Psychological Aspects of Cancer

A Guide to Emotional and Psychological Consequences of Cancer, Their Causes, and Their Management

Jennifer L. Steel
Brian I. Carr
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Second Edition

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He used to say:

If I am not for myself, who will be for me?

And if I am only for myself, what am I?

And if not now, then when?

–Hillel Mishna Avot 1:14

Who is wise? He who learns from every person

–Ben Zoma Mishna Avot 4:1

For my daughters: Ophira and Feridey

Preface

The idea for this book of essays arose after several years during which the co-editors collaborated at the University of Pittsburgh on the medical oncology and psychological care of patients diagnosed with hepato-biliary cancer. Although the need for patient psychosocial support was evident, the time available in an ever-busy clinic was not conducive to the extended discussions that many patients and families wanted. The time pressures on staff in US hospitals are increasing annually, in the name of system and business efficiencies. We noted a dichotomy between ideal total patient care in clinical practice and the realities of limited time per patient for employees of medical organizations. To some extent, patient-enabling Internet communication and services with health-care providers are beginning to be introduced with this dichotomy in mind. Still, the need for real-time, face-to-face contact and sufficient time with health professionals to hear and address their concerns are a patient priority.

The medical/psychological literature has exponentially expanded in the last decade with increasing documentation and sub-set characterization of various aspects of the quality of life of patients and their loved ones. Moreover, feedback from patients has resulted in a further proliferation of research that has extended to family and caregivers, who are rightly seen as important components of the patient environment, as well as subjects in need of study and care in their own right.

The arrival of unwelcome health-related news in the form of a cancer diagnosis would be expected to interrupt a person's self-perception and plans for his or her unfolding life story. Reflection on this interruption will likely result in fear and anxiety about the unknown quality and quantity of life that will now lie ahead. The major part of this book is taken up by considerations of the available resources in support of patient coping with his or her post-diagnosis new life structure as it is imagined and might become. Much of that is worldview driven, as seen in Part 3. Constructing a post-diagnosis new life structure involves concepts of hope, meaning, and spirituality and their various impacts on coping, which in turn may change during the development and course of an individual's disease. All of this is concerned with the various cognitive and emotional aspects of coping with cancer and flows logically from the expected effects of disease on a person's thoughts, hopes, plans, and feelings. An emerging concept, however, is the idea of the potential reversibility of this process, in which thoughts and emotions might influence body function and disease development and its progression. For example, the concept that stress might be involved in and predisposing of cardiac ischemia and peptic dysfunction is very old. Evidence is emerging that these psychological and behavioral processes might also be involved in the development and/or progression of several chronic diseases, such as the inflammatory diseases and cancer. If mental processes can impact the immune and endocrine systems, then they might modulate the inflammatory and tumor growth processes that these systems mediate.

This book opens with two essays on the biological basis of emotion/mental-driven body processes and disease. The consequence of such considerations is that since thoughts and emotions can be modulated and changed with assistance from health-care professionals, then psychological counseling might be seen not only to help patients cope but possibly to influence the disease itself. The book then proceeds to a part on genetic predispositions to cancer and the psychological considerations involved in screening and preemptive therapies and decision-making in cancer therapy. The third part deals with the philosophical and religious underpinnings of psychological factors involved in coping with disease state stressors and the roles of hope in coping. The fourth part is an acknowledgment that patients live in a social context, which often includes a partner and/or caregiver. The fifth part includes several essays on aspects and modalities of caregiving that are designed to help patients coping with their cancer and its aftermath, which increasingly extends for years. This is followed by a part with some considerations of approaches to dying and concerns of those who are left behind. The last part seeks to tie all this together and provide a resource chapter.

This book is not intended as a textbook, but as a set of essays for both health-care professionals and all people whose lives are directly or indirectly affected by cancer, to provide a sense of the activity and several new concepts in the rapidly expanding field of psychological support and psycho-social needs and context of the patient with cancer.

The book is presented in seven parts: A. Biological Basis; B. Prevention and Decision-Making; C. Theory in Psychosocial Oncology; D. The Social Context; E. Patient Support; F. Advanced Cancer; G. Wide-Angle Lens: Resources and Overview.

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Inflammation, Chronic Disease, and Cancer: Is Psychological Distress the Common Thread?

Feridey N. Carr, Elizabeth M. Sosa, and Brian I. Carr

Inflammation is a hallmark of immunological responses to invading microbes and has been implicated in a growing list of major diseases, including rheumatoid arthritis and lupus, inflammatory bowel disease, pulmonary and cardiovascular diseases, obesity, and diabetes mellitus. The focus on chronic inflammation has intensified since it has been linked with specific types of cancer, particularly those associated with viral infection or an inflammatory response. Although some chronic inflammatory diseases have long been acknowledged to increase the risk of malignancy, it is only within the past decade that chronic inflammation has been hypothesized to be a key factor in the development of several cancer types, such as cancer of the pancreas, colon, and liver (hepatocellular carcinoma or HCC). While there is as of yet little evidence to suggest that psychological distress, particularly chronic stress and depression, directly affects the pathogenesis of tumors, there is an increasing amount of scholarship indicating that psychosocial factors directly contribute to the development and maintenance of chronic inflammation. In fact, it is possible that while depression may contribute and increase the levels of circulating pro-inflammatory cytokines, inflammation may itself act on the brain to induce depressive symptomatology. This chapter focuses on the primary disease categories in which inflammation is a known contributor and discusses the mechanisms by which the inflammatory processes interact with carcinogenesis as well as psychological aspects of chronic inflammation. Some clinical considerations are offered for interventions targeting the anxio-depressive symptoms associated with major illness that may also disrupt the chronic inflammatory cycle and its resultant disease process.

Inflammation and Cancer

In 1863, Rudolf Virchow hypothesized that tumors originated at sites of chronic inflammation within the human body [1]. Virchow identified the role of inflammation in carcinogenesis when he noticed the presence of leucocytes in neoplastic tissue and suggested that the "lymphoreticular infiltrate" reflected the origin of malignancies where inflammatory processes occurred [1]. Virchow's claim was not investigated for

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more than a century. Researchers have recently begun examining the hypothesized relationship and directing efforts to research the possible connection between chronic inflammation and cancer. Epidemiological studies have demonstrated that chronic inflammation predisposes individuals to a variety of cancers such as thyroid, bladder, cervical, prostate, esophageal, gastric, pancreas, liver, and colon [1, 2]. About 25% of all deaths from cancer worldwide are attributable to underlying infections and inflammatory responses [3]. Chronic infection and inflammatory responses are known to have associations with the development of certain cancers, such as the human papilloma virus (HPV) and its relationship to cervical cancer or the infection of hepatitis B or C viruses leading to hepatocellular carcinoma (HCC) [4]. Increased risk of tumor growth can be associated with chronic inflammation caused by microbial infections and autoimmune diseases, as in inflammatory bowel disease and the risk of colon and colorectal cancers, as well as inflammatory conditions resulting from uncertain origins such as prostatitis, which can lead to prostate cancer [5–7]. Chronic inflammation contributes to a tumor-promoting environment through various avenues that may include cellular transformation, the proliferation and survival of malignant cells, development of angiogenesis and metastasis, reduction of adaptive immune responses, and tumor response to chemotherapeutic drugs and hormones [7]. The inflammatory response and resultant tumors may be conceptualized as wounds that do not heal [8].

The role of chronic inflammation in the development of cancerous tissue easily becomes convoluted with many aspects that must be considered, such as the contributions of various inflammatory cells, mediators, and signaling pathways in carcinogenesis [7]. The inflammatory process involves the presence of inflammatory cells and inflammatory mediators, which include chemokines and cytokines in tumor tissues, tissue remodeling, and angiogenesis [7]. The prime endogenous promoters include transcription factors such as nuclear factor-kappa B (NF-kB) and signal transducer activator of transcription-3 (Stat3) as well as major inflammatory cytokines, such as interleukin beta (IL-1 b), interleukin 6 (IL-6), interleukin 23 (IL-23), and tumor necrosis factor alpha (TNF-a) [9–12]. TNF-a was the first factor isolated as an anticancer cytokine, but at dysregulated levels within the immune system, its presence mediates a variety of diseases [13]. TNF-a has also been demonstrated to be a major predictor of inflammation [14]. Several pro-inflammatory cytokines have been related to tumor growth, indicating that inflammation is associated with carcinogenesis [1, 15]. These include IL-1, IL-6, IL-8, and IL-18. Interleukins are involved in different steps of tumor initiation and growth. Specifically, Negaard et al. demonstrated that individuals with hematological malignancies have increased bone marrow microvessel density as well as elevated levels of IL-6 and IL-8, possibly contributing to the malignant phenotype [16].

Chemokines are a family of proteins that play several roles in cancer progression, including in angiogenesis, inflammation, cell recruitment, and migration. Chemokines also play a central role in leucocyte recruitment to sites of inflammation [1]. Most tumors produce chemokines that are one of two major groups, alpha and beta chemokines [1]. Evidence from murine models and human tumors support the idea that beta chemokines greatly contribute to macrophage and lymphocyte infiltration in melanoma; carcinoma of the ovary, breast, and cervix; as well as in sarcomas and gliomas [1, 17, 18]. A key molecular link between inflammation and tumor promotion and progression is transcription factor NF-kB, which regulates TNF, interleukins, chemokines, and other molecular factors [9]. Although NF-kB is inactive in most cells, there is an activation state that is induced by a wide variety of inflammatory stimuli and carcinogens that, in turn, mediate tumorigenesis [19].

Inter-Relationship Between Depression and Inflammation

The relationship between the brain and the peripheral organs, often referred to as the “mind–body” connection, is based on alterations in the endocrine and immune systems that lead to the chemical changes that occur in clinical depression. Pro-inflammatory cytokines, particularly IL-6, have been found to occur in greater quantities in depressed patients [20]. It has also been shown that about 45% of patients being treated medically with pro-inflammatory cytokine interferon-alpha (IFNa) developed symptoms of depression that was reversed once the treatment ended [21]. Inflammation is not only a contributing factor in depression but also in many domains of medical illness. Among patients diagnosed with major depression, there is evidence to suggest that relationships exist between severity and duration of depression and increased prevalence of other disease processes, such as cardiovascular disease, type 2 diabetes, a variety of autoimmune diseases, and cancer [22]. Major depressive disorders are also more prevalent in patients who suffer from illnesses that are associated with chronic inflammation than in healthy people [23]. While the presence of an inflammatory disease may initiate depressive symptoms in patients without preexisting psychological disorders, it is also the case that inflammation occurs in depressed patients who are not suffering from concurrent inflammatory disorders [24].

It is now known that the brain is not the “immune-privileged” organ that it was once presumed, as many thought it to be protected by the blood–brain barrier. Rather, the brain is very much influenced by the peripheral immune system where large molecules such as cytokines, chemokines, and glucocorticoids originating in the peripheral organs can affect the neuronal pathways implicated in depression [20, 25]. Recently, it has been shown that symptoms of sickness (fatigue, decreased appetite, social withdrawal, disturbed sleep cycles, and mild cognitive impairment), the normal bodily response to infection, are triggered by pro-inflammatory cytokines, including IL-1a and IL-1b TNF-a and IL-6 [20]. These cytokines are responsible for developing the body’s inflammatory (local and systemic) response to invading microbes. In doing so, they also impact neural circuitry within the brain, resulting in the behavioral symptoms of sickness. Such sickness behavior is remarkably similar to the symptoms of clinical depression. It is generally the role of anti-inflammatory cytokines to regulate the duration of these sickness symptoms, possibly by inhibiting pro-inflammatory cytokine production and interfering with pro-inflammatory cytokine signaling [26].

Despite the evidence to support the mechanism by which pro-inflammatory cytokines act on the brain, the directionality of the inflammation–depression relationship is as yet unclear. As mentioned earlier, there is also research to suggest that depression may predispose people to developing illness. One study attempting to examine the directionality of the inflammation–depression relationship found that baseline depression scores of healthy (no medical illness) patients independently predicted change in IL-6. In contrast, IL-6 did not predict change in depression score [27]. The implication of those findings suggests that depression in previously healthy people may lead to inflammation and inflammation may be the mechanism through which depression potentiates chronic illness.

Rheumatic Disease

Rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), are autoimmune conditions that often involve periods of painful swelling and inflammation in the joints and muscles. The inflammatory stages of RA involve the infiltration by inflammatory cells of the synovial sublining, activating the production of pro-inflammatory cytokines, chemokines, and growth factors that results in synovial lining hyperplasia [28]. This process results in the hyper-activation of macrophage and fibroblast-like synoviocytes, which releases additional cytokines, chemokines, and growth factors [28]. This process leads to systemic inflammation and the production of enzymes that destroy the organized extracellular matrix [29]. IL-6, a cytokine that regulates the immune and inflammatory response, is thought to play pathologic roles in RA [30]. Increased IL-6 levels have been found in both serum and synovial fluid in patients with RA and are also known to correlate with increased disease activity [31, 32]. Baecklund et al. examined disease activity and various secondary symptoms of rheumatic disease, as well as drug treatment to evaluate risk factors for the development of lymphoma, a cancer associated with RA [33]. In a nested case–control study with 41 patients and 113 controls, no association was found between any specific immunosuppressive drug and increased risk of lymphoma. However, a strong association was seen between disease activity and risk of developing lymphoma. In a similar study, Baecklund et al. investigated both RA patient cancer risk and the danger of antirheumatic treatment in lymphoma development [34]. After comparing 378 RA patients positive for malignant lymphoma history with 378 healthy controls, data revealed that individuals with severe disease activity were at increased risk of lymphoma. In addition, increased level of pro-inflammatory cytokines, not drug treatment, predicted lymphoma risk.

Although RA patients' increased risk for developing malignant lymphomas is not completely understood, there are several possible hypotheses that have emerged, including the role of immunosuppression, Epstein-Barr virus infection, and unregulated systemic inflammation [33–39]. In one systematic review and meta-analysis, Smitten et al. characterized the associated risk of four site-specific malignancies that included lymphoma, lung, colorectal, and breast cancer in patients with RA [40]. Results indicated that compared with the general population, RA patients have an approximately twofold increase in lymphoma risk and greater risk of Hodgkin's than non-Hodgkin's lymphoma. There was also data to suggest an increased risk of lung cancer but a decreased risk for colorectal and breast cancer.

The prevalence of psychological distress among patients with rheumatic diseases is a well-known and highly documented phenomenon. Among patients with SLE, there is evidence to suggest a range of 16–65% of patients in active disease states who meet criteria for a psychological disorder [41, 42]. In particular, mood and anxiety disorders appear to be the most frequently occurring [41, 43]. One study showed that 69% of patients diagnosed with SLE were positive for a lifetime history of mood disorder and 52% for lifetime anxiety disorder [44]. Some research links psychological distress, particularly depression, with disease activity in SLE. Segui et al. evaluated patients for depression and anxiety during both active and inactive stages of their disease [42]. Forty percent of participants were diagnosed with a psychological disorder during the acute phase, but only 10% met criteria a year later when the participants no longer displayed disease activity associated with SLE. However, it is often difficult to determine whether this phenomenon has biological influences or is a psychological adaptation to managing a chronic illness. In a study comparing depressive symptoms in patients with RA and patients diagnosed with osteoarthritis (a chronic non-inflammatory degenerative disease), those with the inflammatory disease were found to have significantly higher depressive symptoms [45]. The authors point out that while the two diseases are similar in terms of pain and functional impairments, the difference may be the neuroimmunobiological cytokine mechanism in inflammatory diseases, postulated to play a role in the development of depression. Psychological distress is associated with increased inflammation in both healthy individuals and RA patients [23, 46]. Depression could facilitate the development of inflammation by leading to poor health behaviors, hormonal dysregulation, and vulnerability to atherogenesis [47, 48]. Depression has also been specifically linked to increased levels of CRP and IL-6, as well as increased weight, which itself has been associated with the release of pro-inflammatory cytokines [49, 50].

While results suggest that some depressive symptoms are correlated with CRP and other biomarkers of inflammation, particularly among women with RA, the relationship may be at least partially explained by disease-related factors, such as increased pain among patients with higher levels of inflammation [51]. The proposition that inflammation leads to depression among

RA patients may deserve closer evaluation in longitudinal studies. In addition to experiencing increased pain, patients with RA and SLE often have symptoms such as fatigue and sleep disturbance that may mimic or interact with depression. Results have indicated that depression is a stronger contributor to patient fatigue than self-reported disease activity [52]. Moreover, depression in patients with inflammatory disease predictor of mortality affects quality of life, increases healthcare costs, and contributes to disability [53].

Gastrointestinal Disease

Inflammatory bowel disease (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation and abnormal physiological immune response that flares and then remits throughout an individual's lifetime, often beginning in childhood. Current prevalence rates estimate that inflammatory bowel diseases affect 1.4 million people in the USA [54]. IBD is an example of a disease process where chronic inflammation is known to mediate the risk of cancer and involves both immune deregulation and autoimmunity. The precise mechanisms by which inflammation leads to tumor development are not yet clear; however, patients with IBD, both UC and CD, are at increased risk of developing colorectal cancer [55]. Ulcerative colitis is characterized by the inflammation of the mucosa of the colon and rectum. CD involves inflammation of the bowel wall and may include any part of the digestive tract from the mouth to the anus. Itskowitz and Yio highlight the various predisposing factors that contribute to the link between chronic inflammation and colorectal cancer (CRC) in IBD, explaining how risk of colorectal cancer in IBD increases with longer duration of colitis and with the extent of involvement of the large intestine [56]. There is also a positive association between the severity of colitis and the risk for colon cancer where the risk of colon cancer increases with the severity of disease. Rutter et al. examined risk factors for colorectal neoplasia in patients with UC using a case–control study. Sixty-eight participants were matched with two control patients from the same population on various factors [55]. Results revealed a highly significant correlation between colonoscopic and histological inflammation scores and the risk of colorectal neoplasia, demonstrating that the severity of colonic inflammation is an important determinant of colorectal neoplasia risk. Other studies have shown that IL-6 and STAT3 are activated in the intestinal mucosa in murine models of IBD and colitis-associated cancers [57, 58]. TNF-a concentration is also elevated in the serum and stool of IBD patients [59]. The increased level of TNF-a stimulates the production of other pro-inflammatory cytokines that further promotes the inflammatory process within the microenvironment [60]. Landi et al. examined the specific molecular elements that contribute to inflammatory responses in colorectal cancer and assessed the contributions of IL-6, IL-8, TNF-a, and peroxisome proliferator-activated receptor gamma (PPARG) genes toward the risk of colorectal cancer [61]. Results suggested that a polymorphism in the promoter of the IL-6 gene is associated with a significantly increased risk of colorectal cancer, whereas polymorphisms in the PPARG genes and IL-8 were related to significantly decreased risk. They concluded that IL-6 could be related to CRC through its role in affecting the low-grade inflammation status of the intestine.

The risk of colorectal cancer is much greater in a small subset of IBD patients who also have primary sclerosing cholangitis (PSC), a disorder characterized by inflammation, cholestasis, and fibrosis in the intrahepatic and extrahepatic biliary ducts [56, 62]. Shetty et al. compared patients with ulcerative colitis and co-occurring PSC with a random sample of UC controls without PSC and found that 25% of 132 UC patients with PSC developed colorectal cancer or dysplasia compared with 5.6% of 196 controls [63]. This study demonstrates that UC patients with PSC are at increased risk for developing colorectal cancer or dysplasia and therefore should be closely monitored by their physicians. Research also suggests that some anti-inflammatory medications can reduce the development of colorectal dysplasia and cancer [56, 64]. This last factor provides strong support for the relationship between chronic inflammation and resultant carcinoma and suggests that utilization of anti-inflammatory medications may reduce cancer risk.

Itskowitz and Yio suggest several possibilities that explain how inflammation may result in neoplastic transformation and progression in IBD [56]. One theory suggests that an increase in epithelial cell turnover occurs, perpetuating the molecular and DNA damage caused by heightened levels of pro-inflammatory cytokines and potentially exacerbating the carcinogenic process [56]. Another theory is that the oxidative stress accompanying chronic inflammation among patients with IBD creates an environment that is malignancy prone [65]. While more research is needed to better understand the link, there is mounting evidence demonstrating that chronic inflammatory processes foster an environment where carcinoma is more likely to occur.

Major depression has been shown to occur in 31% of patients diagnosed with CD and in 27% of patients with UC [66]. Compared with patients diagnosed with erosive esophagitis, those with Crohn’s disease (and thus chronic inflammation) have been found to have significantly higher rates of depression (25.4% vs. 8.2%). Depression was also found to be highest among patients with active disease states. Patients with functional gastrointestinal disorders such as irritable bowel syndrome have been shown to have even higher depressive symptoms than patients with organic disorders, such as IBD, as well as more severe depressogenic dysfunctional attitudes [67]. While there is little evidence that psychological distress is related to the onset of IBD, there is more consistent evidence that psychological factors such as depression, anxiety, and chronic life stress contribute to disease course. This may be particularly true of daily life stress and depression among patients with UC and CD [68]. One study evaluating more than 450 patients with CD discovered that the odds of a patient presenting with an exacerbation of their illness increased 1.85 times for 1 standard deviation of perceived stress. After statistically controlling for the mood and anxiety components, the association between perceived stress and exacerbation of illness no longer existed [69].

An interesting theory surrounding the recent increase in reported cases of IBD suggests that lack of exposure to certain microorganisms in industrialized societies may play a role in sensitizing modern immune systems. The theory implicates the over-sanitation of these societies in the rise of major depressive disorder, which may arise from a lack of contact with sources of anti-inflammatory, immunoregulatory signaling [70]. Due to a paucity of immune training, some predisposed individuals may be at greater risk of unnecessary inflammatory attacks on benign environmental and organic antigens. Increased levels of pro-inflammatory and depressogenic cytokines may lead to a higher prevalence of depressive disorders. This theory is often referred to as the “hygiene hypothesis,” and though it is still in its infancy in terms of supporting evidence, the idea is rapidly gaining momentum. To this end, one randomized double-blind study was able to decrease anxiety in patients with chronic fatigue syndrome by introducing a probiotic [71]. Although these are certainly intriguing results, thus far there is little else in the clinical literature to suggest that intestinal microbiota may influence emotional state.

Patients with inflammatory bowel disease are viewed as a population at high risk for developing colorectal cancer, a leading cause of cancer-related mortality. One study evaluating the psychological implications of having such high-risk status found that among patients with IBD, those with higher perceived social support reported lower generalized distress [72]. Additionally, those with first-degree relatives with both colorectal and non-colorectal cancers were found to have higher reported generalized distress. Although there is not yet much research connecting better psychological status with lower incidence of colorectal cancer, it is tempting to surmise whether psychological interventions could improve the course of irritable bowel disease and therefore decrease risk of related cancers.

Obesity and Type 2 Diabetes

The prevalence of obesity is increasing significantly in the USA, and recent estimates demonstrate that nearly two-thirds of the population is currently either overweight or obese [73]. When abdominal obesity is accompanied by other metabolic risks such as insulin resistance, low HDL, and elevated triglycerides, individuals are at increased risk for developing type 2 diabetes, hypertension, hyperlipidemia, and cardiovascular disease [74, 75]. Type 2 diabetes, hypertension, and cardiovascular disease are all complications of disease processes that also involve chronic inflammatory mechanisms. Obesity is associated with a chronic, low-grade inflammation and can itself be viewed as an inflammatory condition since weight gain activates inflammatory pathways [76]. Studies have demonstrated that numerous inflammatory markers are highly correlated with the degree of obesity and insulin resistance [77, 78]. Serum levels of pro-inflammatory cytokines, including IL-6, TNF-a, and CRP, are generally all elevated in individuals with obesity and insulin resistance [79].

It is clear that the adipocyte is an active participant in the generation of the inflammatory state in obesity. Adipocytes secrete several pro-inflammatory cytokines that promote inflammation, including IL-6 and TNF-a [80, 81]. Among patients with type 2 diabetes, these cytokines can enhance insulin resistance directly in adipocytes, muscle, and hepatic cells [82, 83]. Hotamisligil et al. examined the expression pattern of TNF-a in adipose tissue and found that TNF-a plays a role in the abnormal regulation of this cytokine in the pathogenesis of obesity-related insulin resistance [84]. The increased levels of cytokines lead to hepatic production and the secretion of CRP, plasminogen activator inhibitor-1 (PAI-1), amyloid-A, alpha1-acid glycoprotein, and haptoglobin, which are all inflammatory markers that appear in the early stages of type 2 diabetes and increase as the disease progresses [85]. Panagiotakos et al. evaluated the association between various markers of chronic inflammation in a population-based sample of 3042 adults and found that compared with participants with normal body fat distribution, individuals with central fat exhibited 53% higher CRP levels, 20% higher TNF-a levels, 26% higher amyloid-A levels, 17% higher white blood cell counts, and 42% higher IL-6 levels [86]. They also found that all inflammatory biomarkers were related to body mass index (BMI), waist, and waist-to-hip ratios. This study demonstrates a relationship between central adiposity and inflammation that can be associated with increased coronary disease risk. Some research suggests that obesity stimulates inflammation through oxidative stress, which can result either from high levels of free radical production, a decrease in endogenous antioxidant defenses, or both [87–89]. The oxidative stress that is created activates the pro-inflammatory transcription factor, NF-kB, continuing to promote low-grade chronic inflammation [90, 91].

Several epidemiological studies have demonstrated that elevated weight and obesity, defined by a BMI higher than 25, results in significant increase for risk of cancer [92–94]. In a large population-based study, Calle et al. found that the relative risk of cancer-related deaths for men and women was 1.52 and 1.62, respectively [94]. The increase in risk was dependent on the type of cancer, with the largest observed risk being for HCC, the most common form of liver cancer. BMI, in both men and women, was also significantly associated with increased mortality due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney. Moreover, men with higher BMI were at increased risk of death from cancers of the stomach and prostate. Women showed increased risk for death from cancers of the breast, uterus, cervix, and ovary. Park et al. examined how obesity enhanced cancer risk and development by studying HCC in mice [95]. Results revealed that dietary and genetic obesity promoted the growth of tumors associated with the liver. There was a direct association between obesity-promoted HCC development and enhanced production of the tumor-promoting cytokines IL-6 and TNF, both of which cause hepatic inflammation and activate the oncogenic transcription factor STAT3. Such data suggests that inflammatory mechanisms may mediate the association between obesity and cancer development.

The link between depression and obesity is a well-researched one with copious studies supporting it [96–98]. Both obesity and depression are public health problems with high prevalence rates and carry multiple health implications [99]. Evidence suggests that depressed individuals have about an 18% increased risk of becoming obese [96]. An examination of the association between obesity and depression revealed that large waist circumference and class III obesity (BMI >40 kg/m^2) were associated with higher prevalence of depression among female participants only [100]. In a systematic review and meta-analysis of longitudinal studies examining the relationship between depression, weight, and obesity, results suggested a reciprocal relationship between depression and obesity [101]. In a separate review, Taylor and MacQueen examined the role of adipokines (cytokines that are secreted by adipose tissue) in mediating the relationship between obesity and depression [102]. Data revealed that obesity was generally accompanied by the presence of pro-inflammatory cytokines as well as elevated levels of adipokines. Such inflammation increases the risk for individuals with obesity to develop functional bowel disorders such as irritable bowel syndrome, as well as colorectal cancer [103, 104]. Given that sweeping behavioral changes are often necessary to avoid the extensive tissue damage that may result in uncontrolled type 2 diabetes, targeting possible depression in patients with obesity and/or diabetes appears to be an important area for clinical intervention. In fact, assessing overweight or prediabetic patients for depression may also be a crucial step in prevention of serious medical illness.

Pulmonary and Cardiovascular Disease

Pulmonary disease, in particular chronic obstructive pulmonary disease (COPD), deserves special mention due to the fact that it is a progressive illness initiated and exacerbated by inflammatory processes. The illness involves a significant and generally progressive limitation in airflow of the lungs after long-term exposure to irritants and resultant inflammation [105]. COPD is a disease noted for its chronic inflammation in both stable phases and during periods where it becomes exacerbated. It is often associated with comorbidities including cardiovascular disease, diabetes, and hypertension, illnesses involving chronic inflammatory mechanisms. COPD is an important risk factor for atherosclerosis, the beginning stage of heart disease [106, 107]. Several studies have demonstrated that even minimal reductions in expiratory flow volume elevate the risk of ischemic heart disease, stroke, and sudden cardiac death two- to threefold, independently of other risk factors [106–108]. Even though the mechanisms responsible for this link continue to be examined, persistent low-grade systemic inflammation is believed to play a significant role in the development of clot formation [109]. CRP specifically has been implicated in the pathogenesis of plaque formation [110, 111]. Sin and Man (2003) examined data from participants evaluated in the Third National Health and Nutrition Examination Survey to determine whether CRP and other systemic inflammatory markers are present in patients with chronic airflow obstruction and whether they may be associated with cardiac injury [112]. Results indicated that individuals with severe airflow obstruction had circulating leukocyte, platelet, and fibrinogen levels that were higher than in individuals without airflow obstruction. They also discovered that these individuals were more likely to have an elevated circulating CRP level. This data suggests that low-grade systemic inflammation was present in participants with moderate to severe obstruction and was associated with increased risk of cardiac injury.

One of the hallmarks of COPD is a chronic inflammation of the lower airway. COPD increases the risk of lung cancer up to 4.5-fold among long-term smokers [112–114]. Cigarette smokers develop some degree of lung inflammation, but individuals with COPD develop a greater degree that progresses with advanced disease [115]. Cigarette smoke induces the release of several pro-inflammatory cytokines and growth factors including IL-1, IL-8, TGF-beta, and G-CSF through an oxidative pathway [116]. The activation of epithelial growth factor receptor (EGFR) is elevated in bronchial biopsies from smokers with or without COPD compared to nonsmokers [117, 118]. The increased activation of EGFR has been identified to be an early abnormality found in smokers at high risk for developing lung cancer [119]. Moreover, NF-kB is activated by inflammatory processes and by oxidative stress. Since NF-kB is highly activated in both COPD and lung cancer, it is possible that it may provide the molecular association between inflammation and the pathogenesis of tumor in the lung [120].

Among patients with COPD, depression occurs with such a high prevalence that such psychological distress cannot be easily attributed to behavioral factors. In a recent study, prevalence of depression in a Japanese male sample of patients with COPD ranged from just under 30–40%, depending on the screening tool [121]. The severity of COPD also significantly predicted depressive symptoms in participants. In one study investigating whether depression was associated with systemic inflammation in COPD by using a range of biomarkers and several depression and fatigue scales, it was found that TNF-a was correlated with depression score. Patients with a higher TNF-a level had higher mean depression scores. A slightly weaker correlation occurred between TNF-a and fatigue [122]. As COPD results from inflammation and/or changes in immunological repair mechanisms, a “spillover” of inflammatory mediators into circulation often results in greater systemic inflammation [123]. Systemic inflammation may aggravate any comorbid diseases, such as ischemic heart disease, lung cancer, diabetes, and depression. Such co-occurring health problems may increase the severity of COPD, resulting in frequent hospitalizations, increased healthcare costs, and disability. Psychological comorbidities, such as major depression and anxiety, affect the patient’s ability to adhere to their physicians’ recommendations and to cope personally with COPD.

Hypertension is a major risk factor for the development of cardiovascular disease, the prevalence of which is dramatically higher in women with a chronic inflammatory disease, such as SLE. In fact, some studies have shown that up to 74% of their patient samples have significant hypertension [124, 125]. It is likely that the pathogenesis of hypertension involves inflammatory mechanisms, including metabolic factors as well as pro-inflammatory cytokines. The inflammatory process involves adipose tissue, which produces cytokines (leptin and adiponectin) [126]. Blood pressure has been found to correlate with circulating inflammatory cytokines, such as IL-6, TNF-a, and CRP [127]. One study found that the concentration level of circulating IL-6 and adhesion molecules could be modified by decreasing blood pressure in hypertensive subjects. After successfully treating the high blood pressure of participants, the circulating IL-6 was found to be significantly lower [128]. Relationships between inflammation and autonomic function have also been observed: in a sample of cardiac patients, heart rate variability (HRV) was demonstrated to be negatively correlated with inflammatory biomarkers, CRP and IL-6 [129].

Hypertension is a significant risk factor for the development of certain types of malignancies [130–132]. In a study of health records evaluating almost 364,000 men, data revealed a direct relationship between higher blood pressure and increased risk of renal cell carcinoma [133]. Another association was found to occur between obesity and hypertension and higher risk of renal cell carcinoma. Importantly, after the sixth-year follow-up, the cancer risk rose further with increasing blood pressure and decreased with lowered blood pressure. In a systematic review of articles published between January 1966 and January 2000 examining the relationship between hypertension and malignancy, Grossman et al. suggested that individuals with hypertension experienced an increased rate of global cancer mortality, particularly with regard to renal cell carcinoma [134].

Evidence suggests that depression and anger suppression (as opposed to anger expression) are strong predictors of hypertension [135]. Other types of psychological distress that are known to relate to higher blood pressure and poorer cardiovascular outcomes include loss of social support, cultural alienation, and difficulty coping with stressful events [136]. In the USA, historically underserved populations are especially likely to have overlapping psychological distress and higher rates of hypertension, particularly among the urban American Indian and African American communities [137, 138]. Recent research demonstrates that this pattern is also true among newly urbanized peoples, such as urban black South African community. Among a sample of urban black South Africans with hypertension, psychological distress was associated with higher blood pressure as well as left ventricular hypertrophy [139]. It is interesting to note that depression among historically neglected communities is linked not only to hypertension but also to cardiovascular disease, obesity, and chronic inflammatory diseases [140].

Despite increased media attention focused on prevention of cardiovascular disease (CVD), it continues to be the leading cause of death in the USA and the second most common cause of death worldwide [139]. Researchers have recently begun to examine the role of inflammation in atherogenesis and thrombosis and found that inflammatory processes play a role in all stages of atherothrombosis, known to be the underlying cause of approximately 80% of all sudden cardiac deaths [141]. The molecular process involves a response to oxidized low-density lipoprotein cholesterol, injury, or infection whereby leukocytes bind monocytes to the site of a developing lesion. The monocytes become macrophages, forming foam cells and initiating fatty streaks [142]. The macrophages are the main atherosclerotic inflammatory cells that induce a microenvironment that facilitates inflammation. At this stage, activation of macrophages, T lymphocytes, and smooth muscle cells (SMCs) leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis [142, 143]. In a study of carotid artery intima-media thickness (IMT) in hypertensive older adults, researchers found that inflammation, as measured by CRP, was one of the few predictors of arterial IMT [144]. In fact, new therapies aimed at preventing and treating atherosclerosis have targeted cytokine-based inflammatory mechanisms precisely because of the role of chronic inflammation in the development of atherosclerotic plaques [145].

Several studies have shown that elevations in CRP predict future risk of coronary episodes [146, 147]. Specifically, Pasceri et al. examined the effects of CRP on the expression of adhesion molecules in both human umbilical vein and coronary artery endothelial cells and found that CRP induces adhesion molecule expression in human endothelial cells in the presence of serum [148]. These findings support the hypothesis that CRP may play a direct role in promoting the inflammatory component of atherosclerosis. Sakkinen et al. evaluated the relationship between CRP and the development of myocardial infarction (MI) over a 20-year period in men in the Honolulu Heart Program and found that the odds of MI increased not only in the first few years of follow-up but also as far as 20 years into the follow-up period, indicating that inflammation continues to affect the atherosclerotic process throughout all stages [149]. IL-6 is understood to be the principle procoagulant cytokine and can increase plasma concentrations of fibrinogen, plasminogen activator inhibitor type 1, and CRP, thereby amplifying inflammatory and procoagulant responses [148, 150].

Recent attention has focused on the role of mood disturbance among cardiac patients recovering from acute MI as results have suggested that depression contributes to adverse outcomes following cardiac events [151, 152]. In addition to other complications of cardiovascular disease, depression is known to increase the risk of mortality among this population [153]. In fact, the rate of mortality among depressed patients with cardiovascular disease is twice that of their non-depressed peers. Depression has also been demonstrated to have a predictive role in the development of coronary heart disease (CHD) in healthy individuals [154]. The risk of developing CHD has been shown to be about 60% greater in depressed but otherwise healthy patients.

Depression is associated with poor health behaviors, higher life stress, passive coping styles, as well as behavioral risk factors such as smoking, high fat diets, sedentary lifestyle, and lack of adherence to medical advice [153]. Depression also plays a role in the development of local and systemic inflammation, which is associated with CHD [155]. Following episodes of cardiac arrest and cardiopulmonary resuscitation (CPR), survivors often suffer global cerebral ischemia after periods of brain blood flow deprivation. The levels of pro-inflammatory cytokines have been shown to increase dramatically following cerebral ischemia, and this often results in the transportation of circulating immune cells across the blood–brain barrier [156]. Data indicate that the prevalence of depression rises considerably following the occurrence of cerebral ischemia, further exacerbating neuro-inflammation.

Treatment Considerations

Building on the past decade's examination of the psychological contributors to inflammation and consequent disease and cancer, an interesting question is whether psychological intervention may disrupt chronic inflammation and its resultant disease process. A few promising studies have attempted to shed light on the answer by targeting depressive symptoms in patients diagnosed with cancer. In one randomized clinical trial, newly diagnosed breast cancer patients with clinically significant symptoms of depression were assigned to one of two groups: one received the psychological intervention and the other only an assessment. Participants who received the psychological intervention demonstrated significantly reduced levels of depression, pain, fatigue, and pro-inflammatory biomarkers [157]. Interestingly, the effect of the intervention was mediated by its effect on depressive symptoms. In another randomized clinical trial, both depressed and nondepressed women post-coronary artery bypass graft (CABG) surgery were assigned to either home-based cognitive behavioral therapy (CBT) or no intervention [158]. Depressed post-CABG women demonstrated decreased natural killer cell cytotoxicity (NKCC) as well as a higher frequency of infectious illness in the first 6 months after CABG. Depressed women who received the intervention demonstrated an increase in NKCC ($D = 0.67$) and a decrease in IL-6 ($D = 0.61$), CRP ($D = 0.85$), and postoperative infectious illnesses ($D = 0.93$). These results indicate that psychological status is related to impaired immunological functioning and increased rates of preventable illness.

Another angle examined in recent years has been the pharmacological treatment of depression, particularly with regard to selective serotonin reuptake inhibitors (SSRIs) and tricyclics. Researchers have found that activation of the serotonin 5-hydroxytryptamine (5-HT) 2A receptor, known for its role in brain neurotransmission, results in inhibition of TNF-a-mediated inflammation [159]. One clinical trial that involved SSRI treatment of patients with major depression demonstrated a significant decrease in TNF-a and CRP [160]. The changes reflected similar decreases in self-reported depression symptoms. Similarly, other studies found that among patients with major depression treated with an SSRI, IL-6, IL-1 b, and TNF-a, levels were significantly lower posttreatment [161, 162]. It has been demonstrated that the presence of serotonin is required for expression of the inflammatory markers IL-6 and TNF-a. However, it is interesting to note that lower serotonin levels increase, and higher levels decrease, the expression of pro-inflammatory cytokines [163]. The inverted U-shaped trend suggests that serotonin, and therefore mood state in general, is significant in influencing the inflammatory mechanism [159].

HCC: An Example of Multistep Processes: Depression-Obesity-Inflammation-NAFLD-Tumor

Just as there is a relationship between depression and obesity, as discussed above, so there is also a relationship between depression and obesity-associated liver disease or nonalcoholic fatty liver disease or NAFLD [164–170]. Nonalcoholic steatohepatitis (NASH) is a chronic, inflammatory, and progressive form of NAFLD, and its global incidence is increasing. NASH patients are at risk of HCC development. Thus, NASH has become an epidemic and an increasing cause of HCC [171–175]. Thus, not only is inflammation associated with HCC from viral causes [176], but it is also associated with the metabolic syndrome of obesity-associated HCC. Patients with HCC also have increased levels of depression and stress as measured on quality of life questionnaires [177–182]. Furthermore, HCC patients with post-traumatic growth have increased survival compared to those that do not [179], suggesting that psychological factors may play a role in HCC-associated survival. Overall survival was also found in an HCC group of patients who received a comprehensive education and care program, compared to an HCC group that did not [177], lending support to the idea that psychological factors might impact HCC patient survival. Several studies have shown the prognostic significance of anxiety, depression, and quality of life in relation to survival in HCC patients [183–185]. The unanswered question relates to which is cause and which is consequence. If stress and anxiety are causally related to poorer survival in HCC patients, then psychological interventions might have a role in improving HCC patient survival. Regardless, anxiety and especially depression thus are associated with HCC causation (obesity and NASH) and HCC outcomes.

Conclusions and Future Directions

A current major debate among healthcare providers centers on the nature of the role of chronic inflammation in the pathogenesis of cancer. While it appears likely that the inflammatory mechanism is a major contributor toward a tumor-promoting environment that may also involve cellular transformation, the proliferation and survival of malignant cells, development of angiogenesis and metastasis, and reduction of adaptive immune response, direct causation between inflammation and tumor has not yet been established. Due to the rapid expansion of clinical and scientific literature on the topic, it is possible that more decisive evidence will be discovered within the next 5 years. Of perhaps equal interest (though perhaps to slightly different parties) is the interaction between psychological distress and chronic inflammation. While the directionality of this relationship remains unclear, and there is even evidence supporting bi-directionality, data suggests that psychological factors such as major depression, anxiety, chronic and daily life stress, and anger suppression may trigger an inflammatory response. Unregulated, and often aggravated by the contribution of behavioral factors (dietary obesity, smoking, sedentary lifestyle), such immunological response often develops into chronic disease, some of which have been discussed in this chapter. Although there is no evidence to support a direct effect of psychological distress on the development of malignancies, psychosocial factors should be a target of critical importance in clinical settings as they are often modifiable and such intervention may alter or even prevent the course of chronic diseases associated with cancer development. Much of the literature discussed in this chapter indicated that illnesses such as rheumatic disease, gastrointestinal disease, obesity and type 2 diabetes, and pulmonary and cardiovascular disease all have increased risk cancer development associated with chronic inflammation. The obvious and necessary question that follows is whether, and to what extent, reduction of psychological distress could improve the course of certain inflammatory diseases (or diseases where inflammation is a major feature) and therefore decrease risk of cancer.

The interaction between psychological distress and chronic disease is most acute in the health disparities among historically underserved populations in the USA, particularly among some American Indian/Alaska Natives (AI/AN), African American, and Hispanic communities. Various risk factors contribute to such health disparities including ethnicity, social economic status, age, gender, literacy, transportation, and availability of services [186]. Compared with non-Hispanic Whites, AI/AN, Hispanics, Asians, and Pacific Islanders have much higher rates of cancer [187]. National data revealed increased long-term rates of renal cell, HCC, thyroid, melanoma, bladder, and pancreatic carcinomas as well as increased mortality rates from melanoma, esophageal, pancreatic, and liver cancers [187]. Ethnic and racial minority groups in the USA, particularly non-Hispanic Blacks, have a higher prevalence of CVD risk factors. Racial discrimination contributes to disparities in health-related domains, as new studies have linked self-reported experiences of discrimination to adverse cardiovascular health outcomes and hypertension and have been more pronounced for African Americans [188, 189]. In fact, among a sample of older African American adults, experiences of discrimination have been associated with increased levels of pro-inflammatory cytokines [190]. Understanding the role of psychosocial factors can provide important targets for clinical assessment, connection with resources, and interventions. Clinical literature examining health disparities within the context of the interaction between psychological distress and chronic disease is a relatively new but rapidly expanding field and warrants more efforts in this promising direction.

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Psychological Factors and Survivorship: A Focus on Post-treatment Cancer Survivors

Ellen Burke Beckjord, Kerry A. Reynolds, and Ruth Rechis

Psychological Factors and Survivorship: A Focus on Post-treatment Cancer Survivors

Since a “war on cancer” was declared in the 1970s, research and clinical services focused on psychological factors in cancer have followed closely behind medical and epidemiological advances in cancer prevention and control. The field of psycho-oncology, developed to specifically address the “human experience” of cancer (including psychological and emotional experiences), emerged about 10 years after the “war on cancer” began and has been an extremely active area of empirical study and clinical care ever since [1, 2]. Over the past decade in particular, as the number of people alive in the United States with a personal history of cancer surpassed the 10 million mark, psycho-oncology research and practice has increasingly focused on the *post-treatment* phase of the cancer trajectory [3–5]. Fig. 2.1 shows the growth in the number of cancer survivors alive in the United States today over the first decade of the new millennium [6], with a sample of key events that have occurred in psycho-oncology emblematic of the increase in attention paid to life after cancer treatment ends.

The events highlighted in Fig. 2.1 represent significant progress in understanding the experiences of post-treatment cancer survivors and the variety of research and clinical efforts that are underway to ensure that our health-care system is prepared to meet the needs of this population of nearly 12 million (and growing) people. The Biennial Cancer Survivorship conferences held by the National Cancer Institute’s (NCI) Office of Cancer Survivorship [7], in collaboration with the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), and LIVE**STRONG** (the Lance Armstrong Foundation), have created a consistent setting for showcasing cutting-edge research and care practices devoted to post-treatment cancer survivors. The LIVE**STRONG** Survivorship Centers of Excellence represent a platform of diverse cancer centers from which we will derive new knowledge about best practices in post-treatment survi-

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vorship care [8]. Peer-reviewed publications, including *Journal of Clinical Oncology* and *Journal of Cancer Survivorship*, have been created or devoted entire special issues to survivorship care, with an emphasis on the post-treatment period [9, 10]. Surveillance research to document the experiences of post-treatment cancer survivors has been established by LIVE**STRONG** [11, 12], ACS [13], and the CDC, with the inclusion of a cancer survivorship module in the annual Behavioral Risk Factor Surveillance System starting in 2009 [14]. Finally, in the past decade, three landmark reports were released by the Institute of Medicine (IOM): one focused on post-treatment survivorship for pediatric cancers [15]; one devoted exclusively to the transition out of primary treatment for cancer and into post-treatment survivorship [16]; and the third focused on the need for psychosocial care across the cancer trajectory, including in the post-treatment survivorship phase [17].

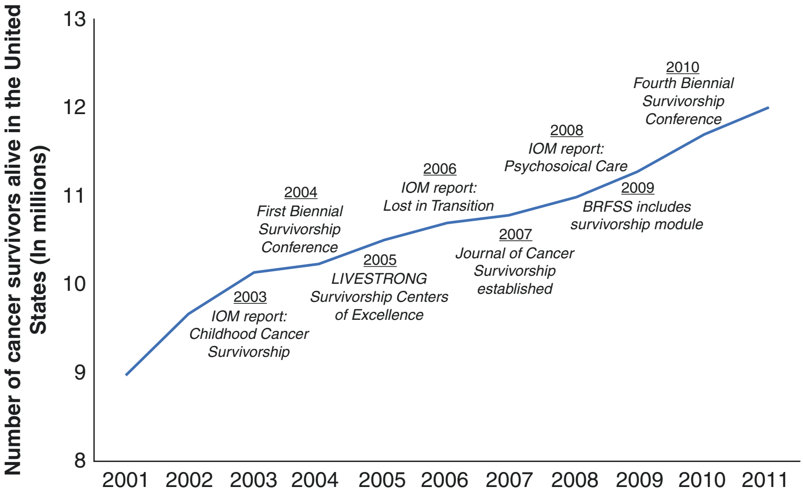

Fig. 2.1 Key post-treatment survivorship events of the past decade

One broad conclusion from the past decade of work devoted to understanding the post-treatment experiences of cancer survivors is that there are numerous physical, emotional, and practical challenges encountered in the post-treatment period [5, 11] and that these challenges are distinct from the experiences people have earlier in the cancer trajectory, near time of diagnosis, or during treatment [16, 18] and require further study to adequately characterize and clinically address [4, 19, 20]. Indeed, even for cancers such as breast cancer – which has been extensively studied from psychological and psychosocial perspectives – we know much more about the psycho-oncology of time near diagnosis and during treatment compared to what we understand about the post-treatment period [21].

This chapter is focused on the psychological experiences of adult post-treatment cancer survivors, which are not as well described or understood in the literature as the physical long-term and late effects of cancer and its treatment [22]. The psychological component of post-treatment cancer survivorship has been referred to by a variety of terms, including psychological health (e.g., [23]); quality of life (e.g., [22]); mental health-related quality of life (e.g., [24, 25]); psychosocial factors (e.g., [21]); depression (e.g., [26]); and broader characterizations of symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD) (e.g., [27]). Here, we will consider a broad range of "psychological factors," certainly not restricted to psychological or psychiatric disorders but more generally a range of emotionally relevant experiences that may cause stress, distress, or disruption in the post-treatment period. As such, we will use terms like "psychological concerns," "distress," "emotional disruption," and the like interchangeably.

At this point, it is worth noting two areas that will not be included in this chapter. There is evidence that *positive* psychological experiences in post-treatment cancer survivorship, such as post-traumatic growth, will not be reviewed in this chapter, though they do represent important psychological factors in cancer survivorship [23, 28] and are commonly encountered in the post-treatment phase. Kornblith and colleagues found that 75% of post-treatment ovarian cancer survivors reported that cancer had had at least one positive impact on their life [29]; Bellizzi and colleagues found that about the same percentage of survivors of non-Hodgkin lymphoma (NHL) reported the same [30]. Yet Bellizzi et al. also found that a similar percentage of post-treatment NHL survivors said that cancer had been responsible for at least one negative impact and that this, rather than positive impact, was associated with (poorer) HRQOL [30]. Other studies have found different results, with associations between post-traumatic growth and more positive psychological outcomes for cancer survivors (e.g., [31]). Overall, we have a better understanding of psychopathology and negative psychological experiences in the context of cancer than we do for positive psychological experiences, and continued methodological and psychometric research is needed to advance what we know about positive psychological outcomes associated with cancer and, in particular, how to promote positive psychological experiences in the post-treatment period [32].

Second, the literature reviewed and data presented will focus on post-treatment survivors of cancers diagnosed in adulthood. Post-treatment survivors of childhood cancers certainly encounter psychological challenges – particularly survivors of central nervous system tumors (compared to hematological malignancies) – and with some evidence that post-treatment psychological adjustment is worse among women, survivors who were treated with cranial radiation therapy, or those who were diagnosed at younger ages [15, 33]. Because the epidemiology of cancer and its treatment for pediatric oncology is relatively distinct from cancers diagnosed during adulthood, this review will focus on post-treatment survivors of adult cancer diagnoses.

Though post-treatment survivorship is an evolving field of inquiry and clinical care [34], there is evidence that psychological concerns are under-addressed in the post-treatment phase [4, 16, 17, 21, 35], with estimates indicating that as many as half of post-treatment cancer survivors do not receive the help they need for emotional or psychological concerns (e.g., [29]). Understanding the psychological experiences of post-treatment cancer survivors is critical to ensuring that our health-care system can better respond to the needs of this growing group. This chapter is divided into three sections: first, we briefly review the literature on the psychological, emotional, and psychosocial experiences of post-treatment cancer survivors, a literature comparatively smaller than studies focused on individuals newly diagnosed or in-treatment (beyond the scope of this chapter). Second, we describe methods and results of a unique data source, the 2010 LIVE**STRONG** Survey for People Affected by Cancer, which provides one of the largest samples of post-treatment cancer survivors' emotional concerns. Finally, we turn to the 2006 and 2008 IOM reports [16, 17] to derive recommendations for addressing psychological factors in survivorship, given the results of the literature to date and the new data provided by the LIVE**STRONG** survey.

Psychological Factors in Post-treatment Cancer Survivorship: A Brief Review

What Do We Know About the Types and Levels of Psychological Distress Encountered in Post-treatment Survivorship?

It is important to begin any review of psychological factors in post-treatment cancer survivorship with an overarching conclusion that has been revealed in numerous studies on the topic: there is no evidence that most post-treatment cancer survivors experience clinically significant levels of emotional distress (i.e., meet diagnostic criteria for a psychiatric disorder) [4, 22–24, 27–29, 35–37]. Further, it is important to qualify this broad conclusion with two other commonly encountered results: there are a not-insignificant number of post-treatment cancer survivors who, though a minority, encounter psychological, psychosocial, and emotional concerns in the post-treatment period that are disruptive and cause for concern [11, 38–43] and the trajectories of psychological experiences of post-treatment cancer survivors are highly idiographic, that is, highly variable and related to a number of premorbid, disease, treatment, and post-treatment factors [19, 35, 36].

Estimates of emotional distress, such as moderate to severe symptoms of anxiety and depression, among post-treatment cancer survivors of multiple cancer types range from in the neighborhood of 15–20% (e.g., [40]) to 20–30% (e.g., [39, 41, 44, 45]) and even as high as greater than 40% (e.g., [42]). Emotional issues typically rank high in lists of post-treatment survivors' unmet needs; in a study of post-treatment ovarian cancer survivors, Kornblith and colleagues found that 30% of women reported that their emotional needs were not fully met, second only to their needs regarding sexual dysfunction [29]. A few studies have used an age-matched control design to determine whether post-treatment cancer survivors have more psychological or emotional problems than their healthy same-aged peers. The results of these studies have been mixed; using nationally representative data from the National Health Interview Survey, Mao and colleagues found that distress was higher among people with a personal history of cancer (26% reported emotional distress) compared to age-matched controls with no history of cancer (16% reported emotional distress) [46]. In a study of individuals enrolled in a managed care organization, post-treatment cancer survivors were statistically significantly more likely to have a psychiatric diagnosis (34%) than age-matched controls (30%), driven largely by higher rates of anxiety or sleep disorders (not including PTSD) among members with a personal history of cancer [47]. In contrast, in a study of post-treatment breast cancer survivors, Ganz et al. showed that HRQOL did not differ between women with a history of breast cancer and age-matched controls, though menopausal symptoms and problems with sexual function were more common in the women with a history of cancer [24]. Other studies have used instruments to measure emotional outcomes among post-treatment cancer survivors that have normative data available for comparison. These studies have generally found that the outcomes for post-treatment cancer survivors are as good as or better than population norms (e.g., [21, 29]).

In addition to symptoms of general anxiety and depression, studies have also specifically examined symptoms of PTSD, which has been shown to be the most commonly diagnosed psychiatric condition among newly diagnosed cancer patients [48]. Clinically significant levels of PTSD symptoms have been estimated at lower levels than anxiety and depression, usually at levels between 10% and 20% (e.g., [27]). However, in a recent study of NHL survivors who were at least 7 years post-diagnosis, PTSD symptoms had persisted or worsened over a period of 5 years after treatment for more than one-third of survivors [49]. In a sample of cancer survivors 1-year post-stem cell transplant, Rusiewicz and colleagues [42] found that symptoms of PTSD were not universally common. In fact, in their sample, some survivors reported high levels of emotional distress and symptoms of PTSD, while others reported high levels of emotional distress with no symptoms of PTSD (i.e., symptoms of more general anxiety and/or depression), suggesting that symptoms of PTSD may represent a distinct psychological experience in the post-treatment period.

In contrast to symptoms of depression, anxiety, or PTSD, a psychological experience that is often found to be prevalent among post-treatment cancer survivors is fear of recurrence [4, 50, 51]. Estimates of the percentage of post-treatment survivors who report fears of recurrence range upwards of 30% [22, 23, 28, 36, 39, 52]. Fears of recurrence are more common among post-treatment survivors with other psychological concerns, such as symptoms of anxiety and depression, but interestingly, fears of recurrence have not always been shown to significantly disrupt quality of life [44]. This may be, in part, due to fears of recurrence occurring in conjunction with follow-up tests and treatments, thereby leaving long stretches of time when post-treatment cancer survivors may be able to keep fears of recurrence successfully at bay [16, 44].

Finally, the length of time that psychological disruptions last for post-treatment survivors varies significantly. There is some evidence that emotional concerns resolve at a slow pace over the first year post-treatment [21]; other studies suggest that distress remains for longer, between 1 and 2 years after treatment ends [38]. Long-term studies of post-treatment cancer survivors have documented the typical 20–30% of participants with emotional problems as far out as 4 years post-diagnosis [27]. We explore the relationship between time since diagnosis and psychological distress more fully in the next section of this review, where we consider the correlates of psychological disruption in post-treatment survivorship.

What Disease and Sociodemographic Factors Are Associated with Psychological Disruption in the Post-treatment Period?

With an understanding of the nature of psychological problems encountered in the post-treatment period, it is reasonable next to consider under what circumstances such problems are most likely to present. A useful framework, introduced by Andrykowski and colleagues [23], identifies a necessary balance or match between the stress and burden associated with cancer and the resources that one has available to cope with or respond to that stress and burden as a critical factor in preventing psychological distress. When these factors are not matched or balanced, either due to an increase in stress or burden, a decrease in resources, or both, psychological problems are likely to occur.

Evidence for this framework's validity in the post-treatment period can be found across a variety of studies involving numerous types of cancer. Regarding factors that increase the stress and burden of cancer and that have been associated with more psychological problems in the post-treatment period, multiple studies have shown that survivors who are experiencing more physical symptoms or problems are more likely to experience more emotional problems as well [4, 23, 46]. The most commonly encountered physical problems in the post-treatment period are fatigue, cardiovascular disorders, fertility, and second malignancies [53]; a full review of these and other physical long-term and late effects is beyond the scope of this chapter, but it is worth noting that a challenge in diagnosing and treating psychological issues in post-treatment survivorship is that commonly encountered physical issues (e.g., fatigue) are also symptoms of psychiatric disorder (e.g., major depressive disorder; [26]). There is some evidence that physical problems that have significant and direct impact on function or physical appearance are more likely to be associated with worse psychological outcomes (e.g., surgical treatment for cancer that results in disfigurement or loss of a specific bodily function; [36]). Further, while the relationship between physical and emotional problems is not unique to the cancer experience, it may be particularly important in the context of post-treatment survivorship. In their study of cancer survivors and age-matched healthy controls, Mao and colleagues found that more physical problems were associated with higher levels of emotional distress only among cancer survivors but not for those without a history of the disease [46].

Also related to the stress and burden of the cancer experience are treatment received and time since diagnosis. A significant amount of evidence has indicated that cancer survivors who undergo systemic treatment with chemotherapy are more likely to experience psychological problems in the post-treatment period [22, 35, 36, 49]. Additional, though not direct, support for this hypothesis can be found in a study by Rusiewicz and colleagues [42], who showed that 43% of cancer survivors 1-year post-stem cell transplant reported clinically significant levels of emotional distress, a percentage that is arguably higher than what is typically observed. This may, in part, be due to the severity of the treatment experience of stem cell transplant that is also more intense than typically experienced in other types of cancer. Still, the association between receipt of systemic treatment and poorer psychological outcomes is not universal: a recent publication by Ganz and colleagues found no significant difference in psychosocial recovery for breast cancer survivors who did and who did not receive chemotherapy (though did note that for women who did receive chemotherapy, symptoms tended to be more severe and to persist somewhat longer; [21]). Other results suggest that survivors' recalled experiences of symptom severity during treatment are better predictors of long-term psychological outcomes, as compared to treatment received per se [44]. This result underscores the idiographic nature of the cancer experience and the relationship between treatment and emotional outcomes – the "emotional fallout" of cancer and its treatment [36] for two people affected by cancer who experience the same type of treatment very differently is likely to be different as well. For time since treatment ended, though there is some reasonable support for the assertion that emotional distress subsides in the first year or two post-treatment (e.g., [4, 35, 52]), other studies have observed no relationship between time since diagnosis or when treatment ends and emotional outcomes [46], or observe relatively high percentages of post-treatment survivors reporting emotional concerns far into the post-treatment period (e.g., [27]).

Andrykowski's framework [23] suggests that resources are required to prevent the stress and burden posed by cancer and its treatment from negatively affecting psychological outcomes. "Resources" can be interpreted fairly broadly but should at least include premorbid psychological distress (which would presumably reduce resources available for dealing with the stress and burden of cancer) and a variety of psychosocial and environmental resources that may provide support during the cancer experience as well. Indeed, individuals with a history of psychiatric disorders have been found to be more likely to experience higher levels of emotional distress during their cancer experience [48], including the post-treatment period [4, 28, 36]. It is worth noting that the percentage of cancer survivors who have a history of a psychiatric disorder has been shown to be comparable to the percentage of the general population with such a history, at a lifetime prevalence rate of about 50% [48, 54]. Other resources associated with better psychological outcomes in the post-treatment period include external and internal factors such as having a spouse or partner (e.g., [22]) or adequate social support [27, 36]; higher socioeconomic status evidenced by level of education attained and annual income [22, 27, 46, 49]; and personality or trait-like variables such as dispositional optimism [4, 44].

Finally, there are some sociodemographic characteristics associated with emotional outcomes in the post-treatment period that do not easily fit into the "stress or burden" or "resource" categories which are age and gender. Female post-treatment survivors have consistently reported more emotional concerns in the post-treatment period as compared to men (e.g., [38, 45, 46]), and younger survivors report more psychological disruption as well [22, 25, 36–39, 45, 46]. For example, though Mao and colleagues found that individuals with a history of cancer reported, on average, higher levels of emotional distress compared to age-matched healthy controls, they found that this difference was largest for cancer survivors under age 44 [46]. The increased distress among younger post-treatment cancer survivors may be a function of a sense of social isolation, as more than 50% of all cancer diagnoses occur in individuals age 65 and older [3]. Finally, race and ethnicity have not consistently been associated with psychological outcomes in the post-treatment period, though in one study [22], they were found to moderate an association between physical and emotional concerns, wherein African American prostate cancer survivors reported more emotional distress than Whites experiencing the same levels of sexual dysfunction in the post-treatment period.

Summary

While clinically significant levels of emotional distress may not be common in a majority of post-treatment cancer survivors, a variety of psychological concerns are encountered in the post-treatment period; some are more common than others (e.g., fear of recurrence) and are more likely to occur for individuals who experience stress and burden associated with cancer in excess of resources available to cope with that stress. Given the idiographic nature of psychological factors in post-treatment cancer survivorship, it would be particularly useful to examine a variety of emotional concerns in a large sample of individuals in the post-treatment period who are asked to reflect on the experience of emotional concerns that are specifically new to them since completing their treatment for cancer. Though framing the question of emotional concerns in this way is not free from problems of potential recall bias (i.e., will survivors accurately recall whether a specific emotional concern did or did not have a pre-treatment onset?), asking about new emotional concerns since treatment ended across a variety of areas and examining the correlates of emotional concerns, their relationship with physical concerns, and patterns of care received for emotional concerns would significantly advance our understanding of the post-treatment emotional landscape. The 2010 LIVE**STRONG** Survey for People Affected by Cancer provides such a data source and will be examined here.

The Emotional Concerns of Post-treatment Cancer Survivors: Evidence from the 2010 LIVESTRONG Survey for People Affected by Cancer

Participants and Procedures

The 2010 LIVE**STRONG** Survey for People Affected by Cancer built upon the 2006 LIVE**STRONG** Survey for Post-treatment Cancer Survivors [12]. The 2006 survey instrument was designed through a process that engaged both cancer survivors and experts in the field of survey methodology and oncology through peer review, focus groups, and a pilot test. The majority of the 2010 survey content was focused on the physical, emotional, and practical concerns of post-treatment cancer survivors; however, there were additional areas of the survey aimed at survivors currently in treatment and individuals affected by cancer who did not have a personal history of cancer. The results shown here are focused on the 3682 post-treatment cancer survivors who completed the 2010 survey. Post-treatment cancer survivors included individuals who had been diagnosed with cancer and who reported that they were currently finished with treatment or were managing cancer as a chronic condition.

The survey was fielded online and opened on June 20, 2010, in conjunction with the release of *Parade* magazine's issue devoted to cancer survivorship. The survey was available on LIVESTRONG.org as well as LIVESTRONGespanol.org. LIVESTRONG constituents, including cancer patient and survivors, were notified about the survey by email and through Twitter and Facebook. Additionally, LIVE**STRONG** reached out to many of its community, national and international partner organizations, and all state cancer coalitions to provide information about the survey and to assist these organizations in reaching potential respondents. LIVE**STRONG** also collaborated with Comprehensive Cancer Centers, such as members of the LIVE**STRONG** Survivorship Center of Excellence Network, to share the survey with their constituents. The study was reviewed and approved by the Western Institutional Review Board.

Measures

Physical and Emotional Concerns The goal of the LIVE**STRONG** survey program is to gather surveillance data from large groups of people affected by cancer, with an emphasis on post-treatment cancer survivors. The surveys assess whether or not survivors are currently experiencing specific concerns, the degree to which those concerns cause functional impairment, and whether or not care is received to help alleviate their concerns. As such, symptom checklists or multi-item measures of physical health or emotional outcomes were not well suited for the LIVE**STRONG** survey efforts; rather, **LIVESTRONG** research staff developed content for the survey (in collaboration with subject matter experts and with feedback from their constituency) that would allow respondents to indicate if they were experiencing a particular physical or emotional concern in the post-treatment period (practical concerns were assessed as well, though will not be addressed here; please see [11] for a full description of the 2006 and 2010 LIVE**STRONG** surveys).

Post-treatment cancer survivors were asked about physical and emotional concerns that had a post-treatment onset; that is, they were asked to endorse physical and emotional concerns that they were experiencing in the post-treatment period that they had not experienced before their treatment began. Physical and emotional concerns were organized into groups of related items, which will be referred to as "collections." For example, one emotional concern collection contained four items related to sadness and depression (e.g., "I have felt blue or depressed"). If a respondent endorsed any item in a collection, then they were counted as having endorsed the concern category. Fourteen collections focused on physical concerns (e.g., incontinence; sexual dysfunction; pain); eight focused on emotional concerns (for a full copy of the survey and complete list of the physical concerns queried, please see [11]).

The eight emotional concerns considered in the 2010 survey were fear of recurrence (three item collection; e.g., "I have been preoccupied with concerns about cancer"); sadness and depression (seven item collection; e.g., "I have felt blue or depressed"); grief and identity issues (four item collection; e.g., "I have felt that I have lost a sense of my identity"); family member cancer risk (three item collection; e.g., "I have worried that my family members were at risk of getting cancer"); personal appearance (three item collection; e.g., "I have felt unattractive"); cancer-related stigma (four item collection; e.g., "I have felt ashamed because I have had cancer"); personal relationships (five item collection; e.g., "I have been reluctant to start new relationships"); and faith and spirituality (two item collection; e.g., "I have felt that I have lost a sense of my faith or spirituality").

Functional Impairment If a respondent endorsed any item in an emotional concern collection, they were counted as having endorsed that emotional concern and were further asked to what degree the concern impaired their daily functioning (*a lot*, *a little*, *not at all*, *don't know*).

Receipt of Care Finally, if a respondent endorsed an emotional concern collection, they were asked whether they had received care for the concern (*yes*, *no*).

Sociodemographic and Medical Variables A number of sociodemographic and medical variables are included in the current study, based on variables that have been associated with psychological factors in post-treatment survivorship and that represent indices of the stress and burden of cancer as well as resources to cope with cancer. These include age; gender; race/ethnicity; level of education; marital status; annual income; time since treatment ended; and type of treatment received.

Data Analysis

Data were analyzed using SPSS 16.0. Descriptive statistics were used to summarize the emotional concerns of post-treatment cancer survivors and their sociodemographic and medical characteristics. Bivariate statistics (*t*-tests; bivariate correlation; analysis of variance) were used to examine associations between number of emotional concerns and sociodemographic and medical variables, including number of physical concerns reported. We used logistic regression to model the endorsement of each of the emotional concern categories separately, where each model included the same independent variables (sociodemographic characteristics; medical variables; and number of physical concerns). Linear regression was used to model the total number of emotional concerns reported in the context of sociodemographic and medical variables and number of physical concerns reported. Finally, we used logistic regression to look at the correlates of having received care for any emotional or physical concern, where dependent variables included sociodemographic characteristics; medical variables; number of physical concerns; and number of emotional concerns. Due to the high number of statistical tests conducted, we chose to conservatively evaluate statistical significance at a level of $p < 0.01$.

Results

Sample Characteristics Table 2.1 shows the sociodemographic and medical characteristics of the 3682 post-treatment cancer survivors who responded to the 2010 LIVE**STRONG** Survey for People Affected by Cancer.

Table 2.1 Sample description ($n = 3682$)

Current age	49.9 years (SD = 12.2)
Gender	65.2% female
Race/ethnicity	93.3% white
Level of education	High school or less: 8.5%
	Some college: 36.4%
	College degree: 31.7%
	Post-college degree: 23.4%
Annual income	$60 K or less: 28.4%
	$61 K to ≤$100 K: 24.7%
	$100 K or more: 27.3%
	Prefer not to answer: 19.6%
Marital status	66.8% married
Age at diagnosis	43.4 years (SD = 13.9)
Time since last treatment	4.37 years (SD = 5.85)
Type of cancer	Breast: 27.5%
	Testicular: 6.4%
	Non-Hodgkin lymphoma: 5.6%
	Hodgkin lymphoma: 4.7%
	Prostate: 6.9%
	Other (includes more than 50 types of cancer, each reported by less than 5% of respondents): 48.9%
Type of treatment	Chemotherapy, radiation, and surgery: 26.3%
	Chemotherapy plus radiation or surgery: 23.8%
	Only chemotherapy: 8.7%
	No chemotherapy: 41.3%
Number of emotional concerns	3.67 (SD = 1.9) (range = 0–8)
Number of physical concerns	3.56 (SD = 2.6) (range = 0–14)

The sample was relatively young, with an average age under 50 years, and more than half were female. The vast majority reported White race/ethnicity, and most (about 55%) had at least a college degree or more education. More than one-quarter had an annual income of more than $100,000 per year (though about 20% preferred not to answer the income query). About 70% of the sample were married or living with a partner.

On average, more than 4 years had passed since respondents' last treatment for cancer, and the average age at diagnosis for the sample was 43 years old. A wide variety of cancer types were represented, the largest being breast cancer survivors (27.5%), though no other cancer type included more than 10% of the sample. Respondents had endured a lot of treatment for their cancer: more than half had received chemotherapy as part of their treatment regimen, and within that group, most received at least on other treatment (surgery, radiation, or both) as well. Finally, respondents reported an average of almost four post-treatment emotional and physical concerns.

Emotional Concerns Figure 2.2 shows the percent of respondents who endorsed each emotional concern.

Overall, 95% of respondents endorsed at least one emotional concern. Fear of recurrence was most common, with more than 70% of respondents endorsing that concern. Half or more of the sample reported sadness and depression, grief and identity concerns, and concerns about family member risk for cancer. More than one-third endorsed having new concerns since treatment ended about personal appearance, personal relationships, and dealing with cancer-related stigma; a small number (10%) reported concerns about faith and spirituality.

Though many survey respondents endorsed these emotional concerns, few reported that the concerns caused "a lot" of functional impairment. Less than 10% of respondents who endorsed any concern said that it caused "a lot" of functional

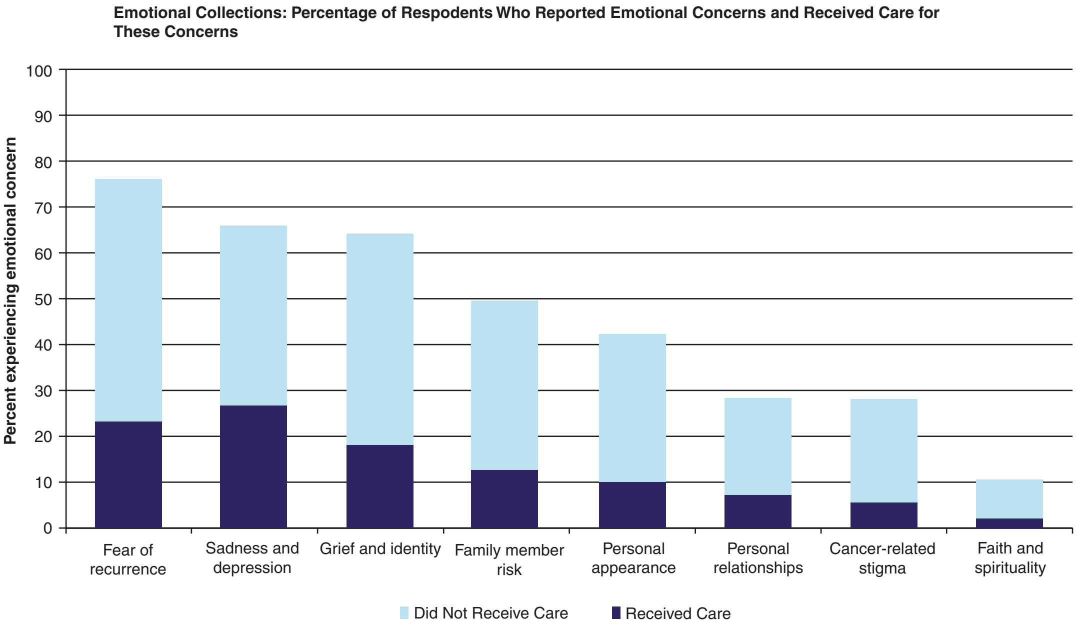

Fig. 2.2 Prevalence of emotional concerns and care received for each

impairment, except for those reporting concerns about personal appearance (10% reported "a lot" of functional impairment); personal relationships (16% reported "a lot" of functional impairment); and concerns about faith and spirituality (12% reported "a lot" of functional impairment). In fact, though fears of recurrence were the most commonly endorsed emotional concern, it was ranked sixth out of eight concerns in terms of functional impairment (only 6% reported that fears of recurrence caused "a lot" of functional impairment), whereas concerns about faith and spirituality were least common but ranked second in terms of functional impairment.

Figure 2.2 also shows, for each group of respondents who reported an emotional concern, the percentage who reported to receive care for the concern. The results here are fairly alarming, given that fewer than half of any group of post-treatment cancer survivors reporting an emotional concern said that they received care for the concern, though in light of the functional impairment data, it may be that for most survivors with emotional concerns, the concerns do not disrupt their lives to a degree that they believe warrants treatment. Further, receipt of care was higher when looking across all emotional concerns: overall, 66% of respondents who reported at least one emotional concern said that they received care for an emotional concern.

In bivariate analyses (data not shown; all $p < 0.01$), more emotional concerns were associated with younger age; female gender; not having a spouse or partner; and by those with annual incomes of $60,000 per year or less (compared to those making $100,000 or more). Regarding medical variables, longer times since treatment ended were associated with fewer emotional concerns; respondents who had received the most treatment (chemotherapy plus radiation and surgery) reported the most emotional concerns; and respondents who reported more physical concerns reported more emotional concerns as well (bivariate correlation = 0.47).

Who Reports Which Concerns? Multivariate Logistic Models of Each Concern Category To examine whether specific sociodemographic and medical characteristics were differentially associated with each of the eight emotional concerns queried in the survey, we used multivariate logistic regression to model the odds of endorsing each concern category separately (Table 2.2). Two variables were consistently associated with

Table 2.2 Logistic regressions modeling endorsement of each emotional concern separately

Study variables		Fear of recurrence	Sadness and depression	Grief and identity	Family member risk
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age		0.98 (0.97, 0.98)*	0.98 (0.97, 0.99)*	0.98 (0.98, 0.99)*	0.99 (0.99, 1.00)
Gender	Male	(reference)	(reference)	(reference)	(reference)
	Female	1.43 (1.19, 1.72)*	1.09 (0.93, 1.29)	1.18 (1.00, 1.40)	1.44 (1.23, 1.68)*
Race/ethnicity	White	(reference)	(reference)	(reference)	(reference)
	Other	0.66 (0.47, 0.92)	0.85 (0.62, 1.16)	0.78 (0.57, 1.07)	1.05 (0.78, 1.41)
Education	College or more	(reference)	(reference)	(reference)	(reference)
	College graduate	0.87 (0.68, 1.10)	1.10 (0.89, 1.36)	0.98 (0.79, 1.21)	1.10 (0.91, 1.34)
	Some college	0.79 (0.62, 0.99)	1.01 (0.82, 1.24)	0.84 (0.69, 1.04)	1.16 (0.95, 1.41)
	≤High school	0.56 (0.41, 0.83)	1.05 (0.75, 1.45)	1.00 (0.71, 1.39)	1.27 (0.94, 1.73)
Marital status	Married/partnered	(reference)	(reference)	(reference)	(reference)
	Other	0.82 (0.67, 1.00)	0.87 (0.72, 1.04)	0.89 (0.74, 1.07)	0.68 (0.57, 0.81)*
Annual income	<$60 K	(reference)	(reference)*	(reference)	(reference)
	$61 K to ≤$100 K	1.07 (0.84, 1.37)	0.93 (0.74, 1.15)	1.01 (0.80, 1.27)	0.93 (0.75, 1.14)
	$100 K or more	1.19 (0.92, 1.54)	1.33 (1.06, 1.69)	0.93 (0.74, 1.17)	0.97 (0.78, 1.20)
	Prefer not to answer	1.08 (0.83, 1.41)	1.11 (0.87, 1.41)	1.02 (0.80, 1.31)	0.84 (0.67, 1.06)
Type of treatment	Chemo, radiation, and surgery	(reference)	(reference)	(reference)	(reference)*
	Chemo and radiation OR surgery	1.08 (0.86, 1.37)	1.08 (0.87, 1.36)	1.01 (0.81, 1.26)	0.78 (0.64, 0.96)
	Chemotherapy only	1.00 (0.71, 1.42)	1.30 (0.94, 1.80)	1.16 (0.85, 1.60)	0.65 (0.49, 0.87)*
	No chemotherapy	1.08 (0.86, 1.37)	1.02 (0.83, 1.25)	0.83 (0.67, 1.02)	0.98 (0.81, 1.19)
Time since treatment ended		0.99 (1.09, 0.99)*	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)*
Number of physical concerns		1.13 (1.09, 1.18)*	1.25 (1.21, 1.30)*	1.28 (1.23, 1.32)*	1.11 (1.08, 1.14)*
		Personal appearance	Personal relationships	Cancer-related stigma	Faith and spirituality
Study variables		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age		0.97 (0.97, 0.98)*	0.98 (0.98, 0.99)*	0.96 (0.96, 0.97)*	0.98 (0.97, 0.98)*
Gender	Male	(reference)	(reference)	(reference)	(reference)
	Female	2.65 (2.21, 3.12)*	0.99 (0.81, 1.20)	1.33 (1.01, 1.60)*	0.88 (0.68, 1.13)
Race/ethnicity	White	(reference)	(reference)	(reference)	(reference)
	Other	0.75 (0.54, 1.04)	0.97 (0.68, 1.37)	0.85 (0.60, 1.21)	1.10 (0.71, 1.71)

(continued)

Table 2.2 (continued)

Study variables		Fear of recurrence	Sadness and depression	Grief and identity	Family member risk
Education	College or more	(reference)	(reference)	(reference)	(reference)
	College graduate	1.21 (0.97, 1.51)	0.95 (0.75, 1.21)	0.86 (0.68, 1.09)	0.79 (0.58, 1.07)
	Some college	1.03 (0.83, 1.28)	0.80 (0.63, 1.01)	0.82 (0.65, 1.03)	0.65 (0.48, 0.89)
	≤high school	1.09 (0.78, 1.53)	0.96 (0.67, 1.37)	0.57 (0.39, 0.83)	0.49 (0.29, 0.84)
Marital status	Married/partnered	(reference)	(reference)	(reference)	(reference)
	Other	1.04 (0.86, 1.26)	2.69 (2.21, 3.27)*	1.32 (1.08, 1.61)*	1.10 (0.85, 1.44)
Annual income	<$60 K	(reference)*	(reference)	(reference)	(reference)
	$61 K to ≤$100 K	0.91 (0.72, 1.14)	0.82 (0.65, 1.05)	1.04 (0.81, 1.32)	0.89 (0.65, 1.23)
	$100 K or more	0.90 (0.71, 1.14)	0.71 (0.55, 0.92)	0.90 (0.70, 1.16)	0.84 (0.60, 1.17)
	Prefer not to answer	0.57 (0.44, 0.74)*	0.70 (0.53, 0.92)	0.91 (0.70, 1.20)	0.73 (0.49, 1.06)
Type of treatment	Chemo, radiation, and surgery	(reference)*	(reference)*	(reference)	(reference)*
	Chemo and radiation OR surgery	0.86 (0.69, 1.07)	0.89 (0.70, 1.13)	0.90 (0.71, 1.14)	0.74 (0.54, 1.02)
	Chemotherapy only	0.71 (0.52, 0.97)	1.19 (0.85, 1.67)	0.98 (0.70, 1.36)	0.57 (0.34, 0.94)
	No chemotherapy	0.61 (0.50, 0.76)*	1.53 (1.21, 1.93)*	1.23 (0.98, 1.56)	1.14 (0.89, 1.54)
Time since treatment ended		0.99 (0.99, 0.99)*	0.99 (0.99, 1.00)*	0.99 (0.98, 0.99)*	1.00 (0.99, 1.00)
Number of physical concerns		1.34 (1.30, 1.39)*	1.41 (1.35, 1.46)*	1.20 (1.16, 1.24)*	1.18 (1.13, 1.24)*

$^{*}p<0.01$

higher odds of endorsing each emotional concern: younger age (except for the concern of family member risk of cancer, which was not associated with age) and reporting more physical concerns (all $p < 0.01$). Education, race/ethnicity, and annual income were not reliably associated with any emotional concerns, except survivors who preferred not to report their annual income had significantly lower odds of reporting concerns about their physical appearance, compared to those who reported less than $60,000 per year (OR = 0.57; 95% CI = 0.44, 0.74; $p < 0.01$).

Compared to men, women had higher odds of reporting fear of recurrence (OR = 1.43; 95% CI = 1.19, 1.72); concerns about family member risk of cancer (OR = 1.44; 95% CI = 1.23, 1.68); concerns about personal appearance (OR = 2.65; 95% CI = 2.21, 3.12); and cancer-related stigma (OR = 1.33; 95% CI = 1.01, 1.60; all $p < 0.01$). Respondents without a spouse or partner were significantly less likely to endorse concerns about family member risk of cancer (OR = 0.68; 95% CI = 0.57, 0.81) but were more likely to report concerns about personal relationships (OR = 2.69; 95% CI = 2.21, 3.27) and cancer-related stigma (OR = 1.32; 95% CI = 1.08, 1.61; all $p < 0.01$).

Finally, for medical variables, respondents who received less treatment had lower odds of endorsing some emotional concerns compared to post-treatment survivors who had received chemotherapy, radiation, and surgery. Survivors who only received chemotherapy had lower odds of reporting concerns about family member cancer risk (OR = 0.65; 95% CI = 0.49, 0.87), and survivors who did not receive chemotherapy had lower odds of reporting concerns about personal appearance (OR = 0.61; 95% CI = 0.50, 0.76) but higher odds of reporting concerns about personal relationships (OR = 1.53; 95% CI = 1.21, 1.93; all $p < 0.01$). Longer times since treatment ended were associated with fewer emotional concerns, including lower odds of reporting fears of recurrence; concerns about personal appearance; personal relationships; or cancer-related stigma (all ORs = 0.99; $p < 0.01$); however, longer times since treatment ended were associated with slightly higher odds of reporting concerns about family member risk of cancer (OR < 1.01; $p < 0.01$).

Who Reports the Most Concerns? Multivariate Linear Regression Model of Number of Emotional Concerns

In looking at the sociodemographic and medical characteristics associated with number of emotional concerns reported (Table 2.3), only younger age (**B** = −0.19), female gender (**B** = 0.11), and reporting more physical concerns (**B** = 0.44) were associated with reporting more emotional concerns (all $p < 0.01$).

Longer times since treatment ended were marginally associated with fewer emotional concerns (**B** = −0.04; $p = 0.02$) as was preferring not to report annual income (as compared to reporting $60,000 or less per year; **B** = -0.05; $p = 0.02$).

Who Is Most Likely to Receive Care for Concerns? Finally, we used multivariate logistic regression to examine associations between sociodemographic characteristics, medical variables, and emotional and physical concerns with odds of receiving care for emotional or physical concerns for respondents who reported at least one emotional concern ($n = 2869$). In the model of receipt of care for emotional concerns (Table 2.4), we found that women were more likely to have received care for emotional concerns compared to men (OR = 1.64; 95% CI = 1.36, 1.97). Longer times since diagnosis were associated with slightly higher, though significant, odds of receiving care for emotional concerns (OR = 1.00; 95% CI = 1.00, 1.01), and compared to survivors who received chemother-

Table 2.3 Linear regression modeling total number of emotional concerns (model adjusted $R^2 = 0.28$)

Study variables		Standardized β (beta)	*p*
Age		**−0.19**	**<0.01**
Gender	Male	(reference)	
	Female	**0.11**	**<0.01**
Race/ethnicity	White	(reference)	
	Other	−0.03	0.10
Education	College or more	(reference)	
	College graduate	0.00	0.98
	Some college	−0.03	0.23
	≤High school	−0.03	0.09
Annual income	<$60 K	(reference)	
	$61 K to ≤$100 K	−0.02	0.42
	$100 K or more	−0.02	0.32
	Prefer not to answer	−0.05	0.02
Marital status	Married/partnered	(reference)	
	Other	0.03	0.09
Type of treatment	Chemo, radiation, and surgery	(reference)	
	Chemo and radiation OR surgery	−0.03	0.06
	Chemotherapy only	−0.01	0.66
	No chemotherapy	−0.01	0.43
Time since treatment ended		−0.04	0.02
Number of physical concerns		**0.44**	**<0.01**

Table 2.4 Logistic regression modeling receipt of care for emotional concerns (for respondents who reported at least one emotional concern; $n = 2869$)

Study variables		OR (95% CI)
Age		0.99 (0.98, 1.00)
Gender	Male	(reference)
	Female	1.64 (1.36, 1.97)*
Race/ ethnicity	White	(reference)
	Other	0.81 (0.56, 1.15)
Education	College or more	(reference)
	College graduate	0.99 (0.79, 1.25)
	Some college	0.89 (0.71, 1.12)
	≤High school	0.62 (0.43, 0.90)
Marital status	Married/partnered	(reference)
	Other	1.07 (0.88, 1.31)
Annual income	<$60 K	(reference)
	$61 K to ≤$100 K	1.20 (0.94, 1.54)
	$100 K or more	1.06 (0.83, 1.37)
	Prefer not to answer	1.35 (1.03, 1.77)
Type of treatment	Chemo, radiation, and surgery	(reference)*
	Chemo and radiation OR surgery	0.64 (0.51, 0.81)*
	Chemotherapy only	0.71 (0.51, 0.99)
	No chemotherapy	0.85 (0.68, 1.08)
Time since treatment ended		1.00 (1.00, 1.01)*
Number of physical concerns		1.19 (1.12, 1.24)*
Number of emotional concerns		1.21 (1.13, 1.28)*

$^{*}p < 0.01$

apy, surgery, and radiation, those who received chemotherapy with surgery or radiation had significantly lower odds of receiving care for emotional concerns (OR = 0.64; 95% CI = 0.51, 0.81). Finally, more physical and more emotional concerns were associated with higher odds of receiving care for emotional concerns (ORs = 1.19 (1.12, 1.24) and 1.21 (1.13, 1.28), respectively, all $p < 0.01$).

In an exploratory analysis (data not shown), we also modeled odds of receiving care for physical concerns for respondents who reported at least one physical concern ($n = 3199$). Overall, 69% of post-treatment survivors who reported at least one physical concern received care. Odds of receiving care for physical concerns were lower among respondents who received chemotherapy without additional treatment or with only one additional treatment compared to survivors who received chemotherapy, surgery, and radiation (ORs = 0.48 (0.33, 0.70) and 0.59 (0.45, 0.78), respectively). Similar to the results of the model of receiving care for emotional concerns, longer times since treatment ended and reporting more physical concerns were both associated with higher odds of receiving care for physical concerns (ORs = 1.00 (1.00, 1.01) and 1.87 (1.74, 2.01), respectively, all $p < 0.01$). However, respondents who reported more emotional concerns had lower odds of receiving care for physical concerns (OR = 0.92; 95% CI = 0.87, 0.98; $p = 0.01$).

Addressing the Emotional Needs of Post-treatment Cancer Survivors

The results of the 2010 LIVE**STRONG** survey suggest that emotional concerns among post-treatment cancer survivors are exceedingly common and that individuals often encounter new emotional challenges after cancer treatment ends that they had not experienced in earlier phases of their cancer journey. The LIVE**STRONG** survey asked about emotional concerns in a way that is different from other investigations of post-treatment cancer survivors, using a format that allowed for a variety of emotional concerns to be fielded to respondents, offering a more in-depth and nuanced picture of the emotional landscape of the post-treatment period. The consistency of the results with previous studies – that younger survivors reported more emotional concerns; that emotional and physical concerns were strongly associated – suggests that the survey structure offered a valid means for assessing cancer survivors' post-treatment concerns.

Also consistent with previous research (e.g., [24, 44]) was the result that while emotional concerns were common, reports of emotional concerns were usually not accompanied by high levels of functional impairment. This finding may ease some of the concern over the difference between the percentage of survivors who reported an emotional concern and the percentage who received care for the concern (95% reported at least one emotional concern; only 66% received care for any emotional concern). It may be that the post-treatment survivors in the study sample did not judge their emotional concerns to be at a level requiring intervention, if their concerns were not consistently and significantly causing functional impairment.

However, the difference between reports of emotional concerns and receipt of care was striking, particularly when considering the results for each concern separately, and other studies have found that there are significant numbers of post-treatment cancer survivors who do not receive psychological or psychosocial care that they need (e.g., [29, 45]). Post-treatment survivors may not be aware of available psychosocial care [27], underscoring the need for psychosocial services to be more fully integrated into routine cancer care [17].

How might this be accomplished? Some have argued for routine screening to provide early identification of distress [2, 17, 23, 55]. Such early identification of distress could have benefits in the post-treatment period as well, as there is evidence that untreated distress during cancer treatment predicts poorer psychological adjustment in the post-treatment period [56]. This approach is also congruent with the most recent conceptualizations of cancer survivorship, which emphasize prevention, in recognition of the increased numbers of people affected by cancer who will go on to live the balance of their full life expectancy [3]. However, it is worth noting that screening for distress in cancer patients is not without risks or burden. There is evidence that screening does not lead to adequate enough numbers of survivors who need psychological services but are not getting them to offset the burden of false-positive screens [57]. Some have suggested that screening should not be aimed at identification of distress but identification of unmet needs [45]. This approach is consistent with the results of this study and the larger literature on psychological experiences of post-treatment cancer survivors, which suggests that survivors may experience a number of concerns in the post-treatment period without having these concerns significantly disrupt their mood or quality of life. Further, a recent study by Arora and colleagues showed that many post-treatment cancer survivors do not feel that their follow-up care providers have an adequate understanding of the ways that cancer has impacted their QOL [58]. The results of routine screening to capture survivors' unmet needs might serve to facilitate better patient-provider communication on these issues.

Andrykowski [59] has recently called for a more tailored approach to psycho-oncological intervention, suggesting that we can do a better job of matching our intervention approaches to the specific needs of people affected by cancer. Indeed, the results of this study suggest that there are patterns of relationships between sociodemographic and medical variables and emotional concerns in the post-treatment period: compared to men, women were more likely to report concerns of an interpersonal nature, such as concerns about appearance, cancer-related stigma, and family member cancer risk. Post-treatment survivors who had been treated with chemotherapy were more likely to have concerns about appearance than those who did not; fears of recurrence, concerns about appearance, and problems with personal relationships were all more common closer to the time when treatment ends. Screening for needs related to these areas before the end of treatment would enable supportive care providers to deliver more personalized psycho-oncology interventions to patients as they transition in to the post-treatment period.

Increases in the use of survivorship care plans (SCPs) may improve the degree to which cancer survivors receive the psychosocial services they need in the post-treatment period. The SCP can contain follow-up recommendations derived from the results of routine psychosocial screening or care received during treatment, thereby helping to integrate psychosocial services into routine care pathways when primary cancer treatment ends [5, 17, 60]. In this way, the SCP may also serve to decrease the stigma that still accompanies psychosocial care [61], which can pose a real barrier to receipt of treatment, particularly if an individual is coping with cancer-related stigma as well (reported by nearly one-third of post-treatment survivors in our study).

SCPs were specifically called for by the 2006 IOM report [16], and the inclusion of psychosocial elements of care into the SCP was defined in the 2008 report [17]. A recent study of the LIVE**STRONG** Survivorship Centers of Excellence overviews the challenges of implementing SCPs in survivorship care [60]: all of the centers failed to meet at least 75% concordance with IOM guidelines in their SCPs or treatment summaries, and regarding psychosocial issues specifically, less than half of SCPs were concordant with IOM recommendations regarding the inclusion of psychosocial elements in the SCP. Additionally, the creation and provision of SCPs were found to be extremely time-consuming for clinical care providers. It may be that increased use of electronic health records and other health information technology applications serves to facilitate the efficient and effective provision of SCPs [62], which in turn can serve as a platform from which to engage in better patient-provider communication about psychosocial issues in post-treatment survivorship [58]. SCPs may also serve to empower cancer survivors by providing them with information they need to reduce emotional concerns related to fears about recurrence or family member risk of cancer [28], both of which were observed in half or more of survivors in this study.

Another function of SCPs is to facilitate receipt of follow-up cancer care and care for symptom management. The results regarding receipt of care in the LIVE**STRONG** data were intriguing; in particular, the association between reports of concerns and receipt of care. For receipt of care for emotional concerns, more emotional concerns and more physical concerns were both associated with higher odds of receiving care, suggesting that post-treatment survivors with higher emotional and physical symptom burdens are more likely to seek care for emotional concerns. However, we observed a different result for receipt of care for physical concerns: here, more physical concerns were associated with higher odds of receiving care for physical concerns, but more emotional concerns were associated with lower odds of receiving care for physical concerns.

This result is worth further study, as we cannot draw inferential conclusions from this cross-sectional, observational data. One hypothesis is that higher levels of emotional distress, evidenced by more emotional concerns, create a barrier to engaging in physical health care. This has been observed in studies of people with mental illness, who are less likely to engage in preventive health care, in part as a function of the ways that psychiatric symptoms may prevent behavioral activation needed to engage in care (e.g., [63]).

There is a large and involved literature on the role of psychological factors in physical health, and in cancer, this topic has been particularly controversial and debated for several decades (e.g., [64–66]). It is beyond the scope of this chapter to address this debate, which is more often focused on the ways that psychological factors may affect biobehavioral mediators of health outcomes (e.g., [67]) than on how psychological factors affect health-care seeking behavior. However, it is worth noting that, given the results of the LIVE**STRONG** survey, the degree to which emotional disruption in the post-treatment period interferes with receipt of follow-up cancer care is an area of investigation that requires further study.

Limitations

There are a number of limitations to the current assessment of psychological factors in post-treatment survivorship and the data presented from the LIVE**STRONG** survey. As noted earlier, we did not include research focused on positive psychological developments in the wake of cancer, nor did we include the experiences of post-treatment survivors of cancers diagnosed in childhood in our review. The respondents to the LIVE**STRONG** survey are a self-selected group of Internet-using cancer survivors and do not represent the majority of cancer survivors alive in the United States today with respect to age, type of cancer, race/ethnicity, or socioeconomic status. The survey did not include measurement of trait-like variables shown to be associated with adjustment in the post-treatment period, such as optimism (e.g., [44]). Finally, it was beyond the scope of this chapter to include results from the LIVE**STTRONG** survey on the practical concerns (e.g., concerns about employment) of post-treatment cancer survivors, though these concerns are certainly relevant to psychosocial experiences in the post-treatment phase.

Summary

Despite these limitations, the LIVE**STRONG** data do offer a large sample of post-treatment cancer survivors, and our results confirm and extend previous work on psychological factors in post-treatment survivorship. Considering Andrykowski's framework that identifies a balance between the stress and burden of cancer against resources available as key to the prevention of psychological disruption [23], given the lack of evidence to suggest that stress and burden significantly increase in the post-treatment period but that the resources provided by the health-care system at time of diagnosis and during treatment significantly decrease when treatment ends [20], the results shown here are congruent with a conceptualization of the post-treatment period as being one in which new stressors and burdens related to cancer emerge but resolve at a pace that is slower than the one at which the resources provided by the health-care system disappear when treatment ends. In this way, SCPs may serve a function to help post-treatment survivors remain aware of and stay connected to the resources provided by their cancer care team, enabling them to avoid significant psychosocial disruption during the post-treatment period.

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Couple Relationships and Cancer

3

Hoda Badr

Introduction

Most cancer patients who are in an intimate relationship identify their spouse or partner as their most important source of support [1]. However, the diagnosis and treatment of cancer can affect every aspect of the patients' and his or her partners' quality of life (QOL). Patients must cope with the role changes and distress brought about by the physical side effects and increased functional disability associated with their disease and treatment. Partners must not only confront the potential loss of the patient but also become adept at providing instrumental and emotional support during a time when they themselves are under extreme stress. Coping with cancer treatment can also challenge couple's established communication patterns, roles, and responsibilities [2, 3]. Thus, it is not surprising that some couples say that cancer brought them closer together, whereas others experience significant adjustment and communication difficulties as a result of their cancer experience [4, 5].

Couple-based interventions hold great promise in cancer because they can simultaneously address patient, partner, and relationship factors that can hinder cancer adjustment. However, they have yet to be routinely implemented in oncology clinical care settings. This chapter will therefore begin with an overview of some of the challenges faced by couples coping with cancer. Next, different perspectives that have shaped descriptive and intervention research on couples' psychosocial adaptation will be described. The chapter will conclude with practice implications and directions for future research.

Challenges Faced by Couples Coping with Cancer

Although the goal of most cancer treatments is to improve or maintain physical functioning and overall QOL, cancer patients often experience physical symptoms that persist long after treatment ends [6]. In addition to the physical challenges experienced as a result of a cancer diagnosis and treatment, many cancer patients experience significant depression and/or anxiety symptoms [7, 8]. Having a supportive partner may buffer the adverse impact of cancer on patient distress and QOL [9]. For example, a study of women with breast cancer found that vulnerability to anxiety was moderated by the degree of felt support from a partner [10]. Likewise, a study of in head and neck cancer found that partners who used positive social influence tactics boosted patient positive mood [11].

Although having a partner may be beneficial to patients, partners may experience decreased

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physical well-being through unhealthy stress management behaviors including increased drug or alcohol use, poor diet, and decreased exercise. Partners, like patients, report a decrease in the ability to sleep and fatigue [12, 13]. One study found that partners of cancer patients had the most sick leave episodes, which may be attributed to higher physical and emotional burdens of care [14]. Partners are also often as distressed as patients, and distressed partners may find it difficult to provide adequate caregiving and support [15, 16]. Factors associated with partner distress include increasing patient functional and caregiving responsibilities [17, 18]. Some studies have also found that patient and partner psychological distress levels are interdependent, such that increases in one partner's distress adversely affect the emotional well-being of the other partner [19, 20]. In addition to the individual stressors experienced by cancer patients and their partners, couples coping with cancer experience a myriad of shared stressors. These include the effects of treatment on sexual function and the need to make healthcare decisions (e.g., regarding treatment choice, cessation, or the pursuit of alternative therapies). Such topics may become a springboard for conflict – especially if partners are not aligned with regard to treatment priorities and goals – and thus require dyadic or collaborative coping [21–23].

Research on Couples' Psychosocial Adaptation to Cancer

Research on couples' psychosocial adaptation to cancer has either taken a resource perspective or a dyadic perspective. The former focuses on understanding the impact of cancer on patients, partners, and their relationships, as well as identifying social/relationship characteristics (e.g., social support, equity) that might buffer couples from the adverse effects of cancer-related stress on psychosocial well-being. The latter focuses on identifying modifiable targets that could be addressed by couple-based interventions (e.g., joint problem-solving, communication patterns, and approaching cancer together as a team). Key research findings and an overview of the different theoretical models that have guided this research are described below.

Resource Perspectives

Research emanating from the resource perspective has examined the roles that social support, perceptions of equity, and coping congruence play in the adaptation of couples coping with cancer.

Social Support. According to Lazarus and Folkman's Transactional Theory of Stress, social support can be viewed as a form of coping assistance. Partners can provide both practical and emotional support to facilitate adaptive coping. Consistent with this model, higher levels of perceived partner support have been associated with lower levels of distress and greater patient and partner well-being [24–30]. Although socially supportive relationships can facilitate cancer adjustment, unsupportive or negative interactions can hinder adjustment, increase distress, and may even have a greater impact on patients' well-being than supportive interactions. One explanation is that unsupportive partner behaviors adversely affect patient coping strategies. Another is that negative partner responses reduce opportunities for patients to talk about cancer concerns. Talking with a supportive partner may facilitate successful cognitive and emotional processing by allowing disclosure of emotions, helping the person learn to tolerate aversive feelings, providing support for effective coping, and assisting with finding meaning and benefit in the cancer experience. Without sharing concerns, it is possible that these processes may not occur or occur with insufficient frequency for successful processing of the event.

Equity Theory Equity theory posits that when the ratio of contributions to rewards for one partner differs from that of the other, the relationship is out of balance; those in inequitable relationships are more likely to become distressed [31], regardless of whether they are over- or underbenefited [32, 33]. Supporting this idea, cancer patients have reported feeling more overbenefited and experiencing more guilt about being over-benefited than healthy individuals [34, 35]. However, couples may also make adjustments to accommodate changes in the balance of give and take brought on by cancer. More work is thus needed to determine for whom (e.g., younger vs older couples) and when (e.g., early vs late stage cancer) equity issues may become problematic.

Coping Congruence Coping congruence focuses on the degree to which relational partners have similar or dissimilar coping strategies. The degree of match/mismatch in partners' coping responses is thought to either complement or destabilize coping efforts and adjustment [36]. Research has found that the use of similar or complementary coping styles is associated with greater patient and partner illness adjustment and marital satisfaction [37, 38]. Likewise, discrepancy in the use of emotion-focused coping strategies by patients and partners has been associated with greater distress and poorer cancer adjustment [39].

Dyadic Perspectives

Below, three dyadic processes are described that research has found to be important for couples' psychosocial adaption – relationship maintenance, dyadic coping, and communication.

Relationship Maintenance Relationship maintenance strategies (e.g., positivity, openness, providing assurances, sharing household tasks) promote important relational characteristics (i.e., liking, commitment) that motivate people to engage in other pro-relationship behaviors over time [40, 41]. Research in lung cancer has shown that efforts to maintain or enhance the couple relationship is positively associated with both partners' psychological and marital adjustment over time [42].

Dyadic Coping Bodenmann's Systemic Transactional Model (STM) of couples coping with stress posits a model of dyadic coping whereby relational partners cope individually and jointly as a unit [22]. Dyadic coping is a process consisting of (1) the communication of problem- or emotion-focused stress by partner A, (2) the awareness or perception of partner A's stress by partner B, and (3) partner B's coping reaction to partner A's behavior. Dyadic coping includes positive actions like sharing practical or emotional concerns (i.e., problem- and emotion-focused stress communication) and supportive actions like helping a partner to engage in positive reframing and problem-solving (problem-focused dyadic coping) and offering empathic understanding (emotion-focused dyadic coping). It also includes negative actions like distancing, blaming, or minimizing the seriousness of a partner's stress (negative dyadic coping). Whereas positive dyadic coping is important for helping couples resolve problems and reduce emotional arousal, negative dyadic coping is considered a maladaptive couples' coping strategy. STM interventions have improved psychological and relationship functioning and distress in breast, gynecological, and head and neck cancer couples undergoing active cancer treatment [43–45]. Common therapeutic elements include (1) education; (2) intrapersonal skills training to address individual coping needs; and (3) interpersonal skills training (e.g., communication) to improve communal or dyadic coping. Research emanating from this perspective has found that both patient and partner psychological and relationship functioning may be improved by enhancing couples' dyadic coping [43, 46–48].

Communication Communication skills training is a critical component of couple-based interventions. The link between spousal interaction and affect is central to the therapeutic process [49, 50]. Most notably, negative cycles of spousal interaction and the inability of distressed couples to maintain supportive emotional engagement have been shown to be more influential than spousal disagreements in maintaining psychological and relationship distress [51]. Patients' and partners' confidence in and ability to talk about cancer has been linked to better marital adjustment and well-being, adaptation to cancer-related role changes, and cancer management [52–54]. With regard to types of communication that have been found to either enhance or impair cancer adaptation, Badr and colleagues found that the use of open and constructive communication is associated with lower levels of patient psychological distress [42, 55]. Others have found that couples who used more mutual constructive communication, less mutual avoidance, and less demand-withdraw communication (where one partner pressures the other to discuss concerns and the other subsequently withdraws) experienced less distress and greater relationship satisfaction [56].

Couples talk about many things when they discuss cancer. For example, they may discuss health-related issues (e.g., symptoms, health decisions, coordination of care, prognosis), psychological/behavioral processes (e.g., thoughts/feelings, wants/needs, plans, behaviors), and interpersonal processes (e.g., role changes, sexual problems, social/family relationships, and support [57]. However, most couple-based interventions emphasize emotional disclosure over other forms of communication [58–61]. The idea that couples should talk about feelings is grounded in social cognitive models of stress and coping [61, 62]. These models posit that successful cancer adaptation can be achieved by disclosing fears and concerns as a means of soliciting partner support and facilitating engagement in active coping strategies [63, 64]. However, findings on the benefits of emotional disclosure have been mixed. Some studies have found that it reduces distress and improves marital satisfaction; others have either found no effects or that effects are contingent on factors like cultural background, role (patient or partner), age, or cancer type [65, 66]. Thus, avoidance of cancer discussions may be damaging, but emotional disclosures about cancer may not necessarily be beneficial.

Existing studies of couples communication in cancer have relied on measures that are not specific to cancer, and contradictions have been noted in self-reports about disclosing [65]. For example, someone might say, "we talk about everything," but go on to report avoiding specific topics. Thus, more observational studies of communication in cancer are needed. Within this paradigm, automatic text analysis approaches are promising because they are less vulnerable to limitations of self-report like social desirability, demand characteristics, and mood effects [67]. They may also yield information that cannot be obtained from self-report about how support transactions unfold and equity is negotiated when couples discuss cancer. One observational study that used such methods to analyze cancer couples' conversations found that emotion word use was not associated with either patient or partner psychological or marital adjustment [57]. Instead, couples reported more positive mood following the discussion and less distress over time when they used more we-talk (i.e., use of first-person plural pronouns such as "we," "us," or "our" when discussing cancer concerns), ($p < 0.01$), suggesting that the manner in which couples discuss cancer – conceptualizing it as either a shared or individual problem – may have implications for both partners' adjustment.

One study found that partners of prostate cancer patients reported increased distress following an intervention that sought to improve the couple's ability to openly share cancer-related feelings and concerns [60]. The authors postulated that the open discussion of feelings may have made partners more attuned or aware of stressors/problems, which could have exacerbated their distress. Another possibility is that a mismatch occurred between the patient's need/desire to talk and the partner's ability to listen and process what was being said. In fact, studies have found that similarity in relational partners' preferences and patterns of talk, their perceptions of mutuality, and their ability to respond with reciprocal disclosures may be more important for alleviating distress than what is actually disclosed or how often disclosures occur [66, 68, 69].

Problems can also occur if both partners do not agree about how to feel or are not prepared to validate each other's feelings [70, 71]. Thus, it might not be as important for a person to disclose emotions as it is to have a partner whom they see as instrumental to their coping process.

Even though talking about cancer may confer a variety of benefits including improving perceptions of closeness, enhancing the coordination of care, and strengthening patients' and partners' commitment to each other and their relationship [72], the emotional, functional, and relationship changes that occur in response to cancer may make couples reluctant or unsure about how to effectively communicate. Research has shown that one-third of cancer patients and partners experience difficulties talking about cancer [73, 74]. This may be due to the desire to protect or shield one's partner from distress, also known as protective buffering. Engaging in protective buffering is usually done with the best of intentions; however, it increases burden, decreases relationship satisfaction, and contributes to poor mental health in the person who is buffering, as well as the person whom the buffering was intended to protect [75–77]. Another possibility is that individuals may perceive their partners as critical, unreceptive, or uncomfortable talking about cancer [64, 74]. Other explanations for why couples may avoid cancer-related discussions include the desire to maintain hope, optimism, and a sense of normalcy and the desire to preserve valued identities and patterns of relating. For example, if a couple has a long-established problem-focused pattern of addressing shared stressors, deviating from that pattern may in itself cause distress [78]. It is also important to keep in mind that even though talking with a partner can serve as a direct means of soliciting social support, the need to ask for support in close, long-term relationships may be the exception rather than the rule and actually indicate a breakdown of the unspoken and shared routines through which couples usually cope [79].

Couple-Based Interventions in Cancer

Given the growing acknowledgement that patients, partners, and their relationships are profoundly affected by cancer, there has been a growing interest in developing and testing interventions that are offered to the couple as the unit of care [80–83]. Couple-based interventions often include psychoeducational and skills training components (e.g., information about cancer and caregiving, self-care/self-management skills, stress management, training regarding caregiving tasks, and/or relationship enhancement skills including communication skills training and dyadic coping) [80, 83]. Therapeutic techniques that have been employed include cognitive behavior therapy (CBT), education, interpersonal counseling, behavioral marital therapy, and emotion-focused therapy [83], and most interventions have been delivered by a nurse or specialist healthcare provider such as a behavioral therapist, psychologist, or mental health professional [80, 83, 84].

Meta-analyses of the dyadic intervention literature [80, 83] have shown that delivery formats have been relatively evenly divided between in-person visits (e.g., either interventionists come to participants' homes or participants come to a clinic/hospital to receive the intervention), telephone contact, and a combination of both. Few studies have involved group formats, videoconferencing, or web-based approaches [85, 86]. The vast majority of interventions have also included print materials, such as instructional manuals or booklets; however, some have also included audio/video materials to reinforce skills taught. Most have involved six sessions; however the number of sessions has ranged from 1 [87] to 16 [88], and session length varies from 20 to 120 minutes [80]. In addition, most studies have compared couple-based intervention to a usual care or wait list control condition as opposed to an active control condition [80].

For the most part, partners have been involved in couple-based interventions in one of two ways. The first method treats the partner as an assistant or "coach" to facilitate learning and coping skills in the patient. This approach conceptualizes the role of the partner in the intervention as being supportive of the patient [89]. The second method seeks to actively involve the partner by focusing on how the dyad functions together as a unit and addressing both partners' needs and concerns [83]. Future research should thus determine whether there are particular patient, partner, or dyad factors that might influence when it is more appropriate to conceptualize the partner's role as either supportive or active.

Overall, couple-based interventions targeting patients and partners have had different effects depending on the outcome being examined [80, 83]. Small to moderate effects have been observed for patient and partner psychological functioning. Small to large effects on marital functioning have been observed for patients, but these effects may only be short term in nature. Effect sizes for marital functioning for caregiving partners have been small. Likewise, small to moderate effects have been observed for patient physical well-being, but this may be largely dependent on stage of cancer, and it may be unrealistic to expect improvement in physical well-being in individuals who have metastatic disease. More work is needed to clarify the definition of clinically meaningful changes in the outcomes examined as even small effect sizes can still be clinically significant and important.

Future Directions

Although the descriptive and intervention research described above have explored and emphasized different aspects of couple relationships and their role in patient and partner adjustment to cancer, several insights can be gleaned and gaps identified that can help drive future research. The first relates to describing partner behaviors that are enacted or intended to help the other partner cope and the results or outcomes of those behaviors. Examples include social support, congruent coping, dyadic coping, and disclosure; and for the most part, these behaviors have been associated with improvements in relationship satisfaction, relationship intimacy, and psychological distress. How and when a particular strategy should be applied and the likelihood of a favorable outcome are currently still unclear. A second insight relates to what couples can do to effectively cope together. Conceptualizing cancer as "our" problem (shared appraisal) rather than "your problem" or "my problem" (individual appraisal) and engaging in dyadic coping by taking collaborative "we"-based actions to address it appear beneficial for psychological and relationship adaptation [23, 90]. However, little is known about how communal coping is communicated or unfolds during couples' discussions about cancer. More work is also needed to understand when and under which circumstances a dyadic coping approach may be beneficial and when individual coping strategies are sufficient.

A third insight relates to the need to refine the prescription for spousal communication. Scholars still know very little about what they should instruct couples to talk about, how often they should talk, and when talking (or not talking) is beneficial (and for whom – the patient, partner, or both) [86]. It may be useful to understand why people choose to talk or avoid cancer-related discussions in the first place. We also need to develop a more nuanced view of couples' communication that acknowledges that there are multiple ways to talk, aspects of the cancer experience to talk about, and pre-existing communication patterns and preferences that may influence the utility of talk for different couples. Indeed, successful adaptation may hinge on the ability of patients and partners to discern when to engage in or suppress disclosures and to develop flexibility regarding the discussion of certain topics in response to situational demands [91].

For example, in situations where patients/spouses are reluctant or unsure how to communicate with their partner about cancer, shifting the focus onto the couples' relationship by talking together about it (e.g., how good it is, relationship memories and how the couple addressed challenges together in the past, and future plans) may help to remind couples of the strengths and resources that they have to deal with the disease [92, 93]. Under conditions where disclosure to a partner becomes challenging or problematic, some patients and partners may benefit from disclosing to a neutral third party or through practicing expressive writing [94, 95]. Indirect methods of communicating such as showing affection through physical touch, having everyday conversations that are not about cancer (e.g., “How was your day?”), and spending time doing shared activities may also provide a more comfortable context for illness-related issues to spontaneously arise. More research is thus needed to identify alternative methods of communicating and to clarify the associations between these communication methods and patient and partner outcomes. Likewise, interventions that replace the generic prescription to talk openly with targeted questions that prompt reflection on the couple’s strengths, communication patterns, and resources may help bolster the impact of couple-based interventions on patient and partner QOL.

Finally, even though couple-based interventions have had many beneficial effects, they are seldom implemented in clinical practice settings. In an effort to inform implementation efforts, Ratcliff and colleagues conducted qualitative interviews with individuals representing different oncology stakeholder groups [96]. Questions focused on existing support services, barriers to integrating couples’ interventions in routine patient care, and possible models for clinical uptake and dissemination. Findings suggested that researchers should evaluate intervention outcomes that are important to stakeholders, including cost/cost savings, healthcare utilization (e.g., readmissions, emergency department visits), and clinical outcomes (e.g., increased adherence, early detection of adverse events, survival) in order to translate effective interventions from research to practice. They also suggested that, given limited personnel and financial resources, more pragmatic trials are needed that allow for flexibility in the delivery of couple-based interventions. Emerging communication technologies (e.g., Internet, mobile health, social media) may allow for more efficient delivery and widespread dissemination, but more research is needed to determine patient and partner intervention preferences; whether factors such as advanced disease status, age, or comfort with technology affect receptivity and uptake; and whether such interventions are feasible and cost-effective. Studies evaluating the relative cost of different modes of administration (i.e., in-person, over the phone, Internet) are also needed.

Conclusion

In conclusion, the couple relationship exerts a major influence on both patients’ and partners’ psychosocial adaptation to cancer and QOL. Future research may benefit from an increased focus on couples’ interactions to address ways that couples can adaptively cope together. In addition, there is a growing need for healthcare providers to view the couple as the unit of care and provide more information and support to partners so they can provide effective caregiving for the patient while also maintaining their own health and well-being. Unfortunately, in current practice, such interventions are rarely offered. Healthcare providers typically have limited time to evaluate patients and may not have adequate training in delivering psychosocial interventions. While research on the development of effective programs for improving the QOL of cancer patients and their partners progresses, change in the healthcare system is needed to integrate these programs into the standard of care.

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4

The Impact of Cancer and Its Therapies on Body Image and Sexuality

Susan V. Carr

Introduction

Sexuality is the combination of gender identity, sexual orientation, sexual attitudes, knowledge, and behavior. While gender identity and sexual orientation are of biopsychosocial origin, sexual behavior is socioculturally determined and will change over the course of a lifetime. The impact of cancer on an individual's sexuality is enormous and overwhelmingly negative in most cases.

For ease of understanding in the clinical context, sexuality can be thought of as being composed of gender identity and sexual orientation together with sexual attitudes and behavior, all of which combined are fundamental to the human sexual response [1].

Gender identity is usually designated at birth with approximately half of the population being male and half female. It is biologically determined and carries legal and societal implications. Gender identity is a fundamental determinant of future biopsychosocial development. A very small proportion of the population are transsexual or intersex; however these conditions do not become apparent until later in life, when a gender identity has already been assigned. Although most of the research and literature in relation to sexuality focus on women's cancers, men are 40% more likely to die of cancer than women, and prostate, testicular, and penile cancers all affect men's sexuality in particular, while all cancers have some negative effects [2].

Sexual orientation describes the likelihood of being attracted sexually to either males, females, or both.

The vast majority of the population are heterosexual, demonstrating clear sexual instincts and attraction to the opposite gender. There are, however, a proportion of men who are sexually attracted to men and who identify as homosexual, a proportion of women who are sexually attracted to women, and around eight percent of the population who are attracted to both. Some individuals declare that they are not attracted to either sex. There is currently a myriad of differing variations on these core definitions, and if clinically relevant, the patient should be asked to self-define their particular orientation.

There is some long-standing evidence to support a biological basis for gender identity mooted as long as 50 years ago [3]. Likewise, there are several biological factors in the origins of homosexuality; however culture and experiences are also influential, and debate still continues on this topic [4].

Cancer will not change sexual identity nor sexual orientation but may well radically change attitudes to sex and to choices and experiences in relation to sexual behavior. All individuals are sexual beings but vary widely in their attitudes

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and beliefs in relation to their own sexuality. They have an absolute right to either be sexual or nonsexual as they choose. Sadly, in some parts of the world, this basic human right is still not yet recognized, especially in relation to women, and even in open societies, most find it difficult to talk about sex or even to accept that they have a right to a pleasurable, pain-free, and autonomous sex life.

Although the majority of people have a problem free sex life, there is a recognized acceptance that a substantial proportion of the population may have a sexual problem at some time in their lives, and sadly, this is more so in individuals with cancer.

It is thus essential that clinicians are aware of sexuality in relation to cancer, the potential problems which can ensue, and strategies which can be adopted, most of which are simple, in order to improve sexual well-being.

The Sexual Response

The human sexual response is fascinatingly complex [5] and has been classically described as the "psychosomatic circle of sex" It depends on endocrine, vascular, and neurological integrity. The female response results from sensory input through the peripheral nerves of the autonomic and somatic nervous system, as well as the cranial nerves. Psychogenic stimulation is crucial to this process. The precise location and mechanism of transmission of afferent information within the brain and spinal cord are, as yet, unknown. The temporal and frontal lobes and anterior hypothalamus also have some role in mediating the sexual response. The generalized motor responses are more obvious. The sexually aroused female has pelvic congestion and vaginal lubrication. During sexual intercourse, the vagina lengthens, the labia swell, the uterus draws back, and there is clitoral hood retraction. In the male, the penile vessels and corpora cavernosa engorge with blood, the testes draw up, and the penis becomes stiff and erect ready for intercourse.

There have been different sexual response models described over the years. Masters and Johnson [6] used a four phase model consisting of excitement, plateau, orgasm, and resolution. This was modified by Helen Singer Kaplan into a triphasic description of desire, arousal, and orgasm [7]. Desire is now thought of as the first stage of sexual arousal. These models have been used for many years as a basis for modes of treatment, such as sensate focus therapy, in which couples employ a series of nonsexual touching exercises to "relearn" intimate sexual contact. In appropriately selected cases, improvements have been shown using this therapy often without the need for any additional interventions.

Prevalence

Sexual problems in people with cancer are far more common than in the general population. The general prevalence of sexual problems is quoted as 30% of males and 43% of females in a US population [8], 20% in an Australian population, and 11% of both males and females in Denmark. The most common sexual problem experienced by women is that of lack of desire, followed by problems such as lack of orgasm and the presence of sexual pain. For males the most common sexual dysfunctions are premature ejaculation and erectile dysfunction [9].

Published evidence shows that at least 50% of cancer patients will have a sexual problem at some time during their cancer journey [10]. Most recognition has been paid to women with breast and gynecological cancers and men with prostate cancer as these are overtly "sexual" areas of the body; for instance, women treated for early stage breast cancer have more sexual problems than the French population in general [11]. Sexual problems, however, can affect people with all cancers, and this is an area of healthcare sadly often ignored or forgotten by the clinical team.

Sexual problems occurring throughout the cancer journey need not be permanent and can improve over time [12] or, conversely, can be ongoing over a long period [13]. This will be dependent not only on physical treatments but also on the emotional and relationship status of the patient, before, during, and after being diagnosed with cancer.

Studies have shown that gynecological cancer survivors have a greater incidence of distressing side effects such as fecal incontinence than controls and also experience less sexual desire and less ability to orgasm [14]. However after 3 years, women who had radiotherapy for gynecological cancers showed improved sexual function over baseline [15], possibly helped by feelings of being "cancer free."

Severe sexual dysfunctions are common for long-term survivors of hematopoietic stem cell transplantation, and women seem to suffer more than the men [16]. This may be because of altered hormonal levels but may also be due to the emotional impact of the severity of the disease and its treatment. A single study of patients with hepatocellular carcinoma showed a higher prevalence of sexual problems than comparison groups, some of which was related to drug therapy [17]. Reduced libido and sexual enjoyment is described in patients with total or partial laryngectomy [18]. With major head and neck cancers, sexual and intimacy problems were not linked to the site of the lesion [19].

Site of cancer, stage of cancer, and different treatments of each cancer all significantly impact sexuality, and no one cancer is without this effect. Interventions commenced de novo from the cancer diagnosis have the potential to reverse this often devastating impact on quality of life and well-being and should be an important part of the overall multidisciplinary approach to patient care.

What Are Sexual Problems?

Physical changes as a result of cancer and its treatments can be many and varied, leading to a wide variety of sexual problems. Women with cancer can experience disruption to sexual arousal, lubrication, and orgasm and develop pain on intercourse particularly if they have experienced menopause as a result of chemotherapy or surgery. This functional disruption leads to lack of pleasure in sex and can result in total loss of libido, or sexual interest, as a subconscious way of avoiding something which has become an unpleasant or painful experience. Men most commonly can experience erectile dysfunction or delayed or premature ejaculation. The emotional impact element of all these factors should never be underestimated.

It is useful to be aware of some of the commonest sexual problems that may be seen in practice and the treatment options available.

Female Sexual Problems

Anorgasmia

This is the clinical term for inability to reach a sexual climax. It is common and affects up to 20% of woman globally. Some women complain of inability to reach sexual climax and report that they have never experienced or are unsure whether or not they have experienced the intense feelings leading up to and culminating in orgasm. Others may experience orgasm only when masturbating but not with a partner during penetrative coitus. There may be underlying reasons for this sexual inhibition such as strong historical, cultural, and religious taboos, which can be explored, and "permission to feel sexual" which can be achieved. Clear education around sexual anatomy and simple masturbation exercises will help, as can the appropriate use of vibrators.

If anorgasmia is the result of antidepressant use such as selective serotonin reuptake inhibitors (SSRIs), then sildenafil treatment may be effective in highly selected cases [20]. Otherwise educational, behavioral, and emotional therapy is of benefit.

Primary Vaginismus

Vaginismus is described as the involuntary contraction of the vaginal muscles and may be psychogenic in origin. Primary vaginismus is a condition where nothing is able to enter the vagina. This woman will never have used a tampon for menstruation or have had any sort of penetrative sex. These are often women who have had a loving, but rather overprotected upbringing and find it difficult to make the leap from being the child at home to the adult woman in a relationship. In this situation, there is no organic disease, the woman has a healthy vagina and vulva, and treatment should focus on the emotional blocks to having sex.

Secondary Vaginismus

Secondary vaginismus, however, is a far more likely diagnosis when a woman complains of inability to have penetrative intercourse after cancer. A woman with cancer may have been able to have penetrative sex prior to diagnosis and treatment, but at some point on her cancer journey, she finds herself unable to have sex as it was before. This can be due to pain after surgery or radiotherapy or discomfort due to vaginal dryness following sudden menopause as a result of ovarian surgery or chemotherapy.

Vaginal dilators are commonly used for women following radiation therapy. It is thought that they help to stretch the vagina and prevent adhesions. Many women, however, don't like using them, and the evidence for their use is flimsy [21]. When dilators are used in women who have no vaginal pathology, as in the women with primary vaginismus, they are known as vaginal "trainers," because they are being used to teach the woman that she can in fact allow something to enter into the vagina and that she herself can be in control. There is often concern about vaginal length in relation to penetrative intercourse, but current literature does not show any association between postsurgical vaginal length and sexual satisfaction [22].

A neurotoxic protein such as Botulinum toxin A, injected intravaginally, has been show to help in vaginismus as part of a multimodal treatment regime [23]. Furthermore, multimodal treatments may be valuable [24].

Dyspareunia

Dyspareunia is pain on sexual intercourse. It may or may not have an organic origin, such as cancer or dermatological problems including atrophic vaginitis and moniliasis. The pain may also derive from surgical scarring or alteration in vaginal length and/or caliber.

Dyspareunia and secondary vaginismus are often linked by cause and effect. Thus diagnosis may be confused leading to inappropriate treatment [24]. If there is pain due to organic problems, the woman will expect pain on intercourse and will subconsciously contract her vaginal muscles, and any attempts at penetration will be met by a strong wall of contracted muscle, "a brick wall." The erect penis tries to penetrate, and further pain is caused, thus distressing both partners. These conditions should be looked at as a possible continuum.

It is essential for the patient to have a thorough clinical examination to ensure that no organic lesion is left untreated.

Painful sexual intercourse is often a distressing feature of the many vulvar pain syndromes which can occur in women with or without cancer. It is generally recognized that the ideal approach to all of these conditions is multidisciplinary, paying as much attention to the emotional as well as the physical dimensions of the problem.

Male Sexual Problems

Erectile failure is described as failure to achieve and sustain penile erections for long enough to have satisfying sexual intercourse and can be a devastating situation for any man. It can be a common side effect of some cancers, especially cancer of the prostate, but is also a common accompaniment to common medical conditions including obesity, diabetes, and vascular disease.

This is a condition which becomes more prevalent with age, with around 25% of men in their 50s and 40% in their 60s having some degree of failure.

As over 60% of erectile dysfunction is organic in origin, the mainstay of treatment is medication such as phosphodiesterase type 5 cyclic GMP inhibitors, which are facilitators not initiators of erections. If a man is not sexually attracted to his partner, the medication is unlikely to work. Locally acting injectables, such as prostaglandin E, can be injected into the base of the penis or used as an intraurethral pellet. The efficacy rates are high.

Vacuum devices together with penile constriction rings can produce an erection but are cumbersome to use and consequently not very popular.

It is important to recognize that 25% of erectile dysfunction is partially psychogenic and 15% purely psychogenic in origin, and even men with wholly organic disease will sustain an emotional impact if having erectile difficulties.

Pharmacological treatments have now become the mainstay of treatment for erectile dysfunction [25], especially post-cancer treatment; however in clinical trials with phosphodiesterase 5 inhibitors, men with posttraumatic stress disorder showed a significant placebo response; this was not the case in cancer patients [26].

Loss of erectile function can be devastating for any man, impacting on his self-esteem and masculinity, and the emotional aspects of this should not be ignored. Psychosexual therapy in which partner can be included if the patient wishes will provide an opportunity to explore any complex underlying emotional issues.

Premature Ejaculation

The commonest male sexual problem worldwide is premature ejaculation. The latency period, i.e., the time between achieving an erection and ejaculation, is too short for satisfying sexual intercourse to take place. This condition can be very frustrating for both partners and can cause a loss of self-esteem for the man and feelings of dissatisfaction for his partner.

Treatment is mainly the use of selective serotonin reuptake inhibitors (SSRIs), which can lengthen the latency period. These have high efficacy rates, and it is easy to take the medication [27]. Behavioral therapy has only short-term benefits which disappear when therapy is concluded. Other techniques such as squeezing firmly at the base of the penis at the point of orgasm are widely recommended, but there is no good published evidence to support their use, and in clinical practice, the technique appears to have minimal effect.

Delayed Ejaculation

This condition has a completely different presentation from that of the premature ejaculation. The condition has often been long-standing and except for a few instances, when it can be a side effect of medication, tends to be due to issues of control. The man has a strong subconscious block to ejaculation, which is often situational. If he can ejaculate through masturbation but not inside his partner, then the problem is clearly psychogenic and should be treated with psychosexual or counseling therapy.

Loss of Libido: Male and Female

This is loss of sexual interest or desire, a clinical condition for which there are no physiological markers. It is sometimes called “sexual desire disorder.” It can affect both males and females, regardless of gender, age, sexual orientation, or ethnicity. It tends to occur more commonly in people with cancer or chronic disease and can be either caused by cancer and its treatments or brought to the surface by underlying emotional issues being highlighted by the cancer.

The only evidence-based drug treatment is for loss of libido following sudden menopause, often as a result of cancer therapy. In these cases, if appropriate, then hormone replacement, with the addition of testosterone, can restore libido. Males with low testosterone levels can benefit from hormone replacement also, but there is no direct measurable link between hormone levels and libido. If a couple has had long-standing relationship problems, some hormones given after menopause will not make these problems disappear!

Emotional issues require appropriate therapies, and psychosexual interventions can help the patient gain insight.

Psychosexual and Behavioral Treatments

A range of treatments can be utilized for sexual problems for all genders. It is essential to treat any organic disease or dysfunction before embarking on therapy for the sexual problem. All cancer symptoms and manifestations have to be expertly clinically assessed and treated before embarking on sexual therapy.

Treatments depend on the etiology of the problem and can be medical, surgical, psychological, analytical, behavioral, or a combination of some of these therapies.

Cognitive behavioral therapy (CBT) is useful in sexual dysfunction, but procedures differ depending on the nature of the problem. Only a few CBT treatments have been empirically investigated, and as a result, it is not known which components of the treatment are most effective [28]. Broader approaches can be taken which focus on the construct of flexibility in behavioral and coping strategies [29]. It is also useful to know that Internet-based CBT was beneficial in the treatment of breast cancer survivors. The current trends among health psychologists to use psychoeducational interventions using combinations of cognitive and behavioral therapy and mindfulness training continue to be effective [30].

Psychosocial interventions can improve sexual outcomes, even if medication is being used. When group therapy was given to men using sildenafil for erectile dysfunction following prostatic cancer, the sexual outcomes were improved [31]; however, greater focus on the psychosocial aspects of this disease has not been adequately researched [32], despite erectile dysfunction having such a major negative impact on these men lives [33]. A supportive-expressive group therapy intervention offered to lesbians with primary breast cancer showed reduced emotional distress and improved coping but had no effect on sexual issues [34]. A peer counseling intervention for African American breast cancer survivors showed improved sexual functioning after 6 months, but not after a year. Peer counseling in this group showed no advantage over telephone counseling [35].

The consensus on therapy for sexual problems, however, is that as sexuality is complex and multifaceted, whatever therapeutic modality is used, then a multidisciplinary approach to treatment must be taken [36]. The delivery of these interventions in the future should evaluate resource friendly modalities such as phone and Internet and careful use of social media in order to educate and provide interventions.

Body Image

Body image and sexual self-confidence are intrinsically linked. Cancer and its therapies can cause major alterations in body image which in turn can have negative impact on sexuality and sexual satisfaction [37]. About 58% of young women with breast cancer experienced sexual problems 2 years after [38]. Fifty-eight percent also had reproductive concerns, and many of these women also experienced problems with body image. Patients who have had mastectomy both for prevention and cancer treatment can experience loss of sexual desire and body image problems for many years after the surgery [39].

The obvious physical changes associated with cancer can be either transient or permanent. They include baldness following chemotherapy, weight fluctuations, body shape changes such as loss of breast, stoma onto the skin, lymphedema, or some disfiguring features following head and neck cancer. One study in Italy showed that the degree of disfigurement in head and neck cancer leads to greater problems with sex, self-image, and relationship with partner compared to those with less obvious outward changes [40]; however, another study showed that age rather than degree of disfigurement was more significant in relation to sexual dissatisfaction, with men under 65 having poorer sexual functioning and satisfaction [41]. Interestingly only 58% of the sample were satisfied with their current sexual partner, the reasons for which were not explained!

In areas such as Africa where presentation of cancer can be late and incurable, sexual problems and body image disturbance, “I don’t look like myself,” were ranked as of prime importance to the patients [42]. It is so easy to dismiss these concerns in the face of the life-threatening potential of the disease, but patients should be given the opportunity to discuss what is important to them, even in the palliative phase of care.

Changes in body self-perception, however, need not necessarily stem from outward change, and for a lot of young women, loss of fertility can greatly lower their feelings of quality of life [43]. The impact on body image following cancer is multifactorial, and issues such as age and physical and psychosocial factors are all relevant [44]. In adolescent and young adult survivors of testicular cancer, sexual function was closely bound to fertility issues and masculinity resulting in body image problems in a proportion of these men [45]. What is encouraging is that many survivors of various childhood cancers successfully go on to produce healthy children [46]. This positive outcome should increase with advances in both cancer treatments and infertility technology. It is therefore crucially important that individuals in this group have access to expert and timely and accurate information about their fertility options, which may well alleviate many of their concerns, and avert negative sexual impact. Adolescents with cancer have particularly difficult issues in relation to body image as it is so integral to romantic attractions and establishing relationships [47]. Fertility issues are yet to become relevant to them, but should be highlighted if fertility-sparing treatment options are available.

Body image can stem from the patient’s own feelings or can be a reflection of real or supposed feelings of a partner. If there is a regular partner, however, couple-based interventions are known to be the better therapeutic option [48] especially if they educate both partners about the cancer and its treatments and support mutual coping.

Can Different Cancer Treatments Alter Body Image and Increase Sexual Difficulties?

Different treatments can cause differing body image and sexual outcomes, for instance, patients treated for rectal cancer have a high rate of sexual problems. These problems both in males and females seem to be exacerbated by nerve damage and are associated with preoperative radiotherapy; however new techniques are being developed, with the intention of minimizing organ damage [49]. Preoperative radiotherapy causes higher levels of poor body image and poorer sexual function in males being treated for rectal cancer than in those having surgery alone [50], and all patients suffered more sexual problems than the non-cancer population. Many cancer patients have a stoma, but it has been shown that not everyone in this situation experiences negative body image and sexual problems [51].

Sexual function post-treatment in men with prostate cancer is an enormously important issue, yet there are still unmet needs for appropriate and accurate information in making treatment choices [52]. Men with nonseminomatous testicular cancer had fluctuations in sexual functioning but not desire in the first year after diagnosis. In this case, the type of treatment did not matter [53].

Women with early stage breast cancer in a US study showed less problems with sexual attractiveness over time than women without cancer; however those with mastectomies had a higher incidence of sexual problems [54]. In Turkey, 41% of women undergoing treatment for breast cancer had a deterioration of sexual functioning; however those undergoing mastectomy had a greater loss of libido than those undergoing breast-conserving treatment. There was no significant change in body image, however, between the two groups [55].

Sexual abuse in childhood can have significant effect on self-esteem and body image. It has been suggested that women opting for breast reconstruction may have a higher likelihood of abuse than those who choose mastectomy alone [56]. This is a very sensitive area which needs more exploration.

Women with breast cancer did not experience a worsening of sexual feelings after surgery but did experience loss of sexual inclination progressively after chemotherapy and hormonal treatment [57]. Interestingly no body image deterioration was noted, but there were many physical changes in contrast to other studies.

A study undertaken in Italy comparing radical hysterectomy by either laparoscopy or laparotomy concluded not surprisingly that radical hysterectomy lessens sexual function, regardless of the type of surgical approach [58]. In another study comparing the treatment of women with early stage cervical cancer with either radical trachelectomy or radical hysterectomy, the measurements of mood, sexual function, and quality of life did not differ by treatment [59]. Women treated with neoadjuvant chemotherapy and type III radical hysterectomy for locally advanced cervical cancer showed no difference in sexual enjoyment to benign gynecological disease patients [60].

Regardless of the type of treatment, across all cancers, the most commonly discussed symptoms in relation to sexual problems were fatigue, hair loss, weight gain, and scarring [61]. Other symptoms which are out of the patients control, such as fecal and urinary incontinence, are major inhibitors to sexual contact, as the sufferer is highly anxious of causing embarrassment to themselves or their partner. This alone can cause avoidance of all sexual contact. Although much of human sexual activity is an intimate and “messy” activity involving body fluids, when faced with flatus, feces, or urine, many people find sex unacceptable.

Symptoms such as shortness of breath due to lung involvement or severe pain are also major physical inhibitors to sex. None of this fails to have an emotional impact on the patient and their partner and should always be recognized when treating anyone with these problems.

Over the last few years, thankfully, there has been more attention paid to the application of evaluated interventions to try to improve the psychosocial aspects of cancer. An intervention using guided imagery within a group therapy approach helped body image but not sexual difficulties [62]. Sexual difficulties may be better addressed in a dedicated cancer and sexuality clinic which can deal with all aspects of the problem [63] using treatments such as couple-based psychosexual therapy [64].

Emotional Aspects of Sex

Many clinicians are well versed in treating sexual problems which seem to have an obvious physical cause. Examples of this include the use of local estrogen for vaginal application following menopause or systemic estrogen and/or progestagens for hormone replacement.

What clinicians find more difficult, however, is dealing with the emotional aspects, either causative or as a consequence of sexual disturbances.

Whether or not a sexual problem has a physical cause, it will have an emotional impact. A man who has suffered erectile dysfunction after prostate cancer will not only have to deal with the potential life-threatening disease, unpleasant treatment, and anxiety for the future, he will find that his sexual life is altered, which impacts on his sense of self and his masculinity. Likewise a woman who finds sex too painful following radiotherapy to the genital area will feel she is “letting herself and her partner down.”

Cancer produces a list of losses which the patient may experience throughout their cancer journey. There are the loss of health, loss of freedom if having to undergo treatment, potentially loss of life expectancy, and loss of plans for the future. Added to this can be the loss of self-esteem, lowering of self-worth, and feelings of being subsumed by the cancer. One of the most common sexual problems, loss of sexual interest, or loss of libido, can follow major life losses and is commonly seen in cancer patients.

As previously stated, there are no physiological markers for this condition. In most cases, it is psychogenic and will respond to appropriate psychosexual, psychological, or counseling therapy.

Even when all physical symptoms have been appropriately diagnosed and treated, the sexual problem may remain. Sexual morbidity in gynecological cancer is associated with poorer psychological adjustment among survivors [65]. Cancer often acts as a trigger for deeply buried emotional issues to come to the fore. Previous losses may often come to light as the client undergoes counseling. These may be past loss of pregnancy, either termination of pregnancy or miscarriage, loss of job, or unresolved bereavement issues around a family member. Many patients throughout therapy confront loss of a carefree childhood, with physical and verbal abuse, alcoholism in the family, or a traumatic parental divorce which may be underlying factors in their current sexual condition. These are just a few examples which serve to underline that dealing with sexual problems in cancer patients may require a broader approach than may be currently available in many centers.

Many sexual problems are of primary psychogenic origin, but with the cancer disease process in the background, there is an anxiety in making this diagnosis in case some organic disease is "missed." There is also a prevailing attitude in some cancer units that sexual problems are being treated, when in fact the depth of the emotional impact has not been recognized. It consequently may take a long time before the patient is able to access appropriate treatment for a psychosexual problem. Increased staff awareness and training, however, should eventually remove some of the barriers to adequate treatment, but current training needs to be improved in order to better elicit the concerns of patients [66].

Partners

When an individual has cancer, not only are they affected, but in most cases, there is a substantial impact on their family, friends, and social and work contacts. Also sadly many have to face the cancer alone. In relation to sexuality, if there is a partner, then the partner will almost invariably be affected. The impact of cancer on a sexual partner is enormous. Seventy-six percent of partners of people with nonreproductive site cancers and eighty-four percent of partners of people with reproductive site cancers had sexual problems [67] . The presence or absence of a partner may be a major issue for the patient, either before, during, or after their cancer treatment.

A Danish population study showed that the male partners of women with breast cancer had an increased risk of severe depression, which was even higher in those whose partners had died [68]. The high rate of sexual problems associated with prostate cancer leads to couples' spousal communication levels dropping significantly [69], as it is easier to avoid the topic than cover emotionally painful ground. The partners of cancer sufferers who had hematopoietic stem cell transplantation suffered more depression and sexual problems than controls [70].

Infertility can be an outcome of cancer or its therapy. This adds another major loss to a couple who are already dealing with loss of health and a possibly altered vision of their future together. In many, parenthood is a natural and primeval drive, and the desire to found and care for a family is profound. When faced with the inability to bear children with one's partner directly or indirectly because of malignancy, the couples are more likely to suffer anxiety, stress, and sexual problems, especially the woman [71]. Service providers should be sensitive to the fact sexual and reproductive concerns may be present, in both couples and single individuals, and should give the patients an opportunity to speak of their difficulties. With increasing current knowledge of both cancer and reproduction, a comprehensive oncofertility program comprising rapid and robust referral pathways to skilled medical and oncopsychology services is the ideal [72], but globally underprovision of these services is still a major problem.

Treatment for sexual problems in relation to cancer should always offer the option of involving the partner, if there is one. Not everyone wishes this, especially in the early stages of discussion where individuals are anxious as to the form of the consultation. In a psychosexual clinic, it is a common fear of the patient that they may be made to have sex in the clinic setting.

Alternatives to penetrative intercourse can be suggested, but some couples find they cannot contemplate such a radical change [73]. Simple suggestions like the use of books and online materials for ideas and information can be helpful and fun, but all of these suggestions need partner compliance. The deeper emotional issues will not be addressed in this way but can provide some positive input into very disrupted sexual lives.

When couples are willingly involved, however, treatment outcomes can be very good. For example, post-breast cancer, it is the quality of the woman's partnered relationship which predicts sexual outcomes [74].

Sexual Minority Groups

As the majority of the population are heterosexual, when talking about sexual and relationship issues, it is sometimes forgotten that the groups with minority sexual orientation and identity such as gay men, lesbians, bisexuals, and trans people are equally or may be more likely to be the victims of cancer. There is not enough data on whether they are more susceptible to cancer than the general population, due to a paucity of good and routinely collected statistics, but it has been suggested that appropriate information could be acquired by using cancer registry data [75]. This is important, because lesbian and bisexual women may perceive their cancer risk to be lower than reality [76] particularly bisexual women, who are having sex with both men and women and are at high risk of HPV infection and consequently cervical cancer. Sadly some healthcare professionals are also unclear about lesbian and bisexual women's needs for cervical screening, despite the fact that there is a clear incidence of smear abnormalities in this group. The women also feel that they are excluded from dominant sexual scripts that inform the negotiation of safer sex practice [77]. Location of residence is another factor regarding screening, and rural women were less likely to accept cancer screening than urban residents [78].

For some years now, lesbian and bisexual women have been shown to have a greater risk of diseases linked to smoking and obesity, both of which have associations with cancer [79]; however despite awareness this may continue to be the case. Tobacco and alcohol misuse has clearly been associated with a variety of cancers. Lesbian and bisexual orientation and sexual abuse before the age of 11 were shown to be associated with an increased risk of tobacco and alcohol use during adolescence, greater than heterosexual women [80].

A comparison of lesbian and heterosexual women's response to newly diagnosed breast cancer showed no substantive differences, and the lesbian women demonstrated adaptive coping [81]. The women who openly identified themselves as lesbian or bisexual had better coping mechanisms and lower distress than women who identified themselves as actually heterosexual but also have sex with women [82].

There have been positive differences demonstrated in sexual minority women and their sexual functioning after cancer. These women may experience less sexual disruption such as lubrication and orgasmic problems and less problems with body image than heterosexual women. Their partners are often more supportive and understanding [83]. It is not unknown for both women in a same sex relationship to suffer the same cancers at the same time and have to cope with a complex patient, partner, and carer role. There can be robust community support for a lesbian woman with cancer, but there have been reports of isolation linked to fear of cancer and homophobia in the greater community [84]. Additional anxiety can be provoked by fear of disclosing their sexual orientation to healthcare providers, and there is often unconscious heterosexual bias in healthcare settings, as physicians do not ask or make assumptions [85] which can make the patient feel uncomfortable in facing the unknown.

Men who have sex with men are at high risk of anal cancer, especially if HIV infected. In general, anal cancer screening was not associated with greater psychological stress in HIV-infected men; however it was an issue among younger men and those whose HIV symptomatology was greater [86]. Although men are traditionally reluctant to come forward for screening, when invited in a healthcare setting, it is feasible without undue psychological stress.

Generally overt homophobia is not experienced by gay and lesbian and trans people with cancer [87], but there can still be an unintended insensitivity to sexual minorities among the caring professions which only appropriate education and training can address. Sensitivity toward differing sexual and gender identities is now a more widespread feature of training for healthcare professionals but is still an under-researched field [88].

Communication About Sex

Many cancer patients wish to communicate about sex to their clinician but find it very difficult to do so [89]. It is also difficult communicating about sex in a routine cancer consultation. There are often family members or close friends present to support the patient, but this can clearly inhibit discussion about sex which concerns the most intimate level of interaction between the patient and their partner.

It has been shown that poor communication levels can stop the patient from getting the help they need. Doctors and nurses know that they should communicate about sexual problems with their cancer patients, but they fail to do so. This can be due to personal feelings of discomfort about sex or an embarrassment at talking about sex to others. Age disparity makes it hard to talk about sex; a young doctor is unlikely to ask an octogenarian if she is having a sexual problem, and the octogenarian lady is unlikely to bring up the subject with a doctor or nurse in their twenties. Older men with prostate cancer said they were rarely invited to talk about sex, and it became a more important issue over time, with the patients saying, “I wish I had told them” [90]. Men find it particularly difficult to talk about intimate issues due to “the barrier of masculinity,” but adequate partner support and stable sense of self can bolster men’s self-esteem [91]. It is therefore incumbent on the professional to make sure they are adequately trained in this field and are able to bring up the subject in a timely and positive way. When students have formal communication training, the outcomes for the patient are better.

Information from the care provider about sex varies depending on the cancer site. In one study, 79% of prostate cancer sufferers were given appropriate sexual information, yet only 23% of lung cancer patients received the same help [92]. Asking routinely if patients have a partner, if they are sexually active, and if they have any problems is a certain way to give the patient permission to discuss the topic. They may not wish to at that particular point, but they know it is an “acceptable” topic and may choose to bring it up later.

In certain situations, it becomes even more difficult to discuss sex. For instance, transgender men may retain female reproductive organs, and screening in particular for cervix cancer is still important and warrants discussion [93].

One of the great taboos in cancer care is still talk of sex during the palliative phase. Some patients who are dying do wish to talk about sex [94]. It is to them a reaffirmation of life and a powerful bond with the person they love. In some enlightened cancer units, a double bed is provided to give comfort and sexual dignity to the dying.

A major problem is the attitude of health professionals who tend to “medicalize” sex [94]. As anyone engaged in psychodynamic work will understand, this is an easy way for the clinician to escape the emotional aspects of the problem and to retreat into nonthreatening areas of clinical discussion. Clinicians are very skilled at “running away” from emotional issues by focusing on physical and physiological signs and symptoms. The standard clinician-led question and answer session in a consultation does not allow the patient any opportunity to express any sensitive or deeper sexual or emotional issues. Allowing silence, time, and space in questioning allows the patient better opportunity to disclose sexual issues.

Problems in professional communication about sex can only be addressed by formal and compulsory training for the whole clinical team, within a fully evaluated framework such as medical or nursing school or in postgraduate training. One cannot opt in or out of training in specific diseases nor be permitted to ignore physical symptoms. Likewise sexual problems should be regarded in the same light and should be a compulsory and integral part of education particularly in the oncological setting.

Conclusion

Sexual problems are now finally being acknowledged by both patients and their clinicians as an intrinsic part of the life of a cancer survivor and deserve as much, if not more, attention than some of the other issues being faced. As research shows, if around half of all cancer sufferers have a problem of a sexual nature, it is imperative that these issues are addressed.

The evidence is clear and prolific in documenting the burden of sexual distress in patients with cancer. These effects can be improved by taking a multidisciplinary approach, not only by clear diagnosis and treatment of the physical aspects of the disease but by approaching the patient as an autonomous individual and accepting the emotional impact on them of sexual problems within their own social, economic, and cultural setting.

Despite this ongoing knowledge, in general the provision of professional training and service provision in this field is still woefully inadequate. Much help, however, can be given by the individual clinician to their patient by utilizing their core professional skills. By encouraging disclosure of sexual concerns, listening empathetically, and treating each one as an individual, much ongoing suffering can be alleviated.

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Use of the Classic Hallucinogen Psilocybin for Treatment of Existential Distress Associated with Cancer

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This chapter will review the potential of a treatment approach that uses psilocybin, a novel psychoactive drug, to ameliorate the psychospiritual distress and demoralization that often accompanies a life-threatening cancer diagnosis. The focus of cutting-edge research beginning in the 1950s, the investigation of classic hallucinogens, had a major impact on the evolving field of psychiatry, contributing to early discoveries of basic neurotransmitter systems and to significant developments in clinical psychopharmacology. While published reports of therapeutic breakthroughs with difficult-to-treat and refractory patient populations were initially met with mainstream professional enthusiasm, by the late 1960s and early 1970s, the growing association of hallucinogens with widespread indiscriminate use led to the temporary abandonment of this promising psychiatric treatment model. After a hiatus lasting several decades, however, regulatory and scientific support has grown for the resumption of clinical research investigations exploring the safety and efficacy of a treatment model utilizing the classic hallucinogen, psilocybin, in a subject population that had previously demonstrated positive therapeutic response, patients with existential anxiety due to a life-threatening cancer diagnosis.

Psilocybin

Psilocybin is a naturally occurring compound that is an active constituent of many species of mushrooms, including the genera *Psilocybe*, *Conocybe*, *Gymnopilus*, *Panaeolus*, and *Stropharia*. Psilocybin-containing mushrooms grow in various parts of the world, including the United States and Europe, but until recently they have been consumed primarily in Mexico and Central America, where they were called by the ancient Aztec name of *teonanacatl* (flesh of the gods). In addition to psilocybin, other naturally occurring classic hallucinogens include mescaline from peyote and dimethyltryptamine (DMT) from various plants. All three of these substances have a long history of ceremonial use by indigenous people for religious and healing purposes. Following the arrival of Europeans in the New World in the sixteenth and seventeenth centuries, however, the use of plant hallucinogens by native peoples was harshly condemned and punished under the strict laws of the Spanish Inquisition

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and forced to go underground. This suppression was so effective that hallucinogenic mushroom use was eventually assumed to be non-existent, until the discovery by amateur mycologist, R. Gordon Wasson, of their extant ceremonial use by indigenous Mazatec people of Oaxaca, in the central Mexican highlands. Invited to participate in a healing ritual using mushrooms as a psychoactive sacrament, Wasson published his observations in the popular American press in 1957, catalyzing both popular and professional interest [71, 91]. Subsequently, the eminent Swiss natural products chemist, Albert Hofmann, succeeded in isolating the active tryptamine alkaloid, psilocybin, from samples of the hallucinogenic mushrooms from Mexico sent to him by Wasson.

Psilocybin is 4-phosphoryloxy-N,N-dimethyltryptamine and possesses a chemical structure similar to the neurotransmitter serotonin (5-hydroxytryptamine). Psilocybin is rapidly metabolized to psilocin, which is a highly potent agonist at serotonin 5-HT-2A and 5-HT-2C receptors [85, 86]. Research suggests that the primary site of action for the psychoactive effects of psilocybin is the 5-HT-2A receptor [79, 105]. During the 1960s, psilocybin was subjected to psychopharmacological investigation and found to be active orally at around 10 mg, with stronger effects at higher doses, and to have a 4- to 6-hour duration of experience. Psilocybin was also determined to be 30 times stronger than mescaline and approximately 100 to 150 times less potent than LSD (lysergic acid diethylamide) [50]. Compared to LSD, psilocybin was considered to be more strongly visual, less emotionally intense, more euphoric, and with fewer panic reactions and less likelihood of inducing paranoia [84]. Similar to other classic hallucinogens, psilocybin was observed to produce an altered state of consciousness that was characterized by changes in perception, cognition, and mood in the presence of an otherwise clear sensorium, along with visual illusions and internal visionary experience (though rarely frank hallucinations), states of ecstasy, dissolution of ego boundaries, and the experience of union with others and with the natural world.

In the late 1990s, psilocybin was subjected to renewed examination by contemporary investigators, including Franz Vollenweider and colleagues at the Heffter Research Center and the University of Zurich, in Switzerland. Careful medical and laboratory evaluations conducted there identified a relatively safe physiological range of action in normal volunteer subjects [42, 101]. Positron emission tomographic (PET) studies also demonstrated that psilocybin induces a global increase in cerebral metabolic rate of glucose, most markedly in the frontomedial and frontolateral cortex, anterior cingulate cortex, and temporomedial cortex [104]. In another recent study, at the University of Arizona, Francisco Moreno examined the use of psilocybin in the treatment of severe, refractory obsessive-compulsive disorder, observing that psilocybin appeared to be safe, well-tolerated, and capable of inducing "robust acute reductions" in OCD symptoms [73]. Further investigations of psilocybin in normal volunteers were conducted at the Johns Hopkins University exploring the emergence of psychospiritual states of consciousness following psilocybin administration [35] (see section below). The Johns Hopkins group also published a set of recommended guidelines for safe conduct of high-dose research with classic hallucinogens [53].

Psychiatric Research with Classic Hallucinogens: Historical Perspective

Hallucinogens consist of a diverse group of biologically active compounds. Hallucinogens in plant form are thought to have been utilized by prehistoric and early civilizations as essential features of their religious, initiation, and healing rituals. Ethnobotanists have catalogued more than 100 species of plant hallucinogens, the majority in the Western Hemisphere, where they played a vital role within indigenous ceremonial practices [98]. In the late nineteenth century, interest in psychoactive plants was catalyzed by discoveries of anthropologists studying native peoples around the world, who shipped specimens to leading European pharmacologists of that era, including Arthur Heffter and Louis Lewin, who succeeded, respectively, in isolating mescaline from the southwest American cactus peyote, *Lophophora williamsii*, and harmine from *Banisteriopsis caapi*, one of the plants brewed to create the Amazonian plant hallucinogen decoction, ayahuasca.

The classic hallucinogens can be divided structurally into two classes of alkaloids: the tryptamines, including psilocin and psilocybin (constituents of *Psilocybe* and several other mushroom genera), DMT (constituent of the plant admixture ayahuasca and other hallucinogenic preparations), and d-lysergic acid diethylamide (LSD), and the phenethylamines, including mescaline (constituent of peyote) and various synthetic compounds. The primary pharmacological effects of these substances are mediated at 5-HT$_{2A}$ receptors where they function as agonists. The first classic hallucinogen to be characterized pharmacologically was mescaline, which was discovered in 1896 and synthesized de novo in the laboratory in 1919 [51]. While some attention was given in the early twentieth century to potential medicinal applications of hallucinogens and there were preliminary efforts to formally classify and analyze visions induced by alkaloids discovered in particular plants [1, 61], widespread medical and psychiatric interest did not emerge until the mid-twentieth century, following Albert Hofmann's serendipitous discovery of LSD at the Sandoz Laboratories in Basel, Switzerland, in 1943 [46].

From the 1950s, when formal study of the range of effect of hallucinogens and their potential in treatment models was initiated, until the early 1970s, when cultural and political turmoil led to the termination of studies, over 1000 clinical and research reports were published in the medical and psychiatric literature describing the response to hallucinogen administration of approximately 40,000 research subjects and patients [38]. While initial research focused on the presumed capacity of hallucinogens to induce psychotic-like experience, interest in this psychotomimetic model waned [2, 37]. By the late 1950s and into the 1960s, however, significant new research activity was catalyzed by studying potential treatment applications of hallucinogens, most notably for several notoriously difficult-to-treat clinical conditions, including alcoholism, drug addiction, obsessive-compulsive disorder, chronic post-traumatic stress disorder, antisocial disorder, infantile autism, and the overwhelming existential anxiety often experienced in the presence of terminal cancer. Two discrete treatment models were proposed, involving the administration of lower versus higher dosages of hallucinogens and the application of different theoretical mechanisms of action for their observed therapeutic effect. The initial treatment structure investigated, the psycholytic model, called for the administration of relatively low dosages of hallucinogens, with the postulated goal of facilitating the release of repressed psychic material, particularly in anxiety states and obsessional neuroses. Using this approach, some clinicians claimed to have achieved breakthroughs in reducing the duration and improving the outcome of psychotherapeutic treatment, presumably by facilitating ego regression, uncovering early childhood memories, and inducing an affective release [10].

As investigators began to explore the effects of higher dosages of hallucinogens on clinical subjects and patients, however, they began to appreciate that hallucinogens were capable of occasioning entirely new and novel dimensions of consciousness. Humphrey Osmond, a Canadian alcoholism researcher, noted that this high-dose hallucinogen, or *psychedelic* (translated from the ancient Greek as "mind revealing") treatment model, appeared to free up the mind from its habitual moorings and allow it to access states of consciousness resembling spontaneous psychospiritual epiphanies. Osmond observed that even after the effects of the administered drug had worn off, individuals were still left with a deeply positive and therapeutic impact from having had a mystical level transcendent experience [80]. With certain conditions in particular, including alcoholism and other addictive disorders, the mysticomimetic capacity of the hallucinogen experience often appeared to have induced remissions from intractable psychological conditions to a greater degree unique than conventional treatment modalities. While the low-dose psycholytic model usually involved active discourse between patient and psychotherapist in the service of analyzing underlying neurotic complexes, the high-dose psychedelic model involved the development of an alternative treatment structure, with the subject lying down, wearing eyeshades, and listening to pre-selected music throughout much of the session. During the session, the patient was encouraged to go deeply into the experience, with the facilitator maintaining an active presence but generally not engaging in verbal dialogue until the concluding phase of the treatment session.

One patient population that demonstrated positive response to the hallucinogen treatment model were individuals with advanced cancer with overwhelming anxiety in reaction to their terminal illness. Beginning with the observations of internal medicine investigators in the late 1950s at the University of Chicago [57, 58] and UCLA [15], and extending by the mid-1960s to psychiatrists and psychologists at the University of Maryland [40, 83, 90] and UCLA [25], a growing consensus within the field of hallucinogen investigations was achieved that patients with advanced-stage cancer treated with this novel approach frequently sustained significant improvements of their psychospiritual status. Moving accounts were reported of patient experiences, including reduced physical pain and lessened need for narcotic medication, improved quality of life, and greater acceptance of the inevitable and in some cases imminent end of their lives. Of particular interest, the most positive therapeutic outcomes, reflected in lowered anxiety, in demoralization and fear of death, and in improved mood and quality of meaningful interpersonal relations, were in patients who during the course of what was often their only hallucinogen treatment session experienced a deeply felt mystical state of consciousness. Unfortunately, these promising observations were terminated prematurely, largely in response to public and political concern about the misuse of these compounds in the 1960s.

Contemporary Psilocybin Research in Patients with Life-Threatening Cancer

Following decades of inactivity, it has been possible in recent years to obtain the regulatory approval and funding necessary to resurrect this long neglected treatment model. While improvements in caring for patients at the end of life have occurred in the intervening years, including the development of the hospice movement and the field of palliative medicine, it is still clear that even with these innovative approaches, many individuals still go through the final phase of their life with high levels of anxiety, depression, and demoralization. Given the pressing need for more effective therapeutic interventions in individuals struggling with cancer and reactive existential crisis, along with the promising preliminary findings of the hallucinogen treatment model from the previous generation of research in patients with terminal medical illness, it is not surprising that this has become a prominent focus for current research efforts as well. Indeed, in recent years, three investigations have been approved in the United States that have examined the use of psilocybin treatment for anxiety and demoralization in patients with a life-threatening cancer diagnosis – at Harbor-UCLA Medical Center, Johns Hopkins University, and New York University School of Medicine. All three sites established guidelines of set and setting, specifically that of interpersonally supportive preparatory sessions, medication session monitoring, and postmedication therapeutic integration sessions first developed at Spring Grove/Maryland Psychiatric Center [41, 53].

In 2004, the Harbor-UCLA psilocybin treatment protocol for anxiety in patients with advanced cancer was initiated. A total of 12 patients were recruited for a double-blind, placebo-controlled investigation, using a moderate dose (0.2 mg/kg) of psilocybin. All subjects enrolled in the study were diagnosed with advanced-stage, metastatic cancer with reactive anxiety and depression. All patients were screened to meet inclusion and exclusion criteria, which included a diagnosis of advanced-stage cancer but still functional enough to undergo full screening, preparation for the psilocybin sessions, and participation in two all-day sessions spaced several weeks apart, one active drug and the other placebo. Potential subjects on the threshold of expiring were not accepted into the study. The primary physicians and oncologists for each screened subject were consulted, and subjects were considered potential study candidates if their life expectancies were considered to be in the 6-month to 1-year range. Support with integration of the experience and collection of follow-up reports and quantitative data analyses continued with each patient for at least 6 months following treatment. Recruitment for all patient into the study, their participation in both psilocybin and placebo treatment sessions, and collection of data concluded in early 2008. Within several years of their participation in this pilot psilocybin treatment of advanced cancer-anxiety study, all enrolled and treated subjects had died.

The report describing the rationale for the investigation, methodology employed, and findings up to 6 months after treatment were published in the *Archives of General Psychiatry* [39]. All patients tolerated the psilocybin experience well, and there were no medical or psychological crises. Repeated administration of quantitative rating scales revealed improved mood and lessened anxiety, reaching significance at some monthly data collection points. Overall, patients reported their participation in the psilocybin treatment study as having been a very valuable experience, allowing them to improve their quality of life and augmenting their capacity to withstand the psychological stressors of their medical condition. Following the completion of the Harbor-UCLA research investigation, approved studies at Johns Hopkins and NYU continued to explore the treatment of cancer-anxiety patients with higher doses of psilocybin. The Johns Hopkins and NYU studies, initiated in 2006 and 2009, respectively, both received regulatory approval to use a significantly higher dose than the Harbor-UCLA protocol, which likely allowed for more in-depth exploration of the psychospiritual dimension of the experience. These studies also offered more flexibility for subject inclusion and allowed for the entry of patients with early-stage cancer that are nonetheless considered potentially life-threatening.

The Johns Hopkins psilocybin treatment research study [32] of 51 patients who had potentially life-threatening cancer diagnoses and symptoms of depression and/or anxiety utilized a randomized, double-blind, cross-over trial contrasting the effects of a very-low-dose psilocybin placebo of 1–3 mg/70 kg subject body weight with a high psilocybin dose range of 22–30 mg/70 kg body weight. Treatment sessions were spaced approximately 5 weeks apart, and follow-up data was collected for 6 months following treatment. Significant findings included marked improvement of mood, decreases in anxiety and depression, increases in a measure of spiritual well-being in chronic illness, and an overall elevated quality of life as reflected in both subject and clinician ratings. These therapeutic effects were observed to sustain in 80% of subjects/participants at over the 6-month follow-up period assessment. Positive outcomes were reflected in significant corresponding changes in ratings by community observers (friends, family, work colleagues) of participant attitudes and behavior. Consistent with the prior Hopkins studies [35, 36, 90], the intensity of the experience along with the emergence of a powerful psychospiritual experience on session days were predictive of enduring positive effects induced by psilocybin administration under optimal conditions of set and setting. Such findings were similar to those of clinical treatment research investigations in the 1960s and early 1970s [40, 83] that reported psychologically therapeutic outcomes in terminally ill patients who reported mystical experiences following high-dose psychedelic treatment. In the recent Johns Hopkins study, psycholgically positive effects were similarly noted to correlate with the occurrence of a mystical experience during the actual treatment sessions.

The NYU clinical trial [94] studied 29 carefully screened cancer-anxiety patients, each functioning as their own control, with a double-blind, randomized cross-over design comparing psilocybin (0.3 mg/kg body weight) with effects of the placebo niacin (250 mg) on primary outcome measures of cancer-related anxiety and depression. Nearly two-thirds of participants (62%) had advanced cancers (stages III or IV). Significant findings from the psilocybin sessions included immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual well-being, and increased quality of life. At the 6.5-month follow-up, psilocybin was associated with enduring and marked decreases in anxiety and depression (approximately 60–80% of participants continued with clinically significant reductions in depression or anxiety), sustained benefits in existential distress and quality of life, as well as improved attitudes toward death. Similarly, at 6.5 months, 70% and 52% of the study volunteers rated what they believed to be the psilocybin session as the singular or top 5 most personally meaningful or the singular or top most spiritually significant experience of their lives, respectively. Eighty-seven percent of the study volunteers reported increased life satisfaction or general well-being. Psilocybin was well tolerated with no serious adverse events. Common adverse effects included non-clinically significant elevations in blood pressure and heart rate (76%), headache (28%), nauseas (14%), and transient or episodic anxiety (17%).

Slightly less than two-thirds of the subjects had advanced, metastatic cancer, while the remainder presented with early-stage cancer. Investigators found at the 6-month follow-up strong indication of enduring reductions of anxiety and depression, along with reduced preoccupation and less anxiety toward death. Of note, and consistent with the Johns Hopkins investigation, NYU researchers demonstrated the capacity of psilocybin under optimal conditions to safely generate mystical experiences. Together, the Johns Hopkins and New York University studies included 80 cancer patients with approximately 80% of the patients demonstrating decreases in anxiety, depression, and measures of existential distress with these improvements sustained at a minimum of 6 months. Of note, and consistent with the Johns Hopkins investigation, NYU researchers demonstrated the capacity of psilocybin under optimal conditions to safely generate mystical experiences. Significantly, both studies demonstrated the mystical experience to be a mediating factor and predictor on enduring changes in outcome measures including anxiety and depressive outcomes.

Such powerful psychospiritual epiphanies were identified as a compelling mediating factor facilitating the emergence of positive therapeutic outcomes as observed in reductions of measurable levels of anxiety and depression reactive to the subjects' diagnoses of life-threatening malignant disease.

It is strongly hoped that additional research groups will also initiate treatment protocols exploring the utility of the psilocybin treatment model with medical patients encountering existential crisis and demoralization at the end of life. Toward that end, efforts are currently underway by investigators at Harbor-UCLA, NYU, and UCSF to develop a pragmatic trial in the palliative setting of psilocybin therapy with patients diagnosed with life-threatening medical illness including though not limited to advanced-stage cancer. In this multi-site study, one goal is to provide training in delivering psilocybin treatment for palliative practitioners, including physicians, psychologists, nurses, social workers, and chaplains who are part of the palliative team. The primary focus for this planned study is to examine impact of psilocybin treatment on the existential and spiritual domain of well-being of this highly vulnerable patient population. The primary target for treatment efficacy will be the relative degree of reported demoralization, which is considered a measurable form of existential distress characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life. Demoralization is associated with physical symptom burden and poor quality of life, and it is highly prevalent among patients with serious and life-threatening medical disease. The experimental design for this planned investigation calls for a double-blind, randomized, placebo-controlled study that will continue to follow subjects/participants for outcome evaluation over a 6-week period. An anticipated cohort of 88 subjects across multiple treatment sites will be recruited into the study. Screened participants/subjects will already have been accepted into a palliative care program for management of their potentially fatal medical illness. Following screening and inclusion into the study, participants/subjects will receive an experimental session and will receive either moderate- to high-dose psilocybin or an active placebo (as yet to be determined). 4–6 weeks post-drug administration, the blind will be broken, and participants/subjects who had been randomized to the placebo condition will receive an open-label psilocybin session. Integration and follow-up evaluation will occur for all participants/subjects for 6 weeks following psilocybin administration.

Comments from Annie L, a 53-year-old woman with a diagnosis of metastatic ovarian cancer, 6 months after her participation in a Harbor-UCLA psilocybin cancer-anxiety study

> I had lost my faith because of anxiety, and I was just terrified. I was so anxious that it was hard to think about anything else. I didn't think I was so worried about death as I was about the process of dying. About suffering and being in pain and having all kinds of medical procedures. I was becoming so irritable with my husband. I was just so anxious… My intention (for participation in the study) was to be able to control my anxiety so I could enjoy the rest of my life. I was not enjoying my life at all.
> As soon as it (the psilocybin) started working I knew I had nothing to be afraid of… It connected me with the universe… It was very gentle… And there were people (the treatment team) right there if I got upset… Everything looked absolutely beautiful. I didn't see things that weren't there. With my eyes closed I saw patterns, and visions and faces. I thought about being involved with people I loved, things I would do with people I knew, things I would tell them… I had an amazing spiritual experience. It re-connected me to the universe.

Comments from her husband 4 months after her death

> Annie's mood remained greatly improved for some time after the treatment. She also had much less anxiety, and her fear of getting sicker and her fear of the dying process also diminished a great deal. Beyond that, she and I got along much better after her psilocybin treatment… I have no doubt that the treatment Annie went through was of great value to her…

Overview and Prevalence of Emotional Distress in Advanced Cancer

For many cancer patients, the advanced stage of illness is fraught with a significant degree of emotional suffering. As the illness trajectory progresses from diagnosis through medical treatment and eventually to the prospect of dying, the patient may be faced with considerable psychological distress and despair. In recent years, there has been a growing focus on the prevalence and clinical treatment of psychological distress in patients with advanced cancer that are facing the end of life [22, 54, 56, 63, 92]. Emotional suffering in advanced illness has been characterized as "severe distress associated with events that threaten the intactness of the person" ([9], p.640).

The occurrence of psychological distress in cancer patients has been well documented with the highest prevalence rates among advanced cancer and end-of-life patients. While some cancer patients may cope effectively with the challenges of the disease, others experience a broad range of psychological stressors and symptoms. The prevalence of psychiatric disorders in cancer patients has been reported at approximately 50% [19, 67, 77] with the presence of any depressive or anxiety disorder at 24% [109]. The prevalence of major depression has been reported at 15% [47, 48, 108] with a range of all depressive disorders in cancer patients at 20% [109] to 26% [21, 30]. Anxiety spectrum disorders have been documented at 14% [109] with the prevalence of any anxiety symptoms at 21% [19]. The prevalence of suicide in advanced and end-stage cancer is twice as high as that found in the general population [11], and an increased desire for hastened death in terminal patients has been established [5]. Kelly et al. [59] found 22% of advanced cancer patients had a desire for hastened death.

Focus on Spiritual and Existential Distress in Palliative Care

With a growing awareness of emotional suffering at the end of life, palliative care has increasingly focused on the specific domain of spiritual and existential distress as a significant component of quality of life in cancer and end-of-life cancer patients [16, 22, 72, 76, 95]. In palliative care, outcomes are no longer focused solely on biomedical or physical measures, such as tumor or disease progression, but have expanded to include quality of life, now considered a central focus. Spiritual and existential factors are currently regarded as determinants of quality of life in advanced cancer and end-of-life patients. Distress in cancer and palliative care patients is viewed as a "multifactorial unpleasant emotional experience of a psychological, social, and/or spiritual nature" that impacts the patient's capacity to effectively cope with the myriad challenges of cancer [77].

Existential or spiritual pain of terminal cancer patients has been defined as "the extinction of the being and meaning of the self due to the approach of death. It can be explained as meaninglessness of life, loss of identity, and worthlessness of living that are derived from deprivation of the future, others, and autonomy of people as beings founded on temporality, beings in relationship, and beings with autonomy" [75]. An individual's search for spiritual and existential meaning is frequently triggered by a diagnosis of cancer and may be intensified as the disease progresses and the patient is faced with myriad challenges that accompany the course of illness [69].

The alleviation of spiritual and existential distress is a primary objective of palliative and end-of-life care. A report by the Institute of Medicine listed spiritual well-being as an essential influence on quality of life and one of the six domains of quality supportive care of the dying [24]. Similarly, a report by the Consensus Conference in association with the National Consensus Project for Quality Palliative Care identified spiritual and existential issues as two of the eight core essential domains of quality palliative care [87]. The World Health Organization describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [110].

Religion Versus Spirituality

Despite the overlap and ambiguity that has existed between the concepts of religion and spirituality, a consensus in the research literature has begun to emerge regarding the distinction between these two research constructs. Religion has been defined as structured belief systems that address universal questions and may provide a framework for making sense of ultimate questions of meaning and for expressing spirituality [100]. Spirituality tends to be a broader, more inclusive category than religion. It can be defined as "that which allows a person to experience transcendent meaning in life" [88] and "a personal search for meaning and purpose in life, which may or may not be related to religion" [102].

Whereas religion may be commonly viewed as a structured framework of beliefs and rituals that may include an expression of spirituality, spirituality may be experienced without the context of an organized religious system as a search for transcendence, meaning, and connection to ultimate meaning, to nature, or to how an individual defines or experiences the concept of God. The Report of the Consensus Conference on spirituality in palliative care suggested the following definition (National Consensus Panel Report): Spirituality is the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred [87].

Spiritual Well-Being and Psychological Distress

The domain of spiritual and existential well-being is now widely accepted as an important determinant in the quality of life in palliative care and end-stage cancer [16, 23, 45, 66, 72, 99]. Coping with terminal cancer is a multifactorial and variable process. Enhanced spiritual well-being and the ability to attain meaning when facing end-stage cancer appear to be a key factor in effectively coping with advanced disease. Psychosocial factors in advanced cancer associated with heightened existential and spiritual distress include anxiety and depression [28, 78], anger, alienation, hopelessness, loss of meaning, loss of dignity, vulnerability, isolation, fear, and shock [45, 106, 107]. Chochinov and colleagues [12] identified specific psychosocial correlates of spiritual and existential suffering in advanced cancer patients that include loss of will to live, loss of a sense of dignity, hopelessness, and feeling as a burden to others. Impaired spiritual well-being has also been associated with a poorer tolerance of physical symptoms, whereas an enhanced sense of meaning and spirituality has been shown to increase an individual's tolerance levels for physical symptoms [3]. Myriad healthcare domains and outcomes have been associated with existential distress including quality of life, symptom and disease progression, psychological distress, depression [92], interpersonal functioning [16, 109], suicidal ideation [69], and demoralization syndrome, defined as "a psychiatric state in which hopelessness, helplessness, meaningless, and existential distress are the core phenomena" (p.13 [60]).

Demoralization is defined by Kissane et al. [60] as a syndrome characterized by hopelessness, loss of meaning, and existential distress. This syndrome, which is delineated as a separate construct, has been identified as a primary risk factor for depression in advanced cancer patients. A desire for hastened death in advanced cancer patients has also been identified with this syndrome. Observed in palliative care and advanced cancer populations, this syndrome is associated with chronic medical illness, fear of loss of dignity, social isolation, and the sense of being a burden on others [60]. Kissane and colleagues propose that for targeted psychotherapies or interventions to be effective, they must aim to explore and restore meaning and hope within the context of advancing disease and impending death.

A desire for hastened death has been associated with lower levels of spiritual well-being [4, 92, 93]. A growing number of studies have presented evidence supporting a model that depression and hopelessness are chief determinants and predictors of a desire for hastened death [5, 54, 92]. For example, in a study exploring the relationships among depression, hopelessness, and desire for hastened death, Breitbart et al. [5] identified depression as a robust predictor of desire for hastened death. In this study, patients with major depression were four times more likely to have a desire for hastened death.

Enhanced Spiritual Well-Being as a Buffer Against Emotional Distress

While there has been a documented relationship between lack of spiritual well-being and elevated psychosocial distress, there is increasing evidence to support the hypothesis that *enhanced* spiritual or existential well-being is associated with *improved* psychological functioning and might even prove to be a buffer against psychological syndromes associated with the end of life.

Exploring the relationship between spiritual well-being, depression, and psychological distress in end-of-life cancer patients, a growing body of research has shown that higher levels of spiritual well-being are correlated with lower levels of emotional distress and serve as a buffer against depression, desire for hastened death, loss of will to live, and hopelessness as well as provide an increase in quality of life [5, 23, 56, 69, 78]. Individuals with an enhanced sense of spiritual well-being are also emotionally equipped to cope more effectively with the physical challenges of advanced and end-stage cancer [3].

The concept of meaning has received considerable attention in palliative care and psycho-oncology research as an important construct related to improved quality of life. Cultivating a sense of meaning in advanced cancer has been shown to improve spiritual well-being and overall quality of life while reducing levels of psychological distress [66, 70, 74]. For some patients, the search for meaning in end-of-life cancer, while a psychologically and spiritually complex, arduous, and courageous process, may provide them with a sense of peace and acceptance. Viktor Frankl, in *Man's Search for Meaning*, wrote that "man is not destroyed by suffering; he is destroyed by suffering without meaning" ([26], p.135). Although not written about the end-of-life struggle with cancer or life-threatening disease, Frankl's landmark book was written from his personal experience of survival during his 3 years in Auschwitz and other concentration camps. His struggle to derive personal meaning in the face of horror and death has resulted in universal life lessons for those facing severe suffering or existential distress. In *The Will to Meaning: Foundations and Applications of Logotherapy* [27], Frankl wrote, "Meaning can be found in life literally up to the last moment, up to the last breath, in the face of death" (p.76).

Meaning-enhancing interventions have been demonstrated to improve quality of life in palliative care and decrease wishes for euthanasia and for hastened death [6, 109]. Dame Cicely Saunders, who gave rise to the hospice movement and emphasized spiritual and psychological factors in palliative and hospice care, introduced the concept of "total pain" of the terminal patient that emphasizes psychospiritual as well as physical aspects of care and distress. Influenced by Frankl, she believed that the "total pain" of the terminal patient was related to a "lack of meaning" [96, 97]. In a quantitative thematic analysis [103] of all published literature on spirituality in palliative care, the most cited themes were meaning and purpose followed by self-transcendence and transcendence.

With an increasing body of evidence [5, 56, 69, 78] supporting the premise that enhanced spiritual well-being provides protection against depression, hopelessness, and desire for hastened death among other psychosocial forms of suffering, there is growing interest in interventions that enhance or improve psychological well-being and provide meaning in terminal patients. In recent years, there have been published reviews of interventions targeted at improving end-of-life psychological well-being and reducing various aspects of psychiatric distress [13, 64, 43, 99].

Interventions aimed at enhanced spiritual well-being, meaning, and dignity in advanced cancer patients are now being developed and studied for effectiveness [6, 14, 44]. Meaning Centered Group Psychotherapy [6], which directly focuses on spiritual well-being and meaning, showed improvements in spiritual well-being and a sense of meaning compared to a supportive group therapy. In a 2007 review of eight manualized interventions for existential distress in terminal patients [64], only a Supportive-Expressive Group Therapy (SEGT) met criteria for a "probably efficacious" treatment. We concur with Breitbart [6] in that "interventions focusing on meaning and spiritual well-being are uniquely powerful for patients facing a terminal illness" (p. 25).

Despite the growing awareness of spiritual and existential distress among end-of-life cancer patients and the impact on quality of life, there remains a paucity of psychotherapeutic approaches and interventions to directly address this suffering. In a study evaluating spiritual and existential needs among cancer patients, Moadel et al. [72] found that from 21% to 51% of patients reported unmet spiritual or existential needs. The unmet spiritual or existential needs cited by patients were overcoming fears (51%), finding hope (42%), finding meaning in life (40%), and finding spiritual resources (39%).

Breitbart [6] notes that while some interventions are aimed at improved mood, none examine the effect of spiritual well-being, and few interventional studies are directed at advanced or end-stage cancer patients. Furthermore, aside from hallucinogen-induced mystical experience (discussed below), none provide the means for a direct intensive alteration in consciousness with the potential for a transformative experience directly related to the sacred or to broad spiritual and existential phenomena. Blinderman and Cherny [7] note, "It has been observed that existential distress is the least studied domain of patient distress. Given the paucity of research in this area, additional qualitative and quantitative studies are needed to help further understand this domain of suffering and the possible areas of intervention by health care professionals" (p. 380). Lethborg et al. [65] suggest that "the specific techniques most effective in enhancing meaning and connection [in advanced cancer] are yet to be defined, and such clarification would require intervention-focused research that, in order to appropriately demonstrate change, would need to be longitudinal" (p.387).

Uniqueness of Psilocybin Mystical Experience Treatment Model

The hallucinogen treatment model, which has been shown to generate a mystical or spiritual experience [35], offers a highly unique and novel therapeutic approach to promote transcendence, meaning, and reduction in anxiety for terminal cancer patients [39]. It is the only approach with the dying of its kind in medicine, psychiatry, and the behavioral sciences. Reviews of the literature on the importance of spirituality in end-of-life suffering [89, 103] identify transcendence and meaning as the most common factors. Of the few spiritual well-being enhancing interventions for end-of-life patients currently available, the hallucinogen treatment model is the only approach that potentially facilitates a radical shift in consciousness yielding a transpersonal, transcendent, spiritual, and mystical experience.

Access to the transpersonal and transcendent non-ordinary dimensions of consciousness is an integral aspect of the enhanced spiritual well-being generated by the hallucinogen induced mystical experience. Eric Cassell, the distinguished internist who has contributed considerably to the conversation on dying in America and who has written extensively about the nature of suffering, medicine, and the compassionate and ethical treatment of the terminally ill, writes in his classic article *The Nature of Suffering and The Goals of Medicine*, "Transcendence is probably the most powerful way in which one is restored to wholeness after an injury to personhood. When experienced, transcendence locates the person in a far larger landscape. The suffering is not isolated by pain but is brought closer to a transpersonal source of meaning and to the human community that shares those meanings. Such an experience need not involve religion in any formal sense; however, in its transpersonal dimension, it is deeply spiritual" [9]. Meaning and transcendence, Cassell suggests, provide unique avenues for the amelioration of suffering at the end of life.

Access to the transpersonal realm has the potential to alter a terminal cancer patient's perspective to their existential suffering. Transpersonal psychology "is concerned with the study of humanity's highest potential, and with the recognition, understanding, and realization of unitive, spiritual, and transcendent states of consciousness" (p.91, [62]). For Aldous Huxley [49], the British writer who dedicated attention to comparative spirituality and to the application of hallucinogens in the dying, the hallucinogen-induced mystical experience may reveal the individual to the "perennial philosophy." This philosophia perennis is the philosophical concept which states that all the world's religions and philosophies traditions share a single truth. Mystical, numinous, and peak states of consciousness have been written about extensively throughout history by observers and investigators of philosophy, religion, and consciousness, including Carl Jung [55], Abraham Maslow [68], Rudolf Otto [81], William James [52], and Richard Bucke [8], and appear within the canon of the major religious and wisdom traditions.

For many cancer patients, the mystical experience provides a profound ontological shift. This ontological or paradigm shift in awareness has the capability to alter and transform a cancer patient's assumptions and beliefs regarding the nature of being, the self, the body, disease, and death itself. Often, for the patient who has had this awareness, the body and cancer are experienced as separate (i.e., "I am not my cancer"). The self-experience or self-image of the patient may be recalibrated into a broader existential view where the meaning of cancer and even death itself may be transformed and may no longer be a profoundly anxiety-provoking experience as it was before. The terror of death may be altered as an individual experiences connection to the transpersonal realm, to others, to nature itself, or to the sacred. Often, the patient may experience consciousness as continuing indefinitely, thereby dramatically modifying or transforming the concept of death of the self.

The primary characteristics of a mystical experience, which are summarized in Table 5.1, appear directly related to the potential for a reduction in existential and psychospiritual distress. The potential primary effects or benefits of mystical or peak consciousness states in cancer patients are (1) improved psychological, spiritual, and existential well-being; (2) ability to cognitively or emotionally reframe the impact of cancer, dying, and death; (3) increased capacity for appreciation of time living; (4) increased appreciation and experience of connectedness to sacredness, nature, relationships, and family; (5) ability to attend to unfinished business; (6) the possibility to conceptualize death as "not the end" but a transition of some manner in continuing consciousness; (7) increased sense of meaning and purpose; and (8) increased acceptance and peace with death.

Table 5.1 Phenomenological features of a mystical-type experience – either naturally occurring or occasioned by a classic psychedelic

Unity: a core feature, a strong sense of the interconnectedness of all people and things – All is one – sometimes a sense of pure consciousness or a sense all things are alive
Sacredness: reverence, awe, or holiness
Noetic quality: a sense of encountering ultimate reality
Deeply felt positive mood: universal love, joy, peace, tranquility
Transcendence of time and space: a sense of timelessness, when past and future collapse into the present moment – an infinite realm with no space boundaries
Ineffability: a sense that the experience cannot be adequately described in words

Johns Hopkins Studies of Psilocybin-Occasioned Mystical-Type Experience

Building on observations made in a study conducted in the early 1960s in seminary students at Harvard [20, 82], several double-blind studies conducted at Johns Hopkins [33–36] have demonstrated that under carefully controlled conditions, high doses of psilocybin caused profound personal and spiritually meaningful experiences in the majority of healthy, normal participants. One study [35, 36] involved 36 volunteers who participated in 2 or 3 day-long sessions during which they received, on separate sessions, a high dose of psilocybin (30 mg/70 kg), or a dose of methylphenidate hydrochloride. The design of the study effectively obscured to volunteers and study staff who monitored the sessions exactly what drug conditions were being tested. A subsequent study [34] involved 18 participants who received, in mixed order, a range of psilocybin doses (placebo, 5, 10, 20, and 30 mg/70 kg) over five sessions. In a more recent study [33], 75 healthy volunteers received 2 psilocybin sessions consisting of either a very low placebo-like psilocybin dose of 1 mg/70 kg ($n = 25$) or high doses of psilocybin (20 and 30 mg/70 kg, sequentially, $n = 50$). Participants in all three studies had a mean age of 44 years and were well-educated and high-functioning. Most participants were hallucinogen naïve, and those who had past use reported that the last such use was about 25 years earlier.


[redacted]
[redacted]

Fig. 5.1 The living room-like session room used in the Johns Hopkins psilocybin research studies. Comfortable, aesthetic environments free of unnecessary medical or research equipment, in combination with careful volunteer screening, volunteer preparation, and interpersonal support from two or more trained monitors, help to minimize the probability of acute psychological distress during sessions. The use of eyeshades and headphones (through which supportive music is played) may contribute to safety by reducing distractions as well as social pressure to verbally interact with research personnel. (Reprinted from Johnson et al. [53])

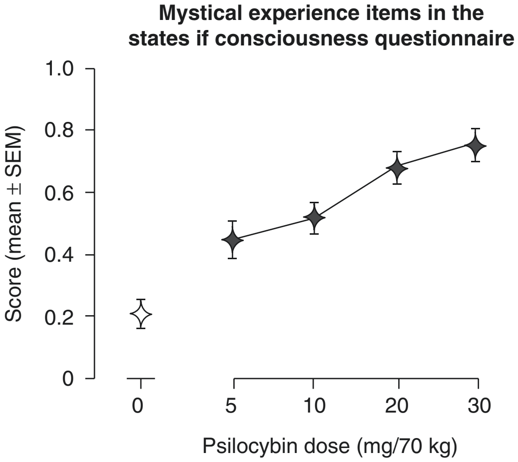

Fig. 5.2 Post-session ratings on a questionnaire designed to assess mystical experience. Psilocybin produced orderly dose-related increases, with most participants fulfilling criteria for having had a “complete” mystical experience. Bars indicate means with brackets showing SEM (N = 18); asterisks indicate a significant difference from the placebo (0 mg/70 kg) dose (Data from [34])

Study monitors met individually with each participant for a total of 8 hours before the first session and for 2 hours between sessions to help develop rapport and trust, which are believed to minimize the risk of adverse reactions to classic hallucinogens. The 8-hour drug sessions were conducted in an aesthetic living room-like environment designed specifically for the study (Fig. 5.1). Two monitors were present throughout the session. For most of the time during the session, participants were encouraged to lie on the couch and use an eye mask and headphones. Participants were encouraged to focus their attention on their inner experiences throughout the session. Details and rationale for screening, preparing volunteers, and managing sessions and aftercare were similar to those described by Johnson et al. [53].

As expected, psilocybin produced increases in measures previously shown to be sensitive to hallucinogenic drugs, including perceptual changes (e.g., visual illusions), greater emotionality (e.g., increased joy and peacefulness and, less frequently, fear and anxiety), and cognitive changes (e.g., changes in a sense of meaning, sometimes suspiciousness). But perhaps the most interesting effect was that psilocybin produced large increases on extensively studied, well-validated questionnaires that were designed to measure naturally occurring mystical-type experiences as described by mystics and religious figures worldwide and throughout the ages, including measures not previously used to assess changes after a drug experience. Figure 5.2 shows that psilocybin produced orderly dose-related increases in a measure of mystical experience obtained at the end of the session day [34]. “Complete” mystical experiences were those in which volunteers met a priori criteria on all six phenomenological dimensions of the mystical experience (Table 5.1). The percentage of volunteers who fulfilled criteria for having had a “complete” mystical experience was an increasing function of dose: 0, 5.6, 11.1, 44.4, and 55.6% at 0, 5, 10, 20, and 30 mg/70 kg, respectively. Seventy-two percent of volunteers had “complete” mystical experiences at either or both the 20 and 30 mg/70 kg session. On retrospective questionnaires completed 1 or 2 months after the psilocybin session and 14 months after the last session, volunteers reported sustained

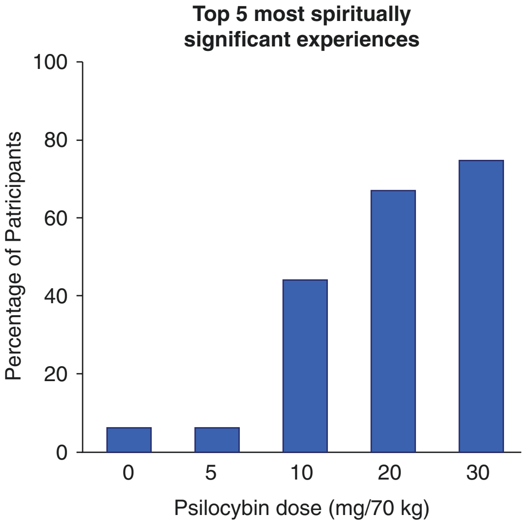

Fig. 5.3 Retrospective ratings of the spiritual significance of the psilocybin experience 1 month after sessions. Bars show percentage of participants (*N* = 18); asterisks indicate a significant difference from the placebo (0 mg/70 kg) dose. Not shown, at 14 months after the last session, 94% of participants rated the experience during the 20 and/or 30 mg/70 kg sessions do be among the top 5 most spiritually significant experiences of their lives, including single most. (Data from [34])

positive changes in attitudes, mood, altruism, behavior, and life satisfaction. Figure 5.3 shows that most participants considered the experience to be among the 5 most spiritually significant experiences of their lives, including single most. Participants also endorsed various domains of change that suggest increased self-efficacy (e.g., increased self-confidence and sense of inner authority) and decreased perceived stress (e.g., decreased nervousness, increased inner peace and ability to tolerate frustration). The more recent study [33] extended these findings by showing that more than 60% of 50 healthy participants who received two high-dose psilocybin sessions (20 and 30 mg/70 kg, sequentially) met criteria for having had a complete mystical-type experience. At 6-month follow-up, compared to the low-dose group, participants who received the higher psilocybin doses showed significant positive changes in moods and trait measures of attitudes and behavior. Importantly, in all three healthy volunteer studies, and similar to the previously described study in cancer patients [32], ratings of the volunteers' behavior by community observers (friends, family members, colleagues at work) were consistent with the volunteer self-ratings, thus indicating that the behavior changes were real rather than imagined.

A robust observation across a range of studies has been that the intensity of mystical-type experience assessed on the day of a psilocybin session predicts subsequent therapeutic and other desirable outcomes. Such effects have been demonstrated in studies with healthy volunteers [33, 36], cancer patients [32, 94], patients with major depressive disorder [17], and patients quitting cigarette smoking [29]. Furthermore, this effect remains after the participant-rated intensity of psilocybin effect has been controlled for [32, 33, 36, 94], suggesting that the qualitative features of the psilocybin experience are critical to the positive outcomes [111]. Recent analyses of data from survey studies suggest that both mystical-type experiences and insightful-type experiences occasioned by psilocybin increase psychological flexibility which mediates therapeutic effects such as decreases in depression [18].

Of further relevance to the use of psilocybin in palliative treatment of existential anxiety associated with terminal illness, Griffiths et al. [33, 34] also showed that the religious subscale of the Death Transcendence Scale was significantly increased over screening levels at 6- to 14-month follow-up. This is notable, because questions on this scale assess a sense of continuity after death (i.e., Death is never just an ending but part of a process; Death is a transition to something even greater in this life; My death does not end my personal existence; I believe in life after death; There is a Force or Power that controls and gives meaning to both life and death).

Clinical Case Vignette of a Patient in an Ongoing Psilocybin Cancer-Anxiety Study

Roy is a 53-year-old white, American-born male. He is married, has no children, and is a college graduate. He produces and directs network television news programs. Roy is a warm, well-related, highly intelligent man with no psychiatric history or mental status alterations aside from existential distress, anxiety, and depressive affects associated with living with cancer. Both his parents are deceased, his father of cancer. Roy's sister in-law died of cancer. He reports a fulfilling and very happy relationship with his wife that was evident when they were together in the preliminary research meetings. He cited that one of the primary sources of emotional distress in contemplating the progression and possibility of eventually dying of cancer is losing time and a future with his wife. In August 2007, Roy was diagnosed with cholangiocarcinoma, a cancer of the bile ducts involving malignant growths in the ducts that carries bile from the liver to the small intestine. In September of that same year, he underwent a partial Whipple and liver resection. His gall bladder, major bile ducts, and parts of the duodenum and pancreas and the right lobe of his liver were removed. Surgery was followed by 6 months of chemotherapy. In November 2008, a CT scan showed metastasis to the lungs.

Since February 2009, chemotherapy was implemented bi-weekly. He reported that this bi-weekly intensive chemotherapy had been extraordinarily difficult causing extreme fatigue, cognitive "cloudiness," pain, overall body aches, discomfort, and psychological distress. He required assistance during weeks when chemotherapy was administered. He has chemotherapy-induced neuropathy in the hands and feet. After 3 years of contending with the physical and psychological effects of cancer along with the debilitating effects of chemotherapy, Roy had grown increasingly anxious and depressed at which point he inquired about the psilocybin research study at New York University School of Medicine and Bluestone Center for Clinical Research.

The patient had two research study sessions, one with psilocybin and the other with placebo. Both the patient and the study therapists were blinded to the study drug administration. During one of the experimental study sessions, presumably the psilocybin session, Roy swallowed the capsule and sat on the couch listening to soft classical music and viewing picture books with images of nature. Two clinical researchers, male and female, were present throughout the session. Thirty minutes after taking the capsule, the patient was encouraged to lie down on a couch prepared like a bed with sheets, pillows, and blankets. Throughout the session, it was recommended that the patient wear eyeshades and headphones. The music played was mostly classical and instrumental. The room replicates a warm and nicely furnished living area with paintings, Asian area rug, soft lighting, flowers, books, and personal items from the patient.

At 2 hours post-ingestion and following a period of silence, the patient stated "Birth and death is a lot or work" repeating it twice and began to cry softly. Five minutes following this, as if observing or deeply engaged in something profound, he said, "Oh God, Oh God." Over the course of the session, which lasted approximately 6 hours, Roy alternated between crying softly, smiling, and laughing. For long periods of time, he lay completely still and silent sometimes uttering short sentences, sometimes with a look of awe on his face. During a 2-hour period while lying completely still, he stated, "it's really so simple," "it's really so simple." All this occurred with eyeshades and headphones on and only with minimal interaction from the therapists. Statements that Roy made during those 2 hours which when compared to his written journal and post-session interviews suggest that he had a "complete" mystical experience by fulfilling all of the major criteria for such an experience (see Table 5.1). He later said to the therapists that, during this period, he experienced himself as completely safe – the safest he had ever felt – and he had an intense experience of maximal love. He indicated that he experienced existence or consciousness as continuing infinitely and it was all filled with love, it *was* love, there was neither death nor a beginning. He reported that these insights and experience gave him enormous comfort and meaning. He appeared at complete peace, but as if engaged in an active internal scene.

Approximately 5 hours after he took the capsule, he sat up as the experience began to wane in its intensity. He reported the experience was "life changing," and he was motivated to live more fully in the present moment. He repeated that the message was "so simple, it is love, it's all about the purity of love, energy of love." He felt as if his cancer and the prospect of dying lost significance with this new "knowledge" or awareness. He stated that he experienced love that was not describable intensity – "like nothing I've experienced here." At one point during the experience, he reported, "I went into my lungs and saw two spots" (referring to the nodules identified by medical imaging), and said he felt "they were 'no big deal'," that the "cancer is not important, the important stuff is love." He continued to discuss his newfound perspective on cancer that grew from the experience stating, "cancer is nothing to fear" and "cancer wasn't very important." He stated the most important "ingredient" in life is "the purity and simplicity of love." His wife rejoined him in the session room. They hugged and cried, and the patient stated to her, "It was amazing, amazing, I saw, I touched…the face of God."

Roy has continued to report and present with sustained and marked positive changes in attitude, coping, and mood 18 weeks after the session. He has characterized this experience as the most important life experience he has had second only to his marriage. Despite his cancer and uncertain future, he remarked, "I am the luckiest man on earth" and that "my quality of life is dramatically improved." He has begun a meditation practice since this experience. He stated that "I experienced infinity that last forever and that is love" and that this insight and awareness has stayed with him and shapes his attitude toward others, his wife, his disease, and the world. Despite the continuing difficult chemotherapy schedule and struggling with sickness for days at a time and additional surgical procedures, he is coping in a highly effective manner. He still feels that "the cancer is irrelevant" within the context of his new awareness, although he remains highly committed and involved in his medical treatments and decisions. Weeks after the session, he stated that "this is the best I've felt in years" and that he felt "the happiest in his life." While realistic about his diagnosis and prognosis, he remains committed to cultivating a positive attitude and has been able to remain emotionally connected to the imagery and existential insights of the psilocybin research session. In the end, he states that the overwhelming message was that of "love, warmth, acceptance" and connection to something greater, eternal, and sacred. The experience of transcendence and the cultivation of meaning appear to be the primary factors contributing to his insight, to the awareness drawn from the session, and to his coping with the existential and spiritual challenges of cancer.

The following are excerpts from a journal entry the patient wrote on the evening and in the days following his experience:

> From here on love was the only consideration. Everything that happened, anything and everything that was seen or heard centered on love. It was and is the only purpose. Love seemed to emanate from a single point of light… It was so pure. The sheer joy… the bliss was indescribable. And in fact there are no words to accurately capture my experience… my state… this place. I know I've had no earthly pleasure that's ever come close to this feeling… no sensation, no image of beauty, nothing during my time on earth has felt as pure and joyful and glorious as the height of this journey…I felt very warm but pleasantly so…
>
> I was beginning to wonder if man spent too much time and effort at things unimportant… trying to accomplish so much… when really, it was all so simple. No matter the subject, it all came down to the same thing. Love. Earthly matters such as food, music, architecture, anything, everything… aside from love, seemed silly and trivial. I was convinced in that moment that I had figured it all out (or it was figured out for me)… it was right there in front of me… love… the only thing that mattered. This was now to be my life's cause. I announced, "OK, I get it! You can all punch out now… our work is done!" But quickly I realized that no… our work… our existence… our energy… is never done… it goes on and on without end.
>
> I thought about my cancer….I took a tour of my lungs. I could see some things but it was more a matter of feeling the inside of my lungs. I remember breathing deeply to help facilitate the "seeing". There were nodules but they seemed rather unimportant… I was being told (without words) to not worry about the cancer… it's minor in the scheme of things… simply an imperfection of your humanity and that the more important matter… the real work to be done is before you. Again love.
>
> [On the day after the experience]…I felt spectacular… both physically and mentally! It had been a

> very long time since I'd felt that good… a serene sense of balance… a level of contentedness, peace and happiness that lasted all day and into the evening. Undoubtedly, my life has changed in ways I may never fully comprehend. But I now have an understanding… an awareness that goes beyond intellect… that my life, that every life, and all that is the universe, equals one thing… love.

Conclusion: Psilocybin Treatment Implications for Palliative Care and Psycho-oncology

While living with advanced cancer may for some patients be a process of depression, despair, and increased distress, for others it can provide an opportunity for personal meaning, enhanced interpersonal relationships, spiritual growth, clarity, and acceptance. Frequently, a life-threatening cancer triggers a search for meaning and transcendence and an awakening of spirituality. A growing body of literature now substantiates the importance and relevance of spiritual well-being and spirituality in palliative and hospice care. For many patients, the search for meaning that is frequently triggered by end-of-life stage cancer is a courageous and difficult journey. Ideally, dying should be viewed, not as a medical problem, but as an important and vital part of life experience with potential for discovery and meaning.

Researchers from several decades ago reported encouraging results from their early efforts developing a hallucinogen treatment model with patients suffering from the psychospiritual distress and demoralization often associated with advanced-stage cancer. More recent efforts to re-explore the judicious application of hallucinogen treatment with patients struggling with existential anxiety in the face of a life-threatening cancer diagnosis have similarly observed significant amelioration of psychological suffering. While valuable knowledge can be gleaned from clinical studies conducted from the 1950s to the early 1970s, it is necessary to conduct modern investigations utilizing state-of-the-art research methodologies in order to definitively establish the safety and efficacy of this novel treatment. To date, contemporary studies conducted at three academic medical centers are producing positive results. While still preliminary, these encouraging reports will hopefully facilitate the development of additional investigations with the hallucinogen treatment model, particularly in patient populations refractory to conventional therapeutic approaches [31].

A unique aspect of utilizing a classic hallucinogen (e.g., psilocybin) to treat the severe psychological demoralization and existential anxiety seen in life-threatening medical illness is its seeming capacity to facilitate powerful states of spiritual transcendence that exert in the patient a profound therapeutic impact with often dramatic improvements in psychological well-being. Recently conducted research at Johns Hopkins University has demonstrated that, under carefully structured conditions in normal volunteer subjects, induction of such transcendent and mystical states of consciousness occurs in most subjects studied. This is a critical advancement in the field because, for the first time, a specific treatment has been developed that is able to reliably facilitate the emergence of a transpersonal level of consciousness that appears to have significant therapeutic value. For a patient population struggling with often overwhelming levels of existential anxiety and demoralization, such a therapeutic intervention may have the capacity to reinfuse a sense of meaning and purpose into their lives. The hallucinogen treatment model therefore offers a novel and potentially valuable approach for addressing the existential crisis often observed in cancer patients, with the potential of significantly improving overall quality of life and psychospiritual well-being for the time that remains in their lives.

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6

Meaning, Spirituality, and Perceived Growth Across the Cancer Continuum: A Positive Psychology Perspective

Crystal L. Park and David Hanna

Cancer Survivorship

Through both public health and public relations efforts, cancer survivorship has come to denote the state or process of living after a diagnosis of cancer, regardless of how long a person lives (National Cancer Institute [1]). By this definition, a person is considered to become a cancer survivor at the point of diagnosis and to remain a survivor throughout treatment and the rest of his or her life [1]. The term "survivor" was chosen with great care by the National Coalition for Cancer Survivorship to explicitly promote empowerment of those with cancer [2]. There are an estimated 18 million cancer survivors in the United States, representing approximately 5% of the US population [3], and an estimated 14.1 million new survivors per year worldwide [3]. Many survivors are in longer-term survivorship, as the overall cancer death rate in the United States has decreased by 20% since the 1990s, leading to an increase in the number of long-term survivors [3].

The cancer experience from diagnosis through longer-term survivorship has been described as a continuum comprising different phases, including living with cancer, living through cancer, and living beyond cancer [4–6]. The demands on survivors differ across these phases, leading to different emotional reactions and coping responses. Further, the roles played by each of the three positive psychology constructs considered here, meaning, spirituality, and perceived growth, may differ across these phases (see Table 6.1).

The first phase, living with cancer, refers to the time of diagnosis and active treatment. Fear, anxiety, and pain resulting from both illness and treatment are common. While in primary treatment, cancer often becomes life's central focus not only for the cancer patient but also for his or her family and friends. Primary treatment may involve intensive and immediate coping with medical issues, decision-making, and the many chaotic emotions that ensue, including fear, hope, pain, and grief [4, 7].

The second phase, living through cancer, refers to the time following remission or treatment completion. The transition period from primary treatment to longer-term survivorship is a critical time, setting the course of psychological adjustment for years to come. While a relief in many ways, this transition is often highly stressful in its own right [8, 9], due in part to reduced frequency of visits and access to medical providers, changes in daily routines, adjustment to treatment-related side effects, and uneasiness about being on one's own after having such close relations with medical providers [8, 9]. Psychologically, survivors are often in a state of

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Table 6.1 The roles of meaning, spirituality, and growth across the cancer continuum

	Living with cancer	Living through cancer	Living beyond cancer
Cancer-related involvement	Diagnosis and active treatment	Transition from primary treatment and regular contact with healthcare providers	Longer-term survivorship
Role of cancer in one's life	Cancer and treatment is life's central focus	Attempts to resume a "new normal" life; cancer focus reduced. Transition from patient role can be jarring	Long-term implications of being a cancer survivor
Potential roles of meaning	Sources of meaning as support Violations of global meaning	Reconsideration and reconstitution of global beliefs and goals	Cancer as part of one's life narrative. Sense of life meaning often enhanced
Potential roles of spirituality	Spiritual crisis. Turning toward spirituality for strength and support	Reconsideration and reconstitution of spiritual beliefs and goals	Revised spiritual global meaning
Potential roles of growth	Possibilities of positive outcomes may provide hope Most reports illusory, function as coping	Reflection on changes experienced; identification of positive changes	Maintenance of life changes or return to pre-cancer baseline

watchful waiting, with high fears of recurrence [9, 10].

The third phase, living beyond cancer, refers to a time when the "activity of the disease or likelihood of its return is sufficiently small that the cancer can now be considered permanently arrested" [5, p. 272]. Even after survivors enter this phase, a sense of vulnerability, fears of recurrence, and psychosocial problems related to their cancer experience are common [11, 12]. However, longer-term survivorship affords individuals opportunities to reflect on and embellish their narratives to include their cancer experience and to feel they have made some meaning from their cancer [13]. Being a cancer survivor often becomes an important aspect of self-identity [14].

The Meaning-Making Model

The meaning-making model addresses two levels of meaning, global and situational [15]. Global meaning refers to individuals' general orienting systems. Situational meaning comprises initial appraisals of a given situation, the processes through which global and appraised situational meanings are revised, and the outcomes of these processes. Components of the meaning-making model are illustrated in Fig. 6.1. In this section, the elements of this meaning-making model are briefly described. This model then serves as the framework to discuss the roles of meaning, spirituality, and growth in the context of cancer.

Global Meaning

Global meaning consists of the structures through which people perceive and understand themselves and the world, encompassing beliefs, goals, and subjective feelings of purpose or meaning in life [15, 16]. Global meaning consists of cognitive, motivational, and affective components, termed, respectively, global beliefs, global goals, and a sense of meaning or purpose [17–19].

Global beliefs concerning fairness, justice, luck, control, predictability, coherence, benevolence, personal vulnerability, and identity comprise the core schemas through which people interpret their experiences of the world [20, 21]. Global goals are individuals' ideals, states, or objects toward which they work to be, obtain, accomplish, or maintain [22, 23]. Common global goals include relationships, work, health,

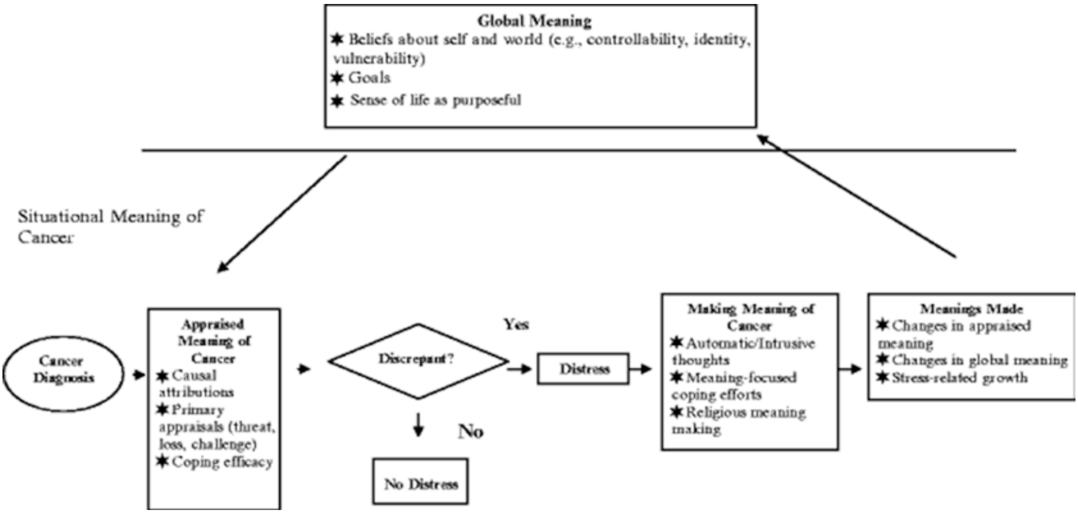

Fig. 6.1 The meaning-making model in the context of cancer

wealth, knowledge, and achievement [24]. Subjective feelings of meaning refer to a sense of "meaningfulness" or purpose in life [19, 25]. This sense of meaningfulness comes from seeing one's life as containing those goals that one values as well as feeling one is making adequate progress toward important future goals [25, 26]. Together, global beliefs and goals, and the resultant sense of life meaning, form individuals' meaning systems, the lens through which they interpret, evaluate, and respond to their experiences.

Situational Meaning: The Meaning of Potentially Stressful Encounters

Meaning is an important part of everyday life [27], informing people's ways of understanding and functioning, although such influences are typically subtle and unnoticed. However, confrontations with highly stressful experiences such as serious illness bring meaning to the fore [28, 29]. People assign meanings to, or *appraise*, potentially stressful situations [30]. These appraised meanings are to some extent determined by the specifics of the particular situation, but are also largely informed by individuals' global meaning.

Stress as Discrepancy Between Global and Situational Meaning

The meaning-making model is based on the notion that stress occurs when people perceive discrepancies between their global meaning (i.e., what they believe and desire) and their appraised meaning of a particular situation [17, 18]. This discrepancy-related stress motivates individuals to resolve their problems and dissipate the resultant negative emotions [31]. Confrontation with a severe stressor is thought to have the potential to violate or even shatter global meaning systems (i.e., individuals' global beliefs about the world and themselves and their overarching goals). Such violations or discrepancies are thought to initiate individuals' cognitive and emotional processing—"meaning-making" efforts—to rebuild their meaning systems. Meaning-making involves efforts to understand and conceptualize a stressor in a way more consistent with their global meaning and to incorporate that understanding into their larger system of global meaning through assimilation and accommodation processes [15].

Resolving stressful events entails reducing discrepancies between appraised meanings and global meanings [32–34]. Discrepancies can be reduced in many ways, and, to this end, people engage in many types of coping (e.g., [13, 35]).

People may engage in problem-focused coping, taking direct actions to reduce the discrepancy by changing the conditions that create or maintain the problem. When encountering stress, individuals can also engage in emotion-focused coping, much of which is targeted at directly alleviating distress, albeit temporarily, by disengaging mentally or behaviorally (e.g., focusing on some distraction). Emotion-focused coping, by definition, does not reduce discrepancies, which may be why it is generally associated with higher levels of distress [36].

Stressful situations vary in the extent to which they are amenable to problem-focused coping, such as planning and actively focusing on changing the problematic situation (e.g., [37, 38]). Problem-focused coping is generally considered the most adaptive type of coping [36], but low-control situations such as trauma, loss, and serious illness are not amenable to direct repair or problem-solving. In such low-control situations, meaning-making coping is particularly relevant and potentially more adaptive [39]. Meaning-making refers to approach-oriented *intrapsychic* efforts to reduce discrepancies between appraised and global meaning. Meaning-focused coping aims to reduce discrepancy either by changing the very meaning of the stressor itself (appraised meaning) or by changing one's global beliefs and goals; either way, meaning-focused coping aims to improve the fit between the appraised meaning of the stressor and global meaning.

Following highly stressful events, individuals' meaning-making processes typically involve searching for some more favorable or consistent understanding of the event and its implications for their beliefs about themselves and their lives. Meaning-making may also entail reconsidering global beliefs and revising goals (see [40]) and questioning or revising their sense of meaning in life [25].

This rebuilding process is assumed to lead to better adjustment, particularly if adequate meaning is found or created (for reviews, see [17, 41, 42]). However, protracted attempts to assimilate or accommodate may devolve into maladaptive rumination over time if satisfactory meanings cannot be constructed [43]. That is, meaning-making is helpful to the extent that it produces a satisfactory product (i.e., *meaning made*) [17].

Meanings Made

The products that result from meaning-making, termed *meanings made*, involve changes in global or situational meaning, such as revised identity, growth, or reappraised situational or global meaning. The outcomes of the meaning-making process involve changes in global or situational meaning. As illustrated in Fig. 6.1, individuals may make many different types of meaning through their meaning-making processes. Among these are a sense of having "made sense" (e.g., [44]), a sense of acceptance (e.g., [45]), causal understanding (e.g., [20]), transformed identity that integrates the stressful experience into one's identity [46], reappraised or transformed meaning of the stressor (e.g., [35]), changed global beliefs (e.g., [47]), changed global goals (e.g., [48]), a revised or reconstituted sense of meaning in life (e.g., [20]), and perceptions of growth or positive life changes [31].

Meaning in the Context of Cancer

Both global and situational meanings influence the processes of coping with cancer across the continuum from diagnosis through treatment and longer-term survivorship. Further, these influences may vary across this continuum (see Table 6.1). A diagnosis of cancer can shatter aspects of a patient's extant global meaning. For example, most people hold views of the world as benign, predictable, and fair and their own lives as safe and controllable [33, 49]. A cancer diagnosis is typically experienced as being at extreme odds with such beliefs (e.g., [50]), setting in motion processes of distress and meaning-making that ultimately lead to changes in survivors' situational and global meaning.

Appraised Meaning of Cancer

People appraise the meaning of their cancer diagnosis based on the information they receive from their healthcare providers and other sources along with their own understanding of the disease of "cancer" (e.g., time course, severity) [51], their appraisals of their ability to manage the illness and its anticipated impact on their future [51], and their general sense of control over their life [52, 53]. Research indicates that the meanings that survivors assign to their cancer experience predict not only their coping and subsequent adjustment but also their treatment-related decisions and their well-being (e.g., [54]). For example, a study of advanced-stage survivors found that those who appraised their cancer positively and with greater optimism had lower levels of mood disturbance, while those who appraised their cancer more negatively and with less optimism had higher levels of mood disturbance [55]. Similarly, a study of survivors of a variety of advanced cancers found that threat appraisals were related to higher levels of distress [56].

Applying Lipowski's [57] taxonomy of illness appraisals in a large sample of breast cancer survivors, Degner et al. [58] found that shortly after diagnosis, most survivors appraised their cancer as a "challenge" (57.4%) or as having "value" (27.6%); few appraised their cancer as "enemy" (7.8%), "irreparable loss" (3.9%), or "punishment" (0.6%). These appraisals were mostly unchanged 3 years later, and survivors who had initially appraised their cancer as a challenge or as having value reported less anxiety at follow-up. Cross-sectionally, at follow-up, women who appraised the cancer negatively (i.e., "enemy," "loss," or "punishment") had higher levels of depression and anxiety and poorer quality of life than women who appraised their cancer in more positive ways. Similar findings were reported by Gilbert et al. [59].

Control appraisals have also been linked to survivors' well-being. For example, in the above-mentioned study of survivors of various cancers [56], appraised uncontrollability of the cancer and low levels of self-efficacy were related to higher levels of distress, although appraised self-controllability of the cancer was unrelated to distress. Similarly, a study of mothers diagnosed with cancer found that women's appraised lack of control over their illness was strongly associated with their psychological distress due to feeling that they could no longer fulfill their roles as mothers [60]. Some research has shown that appraisals are also related to physical health. In studies of colorectal [61] and prostate [62] cancer survivors, having a belief that nothing could cure most cancer was related to all-cause mortality 15 years later, controlling for many confounding factors. The authors speculated that these associations may be due to less engagement in health-protective behaviors, lower adherence to recommended medical protocols, or more lax monitoring of disease recurrence.

Attributions for the cancer are another type of appraisal survivors make [63]. Attributions involve assigning a cause to the cancer; such attributions may change over time through meaning-making processes. When attributions are derived not through a fairly quick and automatic process but through cognitive processing over time, they may be more accurately viewed as reattributions, a product of meaning-making [17]. Unfortunately, virtually no studies have differentiated attributions from reattributions or examined processes of timing and change. Further, most studies assessed attributions long after the initial diagnosis of cancer was made. Thus, survivors in most existing research are reporting on their reattributions rather than their initial understanding of their cancer. Therefore, the majority of research on cancer attributions is reviewed in the subsequent section on meanings made.

Here, we simply note that different types of cancer may elicit different types of causal attributions, which may be evidenced in initial appraisals. For example, Costanzo and her colleagues [64] speculated that because of the lack of information on environmental or behavioral causes of gynecological cancer, women with gynecological cancers were less likely to attribute their cancer to specific causes and more likely to attribute their cancer to chance or God's will. In that study of gynecological cancer survivors, God's will was mentioned as a factor contributing to the development of cancer by 39% of the sample, ranking third only behind genetics/heredity and stress. Further, in the factors perceived to prevent a cancer recurrence, prayer was mentioned by 90% of the sample, ranking third only behind medical checkups and a positive attitude. God's will, assessed as a separate factor, was mentioned by 69% of the sample.

Cancer as Violation of Global Meaning

Receiving a diagnosis of cancer can violate important global beliefs such as the fairness, benevolence, and predictability of the world as well as one's sense of invulnerability and personal control [10, 65, 66]. Further, having cancer almost invariably violates individuals' goals for their current lives and their plans for the future [67, 68].

According to the meaning-making model, the extent to which having cancer is perceived as inconsistent with global beliefs such as those regarding identity (e.g., I live a healthy life style) and health (e.g., living a healthy lifestyle protects people from illness) and global goals (e.g., desire to live a long time with robust health and without disability) determines the extent to which the diagnosis is distressing [67, 68]. Different types of cancer and the specifics of an individual's illness (e.g., prognosis, treatment) likely influence the situational meaning given and the extent of discrepancy with global meaning (e.g., [65]).

Several studies of cancer survivors have examined how global meaning violations may arise from having cancer. For example, a longitudinal study found that colorectal cancer patients appraised their cancer as highly discrepant with their goals; decreases in discrepancies over time related to lower distress [68]. A longitudinal study of survivors of various cancers found that the extent to which the cancer was appraised as violating their beliefs in a just world was inversely related to their psychological well-being across the year of the study [13]. A study of Chinese patients with a variety of different cancers found that meaning-making that related to subsequent changes in situational and global meaning was associated with less depression and anxiety [65]. Similarly, two studies that did not directly measure appraisals of violation but that likely reflects those found women diagnosed with breast cancer reported low levels of perceived control over their lives; findings were especially strong for breast cancer survivors who had received chemotherapy [69, 70]. These links between discrepancy of appraised and global meaning with adjustment in cancer survivorship have seldom been directly examined, and much remains to be learned about perceptions of belief and goal violation.

Making Meaning from the Cancer Experience

Researchers have posited that meaning-making efforts are essential to adjustment to cancer by either helping survivors assimilate the cancer experience into their pre-cancer global meaning or helping them to change their global meaning to accommodate it [66]. Many researchers have proposed, therefore, that meaning-making is critical to successfully navigate these changes [29, 66, 71, 72]. Indeed, it is hard to imagine that survivors could come through a cancer experience without some reconsideration of their lives vis-à-vis cancer [29, 71, 73, 74]. However, some researchers have suggested that survivors sometimes simply accept their cancer experience or, once it has ended, have little need to think or reflect on it [75, 76].

According to the meaning-making model, meaning-making following cancer involves survivors' attempts to integrate their understanding (appraisal) of the cancer together with their global meaning to reduce the discrepancy between them [15, 77]. Yet to assess meaning-making, many studies have employed overly simple questions, such as "How often have you found yourself searching to make sense of your illness?" and "How often have you found yourself wondering why you got cancer or asking, 'Why Me?'" (e.g., [78]).

Such assessments do not adequately measure meaning-making [17]. Survivors' meaning-making processes involve deliberate coping efforts, such as reappraising the event, reconsidering their global beliefs and goals, and searching for some understanding of the cancer and its implications for themselves and their lives (e.g., [66, 79]). In addition, meaning-making processes apparently often occur beneath the level of awareness or without conscious efforts (e.g., in the form of intrusive thoughts; [32, 66]).

In addition, although meaning-making is presumed to be adaptive [17, 66], many studies have found that survivors' searching for meaning is typically related to poorer adjustment (e.g., [78, 80, 81]). For example, a study of breast cancer survivors completing treatment found that positive reinterpretation, attempting to see the cancer in a more positive light or find benefits in it, was unrelated to adjustment, while emotional processing, attempting to understand the reasons underlying one's feelings, was actually associated with subsequently higher levels of distress [17]. A cross-sectional study of long-term breast cancer survivors found that searching for meaning was related to poorer adjustment [74], and a study of prostate cancer survivors shortly after treatment found that meaning-making efforts were related to higher levels of distress both concurrently and 3 months later [78].

Such findings are not inconsistent with the meaning-making model, however, because these studies not only failed to adequately assess meaning-making, but they also failed to comprehensively examine all of the components of the model, such as belief and goal violation. Further, many were conducted cross-sectionally, although longitudinal assessments of appraised meanings and discrepancies between situational and global meaning and examination of change in them over substantial periods of time are necessary to truly capture this assimilation/accommodation process.

In addition, the meaning-making model proposes that meaning-making per se is not necessarily adaptive and, in fact, may be indistinguishable from rumination, without attention to whether meaning has actually *been made*. Few studies have distinguished between adaptive meaning-making and maladaptive rumination; this lack of discrimination may account for the lack of more consistently favorable effects of meaning-making [13, 43]. According to the meaning-making model, when cancer survivors search for meaning, either through deliberate efforts or through more automatic processes, and achieve a reintegration of their cancer experience and their global meaning, they experience less distress *and* engage in less subsequent meaning-making [13]. However, when meaning-making efforts fail, the cancer experience may remain highly distressing. Unable to assimilate their cancer experience into their belief system or accommodate their previously held beliefs to account for their experience, survivors may experience a loss of personal or spiritual meaning, existential isolation, and apathy [10] and may persist in meaning-making efforts even years afterward (e.g., [74]), accounting for the positive relationship between searching for meaning and distress.

To date, few studies of cancer survivorship have assessed both the search for and the finding of meaning and tested their combined effects on adjustment in survivors. A study of breast cancer survivors in the first 18 months post-diagnosis found that women who never searched for meaning and those who searched and found meaning did not differ on negative affect, but both groups had less negative affect than women who were searching but had not found meaning over time [81]. Further, the abovementioned study of younger adult survivors of various cancers assessed meaning-making (as positive reappraisal) and meanings made (perceived growth, reduced discrepancies with global meaning). Results indicated that positive reappraisal led to increases in perceived growth and life meaning, which was related to reduced violations of a just world belief. This process was related to better psychological adjustment [13].

An intriguing but largely overlooked aspect of meaning-making in cancer survivorship is that meaning-making efforts may have different effects on well-being at different points along the survivorship continuum. For example, some researchers have proposed that during primary treatment, when patients are dealing with the impact of the diagnosis and making treatment decisions, effective coping may be more problem-focused, dealing with the immediate demands of the crisis, while meaning-making may be especially important during the transition to longer-term survivorship [10]. The transition to longer-term survivorship, as survivors return to their everyday postprimary treatment lives, may allow more time and energy for more reflective approaches to longer-term psychosocial and existential issues and may change the effects of such processing [74, 82].

Meaning Made from the Cancer Experience

People are thought to make meaning of stressful experiences primarily by changing the meaning of those experiences (i.e., their situational meaning), but sometimes violations of global meaning are too great to be assimilated, and people must turn to processes of accommodation, which produce shifts in global meaning [20]. Researchers have identified a number of products of meaning-making in cancer survivorship. The global meaning change most studied among cancer survivors is that of perceived stress-related growth, the positive changes people report experiencing as the result of stressful encounters [31]; perceived growth is so widely studied that it warrants its own section below. In addition, researchers have identified other psychological phenomena that may be conceptualized as outcomes or products of the search for meaning in cancer survivors. Among these are understanding regarding the cancer's occurrence (usually assessed as reattributions) and the integration of cancer and survivorship into one's identity [46].

Causal understanding of cancer. As noted above, many studies have focused on the attributions cancer survivors make; because these studies are usually conducted long after the diagnosis, survivors' reported attributions likely reflect considerable meaning-making. Research with cancer survivors has indicated that most survivors have ideas or explanations regarding the cause of their cancer (e.g., [63]). However, simply possessing an explanation does not necessarily reflect adequate meaning; in fact, many causal attributions are associated with *greater* distress (e.g., [64, 83]). Instead, the specific cause referred to determines an attribution's ability to establish meaning and thus its relations with adjustment. For example, one literature review on attributions made by breast cancer survivors concluded that attributions to predictable and controllable causes such as pollution, stress, or lifestyle factors such as smoking were associated with better adjustment [84]. However, feeling that one caused one's own cancer (self-blame) has consistently been shown to be negatively associated with adjustment among cancer survivors (e.g., [85]).

The link between having made meaning by identifying causes of the cancer and adjustment is therefore more complicated than it might first appear. This notion is illustrated in the above-mentioned study of women with gynecological cancers [64], in which most attributions (e.g., genetics/heredity, stress, hormones, and environmental factors) were related to elevated levels of anxiety and depression. However, survivors who attributed their cancer to potentially controllable causes were more likely to be practicing healthy behaviors. Similarly, women citing health behaviors as important in preventing recurrence reported greater anxiety, but were also more likely to practice positive health behaviors. Further, health behavior attributions interacted with health practices in predicting distress. For example, among women who had not made positive dietary changes, appraising lifestyle as important in preventing recurrence was associated with greater distress, whereas for those who had made a positive change in diet, lifestyle attributions were associated with less distress. Thus, it appears that behaviors consistent with attributions can be effective in reducing discrepancies in meaning and therefore related to better adjustment.

Integration of cancer and survivorship into one's life narrative and identity. Another potentially important outcome of meaning-making involves the integration of the experience of cancer into survivors' ongoing life story and sense of self [86]. Surviving cancer has been described as a process of identity reconstruction through which survivors integrate the cancer experience into their self-concept, developing a sense of "living through and beyond cancer" [87, 88]. The extent to which having cancer becomes interwoven with other experiences in survivors' narratives may reflect successful making of meaning, having come to terms with the cancer. Such narrative integration is widely viewed as an important aspect of recovery (e.g., [66]) and is being used in interventions with cancer survivors (e.g., [89]). However, further quantitative research regarding the cancer recovery process in terms of narrative reconstruction is needed before firm conclusions can be drawn.

A few studies have examined the extent to which cancer survivors embrace labels that refer to their cancer status and how that identification relates to their well-being. An early study by Deimling and his colleagues [88] examined cancer-related identities in a sample of older, long-term survivors of a variety of cancers. Asked whether they identified themselves as survivors (yes or no), 90% answered affirmatively. Other labels were endorsed less frequently: 60% identified as ex-patients, 30% as victims, and 20% as patients. However, considering oneself a victim or a survivor was unrelated to aspects of adjustment, such as mastery, self-esteem, anxiety, depression, or hostility. It should be noted that this study was conducted prior to the mid-1990s, when the term "survivor" began to be actively promoted [2]. A more recent study of long-term survivors of colon, breast, or prostate cancer by the same group of researchers using the same measurement strategy found that 86% of the sample identified as a "cancer survivor," 13% saw themselves as a "patient," and 13% identified as "victim" [90].

Several other studies have addressed post-cancer identities. Asked which term best described them, over half of a sample of longer-term prostate cancer survivors chose "someone who has had cancer," and a quarter chose "survivor," with smaller numbers choosing "patient" or "victim" [75]. Only identifying as a survivor was related to having more positive affect, and no identity was related to negative affect. Finally, in a study of younger adult cancer survivors asked about their post-cancer identities, 83% endorsed "survivor" identity, 81% the identity of "person who has had cancer," 58% "patient," and 18% "victim" (all at least "somewhat") [14]. Endorsements of these four identities were minimally correlated with one another. Those who more strongly endorsed "survivor" and "person who has had cancer" identities were more involved in many cancer-related activities, such as wearing cancer-related items and talking about prevention, and survivor identity correlated with better psychological well-being and victim identity with poorer well-being [14]. The timing of adopting the survivor identity may matter too. A review found that earlier adoption of survivor identity was associated with higher levels of self-esteem and lower levels of anxiety and depression [86]. This review also found that identifying as a survivor was associated with higher levels of perceived posttraumatic growth, lower threat appraisal, and higher life satisfaction, while the victim identity was associated with intrusive thoughts, lower life satisfaction, and higher levels of hostility [86].

Spirituality and Cancer Survivorship

The proliferating literature on spirituality in cancer survivorship provides strong evidence that spirituality typically plays myriad roles in the lives of those with cancer (for reviews, see [91–94]). Spirituality is often pervasively involved in survivors' global and situational meaning, including their making meaning of the cancer, across the phases of survivorship [95]. Because the present chapter focuses specifically on cancer survivorship, information on how religiousness and spirituality are more generally involved in global meaning is not reviewed here; readers are referred to Park [47]. This section specifically focuses on meaning in the situational context of cancer survivorship.

Spirituality and Appraised Meaning of Cancer

At diagnosis, individuals' pre-cancer spirituality may influence the situational meaning they assign to their cancer, including its appraised meaning and the extent to which their global meaning is violated by that appraisal. Some studies have found that global religious beliefs are related to the ways that cancer patients approach their illness. For example, a study of patients in treatment for a variety of cancers found that although religious beliefs (e.g., "I believe that God will not give me a burden I cannot carry") were not directly related to psychological adjustment, those with higher religious beliefs had a higher sense of efficacy in coping with their cancer, which was related to higher levels of well-being [96]. Another study found that men diagnosed with prostate cancer who viewed God as benevolent and involved in their lives appraised their cancer as more of a challenge and an opportunity to grow [67].

Religious beliefs about God's role in suffering, also known as theodicies, may also play an important role in how patients deal with their cancer. One study identified five types of theodicy beliefs: that their suffering is God's punishment for sinful behavior, that they will become a better person as a consequence of their suffering, that a reward for suffering will come in Heaven, that God has a reason for suffering that cannot be explained, and that by suffering with illness, one shares in the suffering of Christ [97]. One qualitative study examined different theodicies and presence of spiritual struggles in Evangelical Christians diagnosed with cancer. Results indicated that spiritual struggles, especially "anger at God," was associated with higher levels of distress. Furthermore, addressing and resolving the spiritual struggle led to lower levels of distress [98]. More research is needed to determine the relationship between different theodicies and coping with and adjustment to cancer.

Studies assessing associations of religious causal attributions and control appraisals with well-being in cancer survivors have produced mixed results. In a sample of young to middle-aged adult survivors of various cancers receiving chemotherapy, appraisals that God was in control of the cancer and that the cancer was due to chance were related to higher self-esteem and lower distress regarding the cancer, and control attributions to self and religion were positively correlated with positive aspects of adjustment [99], and another study focusing more specifically on different types of religious attributions in a sample of breast cancer survivors found that attributing the cancer to an angry or punishing God was related to more anger at God and poorer psychological adjustment [100]. However, in a sample of prostate cancer survivors, causal attributions to God, regardless of their negative (God's anger) or positive (God's love) nature, were related to poorer quality of life. In addition, prostate cancer survivors who reported having a more benevolent relationship with God reported perceiving less control over their health [67]. Attributions of the cancer to God's will in the abovementioned study of gynecological cancer survivors were related to worry about recurrence, but not to anxiety or depressive symptoms [64].

Spirituality and Meaning-Making from the Cancer Experience

Meaning-making often involves spiritual methods. For example, people can redefine their cancer experience as an opportunity for spiritual growth or as a punishment from God or may reappraise whether God has control of their lives or even whether God exists [101]. Researchers typically assess religious meaning-making with subscales from the RCOPE measure [102], which includes a benevolent religious reappraisal subscale (sample item: "saw my situation as part of God's plan") as a component of a broader "positive religious coping" factor and a punishing God reappraisal subscale (sample item: "decided that God was punishing me for my sins") as a component of a broader "negative religious coping" factor.

Studies of people dealing with cancer have generally indicated that positive religious coping is weakly and inconsistently related to adjustment and well-being in cancer survivorship [91, 93]. In contrast, negative religious coping, although less frequently used, tends to be strongly and consistently associated with poorer adjustment and quality of life (e.g., [103, 104]). However, studies of coping with cancer have not separated out the religious meaning-focused coping subscales from other types of positive or negative religious coping nor examined the resultant meanings made through processes of meaning-making.

Further, different types of spiritual and religious coping efforts may differentially relate to well-being depending on the particular phase of the continuum under study. For example, one study suggested that during the diagnostic phase, private spirituality may be particularly relevant [105]. However, few studies have examined spirituality and meaning-making across phases. One important exception, a prospective study of breast cancer patients from pre-diagnosis to 12 months post-diagnosis, found that the use of different religious coping strategies changed over time and that during particularly high stress points such as presurgery, religious coping strategies that provided comfort, such as active surrender of control to God, were highest, while religious coping processes reflecting meaning-making remained elevated or increased over time [106].

Spiritual Meanings Made from the Cancer Experience

Through the meaning-making process, survivors often make changes in how they understand their cancer (changed appraised meaning). They may also make changes in their global beliefs and goals. These changes often have a religious aspect. For example, through meaning-making, survivors may revise their initial understanding of their cancer; these reappraised meanings may be of a religious nature. Summarizing findings from a qualitative study of breast cancer survivors, Gall and Bilodeau [107] noted, "Breast cancer patients are turning to a higher power in a search for emotional support and comfort at a time when they may not feel in control of their illness and related treatment demands. Women with breast cancer are faced with a greater need to make sense of their situation and to situate their illness within a larger context (e.g., seeing it as part of God's plan)" (p. 112). At this point, little quantitative research on reappraised religious meanings in the context of cancer has been conducted.

Changes in global religious or spiritual meaning in cancer survivorship are also common [98]. Bourdon and her colleagues found melanoma cancer patients reported having become more spiritual and developed a stronger sense of the sacred directing their lives; however, survivors also reported believing less strongly in their faith or feeling spiritually lost because of their cancer [108]. Interestingly, these two directions of perceived change were uncorrelated in a sample of survivors of a variety of cancers, although positive spiritual transformations were related to higher levels of emotional well-being and quality of life, while negative spiritual transformations were inversely related to well-being and quality of life [109]. Such changes in spirituality are usually studied as part of the broader phenomenon of perceived stress-related growth, discussed in the following section.

Perceived Stress-Related Growth and Cancer

Perceived stress-related growth, the positive life changes that people report experiencing following stressful events, has garnered increasing research interest in recent years (see [110, 111], for reviews in the context of cancer). Myriad studies of survivors of many types of cancer have established that a majority report experiencing stress-related growth as a result of their experience with cancer [111]. Reported positive changes may occur in one's social relationships (e.g., becoming closer to family or friends), personal resources (e.g., developing patience or persistence), life philosophies (e.g., rethinking one's priorities), spirituality (e.g., feeling closer to God), coping skills (e.g., learning better ways to handle problems or manage emotions), and health behaviors or lifestyles (e.g., lessening stress and taking better care of one's self) [111].

Stress-related growth has also been referred to as "posttraumatic growth," "perceived benefits," "adversarial growth," and "benefit-finding" [110]. Perceptions of growth are thought to arise as people attempt to make meaning of their cancer experience, seeking to understand their cancer and its implications for their lives within the framework of their previous global meaning system or coming to grips with it by transforming their understanding of the world and themselves to enable the integration of the cancer experience into their global meaning system [110, 112].

Stress-related growth is a subjective phenomenon; that is, it reflects a survivor's *perceptions* of change rather than directly reflecting objective change. This subjective nature creates one of the controversies surrounding stress-related growth: Is it "real" or illusory [113]? Research from other areas of psychology suggests a substantial gap between perceptions of positive change and measured change [114], which has also been demonstrated in the few studies that have compared self-reported and actual growth [115, 116].

Some researchers have suggested that stress-related growth may be either an effort to cope (i.e., a form of meaning-making) or an actual outcome of coping (i.e., a form of meaning made), depending on the specifics of the person and the point at which he or she is in the cancer continuum and meaning-making process [110]. For example, a cancer patient experiencing distress who is struggling to deal with difficult treatments may search for some more benign way to understand the experience, voicing how in some ways this experience is a good one because of the positive changes he or she is experiencing. Another may look back at his or her cancer experience from the vantage of posttreatment and identify ways that the experience has favorably changed him or her. The former may be more suspect as an actual meaning made, while the latter may more accurately reflect meaning made from the experience. However, more research is needed to determine the conditions under which reported growth reflects meaning-making versus meaning made. One study examining growth in survivors from presurgery to 1 year later found that growth was unrelated to well-being at any point cross-sectionally, but increases in growth over time were related to higher levels of well-being [117], suggesting that "real" or adaptive growth may occur only over time.

Another controversial issue regarding stress-related growth is its relationship with indices of well-being. Although some have argued that perceptions of growth constitute a positive outcome in and of themselves (e.g., [118]), most researchers have endeavored to ascertain relations between perceptions of stress-related growth and indices of well-being. Although extensive research has been conducted on this topic, results are inconclusive. Cancer survivors' reports of growth following their cancer experience are sometimes (e.g., [119]), but not always (e.g., [120–122]), related to better psychological adjustment. Many studies on this topic fail to control for potential confounds such as optimism, positive affectivity, or neuroticism, which may account for some of the inconsistency. Also drawing skepticism regarding the relevance of stress-related growth for adjustment are the emerging findings that survivors' reports of negative changes wrought by the cancer appear to be much more potent predictors of well-being than do reported positive changes [123].

Positive Psychology and Interventions with Cancer Survivors

Along with the increasing recognition of the importance of meaning-making in the lives of cancer survivors has come the development of meaning-based psychosocial interventions for those with cancer. Some of these interventions are existential in nature, focusing on broader issues of meaning in life (see [124, 125] for a review). For example, Winger and his colleagues [126] developed a palliative care therapy for those with cancer, aiming to identify and enhance sources of meaning and patients' sense of purpose as they approach end of life.

Other interventions more explicitly target processes of meaning-making. For example, Lee and her colleagues developed a brief, manualized intervention, the Meaning-Making intervention (MMi), designed to explicitly promote survivors' exploration of existential issues and their cancer experiences through the use of meaning-making coping strategies [127]. Cancer survivors receive up to four sessions in which they explore their cognitive appraisals of and emotional responses to their cancer experience within the context of their previous experiences and future goals. In several pilot studies, participants in the experimental group reported higher levels of self-esteem, optimism, and self-efficacy [125] and meaning in life [127], demonstrating preliminary effectiveness of a therapy that explicitly promotes meaning-making. Interventions specifically focusing on spirituality in survivorship have also been developed (e.g., [128]) although little empirical evaluation of such interventions is yet available.

Chan et al. [129] noted that while meaning-based interventions are proliferating, "there is a lack of a corresponding body of controlled outcome studies, without which we cannot answer two central questions: (1) Can meaning-making interventions facilitate or catalyze the meaning construction process? (2) How much (if any) improvement of the psychosocial well-being of patients is attributable to the catalyzed meaning construction process?" (p. 844). An important challenge for interventionists is conducting well-designed outcome studies evaluating meaning-making interventions in terms of not only their effects but also the mechanisms bringing about those effects.

Noting that some interventions focused on broader issues of stress management have demonstrated that stress-related growth is often a by-product of those interventions (e.g., [125]), some researchers have advocated for interventions that explicitly promote stress-related growth (e.g., [130]). However, given the lack of correspondence between perceived growth and other indices of adjustment, such efforts to promote these perceptions of growth appear to be premature and potentially misguided.

Future Research in Positive Psychology and Cancer Survivorship

As this chapter makes clear, much remains to be learned about cancer survivors' meaning-making processes, spirituality, and stress-related growth. The present review is based on the meaning-making model, which provides a useful framework for examining many different phenomena relevant to survivors' psychological adjustment. To date, the literature on meaning-making does not provide strong support for meaning-making processes as requisite for psychological adjustment in cancer survivorship. However, as noted earlier, extant studies have not adequately tested the model. An adequate test of this model awaits studies that thoroughly assess the range of meaning-making efforts, both deliberate and automatic, and whether there are any meanings made (e.g., adaptive changes) resulting from efforts at meaning-making. To date, no study of cancer survivors has fully assessed the components of the meaning-making process, and much remains to be learned about meaning and meaning-making in cancer survivorship. Such studies will need to attend closely to the specific characteristics of the survivors under study and the demands placed on them depending on their location within the survivorship continuum.

Research on issues of spirituality suggests that this is a very important part of survivors' adjustment across the continuum. Both existential and more traditionally religious aspects of spirituality appear to be important [131] and should be examined separately and in combination. A better understanding of spirituality and its unique place in survivors' meaning-making and adjustment across the phases from diagnosis through survivorship is desperately needed. In addition, the phenomenon of stress-related growth, which often reflects spirituality as well as many other aspects of life, is poorly understood. The questions raised here (How do these appraisals reflect reality? Is growth helpful?) await sophisticated research approaches.

Acquiring a better understanding of the ways by which survivors create meaning through their experiences with cancer holds great promise for better appreciating the ways in which survivors differ in their adjustment and the myriad influences on this process. This knowledge should help to identify those needing more assistance in adjusting to survivorship including informing interventions for those who may need help returning to their "new normal" lives.

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7

Stress, Coping, and Hope

Susan Folkman

Hope

Hope is the thing with feathers
That perches in the soul
And sings the tune without the words
And never stops at all
And sweetest in the gale is heard;
And sore must be the storm
That could abash the little bird
That kept so many warm.
I've heard it in the chillest land
And on the strangest sea;
Yet, never, in extremity
It asked a crumb of me.
Emily Dickinson

Few would question the critical importance of hope when facing serious and prolonged threats to psychological or physical well-being, whether our own or that of a loved one (for review, see [1]). The significance of hope is perhaps best understood by the consequences of its absence. Hopelessness is a dire state that gives rise to despair, depression, and ultimately loss of will to live. The assumption of the fundamental importance of hope in confronting serious threats is so embedded in our belief system that hope approaches the status of an evolutionarily adaptive mechanism wired into our genome. Indeed, that might be the case. But it is another matter to assume that hope is an automatically self-renewing resource, as suggested in the frequently quoted passage by Alexander Pope, "Hope springs eternal in the human breast." On the contrary, hope needs to be nurtured; at the very least, it needs something from which to spring as well as something to spring toward.

In this chapter, I view hope from the perspective of stress and coping theory. Hope usually appears in the stress and coping literature in the form of hopelessness, frequently as a predictor of depression or suicidal ideation (for reviews, see [2, 3]). A more interesting story about hope may be the one told in terms of its dynamic and reciprocal relationship with coping in which each supports, and in turn is supported by, the other.

To provide a framework for this discussion, I begin with a very brief account of stress and coping theory. Then I shall incorporate hope, illustrating the interplay between coping and hope as stressful situations unfold over time. I have chosen the context of serious illness for this discussion, but the ideas and hypotheses I propose are likely to apply to any situation that involves prolonged psychological stress.

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Stress and Coping Theory

Stress and coping theory [4] is a framework for studying psychological stress. The theory holds that stress is contextual, meaning that it involves a transaction between the person and the environment, and it is a process, meaning that it changes over time. Stress is defined as a situation that is appraised by the individual as personally significant and as having demands that exceed the person's resources for coping.

Appraisal

Primary appraisal is the term applied to the appraisal of the personal significance of a situation—what is happening and whether it matters and why. Primary appraisal is shaped by the person's beliefs, values, and goals. Secondary appraisal refers to the person's evaluation of options for coping. These options are determined both by the situation, such as whether there are opportunities for controlling the outcome, and by the person's physical, psychological, material, and spiritual resources for coping. The two forms of appraisal determine the extent to which the situation is appraised as a harm or loss, a threat, or a challenge, each of which is a stress appraisal. The appraisal process generates emotions. Anger or sadness, for example, is associated with loss appraisals; anxiety and fear are associated with threat appraisals; and anxiety mixed with excitement is associated with challenge appraisals. The personal quality of the appraisal process explains why a given event can have different meanings for individuals. A job interview, for example, may be considered a threat by one person and a challenge by another.

Coping

Coping refers to the thoughts and behaviors people use to manage the internal and external demands of stressful events. Stress and coping theory originally posited two kinds of coping: problem-focused coping such as planful problem to address the problem causing distress using strategies such as information gathering, and decision-making, and emotion-focused coping to regulate negative emotion using strategies such as distancing, seeking emotional support, and escape-avoidance.

A third kind of coping, "meaning-focused coping," was introduced into the model based on findings that positive emotions occur alongside negative emotions throughout intensely stressful periods, including caregiving and subsequent bereavement [5–7], and in cancer patients during the months preceding their deaths [8]. As suggested by Fredrickson's [9] "Broaden and Build" theory of positive emotion, these positive emotions serve as important functions in the stress process by restoring resources for coping, thereby helping to transform threat appraisals into challenge appraisals and motivating and sustaining coping efforts over the long term. Meaning-focused coping strategies are qualitatively different from emotion-focused coping strategies, such as distancing or seeking social support, that regulate negative emotions. Meaning-focused coping draws on deeply held values and beliefs in the form of strategies such as goal revision, focusing on strengths gained from life experience, and reordering priorities.

The various types of coping often work in tandem, such that the regulation of anxiety (emotion-focused coping) will allow the person to concentrate on making a decision (problem-focused coping), which in turn is informed by a review of underlying values and goals (meaning-focused coping). Ideally, there would be independence among these processes so as to permit prediction. In reality, however, we are looking at a dynamic system of processes that are highly interactive.

Hope

Hope has been defined in many ways and in many literatures. (See [10] for an excellent review of definitions from diverse literatures.) In the psychology literature, for example, hope is defined as yearning for amelioration of a dreaded outcome [11], a theological virtue along with faith and charity [12], and as a positive goal-related motivational state [13]. Hope has also been characterized in the nursing literature as having a "being" dimension, something that is deep inside one's self that remains positive whatever happens; a "doing" dimension, a pragmatic, goal-setting entity in response to situations; and a "becoming" dimension, anticipating future possibilities, positive results [14]. In the medical literature, maintaining and restoring hope is seen as an important function of the physician [15].

Hope and psychological stress share many formal characteristics. Hope, like stress, is appraisal-based; it waxes and wanes, it is contextual, and, like stress, it is complex. Hope has a cognitive base that contains information and goals; it generates an energy, often described as "will" that has a motivational quality; it has both negative and positive emotional tones due to the possibility that what is hoped for might not come to pass; and for many people, hope has a basis in religion or spirituality whereby it is equivalent to faith. Although I think of hope as aligned with positive emotions, I consider it to be a state of mind that has emotional tones rather than an emotion per se.

Coping and Hope: Dynamic Interdependence

A number of writers speak of hope in relationship to outcomes over which the individual believes he or she has some control. Jerome Groopman represents this point of view in his book *The Anatomy of Hope* [16]: "To have hope, then, is to acquire a belief in your ability to have some control over your circumstances" (p. 26). However, psychological stress is at its peak in precisely those situations that offer few, if any, options for personal control [4], meaning that the situations in which hope is most needed are the ones in which hope is most likely to be at low ebb or even absent.

The revival of hope in intensely stressful situations depends at least in part on cognitive coping processes. In turn, the person's capacity to sustain coping with intensely stressful situations over time depends at least in part on having hope with respect to the desired outcome.

The interdependence of coping and hope is played out in many ways over the course of prolonged stress, as can be illustrated in the case of serious disease. Learning that one has a serious disease changes how things are for the patient and the patient's family members and close friends, especially those who are involved directly with the patient's caregiving. The world is different. The future is suddenly filled with unknowns about what lies ahead and how it will affect the physical, psychological, and spiritual well-being of the patient and the patient's close others. The challenges to well-being may differ according to diagnosis and patient characteristics such as age, health, access to care, social support system, and psychosocial and psycho-spiritual resources. But certain adaptive tasks are common to virtually all seriously ill patients and their family members. I have chosen two of these tasks—coping with uncertainty and dealing with a changing reality—to illustrate the dynamic, interdependent relationship between hope and coping and how each would at times be difficult, if not impossible, without the other.

Coping with Uncertainty

Uncertainty travels with psychological stress. There can be uncertainty about when something will happen (temporal uncertainty), what will happen (event uncertainty), what can be done (efficacy uncertainty), and the outcome (outcome uncertainty) [4]. Although not all aspects of uncertainty are relevant in every situation, it is safe to say that every stressful situation involves some uncertainty.

The process of coping with uncertainty in the context of illness begins when the person becomes aware of a change in the status quo, such as when he or she receives a diagnosis or learns of the progression of an established condition. The initial response for some patients will be to minimize the significance of what they were told or to avoid thinking about it altogether. I discuss these emotion-focused strategies below. But I believe the more typical response of patients is to search for a frame of reference that allows them to appraise the seriousness of their condition. "Am I in danger? Will I be okay? How bad is this?" Answers are often in the form of odds—the odds associated with treatment options and their outcomes, the odds associated with the nature and speed of disease progression, or the odds associated with the prognosis more generally.

Odds are estimates, statements of probabilities, often conditional probabilities that are open to interpretation. Statements about odds, and the range of possibilities they imply, invite hope. Hope gains a strong toehold when the odds of a good outcome are favorable. But as noted earlier, hope is likely to be at low ebb or even absent when the odds are unfavorable. Based on the assumption that hope underlies any effort to cope with the demands posed by the illness, I suggest that when odds are unfavorable, people initiate a reappraisal process of their own personal odds that improves them. This process is significant because it gives hope its toehold within the individual's psychological milieu. I refer to this reappraisal process as "personalizing the odds." This coping strategy not only creates a toehold for hope, but it also reduces threat.

The rationales people use to personalize the odds are familiar to anyone who has been involved in conversations about diagnoses with patients and their family members. For example, the person may:

1. Identify reasons why the odds do not apply in this case. For example, a person might reason that the odds do not apply to him or her because of personal attributes ("I am a strong person," "I am lucky"), attributes of the environment ("I have the best doctor, the best medical care, the best hospital in the city/state/nation"), or because of existential beliefs ("God will protect me").
2. Search for information that contradicts the odds that were given. The Internet is a major source of such opinions. Friends and family members may also share information, advice, and beliefs that affect the patient's appraisal of his or her personal odds. Another physician may have a different assessment of the odds.
3. Read the medical literature to determine whether there are other ways of interpreting findings.

Stephen Jay Gould, the internationally renowned geologist, zoologist, paleontologist, and evolutionary biologist, illustrated the process of personalizing odds in an article he wrote about his reactions when he was diagnosed in 1982 with a rare and deadly form of cancer, an abdominal mesothelioma [17]. When he revived after surgery, he asked his doctor what the best technical literature on the cancer was. She told him that there was really nothing worth reading. His reaction was as soon as possible to go to the nearby Harvard Countway medical library. He soon realized why his doctor had tried to discourage him from looking, "The literature couldn't have been more brutally clear: mesothelioma is incurable, with a median mortality of only 8 months after discovery. I sat stunned for about 15 min … Then my mind started to work again, thank goodness." Gould, who knew about statistics, wanted to find out his chances of being in the half that survived more than 8 months, and especially its tail. "I read for a furious and nervous hour and concluded, with relief: damned good. I possessed every one of the characteristics conferring a probability of longer life: I was young; my disease had been recognized in a relatively early stage; I would receive the nation's best medical treatment; I had the world to live for; I knew how to read the data properly and not despair."

I wonder whether Dr. Gould felt any hope during the 15 min when he sat stunned. But by the end of his hour of reading and using many of the cognitive coping strategies listed above to interpret his personal odds more favorably, Dr. Gould was certainly feeling hopeful. Dr. Gould did in fact survive until 2002, when he died of an unrelated cancer.

Uncertainty and distortion of reality. Coping with uncertainty, and especially the process of personalizing odds, can involve distortion of reality, which is a red flag to those who believe that veridicality—adherence to reality—is essential for good mental and physical health. Traditionally, failure to adhere to veridicality was equated with denial. The concern was that if people engage in denial, they will fail to engage in appropriate medical treatment and also that a person engaging in denial has to expend energy on avoiding evidence to the contrary [4].

The issue about veridicality and denial actually involves two questions: Denial of what? And, what are the consequences? Breznitz [18] presents a hierarchy of denial and denial-like processes that offers options for the question: "Denial of what?" The most serious of these is the denial of information, which is probably the closest to the definition of denial of external reality, considered a psychotic defense mechanism [19]. But Breznitz goes on to list other denial-like processes in which information as such is not denied, but its implications are. Breznitz' hierarchy of denial-like processes descends from the denial of threat to the denial of personal relevance, urgency, vulnerability/responsibility, affect, and affect relevance.

Any of these denial-like processes might disturb the physician, who wants to make certain that the patient is fully informed so that the patient can make good decisions. On the other hand, the patient's need to maintain at least an approximation of equilibrium may call for regulating the flow of information into awareness, whether knowingly or unconsciously. A number of articles have been written about achieving this delicate balance [1].

It is understandable that physicians would be concerned if unrealistic hopes lead to treatment decisions that harm the patient or consume scarce resources the patient will need in the future. But the literature suggests that most people do not distort reality to this extent. In general, people's illusions tend to depart only modestly from indicators of their objective standings, show a high degree of relative accuracy, and are kept from becoming too extreme by feedback from the environment [20]. Indeed, the social psychology literature shows not only that people tend to have unrealistic optimism about their ability to manage traumatic events but also that these illusions are associated with effective coping and psychological adjustment [20] and a sense of agency [21]. And, as Snyder and his colleagues note, people who have lofty goals often attain them [21].

The medical literature often uses the term "false hope" to refer to unrealistic hope. A more literal interpretation of false hope is suggested by Klenow [22] who refers to false hope as hope that originates from deliberate deception by the physician, as when a physician tells a patient that he or she has a less serious illness than he or she actually does. Let us assume that this form of deception is rare.

Efforts to discourage unrealistic expectations may push the patient and his or her caregivers to consider a more realistic appraisal of what the future holds. Whether this is important for the patient's health, however, depends on the reasons compelling the more realistic appraisal and the costs of not doing so. Unrealistic hope, for example, may be what the patient needs at the outset in order to have any hope at all, what I referred to earlier as giving hope a toehold, in which case the unrealistic hope may be serving an important adaptive function. Over time, as the patient and the patient's family caregivers absorb more information and its meaning, I would expect them to begin formulating more realistic expectations and to shift their focus away from hoping for unrealistic outcomes, such as a cure, to hoping for more plausible outcomes such as hope of living longer than expected, being well cared for and supported, having good pain and symptom control, and hope of getting to certain events [1].

Managing uncertainty over time. Whether uncertainty lasts just a few hours, as when a parent waits for a teenage driver to return home at night, or years, as when a cancer patient has to wait to learn whether the cancer is in remission, uncertainty is often an aversive condition that is difficult to tolerate. Uncertainty can provide a fertile milieu for doubts based on what one hears, sees, reads, or imagines. Well-intended friends can share anecdotal accounts that have the unintended effect of creating more anxiety rather than reducing it.

Theoretically, hope provides a counterbalance to both intrapersonal and interpersonal events that feed anxiety during periods of uncertainty. In this sense, hope (e.g., as faith) or hoping (e.g., actively focusing on reasons for feeling hopeful) acts as emotion-focused coping strategies. The calming effects of hope can be reinforced by other kinds of emotion-focused coping strategies that are appropriate for managing anxiety in waiting situations, for example, distracting one's self by turning to other activities such as exercising, work, or gardening [23]. This example further illustrates the interplay between hope and coping, whereby each can facilitate the other.

Hope has a very special quality that is especially important in managing uncertainty over time: it allows us to hold conflicting expectations simultaneously. For example, we have reliable information that a hurricane is approaching, so we take necessary precautions—tape windows, get sandbags to ward off flooding, stock up on water, to name a few—and then relax because we also believe the hurricane will veer off its predicted path.

The concept of hope *legitimizes* holding conflicting expectations. The person who holds these conflicting expectations is not thought to be confused or delusional; the person is labeled *hopeful*. Holding both possibilities also facilitates adaptive problem-focused and emotion-focused coping. The belief that the hurricane is coming frees the person to prepare for the hurricane (problem-focused coping). The expectation that the hurricane will veer off path regulates anxiety (emotion-focused coping). By combining both expectations, the person is also likely to continue attending to information about the hurricane's path (problem-focused coping).

Dealing with a Changing Reality

When circumstances change with time, previous expectations and hopes may no longer be relevant. A cancer patient, for example, may learn that the course of chemotherapy was not effective and that a new treatment with more aversive side effects is required, or that there are no further treatments available at the moment. Perhaps the patient learns that his or her cancer has metastasized, or that there has been a recurrence following a period of remission.

The patient and the patient's family members are faced with the dual challenges of sustaining hope while coping with a changing reality. Recognizing that things are not going well means giving up hope with respect to what had been, but hope itself is not necessarily quashed. Generalized hope—hope that is based on faith, personality disposition, or developmental history—can act as a reserve that supports the efforts to revise expectations in the present situation. For example, when there is little that can be done by the patient to affect a particular outcome, religious faith can support hope by providing a sense of ultimate control through the sacred [24] or through affirming beliefs about the sacred such as "God will be by my side." Individuals who rate high on hope as a trait have the advantage of approaching situations with a hopeful bias that is protective; they show diminished stress reactivity and more effective emotional-recovery than those low in dispositional hope [25]. And a developmental history that includes experience confronting stress and coming through quite well provides the individual with confidence that the present situation can also be managed well [26, 27].

The reserve of generalized hope is important for the patient as he or she begins coping with the demands spawned by advancing illness that must be addressed to preserve physical, psychological, and spiritual health. These demands define an array of goals for the patient, ranging from proximal, concrete goals such as the ones on the weekly to-do list, to distal, abstract aspirational values, goals, beliefs, and commitments. In what might be called ideal "normal" day-to-day life, distal and proximal levels are in harmony. Proximal goals (e.g., producing an excellent report on time at work, volunteering service to a community organization) are expressions of distal values, beliefs, and commitments (e.g., valuing excellence and honoring commitments, and belief in communal responsibility) [7].

But illness has a way of perturbing the goals that organize day-to-day choices and behavior—

the routine weekly to-do list. The individual needs to revise these goals [28, 29] and revisit the distal values and higher order goals that guide day-to-day choices and infuse them with meaning [7]. For example, a mother diagnosed with cancer whose top priority had been her children may now need to put attending to her own health at the top of the list in order to restore her health so that she can resume care of her children. For now, by making her own health her immediate top priority, this mother will be able to focus her time and attention on necessary tasks such as arranging for appropriate medical care, arranging finances, preparing for debilitating surgery and for side effects of a course of chemotherapy, and, in some cases, even preparing for a shortened life expectancy.

Overall, the process of revising goals—letting go of goals that are no longer tenable and identifying meaningful, realistic goals that are adaptive for coping in the present circumstances—is an important form of meaning-focused coping that helps sustain a sense of control, creates a renewed sense of purpose, and, of relevance here, allows hope with respect to new goals. I call these goal-specific hopes "situational hope." The seeming simplicity of goal revision processes belies their actual complexity. As the narratives that follow illustrate, the process of goal revision may proceed in fits and starts or happen rather quickly, and the process may be intensely emotional or relatively matter-of-fact. A number of factors influence the process including beliefs, personality disposition, and previous experiences with stress as noted above; the meaning of what is now at stake; what else is going on in the person's life; interactions with close others; and the quality and sensitivity of patient-physician communications during this transition.

The following narrative from the Care Preference Study conducted by Judith Rabkin, myself, and our colleagues in New York and San Francisco [8] illustrates the outcome of a process of goal revision. Participants in this study were diagnosed with terminal illness. Note that the patient's revised goals are not trivial and reflect underlying meaning. The patient's name is Rob, and he had advanced AIDS:

> Rob—Look at you. You're still here! You can't do all the things you used to do—you used to have all the diamonds, and gold, and all the fun you wanted—you can't do that anymore. Those days are gone. And so I try to think about, what now? What do I do now with the time I have left? In my actions—in my spiritual life—pray more, be nicer to other people, give.

Not everyone succeeds in the goal revision process. Some are unwilling to relinquish untenable goals, as illustrated by another patient with advanced AIDS from the Care Preference Study who was asked how he had spent his day. His response: "Moping, depressed, trying to get as close to the life I had before I got sick." This patient was obviously unwilling or unable to relinquish goals that are now unrealistic.

In a dialog between a patient and his wife, transcribed from a documentary about the caregivers of patients with brain tumors [30], the patient does not know what he wants, while his wife has strong feelings about what he *should* want. The exchange illustrates how interpersonal dynamics can further complicate the process of goal revision and create additional stress.

Tony was diagnosed with a glioblastoma multiforme, a brain tumor that few survive. Lisa is his wife and primary caregiver. Following Tony's surgery, Tony's doctor told him that the surgery was "a success, a complete resection."

> Tony: When I asked what did that [*a success, a complete resection*] mean, will it grow back, the doctor said to me the tumor would grow back. He said he couldn't say when, but it would definitely grow back.
>
> Lisa: I just felt contempt for that point of view. When I hear the doctor say it will definitely grow back I say, "Oh no, there is a *95 % chance* the tumor will grow back. But Tony is a 5 percenter."
>
> Tony: And I don't want to say to her "I'm going to die," but I am going to die. Lisa wanted me to think positive. She wanted me to ally myself with anecdotal others who had beaten the odds so to speak … The trouble is, I don't know WHAT I want."

Tony's refusal to think more positively became unbearable for Lisa, and she left Tony, although she eventually returned to take care of him.

Notice that Tony cannot name a goal. He says he does not know what he wants. Tony's conundrum raises an important issue. I have been discussing goal revision as an important coping strategy for dealing with a changing reality. The underlying assumption is that goals give the person something to hope for. And in fact a body of research in psychology is based on a definition of hope offered by the late C.R. Snyder [13] that is entirely related to goals: "a positive motivational state that is based on an interactively derived sense of successful (a) agency (goal-directed energy), and (b) pathways (planning to meet goals)" (p. 287).

However, I consider the boundaries defining hope to be more porous than those defining goals. Hope's more porous boundaries open the way to exploring existential issues that clarify underlying meaning. In the case of patients whose reality is changing, for example, we need to ask questions about *what patients hope for.* Although the initial response is likely to be a response such as "a miracle cure" or "that I beat the odds and land in the tiny percentage that has a lasting remission" (see [31] for a thoughtful discussion of philosophical underpinnings of such hopes), asking patients what they hope for may also inspire them to move beyond those immediate responses and express what matters to them now in their new reality, what they value, and what they yearn for (Rachel Remen, personal communication, March, 2010). Examples might include "maintain my dignity," "be at peace with my God," or "avoid suffering." Or responses may express cosmologic hopes such as being reunited with loved ones who have died, being with their God, or entering a divine world. These aspirations give definition to underlying meaning, the foundation for hope and sustained coping. Technically, these aspirations could be termed higher-order distal goals. Responses to a question about hopes may also be expressed in the form of more concrete, proximal goals such as "to find the best doctor," "to attend my grandson's graduation," or "to have a successful conversation with my insurance carrier."

Regardless of the response, the key is to allow the patient the opportunity to consider existential issues that clarify meaning and for this purpose I believe it is important to ask about hopes in addition to goals. This meaning-clarification function may in fact be a key to the whole process of goal revision, serving to give it a jump start much as I proposed that personalizing odds can give a toehold for hope. With this idea in mind, consider how the following participant in our study of the caregiving partners of men with AIDS [5] might have responded had he been asked about his hopes for himself and his partner:

> Michael: As time passes, we reach different plateaus. And Josh and I view this as if we are climbing down a canyon. And each time he hits a certain health problem it is another plateau that you have to kind of adjust to and face. And we know that his death is the bottom of the canyon. And then it is up to me to start my new existence.

Conclusion

I have discussed hope from the vantage of stress and coping theory and explored the dynamic and reciprocal relationship that hope has with coping. I began with the assumption that hope is essential when we need to confront stressful circumstances but that hope is not always available. Coping plays a critical role in fostering hope when it is at low ebb, as when an individual is confronted with information that threatens well-being. Hope in turn can sustain coping, as when the individual moves forward to deal with the demands of his or her new reality. But hope is more than what is implied by this analysis.

In his *New York Times* column of March 26, 2010, David Brooks highlights the shortcomings of modern economics, most recently those of behavioral economics in which economists are interested in "those parts of emotional life that they can count and model (the activities that make them economists)." He warns "But once they're in this terrain, they'll surely find that the processes that make up the inner life are not amenable to the methodologies of social science. The moral and social yearnings of fully realized human beings are not reducible to universal laws and cannot be studied by physics."

David Brook's comment applies as well to hope. No single interpretation, perspective, or discipline has proprietary rights to hope. Hope belongs to the arts as much as it does to the sciences; its meanings range from the ordinary to the transcendent. We can study certain aspects of hope with behavioral and social science techniques, but we cannot capture all of its aspects. However, what we do learn from those aspects we are able to study can be used to help people sustain well-being through difficult times.

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8

Religiousness and Spirituality in Coping with Cancer

Ingela C. V. Thuné-Boyle

Definitions of Religiousness and Spirituality

There has been much debate in the literature over exactly how religiousness and spirituality should be defined. Religion is often described as institutional and formal, while spirituality is seen as more informal, existential, and personal [1]. This may not always be the case however. Indeed, religion is a multidimensional construct that may involve spiritual experiences, meaning, values, beliefs, forgiveness, private and public religious practices, religious coping, religious support, commitments and preferences [2]. Spirituality may also be viewed as a multidimensional construct that can be divided into three main dimensions: (1) a God-orientated spirituality where thoughts and practices are premised in theologies; (2) a world-orientated spirituality stressing relationships with ecology or nature, and (3) a humanistic spirituality (or people orientated) stressing human achievement or potential [3].

The use of the term "spirituality" as being apart from religion has a surprisingly short history [4, 5] and evolved mainly from a growing disillusionment with religious institutions in Western society during the 1960s and 1970s. Today, it is often associated with more favorable connotations to religion [6] and appears to be the terminology favored by healthcare professionals, especially within oncology and palliative care. However, viewing religiousness and spirituality as distinct and separate constructs may potentially ignore the rich and dynamic interaction between the two [7]. Studies have generally found defining religiousness and spirituality problematic, and empirical studies examining people's understanding of these concepts have produced conflicting results to the notion of separate constructs. For example, Zinnbauer et al. [8] found that religiousness and spirituality were not totally independent and that as many as 74% considered themselves both religious and spiritual. A large overlap between the two concepts, with many similarities in terms of beliefs, time spent in prayer, guidance, a sense of right and wrong, and a connection to God, also exists [9]. Indeed, Scott [10] found that definitions of religiousness and spirituality were evenly distributed across nine content categories: (1) experiences of connectedness or relationships; (2) processes leading to increased connectedness; (3) behavioral responses to something sacred; (4) systems of thoughts or set beliefs; (5) traditional institutional or organizational structures; (6) pleasurable states of being; (7) beliefs in the sacred or transcendent; (8) attempts at or capacities for transcendence; and (9) concerns for existential questions or issues. This further

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demonstrates a substantial diversity in the content of people's understanding of religiousness and spirituality and signifies a considerable overlap between the two constructs. Both may involve a search for meaning and purpose, transcendence, connectedness, and values. Religious involvement can therefore be similar to spirituality. Equally, spirituality may also have communal or group expressions. When these expressions are formalized, spirituality is more like an organized religion [11].

Most studies examining definitional issues surrounding religiousness and spirituality have been conducted in the USA. Therefore, before commencing research in this area at UCL in London, UK, my colleagues and I conducted a brief assessment into the definitional views of religiousness and spirituality in a London population to gain a clearer idea of how people in the UK view these concepts [12]. Although we are not in a position to generalize these findings to the UK population as a whole, in line with previous US findings, results from these interviews show that people in the UK may also have different, and often overlapping, understandings of religiousness and spirituality, although most did not view these terms in any great detail. Being religious was understood in three different ways: having a belief in God or devotion to one's faith (non-organizational), belonging to an organized religion (attending church and adhering to the doctrine of a particular religion) or it may also incorporate both of these. Equally, spirituality was viewed in different ways, as being separate from religion, where it was seen as a broader non-organizational concept with a strong dedication to one's faith. Some viewed it as providing meaning to a person's life and as being similar to religion, describing spiritual people as practicing in much the same way as a religious person might. Others found spirituality difficult to define with some tending toward a "New Age" or Eastern philosophy rather than associating it with more organized religions. Finally, some felt that spirituality was something they associated with people being "a bit phoney."

The variations in people's ideas about these concepts show that it may be more useful to concentrate on the content behind their understanding of religiousness and spirituality rather than focusing on the label itself. Indeed, within medically ill populations, how patients use their spirituality or religiousness in the coping process has been a growing area of interest to healthcare researchers.

Religious/Spiritual Coping

Since 1985, 30% of coping studies in the literature have examined some aspect of coping with cancer [13]; yet despite significant interest in the coping process being evident in the last 30 years, the role of religion and spirituality in coping with illness has received relatively little attention as an area of study in its own right. For example, up until 1998, only 1% of coping studies had examined the use of faith in coping [14]. This is surprising, especially as its role in the appraisal process may lead to both cognitive (e.g., appraising an illness as part of God's plan) and behavioral (e.g., praying or attending religious services) aspects of coping. Religious/spiritual coping can therefore be defined as "The use of cognitive and behavioral techniques, in the face of stressful life events, that arise out of one's religion or spirituality" [14]. The term "religious coping" will be used throughout this chapter simply because it is the term generally used in the literature. However, it does, of course, incorporate the coping of people who view themselves as spiritual and not religious. Other terms such as "spiritual needs" will be used as it is also the term generally used in the literature. It too includes those who regard themselves as religious and therefore have religious needs.

Nature of Religious Coping

Turning to religion during times of difficulty has been described in the literature as a form of escapism, defense, denial, avoidance, passivity, or dependence [15], and the notion that religious coping is a maladaptive avoidant coping strategy was first argued by Freud [16] who believed that people who turn to religion do so from a sense of helplessness with the aim of reducing unwanted tensions and anxieties: “Religion is a universal obsessional neurosis … infantile helplessness … a regression to primary narcissism.” By 1980, attitudes had changed little; the US psychologist Albert Ellis wrote: “Religiosity is in many respects equivalent to irrational thinking and emotional disturbance … The elegant solution to emotional problems is to be quite unreligious … the less religious they are, the more emotionally healthy they will be” [17]. However, this view is simplistic and stereotypical and fails to consider the diverse roles religious/spiritual beliefs, practices, and communities play in people’s attempts to find some sort of significance in their lives [15]. Although religious coping can be avoidant, passive, ineffective, and maladaptive, it may also be adaptive, active, and problem-focused in nature [18]. Public religious/spiritual practices (e.g., attending religious services at church/synagogue/mosque/temple, Sufi meetings or bible study) and private religious/spiritual practices (e.g., prayer or meditation without the influence of other like-minded people) may be conceptualized as a form of religious coping, but religious coping may also describe various religious coping cognitions. These can further be divided into positive and negative religious coping strategies. Positive religious coping is considered to be an expression of a secure relationship with a supportive God/higher power. Seeing the situation as part of God’s plan and seeking God’s love and care or working together with God to solve problems are examples of positive religious coping strategies. Negative religious coping (sometimes referred to in the literature as “religious struggle”) is viewed as an expression of a less secure relationship with a God/higher power that is distant and punishing, or as a religious struggle in the search for significance [19]. Feeling punished or abandoned by God and reappraising God’s powers or feeling let down by God are examples of negative religious coping strategies. In this chapter, the terms “negative religious coping” and “religious struggle” will be used interchangeably.

Pargament et al. [20] argue that the exploration of religious coping should be theoretically based and functionally orientated. They consider five key religious functions in coping based on various theories:

1. *Meaning*. According to theorists (e.g., Clifford Geertz, [21]), religion plays a key role in the search for meaning during suffering or during difficult life experiences. Religion offers a framework for understanding and interpretation.
2. *Control*. Theorists such as Eric Fromm [22] have stressed the role of religion in the search for control over an event that pushes an individual beyond his or her own resources.
3. *Comfort*. According to classic Freudian theory [23], religion is designed to reduce an individual’s apprehensions about living in a world where disaster can strike at any moment.
4. *Intimacy*. Sociologists such as Durkheim [24] have generally emphasized the role of religion in facilitating social cohesiveness. Religion is said to be a mechanism for fostering social solidarity.
5. *Life transformation*. Religion may assist people in making major life transformations where individuals give up old objects of value to find new sources of significance [25].

Table 8.1 shows various religious coping strategies falling within Pargament et al.’s [20] five functional dimensions, and examples of each are given. Researchers should not expect to find five different factors of religious coping according to these five functions as any form of religious coping may serve more than one purpose. For example, meaning in a stressful situation can be sought in many different ways: redefining the stressor as an opportunity for spiritual growth (“benevolent religious reappraisal”), or redefining the situation as a punishment from God (“punishing God reappraisal”) where the former is a potentially adaptive positive religious coping strategy, while the latter is a potentially maladaptive negative religious coping strategy. Empirical studies have indeed confirmed that different forms of religious coping have different implications for adjustment, at least in the short term [26, 27]. For example, collaborative religious coping has been associ-

Table 8.1 Examples of the functions of coping and associated religious/spiritual coping strategies along Pargament et al.'s [20] five dimensions

Religious coping strategies under the five different functions	Positive/ negative	Example of coping strategy
1. *To find meaning*		
Benevolent religious reappraisal	Positive	"Saw my situation as part of God's plan"
Punishing God reappraisal	Negative	"I wondered what I did for God to punish me"
Demonic reappraisal	Negative	"Believed the devil was responsible for my situation"
Reappraisal of God's powers	Negative	"Questioned the power of God"
2. *To gain control*		
Collaborative religious coping	Positive	"Tried to put my plan into action together with God"
Active religious surrender	Positive	"Did my best, then turned the situation over to God"
Passive religious deferral	Negative/ mixed	"Didn't do much, just expected God to solve my problems for me"
Pleading for direct intercession	Negative	"Pleaded with God to make things turn out okay", "Prayed for a miracle"
Self-directing religious coping	Mixed	"Tried to deal with my feelings without the help of God"
3. *To gain comfort*		
Seeking spiritual support	Positive	"Sought God's love and care"
Religious focus	Positive	"Prayed to get my mind off my problems"
Religious purification	Positive	"Confessed my sins"
Spiritual connection	Positive	"Looked for a stronger connection with God"
Spiritual discontent	Negative	"Wondered whether God had abandoned me"
Marking religious boundaries	Positive	"Avoided people who weren't of my faith"
4. *To gain intimacy with others/God*		
Seeking support from clergy or members	Positive	"Looked for spiritual support from religious leaders/ clergy"
Religious helping	Positive	"Prayed for the well-being of others"
Interpersonal religious discontent	Negative	"Disagreed with what the church wanted me to do or believe"
5. *To achieve a life transformation*		
Seeking religious direction	Positive	"Asked God to find a new purpose in life"
Religious conversion	Positive	"Tried to find a completely new life through religion"
Religious forgiving	Positive	"Sought help from God in letting go of my anger"

ated with better physical and mental health [18, 28, 29], while religious coping strategies such as punishing God reappraisal, demonic reappraisal, spiritual discontent, interpersonal religious discontent, and pleading for direct intercession are all associated with greater levels of distress [25]. However, there is also evidence that not all forms of religious coping fall easily into negative and positive categories but may be associated with both positive and negative outcomes. For example, self-directing (i.e., dealing with a situation without relying on God) and deferring religious coping strategies (giving over control to God) have demonstrated mixed results [19], as has pleading religious coping strategies (i.e., pleading and bargaining with God or praying for a miracle) [25].

Measurement of Religious Coping

Early studies have tended to use public religious/spiritual practices such as congregational attendance as a measure of religious coping [30, 31]. Using frequencies of religious service attendance as a coping measure is generally problematic for a number of reasons. For example, public religious/spiritual institutions/group attendance that involves meeting other like-minded people potentially expose people to social support, a variable known to predict illness adjustment which may therefore confound the results, whether the attendance is at a place of worship of an organized or non-organized religion or in someone's home (e.g., Bible study). People may also follow religious/spiritual practices for social reasons, for example, for social approval or social status often referred to as extrinsic religiousness [32]. Measuring public religious practices may therefore not necessarily inform much about *how* people use their faith in coping and how much it is involved in, for example, their cancer diagnosis or during cancer treatment. A distinction needs to be made between habitual religious/spiritual practices and those actively involved in coping with illness. Indeed, simply enquiring about service attendance does not inform about its intended purpose. It is also important to consider that people who are ill may not be well enough to take part in public religious/spiritual practices [33]. An example of a validated public religious practice scale [34] is shown in Table 8.2.

Table 8.2 Instruments examining religious coping strategies

Authors	Measures	Description
Religious coping:		
Idler [34]	Organizational Religiousness Scale	2 items examining frequency of attendance at religious services and participation in religious/spiritual activities with other people. Cronbach’s alpha = 0.82
Levin [35]	Private Religious Practices Scale	4 items examining how often people pray or meditate, read religious or spiritual literature, watch or listen to religious programs on TV or radio, and say grace before meals. Cronbach’s alpha = 0.72
Lazarus and Folkman [38]	The Ways of Coping Scale	2 items, 1 item as part of the “‘Escape-Avoidance” dimension; “Hoped a miracle would happen” and 1 item as part of the “positive reappraisal” dimension; “I prayed”
Carver et al. [36]	The COPE	4 items from the “‘Turning to religion” sub-scale, e.g., “I try to find comfort in my religion” “I seek God’s help. Cronbach’s alpha = 0.92.
Carver [37]	The Brief COPE	2 items from the “‘Religion” sub-scale, e.g., “I have been trying to find comfort in my religious beliefs” “I’ve been praying or meditating” Cronbach’s alpha = 0.82
Pargament et al. [18]	The Religious Problem-Solving Scale	22 items, 3 sub-scales labeled, (1) collaborative, (“When it comes to deciding how to solve problems, God and I work together as partners” Cronbach’s alpha = 0.93); (2) self-directing, (“When I have difficulty, I decide what it means by myself without relying on God” Cronbach’s alpha = 0.91); (3) deferring (“Rather than trying to come up with the right solution to a problem myself, I let God decide how to deal with it” Cronbach’s alpha = 0.89)
Pargament et al. [43]	The Religious Coping Activities Scale	15 items, 6 sub-scales: (1) spiritually based (e.g., “Trusted that God would not let anything terrible happen to me”); (2) good deeds (e.g., “Tried to be less sinful”); (3) discontent (e.g., “Felt angry with or distant from God”); (4) religious support (e.g., “received support from clergy”— – note, not a coping strategy but its consequence); (5) plead (e.g., “Asked for a miracle”); and (6) religious avoidance (e.g., “Focused on the world to come rather than on the problems of this world”). Cronbach’s alpha = 0.61–0.92
Boudreaux et al. [42]	The Ways of Religious Coping Scale	25 items, 2 sub-scales; (1) internal/private (e.g., “I pray” “I put my problems into God’s hands”); and (2) external/social (e.g., “I get support from church/mosque/temple members” “I donate time to a religious cause or activity.” Cronbach’s alphas = 0.93 and 0.97
Pargament et al. [20]	The RCOPE	105 items measuring positive and negative religious coping cognitions along 5 key religious functions in coping: (1) religious coping to give *meaning* to an event; (2) to provide a framework to achieve a sense of *control* over a difficult situation; (3) to provide *comfort* during times of difficulty; (4) to provide *intimacy* with other like-minded people; and (5) to assist people in making major *life transformations*. Cronbach’s alpha = 0.65 or greater
Pargament et al. [19]	The Brief ROPE	14 items divided into 2 clusters of positive and negative religious coping strategies. Cronbach’s alpha = 0.87 (positive sub-scale) and 0.78 (negative sub-scale)
Exline et al. [45]	The Religious and Spiritual Struggles Scale	26 items examining 6 domains of struggle: divine, demonic, interpersonal, moral, doubt, ultimate meaning. Cronbach’s alpha = 0.80 to 0.96

Private religious/spiritual practices such as prayer have also been used in research to represent religion/spirituality in the coping process [30, 31]. Using this approach is limited in that it only informs about the frequency of prayer and not its content, nor does it tell us about the actual cognitions used, whether they were adaptive or maladaptive. It can, however, inform researchers about the frequency of engaging in private religious practices such as frequency of prayer and whether these change as a result of being diagnosed with cancer. As with public religious practices, attention needs to be given to whether a practice is a coping or a habitual behavior or whether it involves praying with other like-minded people whose support may contaminate the findings if not controlled for adequately in the study analyses. An example of a validated private religious practice scale [35] is shown in Table 8.2.

The importance of religious coping strategies is reflected in several commonly used coping questionnaires (e.g., the COPE by Carver et al. [36]; the Brief COPE by Carver [37]; the Ways of Coping Scale by Folkman and Lazarus [38]—Table 8.2). These questionnaire items usually involve explicit terms such as “I prayed” or “I have been trying to find comfort in my religious/spiritual beliefs.” However, attempts made by “nonreligious” coping scales to classify religious coping highlight some difficulties. For example, this form of coping is often conceived as emotion focused [38], but can, as mentioned previously, also be problem focused [18]. Statements about prayer do not tell us about its content, nor does it inform about the actual coping cognitions that are used. Also, prayer is treated as a unidimensional construct when different forms of prayer may be associated with different outcomes. Some general coping measures (e.g., the Ways of Coping Scale) also ignore the possibility that religious coping might entail a unique coping dimension [37, 39–41], where religious coping items are combined within nonreligious sub-scales such as “positive reappraisal” and “escape-avoidance.” However, the distinct nature of religious coping in comparison to other forms of coping is evident in empirical studies. For example, the religious coping items of the COPE and Brief COPE load exclusively together onto one sub-scale [36, 37]. The specific content of potentially adaptive or maladaptive coping strategies (usually cognitive in nature but also some behavioral such as seeking religious support) can be measured using the Ways of Religious Coping Scale by Boudreaux et al. [42], the Religious Problem-Solving Scale by Pargament et al. [18], the Religious Coping Activities Scale by Pargament et al. [43], and the RCOPE by Pargament et al. [20] (Table 8.2). The Ways of Religious Coping Scale includes two sub-scales: (1) internal/private (e.g., “I pray,” “I put my problems into God’s hands”) and (2) external/social (e.g., “I get support from church/mosque/temple members,” “I donate time to a religious cause or activity”). (Note that the former example is not a coping strategy, rather the possible consequence of seeking support from religious groups which, in turn, reduces the validity of this questionnaire.) Prayer is also treated as unidimensional. Although this scale has good psychometric properties (e.g., a two-factor structure and Cronbach’s alpha scores of 0.93 and 0.97), it has not been extensively used.

The Religious Problem-Solving Scale [18] includes three sub-scales examining various religious coping cognitions. These are labeled as follows: (1) collaborative (where the individual and God actively work together as partners, e.g., “When it comes to deciding how to solve problems, God and I work together as partners”); (2) self-directing (where people are religious/spiritual but use coping strategies that do not involve God, e.g., “When I have difficulty, I decide what it means by myself without relying on God”); and (3) deferring (where the responsibility of coping is passively deferred to God, e.g., “Rather than trying to come up with the right solution to a problem myself, I let God decide how to deal with it”). During development, the items from the scale loaded onto three separate factors, and the sub-scales had Cronbach’s alpha scores from 0.89 to 0.93. However, nonreligious people would have trouble responding to items from the “self-directing” religious coping sub-scale as this scale assesses coping strategies of religious/spiritual people who use coping strategies without involving their faith in the coping process. The assumption is therefore that everyone has a belief in God or a higher power. It is, however, important to make sure that nonreligious people can respond to religious coping items as many may indeed turn to a higher power during periods of severe illness despite not admitting to believing in a God.

The Religious Activities Scale [43] includes six sub-scales: (1) spiritually based (e.g., "Trusted that God would not let anything terrible happen to me"); (2) good deeds (e.g., "Tried to be less sinful"); (3) discontent (e.g., "Felt angry with or distant from God"); (4) religious support (e.g., "received support from clergy"—note, not a coping strategy, rather, its consequence); (5) plead (e.g., "Asked for a miracle"); and (6) religious avoidance (e.g., "Focused on the world to come rather than on the problems of this world"). The items from the scale loaded onto six separate factors during development, and the sub-scales had Cronbach's alpha scores from poor (0.61) to excellent (0.92).

The RCOPE [20] is the most comprehensive measure to date. It includes 21 sub-scales (see Table 8.1 for examples of items from each sub-scale and Table 8.2) and is a theoretically based measure that examines much more wide-ranging religious coping methods, including potentially harmful religious expressions. It examines the functional aspects of religious coping and attempts to answer how people make use of their religion or spirituality to understand and deal with a stressful event which includes the five key religious functions in coping mentioned earlier (e.g., to gain meaning, control, comfort, and intimacy and to achieve a life transformation). It is, however, very long (105 items), but the authors recommend that researchers can pick sub-scales of interest or pick sub-scales that are relevant to the research purpose and can use three items (instead of five) with the highest loadings from each sub-scale (as indicated by the authors). The RCOPE was originally validated by Pargament et al. [20] using a college sample (five items per sub-scale) and a hospital sample (three items per sub-scale). The psychometric properties of the former, based on a 17-factor solution, were found to be acceptable with a Cronbach's alpha of 0.80 or greater for all but two scales: "marking religious boundaries" and "reappraisal of God's power," which had an alpha score of 0.78. The psychometric properties of the latter study, using a hospital sample, were also found to be acceptable showing alpha levels of 0.75 or greater for most factors.

Studies have found that several religious coping methods are moderately intercorrelated [19]. Therefore, specific clusters or patterns of religious coping strategies have more recently been explored using the Brief RCOPE [19]. This means that people do not make use of specific religious coping methods alone but apply them in some combination. Items are divided into positive and negative religious coping patterns (i.e., two sub-scales) and may be useful if researchers are interested in focusing on several methods and how these relate to outcome, rather than focusing on one method in detail [19]. All of the items from this scale can be found within the sub-scales of the RCOPE. The negative sub-scale includes items measuring spiritual discontent, punishing God reappraisal, interpersonal religious discontent, demonic reappraisal, and reappraisal of God's powers (see Table 8.2) and have all been empirically examined and associated with negative outcomes in the USA [25]. The positive sub-scale includes items measuring spiritual connection, seeking spiritual support, religious forgiveness, collaborative religious coping, benevolent religious reappraisal, and religious purification. Again, all these sub-scales have been empirically associated with positive outcomes in the USA [25]. During development, the Brief RCOPE showed a clear two-factor structure and acceptable alpha scores of 0.87 (positive sub-scale) and 0.78 (negative sub-scale). However, considering the current lack of research outside of the USA, one potential problem with this approach is that it makes a priori assumptions about which religious coping strategies are adaptive and which are maladaptive rather than treating this as an empirical question. Also, some items may not be as relevant outside of the USA. For example, demonic religious reappraisal (e.g., "Decided that the devil made this happen") may seem alien to many people in Western Europe [44]. This combination of items may therefore not translate well to other cultures.

Finally, and more recently, the Religious and Spiritual Struggles Scale [45] was developed to examine the negative aspects of religious coping only. It has 26 items along 6 different domains: *divine* (negative emotions about God and the relationship with God); *demonic* (concerns about the influence of the devil or evil spirits); *interpersonal* (concerns about negative experiences with religious people or institutions); *moral* (worry or guilt about perceived offences); *doubt* (questioning one's religious/spiritual beliefs); and *ultimate meaning* (not perceiving much meaning in one's life). Using a student sample, the psychometric properties of this scale were found to be acceptable showing Cronbach's alpha scores from 0.80 to 0.96.

Most of these scales were developed on Christian populations and often use terms such as "church attendance" which may not be applicable to all patients with cancer. However, researchers can substitute these with more neutral terms such as "religious/spiritual service attendance" if patients from different religions or spiritual leanings are included in studies. It may also be necessary to ask patients to substitute the word God for a term they are more comfortable with (e.g., a higher power, the universe, spiritual force, etc.). Indeed, my colleagues and I have found that most patients from a variety of cultural backgrounds and religious/spiritual affiliations have no problem responding to these types of questionnaires when these minor adaptations are made.

Prevalence of Religious Coping in Cancer

Studies have reported that religious coping is one of the most commonly used coping strategies in the US cancer patients where up to 85% of women with breast cancer indicate that religion helped them cope with their illness [46]. Negative religious coping strategies on the other hand are used less often [20, 47, 48]. Fitchett et al. [48] found that only 13% of patients used "reappraisal of God's powers" in the coping process. However, religious/spiritual beliefs and practices are very different across cultures, and these findings may therefore not generalize to cancer patients outside the USA; 75% of North Americans feel God is important in their lives compared with 49% of people in Europe; 45% attend a place of worship regularly in the USA in contrast to 10% in the UK [49, 50]. In the USA, only 7% of the population are reported to be atheists [51] compared with 33% in the UK [52]. Indeed, Harcourt et al. [53] found that only 23% of the UK patients with breast cancer used religion in coping 8 weeks after diagnosis. However, this study examined religious coping in a simplistic way (e.g., by using generic questions from the Brief COPE) [37].

My colleagues and I examined various specific religious coping strategies (taken from the RCOPE), and we found a very different pattern; the use of nonreligious coping strategies was, overall, more common and religious coping, despite being used by 66% of the sample, was one of the least used coping strategies when assessed using a comparable general coping measure [54]. This is probably due to a much larger proportion of nonreligious/spiritual people in the UK. Indeed, 28% of patients in our study reported not having a belief in God or being unsure of God's existence. Using items from the RCOPE, we also found consistently high levels of positive religious coping strategies throughout the first year of illness. For example, "active and positive religious coping" was the most common religious coping strategy (with 73% of the sample using it to some degree at surgery), where patients attempted to find meaning, a sense of control, comfort, and intimacy in their illness. This was followed by coping methods to achieve a life transformation (used by 53% of the sample), where patients used religious coping to find a new purpose in life. Indeed, the majority of patients used active nonreligious coping by taking actions to try and make their situation better. It is therefore not surprising that the proportion of the sample who considered themselves religious/spiritual also used their religious/spiritual resources to achieve this. In contrast, negative religious coping strategies were, overall, relatively less common. These findings support previous US results as well as a German study, where negative religious coping strategies were found to be overall less common than positive religious coping [20, 45, 47, 48]. However, despite being less common, negative religious coping strategies were used by as many as 53% of patients (e.g., reappraised God's powers). In addition, 37% of the sample felt, to some degree, punished and abandoned by God. This number is much higher than those reported by the US studies and may reflect the secular nature of the UK where God and religion may be viewed in more negative terms by those not practicing their faith in a more organized manner and may, as a result, have a less secure relationship with a God or may be struggling with their faith in their search for significance during periods of stress.

Change in Religious Coping Strategies Across the Illness Course

According to the "mobilization hypothesis" [55, 56], under stressful circumstances (e.g., a health threat), people are more likely to turn to their faith for coping in response; yet there is inconsistent evidence in cancer patients that this is the case [57]. There are also inconsistencies regarding how religious coping changes during the illness course in cancer. Using a general simple measure of religious coping, Carver et al. [58] and Culver et al. [59] found that religious coping decreased over time. In contrast, Alferi et al. [31] found that levels of religious coping ("extent of turning to religion for comfort") remained stable across a 12-month period. Other studies have examined the trajectory of religious coping across a range of specific religious coping strategies in cancer patients (breast cancer) [54, 60]. Gall et al. [60] found various patterns of change during the first 2 years of illness in ten specific religious coping strategies from the RCOPE. "Active religious surrender" and "spiritual support" showed an increase pre-surgery, and then a steady decline at follow-up. "Religious helping," on the other hand, increased from pre-diagnosis to 1-week pre-surgery but remained stable from pre-surgery throughout 2 years post-surgery, while "religious direction" increased pre-diagnosis to pre-surgery, followed by an increase until 6 months post-surgery, where it stabilized. "Religious focus" increased from pre-diagnosis to pre-surgery and from 1 to 6 months post-surgery, followed by a decrease from 6 months to 1 year. Other religious coping strategies such as "passive religious deferral," "spiritual discontent," "pleading," "benevolent religious reappraisal," and "collaborative religious coping" all remained stable. The pattern of change may therefore depend on the type of religious coping that is used.

My colleagues and I [54] compared the use of specific religious coping strategies in the UK in patients with early-stage breast cancer at the time of surgery and examined how these changed in the first year of illness. In support of previous findings by Alferi et al. [31], we found nonsignificant changes in four of the more specific religious coping strategies from the RCOPE; "religious coping to achieve a life transformation"; "passive religious deferral"; "reappraisal of God's powers"; and "pleading for direct intercession." Gall et al. [60] also found that "passive religious deferral" and "pleading" remained stable across time. However, they found significant changes in "seeking religious direction" (included in the "religious coping to achieve a life transformation" sub-scale in this study as they loaded together onto one factor) where it increased in use until 6 months post-surgery when it stabilized. This demonstrates that findings from one culture may not generalize to another. We also found a significant reduction in some religious coping strategies across time; "active and positive religious coping" and "seeking support from religious leaders and members of religious group" were significantly higher at the time of surgery than at follow-up. This suggests that patients were significantly more likely to seek support from God, actively surrendering to the will of God; work together with a benevolent God to solve problems; and seek support from religious/spiritual leaders and members of religious/spiritual groups in the early stages than further into the illness course. The value of emotional support in patients with breast cancer is well established and appears to have the strongest associations with illness adjustment [61, 62]. For those with a close attachment to God, asking God for support could serve as an added support resource or even a support substitute. Seeking support from God or from religious/spiritual leaders/members early in the illness course is therefore not surprising considering the potential difficulties associated with a breast diagnosis and subsequent surgery. Indeed, Gall et al. [60] also found higher levels of seeking spiritual support early in the illness course. However, in our study, religious struggles such as "feeling punished and abandoned by God" and "searching for spiritual cleansing" were both significantly higher at surgery and 12 months compared with 3 months post-surgery. Gall et al. [60] found no change in spiritual discontent coping strategies across time (combined in our study with "punishing God reappraisal" as these loaded together onto one factor). Finally, the generic religious coping subscale from the Brief COPE only demonstrated that religious coping strategies were more common earlier in the illness course, confirming its limited usefulness as a measure of religious coping.

The above findings provide partial support for the mobilization hypothesis. Indeed, increasing the use of religious/spiritual resources in the coping process, when faced with uncertainties about the future after a cancer diagnosis, may be the case. The majority of our participants were unaware of their prognosis at baseline assessment. Religious coping may therefore be higher as a result and may decrease as the patients become aware of the good prognosis that is associated with early-stage breast cancers. However, the mobilization hypothesis does not explain why some religious coping strategies showed a tendency to increase at 12 months. Indeed, patterns of change may depend on the type of religious coping strategy that is used, and some of these may be particularly volatile. They are also likely to be influenced by co-occurring life events. The Cognitive Phenomenological Theory of Stress and Coping by Lazarus and Folkman [63] describes coping as process-orientated that is directed toward what an individual thinks and does within the context of a specific encounter and how these thoughts and actions change as the encounter unfolds. During the first year of cancer treatment, patients with breast cancer often undergo lengthy treatment protocols with distressing side effects and regular medical surveillance, and worries about treatment and cancer recurrence are common [64]. The postoperative period is one of recovery from the procedure but also of confrontation with, and adaptation to, loss and possible death [65]. It is likely that, as a result of searching for spiritual cleansing through religious actions earlier in the illness course, a need to repent or feelings of being punished and abandoned by God may no longer be salient a few months later. However, as a result of being under close surveillance by hospital staff, this care and attention may serve to substitute feelings of being abandoned or punished and may reduce efforts of religious purification. As this close level of attention is reduced around 12 months, negative feelings of being punished and abandoned, and a need for religious purification, may resurface as a reaction to the loss of care. There is related evidence that end-of-treatment distress may occur as a result of patients feeling vulnerable to tumor recurrence, as they are no longer monitored closely by hospital staff [66]. Indeed, patients may experience a loss of security from having treatment and loss of support relating to ongoing communication with healthcare providers [67–69]. What is clear from these findings is that cancer patients have different spiritual needs at different times during their illness course depending on their coping appraisals.

Cultural and Denominational Differences

It is important to note that specific religious coping strategies may vary between different ethnic groups and religious affiliations; Alferi et al. [31] found that US Evangelical women with breast cancer reported higher levels of church attendance and religiosity across a 12-month period post-surgery compared with Catholic women. Religious denominations may also differ in the extent to which they focus on supporting and fostering the emotional well-being of their members and in their focus on the expiation of guilt and the preparation for the hereafter [31]. There may also be differences between those who are affiliated and those who are not in how they use religious coping strategies. There is evidence that non-affiliates are less likely to express "religious consolation," that is, seeking spiritual comfort and support. Religious affiliates, on the other hand, are more likely to be exposed to support by religious group members and rituals which may enhance the use of positive religious coping [70]. However, one cannot assume that those reporting an affiliation with a particular religious denomination actually practice their faith, as they may simply be referring to their identity rather than their religious involvement, especially in countries such as the UK where regular religious service attendance is relatively low. Therefore, establishing that religious affiliation refers to the actual practice of faith is vital.

There may be differences between those who are affiliated (e.g., Catholic, Protestant) and those who are not (e.g., those who believe in God but do not see themselves as belonging to a particular denomination) in how they use religious coping strategies. There is evidence that non-affiliates are less likely to express "religious consolation," that is, seeking spiritual comfort and support and are less likely to be connected to religious groups and therefore less likely to use religious coping strategies, even in the light of a serious illness such as cancer. Religious affiliates, on the other hand, are more likely to be exposed to rituals which may enhance the use of religious coping [70]. In addition, in countries where a large proportion of the population do not believe in a God, it is important to include all patients in studies examining religious coping, as "non-believers" may nevertheless use religious coping during difficult and desperate times, just as those who believe may exclude their faith in the coping process [54].

There is also evidence that relying on faith during illness in the USA is also greater in some groups such as African Americans [71–73] and Hispanics [36] compared to Caucasians [59, 74]. Indeed, one study found that Black men in the USA with prostate cancer used positive religious coping more often than white men [75].

Religious Coping and Adjustment in Cancer

Various religious coping strategies adopted by people and how these change during the illness course have implications for illness adjustment in cancer [44, 60, 74]. Indeed, there is increasing evidence of the importance of drawing on religious/spiritual resources in the coping process during illness. However, few studies have adequately examined these in patients with cancer, especially outside the USA [76]. A systematic review published in 2006 examining the relationship between religious coping and cancer adjustment found that many studies report mixed findings, but most have various methodological shortcomings using, for example, mixed cancer groups at different stages of their illness [76]. This makes it difficult to discern the impact of the relationship between religious coping and time, as it is possible that at crucial times during the illness course, patients may rely more on their religion/spirituality as they adapt to their diagnosis, treatments, and an uncertain future. Another issue is how religious coping has been conceptualized and measured. However, the potential confusion between religious coping cognitions versus behavior such as religious service attendance is particularly important in societies with high religious service attendance, where an effect could be caused by perceived social support from the religious community rather than religious coping. Many studies have also used generic instruments (e.g., the Brief COPE [37]) that do not identify the content of prayer or the specific religious coping strategies used. Only three studies used measures developed specifically to examine religious coping [77–79], all of which produced significant results in the expected direction.

Since the review was published, further studies have been conducted examining the efficacy of religious coping on well-being in patients with cancer [44, 47, 48, 60, 74, 75, 80–86]. These additional studies reinforce the suggestion that when better ways of measuring religious coping are used, more significant findings are evident. Particularly noticeable is the consistent relationship between negative religious coping and poorer outcomes. However, all of the above studies except Derks et al. [81], Hebert et al. [84], Sherman et al. [85], Gall et al. [60], and Gall [87] were cross-sectional in design, and most (except Gall et al. [60]) used the Brief RCOPE to measure religious coping. Some had very large refusal rates or attrition [44, 74, 81]. Five were conducted outside the USA and found the effects of religious coping to be comparable [44, 60, 81, 83, 86]. Although some controlled for demographic and medical variables [47], only one study [84] controlled for the potential confounding effect of perceived social support.

The Role of Nonreligious Variables

Studies examining religious coping in cancer using more appropriate measures have rarely assessed the role of other important psychological variables (e.g., perceived support, nonreligious coping, and optimism) and how these features in explaining the link between religious coping and adjustment. For example, Gall [80] and Sherman et al. [47] used regression analysis to assess the efficacy of religious coping in predicting adjustment. These studies controlled for demographic variables and found a significant independent effect of religious coping (Brief RCOPE) on adjustment. However, it is not known how these significant effects would appear if other variables known to affect adjustment in patients with cancer had been entered into the regression model. Indeed, researchers need to be thoughtful about which other variables should be measured alongside religious/spiritual variables and consider the order in which these are entered if regression analysis is used. Entering religious coping strategies last, after other nonreligious variables, can only produce two results: an independent effect or a nonsignificant effect of religious coping. If a mediating effect has occurred, it would not be visible; rather a nonsignificant finding would be evident leading to a false conclusion.

Few studies have examined the mechanism through which religious coping affects outcome in patients with cancer. However, there is evidence from non-cancer studies that perceived social support is correlated with various religious factors such as church attendance, church membership, subjective religiosity, religious affiliation [88], and even private religious practices such as prayer [89]. Indeed, perceived social support as well as hope and optimism were found to completely mediate the effect of positive religious coping on better adjustment in cardiac patients [90–92]. Other studies have found inconsistent results. For example, Koenig et al. [89] found that religious activity as a single construct was correlated with social support but was unrelated to depression in a sample of patients over the age of 65. In the same study, frequency of church attendance was negatively related to depression but was surprisingly unrelated to social support. Private prayer was, however, positively related to social support but unrelated to depression. In addition, Bosworth et al. [93] found that social support was related to lower levels of negative religious coping strategies (Brief RCOPE) in a geriatric sample, but negative religious coping was independently related to lower levels of depression. They also found that public religious practice was related to social support but independently related to lower levels of depression in the regression analyses once social support was controlled for.

There are cancer studies examining how religious/spiritual resources other than religious coping strategies are linked to outcome (e.g., religious involvement, strength of faith, or levels of religiosity/spirituality). For example, Sherman and Simonton [94] found that optimism played a mediating role in the relationship between general religious orientation and psychological adjustment in patients, but social support did not seem to play a comparable role. Sherman et al.

[94] found that strength of faith was related to optimism but not to social support. However, Carver et al. [58], using a generic measure of religious coping (the Brief COPE), found that religious coping in patients with breast cancer was not related to optimism at any time point of assessment. This suggests that how religiousness/spirituality is operationalized and measured determines how and whether it is significantly related to outcome.

Various religious coping strategies are also both positively and negatively related to nonreligious coping strategies such as active coping, suppressing competitive activities, planning, the use of social support [58], positive reinterpretation and growth [36], positive and negative appraisal of the cancer situation, distancing coping and focusing on the positive, seeking support, behavioral avoidance, cognitive avoidance, and focusing on the positive [77]. Qualitative work has also found a link between humor and spirituality [95]. Indeed, there is evidence that active coping mediates the link between religion/spirituality and functional well-being in patients with ovarian cancer [96] and between religious involvement and psychological distress in patients with HIV [97]. In addition, religious/spiritual beliefs have been shown to have a positive association with active rather than passive nonreligious coping strategies in cancer patients [98, 99], and those who have strong religious/spiritual beliefs are more likely to use cognitive reframing (i.e., focusing on the positive) as a coping strategy during cancer [100].

There is also evidence of a mediating role of nonreligious variables between religious coping and adjustment in patients with cancer [44, 101]. For example, Zwingman et al. [44] found a mediating effect of nonreligious coping between positive and negative religious coping and psychosocial well-being. They also found that negative religious coping moderated the effect of religious commitment and anxiety. The second study was conducted by my colleagues and I. We examined the role of various specific religious coping strategies on anxious and depressed mood [97]. Previous studies have tended to find negative religious coping, as measured by the Brief RCOPE, to be related to higher levels of anxious mood in patients with cancer [44, 47, 48, 83, 85]. As mentioned earlier, this 7-item sub-scale clusters together various negative religious coping strategies. It is therefore not known which negative religious coping strategy is responsible for this effect. We were indeed able to demonstrate which negative religious coping strategy was important in predicting anxiety in patients with breast cancer living in the UK and also how religious coping was related to this mood variable. First, it appeared that feeling punished and abandoned by God significantly explained 5% of the variance in higher levels of anxiety, but this effect was partially buffered by acceptance coping, reducing levels of distress. The effect of feeling punished and abandoned by God on anxiety was also partially mediated by denial coping, which was significantly associated with higher levels of anxiety. This suggests that a “negative” religious coping strategy can be associated with both higher and lower levels of anxious mood depending on which combination of nonreligious coping strategies is used and shows that religious coping may be related to outcome in more complex ways. Referring to it as a negative religious coping strategy could therefore be misleading in some instances. These findings also reject the usefulness of clustering questionnaire items based on a priori assumptions of which coping strategies are negative and which are positive.

Previous findings have also demonstrated that negative religious coping strategies are associated with higher levels of depressed mood in patients with cancer [44, 47, 48, 85]. However, as with anxiety, most previous studies have used the Brief RCOPE to examine negative religious coping in relation to depression. It is therefore currently not known which negative religious coping strategy is responsible for this effect. In our study, “feeling punished and abandoned by God” was an independent predictor of depressed mood explaining 4% of the variance. We also found that self-blame coping was the only nonreligious coping strategy to predict higher levels of depressed mood and was responsible for 5% of the variance. This demonstrates that religious coping was of equal importance to nonreligious coping in predicting depressed mood in patients with breast cancer in the UK. It is important to mention, however, that these analyses were cross-sectional, so we cannot infer causality at this stage. It is, for example, possible that depressed mood may cause people to appraise their situations within a negative religious framework.

We were unable to find a significant effect of positive religious coping on adjustment in patients with breast cancer. Similar and mixed results in cancer populations are seen elsewhere [44, 47, 85]. The reason for inconsistencies is not yet clear, and the presence or the absence of an effect may simply be due to difficulties in selecting the right outcome measure. Positive religious coping strategies may, for example, be more likely to be related to positive outcomes such as positive affect and life satisfaction. It is also worth mentioning that different patterns of religious coping and how these relate to various adjustment outcomes may be expected from different ethnic groups with different religious backgrounds. For example, the literal meaning of "Islam" means submission and peace which is found by accepting the will of God and accepting events that are outside of our control. For this reason, Islamic theology does not accept anger toward God as an acceptable response to suffering [102]. Currently, more research is needed to understand ethnic differences in relation to religious coping and psychological well-being.

In our studies, perceived social support did not play an important role in explaining how religious coping is associated with adjustment variables. Indeed, previous studies have found inconsistent evidence of social support as a mediator between religious/spiritual resources and adjustment. This inconsistency raises more questions than answers. There is some evidence that church attendance and seeking support from a priest/minister are more advantageous in some denominations. For example, there is evidence that it is beneficial for Evangelical women, but detrimental for Catholics, and that obtaining emotional support from church members is related to less distress in Evangelical women only [31]. Differentiating between the sources of perceived social support may be important as these sources may serve different support functions with different types of consequences. Perhaps a support measure needs to be more explicit regarding which type of support it is measuring, that is, specifically examine support from religious/spiritual communities. However, this is problematic in studies assessing support in a large proportion of individuals who simply do not belong to a religious community (e.g., a European sample). Future studies, especially in the USA, may nevertheless attempt to be more specific in terms of how they enquire about patients' perceived support and examine specific support from religious/spiritual communities using a measure designed specifically for this purpose [103].

Religious Coping and Growth

Until recently, research had largely focused on the negative consequences of a cancer diagnosis (e.g., negative mood) [104]. Indeed, many cancer patients experience clinical levels of distress and dysfunction including anxiety and depression, and some may even suffer from post-traumatic stress disorder [105, 106]. However, there is evidence that cancer should not be viewed as a stressor with uniformly negative outcomes but rather as a transitional event which may create the potential for both positive and negative change [107, 108]. Despite the stress of coping with a cancer diagnosis and dealing with often lengthy treatment protocols, many patients are able to find meaning in their illness such as experiencing profound positive changes in themselves, in their relationships, and in other life domains after cancer [109]. It is even suggested that finding meaning in a stressful event is critical for understanding illness adjustment [110].

Researchers have used a number of terms to describe individual reports of finding meaning in the face of adversity [111]. These include related concepts such as "benefit finding" [104, 112], "stress-related growth" [113], "post-traumatic growth" [114], and "gratitude" [115, 116]. Post-traumatic growth has been defined as "positive psychological change experienced as a result of the struggle with highly challenging life circumstances" [111]. Benefit finding has been described as "the pursuit for the silver lining of adversities" [104], while gratitude has been defined as "the willingness to recognize the unearned increment of value in one's experience" [117]. Although these concepts are similar and related to a large extent, gratitude is considered a broader concept while benefit finding, stress-related, and post-traumatic growth are seen as examining more specific aspects of growth and positive changes arising from a stressful event [118].

Finding meaning in the cancer experience in the form of positive benefits is a common occurrence [119]. There is also evidence that a higher level of faith/religiousness is linked to greater levels of perceived cancer-related growth and benefit finding [114, 120, 121]. However, very few studies have examined the link between religious coping and growth/benefit finding in patients with cancer although some have provided some insight using the Brief COPE. For example, studies have found that patients with breast cancer scoring high on religious coping also scored high on growth [122, 123], and religious coping pre-surgery has also been found to predict higher levels of growth 12 months later in patients with prostate cancer [124]. My colleagues and I, however, addressed which aspects of religious coping may facilitate growth. We used a prospective study examining the effects of religious/spiritual coping resources on benefit finding in breast cancer along with other potentially influencing variables such as nonreligious coping, optimism, and social support [125]. We found that religious coping to achieve a life transformation predicted 14% of the variance but was partially mediated by strength of faith. Strength of faith at surgery on the other hand was an independent predictor of benefit finding 3 months later, predicting 6% of the variance. Seeking emotional support coping at surgery was the only nonreligious variable to predict outcome, explaining 3% of the variance in higher levels of benefit finding 3 months later. Our results show that religious coping was far better than nonreligious coping or indeed, other psychological variables, in predicting a positive outcome such as benefit finding. Again, this study highlights the importance of examining religious/spiritual resources in combination with other variables to fully understand their relationship to adjustment in cancer.

Addressing Cancer Patients' Spiritual Needs

Assessing the psychological needs of patients with cancer has become commonplace in clinical practice in recent years. Also, as a result of studies showing social support to be important in the adjustment process, providing support groups for those patients lacking in support is also widespread. Addressing patients' spiritual concerns is also, in relative terms, commonplace within palliative care, but, as research shows, spiritual concerns can occur at any time during the cancer course. However, how and whether religious/spiritual concerns should be addressed in patients with serious illness has been much debated [126, 127]. Indeed, some academics/physicians believe that there is no place for religion/spirituality within medicine [127, 128]. Then again, critics often fail to differentiate between subjective religiousness/spirituality studies (e.g., spiritual beliefs and behaviors) and those of an objective approach examining, for example, the effect of intercessory prayer on recovery where patients in the experimental group are usually not aware they are being prayed for. Intercessory prayer studies do not examine the effect of patients' own cognitions and behaviors in relation to outcome such as psychological well-being or quality of life but attempt to test the existence of God through the power of prayer. These studies are therefore not psychological in nature; rather they belong within the theological realm. A psychological study assesses the effect of patients' own *subjective* beliefs, perceptions, and behaviors on outcome. Often, these two types of studies are discussed together as if they were, in some way, comparable. It should be mentioned, however, that the effect of intercessory prayer can be important if, during a difficult time, a person is aware of others praying for him or her, as it can instill a sense of comfort from communal caring, and may reinforce a sense of belonging and personal worth in relation to significant others [129]. In addition, when critics discuss patients' subjective religious/spiritual beliefs and practices in relation to health as being problematic, the focus tends to be on the efficacy of religious/spiritual practices such as prayer in assisting with the physical recovery from disease. Prayer in this case is a form of alternative therapy, where it is used as a substitute for conventional medicine. In this instance, religion/spirituality may have severe implications for recovery [128]. If there is evidence of a conflict between religious beliefs and recommended treatments, the National Comprehensive Cancer Network's (NCCN) clinical practice guidelines in oncology—distress management [130]—describe how to deal with this issue. Indeed, Koenig [131] argues that if religious/spiritual resources serve to influence medical decision-making in powerful, negative ways, these need to be understood.

It is suggested that an understanding of patients' religious/spiritual foundation can guide appropriate care [132]. If religious coping turns out to be helpful or even harmful to patients, it may be beneficial for healthcare professionals to acknowledge and support patients' spirituality or religious leanings [133]. For example, patients who perceive their illness as a punishment may become unable to use their faith as a coping resource. God may be seen as weak, distant, or uncaring which may lead to an existential crisis. Plotnikoff [134] has provided a few specific examples of spiritual struggles and their implications: (1) spiritual alienation ("Where is God when I need him most? Why isn't God listening?"); (2) spiritual anxiety ("Will I ever be forgiven? Am I going to die a horrible death?"); (3) spiritual guilt ("I deserve this. I am being punished by God. I didn't pray often enough."); (4) spiritual anger ("I'm angry at God. I blame God for this. I hate God."); (5) spiritual loss ("I feel empty. I don't care anymore."); and (6) spiritual despair ("There is no way God could ever care for me."). However, deciding how to best respond to a patients' spiritual needs can raise professional and ethical issues for healthcare professionals about how they interact and deal with patients [126]. For example, should health professionals really discuss spiritual issues with patients and do patients want them to? If so, who is best placed to do this and what should the professional boundaries be between healthcare professionals and chaplains?

There is some evidence suggesting that addressing spiritual concerns with a physician appears to have a positive impact on perception of care and well-being in patients with cancer [135, 136] and may enhance recovery from illness [137] and improve quality of life [138–140]. Further, 65% of non-cancer patients in a US pulmonary outpatient clinic said that if physicians enquired about spiritual beliefs, it would strengthen their trust in their physician [141]. Therefore, having clinical respect for patients' spirituality as an important resource for coping with illness is important. In the USA, between 58% and 77% of hospitalized patients want physicians to consider their spiritual needs [142, 143]. Further, 94% of patients want their physicians to ask about their religious/spiritual beliefs if they become gravely ill [141], and 45% of patients who did not have religious/spiritual beliefs still felt it appropriate that physicians should ask about them [144]. However, Koenig et al. [145] also found that up to one-third of the US patients do not want physicians to discuss spiritual issues with them. Therefore, physicians (or other healthcare professionals such as a nurse) may initially explore patients' general coping methods in order to discover whether their religious/spiritual beliefs play an important role in their medical decisions.

Most studies examining religious/spiritual needs in patients with medical illnesses have been conducted in the USA. There is some evidence from a German study that the majority of patients who were asked wanted their doctor to be interested in their spiritual orientation [146]. The proportion of patients in other European countries who want their spiritual needs assessed and how these issues should be addressed and by whom is unclear. However, a recent systematic review of the European literature exploring spiritual care within palliative care in general found positive effects of spiritual care, yet the empirical evidence for its efficacy remains low [147].

Spiritual Needs Assessments

A spiritual assessment may contain numerous questions about religious denomination, beliefs or life philosophies, important spiritual practices or rituals, the use of spirituality or religion as a source of strength, being part of a faith community of support, the use of prayer or meditation, loss of faith, conflicts between spiritual or religious beliefs and cancer treatments, ways that healthcare providers and caregivers may help with the patient's spiritual needs, concerns about death, and the afterlife and end-of-life planning [148]. There are several tools in existence that attempt to address patients' spiritual needs (see Table 8.3). These have been developed mainly by the US researchers and provide guidelines on how to conduct a spiritual history. The earliest is the Kuhn's Spiritual Inventory [149]. This brief assessment tool enquires about religious/spiritual beliefs, how illness has influenced beliefs, how patients exercise their beliefs in their lives, and how faith has influenced their behavior during illness and regaining health. Further, Matthew and Clark [150] suggest that physicians should ask about three fundamental questions as part of the initial evaluation. Their assessment tool—the Matthew's Spiritual History—examines the importance of spirituality to the patient, how this influences the way they look at their medical problem/think about health, and whether they would like the physician to address these issues. A similar tool is the FICA Spiritual Assessment Tool [151] which, again, addresses patients' religious/spiritual traditions, the importance of faith, how it is practiced, how it is applied to health and illness, and how these should be addressed. Another much more thorough instrument is the Maugans's SPIRITual History [152]. This covers six areas (SPIRIT): the *s*piritual belief system (e.g., affiliation), *p*ersonal spirituality (includes accept-

Table 8.3 Instruments providing guidelines on how to take a spiritual history, thereby addressing patients' spiritual needs

Authors	Measures	Description
Kuhn [149]	Kuhn's Spiritual Inventory	Meaning, purpose, belief, faith, love, forgiveness, prayer
Matthews and Clark [150]	Matthew's Spiritual History	Importance and influence of religious beliefs and practices and desire of physician addressing these
Puchalski [151]	FICA Spiritual Assessment	FICA: F, faith – what tradition; I, importance of faith; C, church – public religious practices; A, apply – how these apply to health and illness; and A, address – how these should be addressed
Maugans [152]	Maugans's SPIRITual	Includes six areas (SPIRIT): the spiritual belief system, personal spirituality, integration within a spiritual community, ritualized practices and restrictions, implications for medical care, and terminal event planning
Anandarajah and Light [154]	HOPE Questionnaire	Source of hope, meaning and comfort, organized religion, personal spirituality and practices, the effect of these on medical care and illness, and how these should be addressed
Lo et al. [155]	ACP Spiritual History	Includes four questions: The importance of faith, when and for how long, availability of someone to talk to about religious/spiritual matters, and whether the patient wants to explore issues with someone
Frick et al. [146]	SPIR	A semi-structured interview assessing 4 main areas: belief/spirituality/religiosity of patients; the place of spirituality in patient's life; integration into a spiritual community; preference of the role of healthcare professionals in dealing with spirituality
Büssing et al. [157]	Spiritual Needs Questionnaire (SpNQ)	19 items assessing religious needs (e.g., praying), inner peace, existential (reflection/meaning), and actively giving
van Bruggen et al. [158]	Existential Concerns Questionnaire (ECQ)	22 items measuring death anxiety, intolerance of uncertainty, neuroticism, distress, meaning, life events
Exline et al. [45]	The Religious and Spiritual Struggles Scale	26 items examining 6 domains of struggle: divine, demonic, interpersonal, moral, doubt, ultimate meaning

ability of beliefs and practices), *i*ntegration within a spiritual community, *r*itualized practices and restrictions, *i*mplications for medical care, and *t*erminal events planning. This is probably the most comprehensive tool to date covering the most important areas of spiritual needs [153]. Equally, the HOPE questionnaire [154] also examines a broad range of issues considered important in medical illness and decision-making: source of hope, meaning and comfort, organized religion (e.g., being a member of a religious community), personal spirituality and practices, the effect of these on medical care and illness, and how they should be addressed. Finally, the ACP Spiritual History tool [155] asks patients with a serious medical illness four simple questions: the importance of faith during their illness, the importance of faith at other times of their lives, the availability of someone to talk to about religious matters, and their need to explore religious matters with someone. This assessment is patient centered and brief. However, it fails to gather information in several key areas such as identifying spiritual needs, connection with religious/spiritual communities, and beliefs affecting medical decision-making. It was also developed for patients in a palliative care setting only.

It is important to reiterate that these tools were developed in the USA, and it is therefore not currently known to what degree these questions would be perceived as acceptable in the hospital environments of other countries and cultures. Indeed, the crisis of religious institutions is more noticeable in Western Europe than in the USA [146] where Davie et al. [156] have described the phenomenon of "believing without belonging." This means that religious/spiritual beliefs become increasingly personal, detached, and heterogeneous in nature, and this must be taken into account when patients' religiousness/spirituality is assessed in a European context [146]. However, two European (German) assessments exist: the SPIR, a semi-structured spiritual needs interview guide [146] that examines four main areas of patients' spiritual needs and how patients would describe themselves (e.g., a believer/religious/ spiritual), the place of spirituality in their lives, whether they are integrated into a spiritual community and the role they would like to assign their healthcare professional in the domain of spirituality.

The second is the Spiritual Needs Questionnaire [157] which is suited to both secular and religious societies and attempts to address four aspects of cancer patients' spiritual needs: the religious (e.g., praying with others or by themselves), inner peace (e.g., a need to find peace or dwell in a quiet place), existential (e.g., reflections about a previous life or the need to talk with someone about the meaning of life), and actively giving (e.g., to give away something of yourself). There is currently no data to assess its general usefulness. It is also important to appreciate that, after a cancer diagnosis, a nonreligious/spiritual person may, for example, interpret concepts such as finding meaning and purpose in existential or humanistic terms, while a religious/spiritual person would view the same construct as religious or spiritual in nature [157]. Nonreligious cancer patients may therefore have similar needs to religious/spiritual patients but may not label these as such. This may be especially prevalent in European cancer patients. Indeed, examining patient's existential needs may be more appropriate for such a sample. Existential anxiety (EA) is a construct that refers to fears that are provoked by core threats of human existence, such as death, meaninglessness, and fundamental loneliness [158]. Existential distress may be confined to distress that arises when the meaning and value of one's life is unclear and is comorbid with feelings of loneliness and low self-worth [159]. There is evidence that adult patients with cancer across all stages and types benefit from existential interventions [160]. Indeed, the most recent US NCCN guidelines [130] recommend the use of the Existential Concerns Questionnaire (ECQ) [158] in such instances.

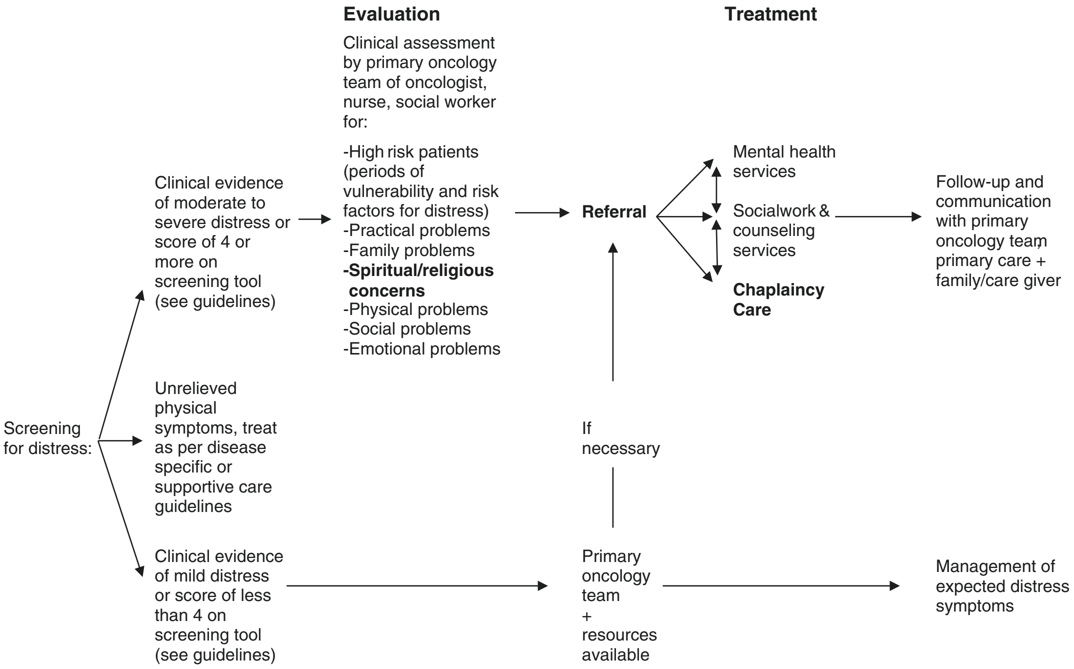
Finally, the most recent NCCN guidelines [130] also recommend the use of the Religious and Spiritual Struggles Scale [45] to examine patient's spiritual needs. As mentioned earlier in this chapter, this 26-item scale measures spiritual struggles only, and it is currently not known how these items generalize to other non-US cultures nor do we know how well its six domains are suitable for different religious traditions. It also does not inform about patient's religious/spiritual affiliation and history—past and present. It should therefore probably be viewed as an additional complimentary measure unless spiritual struggles are of interest only.

Spiritual Distress Management

It is suggested that negative events are easier to bear when understood within a benevolent religious framework. Indeed, the current findings show that positive aspects of religious coping may be related to better adjustment. Therefore, religious counselors, that is, hospital chaplains, can help by reframing negative events within the will of a loving and compassionate God and help patients (who show evidence of religious struggles) to utilize more effective religious coping methods. It has been suggested that this can help individuals to maintain a theologically sound understanding of suffering and to experience better mental health outcomes in terms of their psychological adjustment in the face of stressful events [134]. The UK National Institute for Clinical Excellence (NICE) guidelines on spiritual support services in cancer care [161] state that provider organizations should adhere to the framework of best practice in meeting the religious and spiritual needs of patients and staff outlined in the UK's NHS Chaplaincy Guidelines [162]. For example, on (or before) admission to hospital, patients should be asked whether they would like to have their religious affiliation recorded. They should be informed that this data will be processed for one or more specified purposes. Patients should be asked for permission to pass this information on to the chaplaincy service for the purposes of spiritual care. A staff member, usually a healthcare chaplain/spiritual caregiver, should be nominated to be responsible for liaising with local faith leaders. In addition, while recognizing that one individual may hold specific responsibility for ensuring the provision of spiritual care, this should also be seen as the responsibility of the whole team. Further, individual team members responsible for offering spiritual care should contribute to the team's regular review of care plans, especially for those patients with already identified spiritual needs. These guidelines also state that chaplaincy services should be available in the primary, secondary, and palliative care setting as well as in the community (e.g., home visits) and highlights the importance of including all religious and spiritual beliefs including those without.

In the USA, the NCCN's Clinical Practice Guidelines in Oncology—distress management [130]—also include very clear guidelines on how to manage spiritual distress. The initial evaluation process describes various pathways for screening for distress: the evaluations process, through to referral, treatment, and follow-up. For example, during the evaluation process, any indication of spiritual/religious concerns must be noted, and appropriate referrals made to pastoral services. However, their screening tool for measuring religious/spiritual distress asks only one very basic question, "Please indicate if any of the following has been a problem for you in the past week including today" followed by a yes/no answer for religious/spiritual concerns. Therefore, a more thorough tool (if time allows), such as those mentioned earlier in this chapter, may be implemented after the initial assessment. These assessments should also include a thorough exploration of patients' coping strategies.

Evidence described in this chapter shows that cancer patients' spiritual needs may vary depending on how their situation is appraised. For example, support from their religious community may be more important early on in the illness course while religious/spiritual struggles, although more prevalent in some cancers early on, may resurface much later when healthcare professionals are no longer involved in their patients' care to the same degree. This suggests that interventions should, overall, target patients early but that healthcare professionals should also be aware of the potential resurfacing of some religious struggles later on in the illness trajectory and that these need to be reexamined and addressed at regular intervals.



Barriers to Spiritual Needs' Assessment and Management

Addressing religious/spiritual concerns is not commonplace despite the US NCCN's [130] Clinical Practice Guidelines in Oncology and the UK NICE Guidelines [161] stating the importance of supporting patients' spiritual needs during the course of cancer. The UK Clinical Standards for Working in a Breast Speciality [163] further highlights the importance of understanding psychological risk factors associated with morbidity during breast cancer by understanding a variety of helpful or unhelpful coping strategies, being aware of spiritual conflicts, providing patients with appropriate emotional support and offering intervention strategies, for example, advice regarding coping strategies or referral to other agencies. However, a US study found that as many as 72% of patients with advanced cancer said that their spiritual needs were either minimally met or not met at all by the medical system and 47% said that they were supported minimally or not at all by their religious community [138]. However, healthcare professionals have expressed concern about lack of time, lack of skills (e.g., not knowing how to take a spiritual history), and the appropriateness of such discussions within the context of the medical encounter [143, 164, 165]. Indeed, in the USA, physicians' discomfort at addressing spiritual needs is the best predictor of whether these discussions take place or not [164]. It is also well established that religiosity/spirituality and a belief in God are much lower among physicians, healthcare professionals, and academics compared with their patients or with the general population [8, 166–173]. In the UK, around 70% of people have some belief in God [50]. However, a study examining religiosity among 230 psychiatrists working in London teaching hospitals found that only 27% reported a religious affiliation and 23% reported a belief in God [174]. Another study assessing religious faith in healthcare professionals at a London teaching hospital found that 45% of hospital staff reported that they had a religious faith [175].

There is also a higher level of atheism among physicians. Neeleman and King [174], for example, found that 25% of doctors reported that they were atheists compared to only 9.5% of their patients. Also, Silvestri et al. [176] found that cancer patients and their caregivers ranked doctor recommendations as most important followed by faith in God second, whereas physicians placed faith in God last. These lower levels of religiosity/spirituality and higher levels of atheism may lead healthcare professionals to underestimate the importance of faith for their patients and may also explain the lack of mainstream research in the area until recently. Indeed, physicians who report addressing patients' spiritual concerns do so because of their own spirituality and because of an awareness of the scientific evidence associated with spirituality and health. Empirical findings do suggest that barriers to spiritual assessment include upbringing and culture, lack of spiritual inclination or awareness, resistance to exposing personal beliefs, and the belief that spiritual discussion will not have an impact on patients and their lives [177–179]. It has also been suggested that faith may be a very personal matter for physicians due to the potential stigma associated with admitting being spiritual/religious [180]. Klitzman and Daya [180], using a qualitative methodology, examined spirituality in doctors who themselves had become seriously ill and found that they too had beliefs that ranged from being spiritual to start with; to being spiritual, but not thinking of themselves as such; and to wanting, but being unable to believe. Some continued to doubt. The contents of beliefs ranged from established religious traditions to mixing beliefs, or having nonspecific beliefs (e.g., concerning the power of nature). One group of doctors felt wary of organized religion, which could prove an obstacle to belief. Others felt that symptoms could be reduced through prayer. Unfortunately, there is no comparison data available for non-physicians suffering from a similar condition. However, understanding spiritual-cultural influences on health-related behaviors, and illness adjustment is essential if healthcare professionals are to provide effective care to their patients. Overcoming barriers is therefore important as it would allow a more accepting and open discussion about patients' lives beyond the social and the psychological. Nevertheless, many physicians still practice under the biomedical model where spiritual matters may seem less relevant [137].

There are also some practical problems in meeting patients' spiritual needs. For religious/spiritual counseling to take place, someone needs to identify patients with spiritual concerns in order to refer those who struggle with their faith to a degree that it is detrimental to well-being. Current UK guidelines [162] view hospital chaplaincy as central to this role. However, despite recommendations, chaplains may not be available in smaller hospitals or in outpatient clinics where most care is delivered, especially early in the cancer course where religious/spiritual issues may first arise [148]. In addition, patients struggling with their faith may not want to speak to hospital chaplains as they may feel alienated from religion and anyone associated with it [153]. Also, patients' spiritual concerns may not be "religious" in nature (in terms of organized beliefs and practices) but may take the form of existential and philosophical issues [181]. Therefore, having an intermediary trained to assess and deal with spiritual/existential issues may be more appropriate in the first instance. However, should more complex spiritual needs arise, or should patients wish to speak to religious/spiritual counselors, appropriate and agreed referrals could be made. In a country such as the UK, it may be more appropriate for a senior specialist oncology nurse (e.g., a breast care nurse) to deal with spiritual needs as these healthcare professionals are already trained to assess and address patient's psychological and social needs. Indeed, if patients who have turned away from institutional religion would prefer to talk to a healthcare professional about their spiritual needs rather than a trained and certified chaplain or pastoral counselor, there is a genuine need to provide adequate education and training to allow these professionals to competently address and uncover spiritual needs within this patient group [157].

Conclusions and Future Directions

The focus of this chapter has been on religious coping, its nature, measurement, prevalence, and how it relates to adjustment in cancer. The use of religiosity and spirituality in coping is indeed common in cancer patients throughout the illness course and not just in the USA but also in European cultures where the abandonment of organized religious institutions is much more prevalent. It is also increasingly clear that it plays an important role in illness adjustment, especially the use of negative religious coping strategies. With increasing evidence of its importance, there is an argument for introducing appropriate spiritual need interventions within oncology clinics. Indeed, addressing the psychosocial needs of patients with cancer has become routine in clinical practice in recent years. However, addressing religious/spiritual concerns is not commonplace despite recommendations. Barriers to why this may be the case should be highlighted and overcome and training is needed to allow healthcare professionals to have confidence in their ability to assess and address cancer patients' spiritual needs within clinical practice. There is also a need to develop and test spiritual needs interventions tailored to suit the environment in which they will be implemented. Few such interventions currently exist (but see Kristeller et al. [135]).

The relationship between religious coping and adjustment in cancer is complex [182]. Future studies should examine the mechanism through which various religious coping strategies operate on outcome by examining individual religious coping strategies rather than clusters of coping that has a priori assumptions of what is adaptive or maladaptive. Indeed, much more work is needed examining specific religious coping strategies and how these are linked to various outcomes by examining mediating/moderating relationships using longitudinal designs; studies should examine psychosocial variables in relation to religious/spiritual variables and cancer adjustment and should further explore the relationships between religious coping and positive outcomes. This may provide a clearer understanding of the importance of various religious coping strategies and to which outcome they are related to.

Although there is some evidence that religious coping is more often tied to psychosocial functioning than physical functioning in patients with cancer [94], other studies have found that negative religious coping (using the Brief RCOPE), after controlling for demographic and medical variables, is associated with significantly higher levels of pain and fatigue [47]. Future studies may like to examine the link between religious coping and physical functioning further and in a more thorough manner. In addition, very little is known about differences in religious coping across cancer stages and cancer types. There are also few studies available informing us about differences in religious coping across ethnic groups, different religious traditions, and religious affiliations and how these variables impact on illness adjustment.

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9

Psychoneuroimmunology and Cancer: Mechanisms Explaining Incidence, Progression, and Quality-of-Life Difficulties

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Introduction

Psychological correlates of cancer incidence, progression, and quality-of-life difficulties have been well-documented in the literature; however, recent developments in psychoneuroimmunology (PNI) may provide further confirmation for the relationship between psychological factors and cancer. In this chapter, we review the current literature on how psychosocial factors (e.g., depression, marital support) and physiological processes (e.g., glucocorticoids) impact cancer incidence and progression. We then explore cutting-edge research on the biological mechanisms (e.g., bioenergetic health) that may explain quality-of-life difficulties among cancer survivors. Finally, we review studies that use biomarkers (e.g., pro-inflammatory cytokines) to evaluate the effectiveness of psychosocial intervention strategies.

Psychosocial Associations with Cancer Incidence and Progression

Abnormal levels of psychosocial stress can indicate a variety of health problems [1], including cancer. Cancer patients are more likely to meet clinical criteria for major depressive disorder and/or an anxiety disorder (e.g., generalized anxiety disorder) than the general population [2]. Evidence suggests that such disorders play a causal role in cancer incidence and the likelihood of mortality [3]. Indeed, a recent meta-analysis including more than 2.5 million participants in cohort studies indicated that those with a clinical diagnosis of depression and/or anxiety experienced higher cancer incidence and cancer-specific mortality than those who did not have a clinical diagnosis [4]. Subclinical levels of depression and anxiety were not associated with cancer incidence; however, greater subclinical depression and anxiety were associated with poorer survival and higher cancer-specific mortality [4]. Therefore, clinical levels of depression and anxiety appear to be significant at all stages of cancer incidence and progression, while subclinical levels may be associated with survival and mortality.

Health behaviors are thought to partially explain the association between clinical depression and/or anxiety and cancer incidence and

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progression. For instance, individuals with depression and anxiety are more likely to be sedentary [5], drink excessive alcohol and/or smoke cigarettes [6, 7], meet criteria for being overweight/obese [8], and have poor diet quality [9]. Each of these health behaviors is associated with increased cancer incidence and mortality [10–13]. Moreover, individuals with clinical depression and/or anxiety are less likely to attend scheduled medical appointments or adhere to their treatment regimen [14], behaviors that further enhance risk for poor outcomes.

In addition to individual-level risk factors, interpersonal psychosocial dynamics have also been linked with cancer incidence, survival, and mortality. For instance, low social support is associated with colorectal incidence and mortality [15]. Those who are in a marital relationship have routinely been found to have better cancer survival across a variety of cancer types [16–18]. Yet, the quality of an individual's social support is also important. For example, greater marital distress is associated with poorer health and reduced physical activity among breast cancer survivors [19]. Furthermore, cancer patients who self-report poor satisfaction levels with the social support they are receiving have greater mortality risk than those who report better social support satisfaction [20, 21]. Therefore, both the nature and quality of interpersonal relationships appear to be important at all stages of cancer initiation and progression.

Although considerable evidence exists in support of associations between stress-related psychosocial factors and cancer incidence and progression, evidence both for and against specific associations (e.g., post-traumatic stress disorder and cancer initiation) is common [22, 23]. This is not necessarily surprising given the large number of factors that have been identified as being both protective against and causative agents of cancer [24]. Evaluating biologically plausible mechanisms underlying associations between psychosocial factors and cancer is important for understanding cancer risk.

Stress and Cancer Progression

One potential explanation for stress leading to increased risk of cancer is through dysregulation of the immune system. Stress is both a psychological experience and a biological response to danger. Momentary bursts of stress hormones during fight or flight responses have been critical to our survival as a species, and acute stress has been shown to enhance the immune response and protect against disease [25]. However, sustained psychological stress can lead to potentially damaging cycles of immune dysfunction [26].

Certain tumors are more impacted by stress-induced immune dysregulation. These tumors are "highly immunogenic" or more recognizable to the body's immune system than others [27]. Adults with basal cell carcinoma (BCC), a highly immunogenic tumor, who were maltreated as children and experienced significant life stressors in the previous year showed a poorer immune response to the BCC tumor than others [28]. Ovarian tumors, another highly immunogenic tumor, are also highly impacted by psychological processes such as social support, depression, and stress [29, 30]. In this section, we will look at two types of stress hormones, glucocorticoids and catecholamines, which can impact cancer incidence and progression.

Glucocorticoids

The cellular immune system can be dysregulated by excessive cortisol production, a stress hormone produced by the neuroendocrine system [31]. Cortisol, a type of glucocorticoid that is released in humans, is immunosuppressive, which can impact cell-mediated immunity [32]. Indeed, a robust T-cell response is critical when neutralizing abnormal cells that display atypical major histocompatibility complex markers, such as those seen in tumors [33]. Intentional pharmacological immunosuppression with glucocorticoids has been shown to result in higher cancer incidence [26]. Thus, patients with high levels of cortisol due to stress may be at an increased risk for cancer. Though cortisol is immunosuppressive, chronic exposure to cortisol desensitizes the receptors on immune cells that cortisol binds to; thus, immune cells produce inflammatory cytokines in an unregulated environment, leading to a chronic inflammatory state [34]. Chronic low-grade inflammation has been linked to all stages of tumor progression from incidence, survival to metastasis [35].

Catecholamines

Catecholamines, which are produced by the sympathetic nervous system, are another class of stress hormones that have been implicated in cancer research because of their chemotactic properties [36]. Catecholamines appear to stimulate cancer cell migration [37]. Thus, excess catecholamines due to stress may increase risk for metastasis (i.e., the spread of cancer from the original site to another place in the body). Organs that are central hubs for catecholamines, such as the brain and adrenal gland, are common sites of metastases [38]. Additionally, upregulation of adrenergic receptors, a class of receptors targeting catecholamines, has been associated with tumor progression and metastasis [39]. This has been demonstrated in prostate, lung, pancreatic, melanoma, and breast cancer. Adrenergic receptors also boost tumor formation and characterize tumors that are more likely to grow and spread (i.e., tumors that are "graded high") [40].

Biological Mechanisms of Quality-of-Life Issues Among Cancer Survivors

For the nearly 17 million cancer survivors in the United States, persistent symptoms posttreatment are common [41]. For example, one in four cancer survivors will experience distressing physical symptoms such as fatigue, pain, poor sleep, and an inability to complete activities of daily living (ADLs) after treatment [42–44]. Additionally, one in ten survivors reports persistent mental and psychological problems such as poor memory, depression, anxiety, or negative body image [45, 46]. These symptoms can last for years after the patient has recovered from cancer [47]. Notably, such quality-of-life issues have not been reliably associated with the type (i.e., breast, prostate, lung, etc.), stage (0 − IV), or severity of cancer, nor the dose, regimen, or length of treatment [44, 48–50]. Maladaptive biological responses to cancer and its treatment such as chronic low-grade inflammation and mitochondrial dysfunction may be responsible for unpleasant symptoms that ultimately inhibit healthy behaviors (e.g., adequate diet, exercise, and sleep) that could help reduce symptom severity [47, 51–56].

Chronic Inflammation

Inflammation is typically a self-limiting process [54]. During an acute infection, the body releases signaling molecules called pro-inflammatory cytokines (i.e., IL-6, IL-8, TNFα, IL-12) to attack pathogens and foreign bodies. After the threat is addressed, anti-inflammatory cytokines (i.e., IL-10, IL-19, and IL-20) are released to de-escalate the response and return the body to homeostasis [53]. The body can become desensitized to high levels of pro-inflammatory cytokines, fail to release anti-inflammatory cytokines in response to inflammatory cytokines, and ultimately sustain unproductive pro-inflammatory cascades long after recovery [53, 57, 58]. Chronic inflammation has been widely studied as an underlying mechanism of illness [59]. High levels of inflammation have been found in symptomatic cancer survivors. Compared to their peers who have never had cancer, survivors demonstrate more inflammation and poorer cognitive performance even 20 years after their final chemotherapy treatment [60]. Such quality-of-life difficulties have been shown to be more frequent in breast cancer patients with a history of adverse childhood experiences [61], which is a known predictor of immune dysregulation. In mice, enduring inflammation and elevated anxiety behaviors are associated with cancer survivorship problems, suggesting long-term physical and psychological consequences may be a more expected outcome after cancer remission than once thought [62].

Pathways from Chronic Inflammation to Fatigue

Prolonged inflammation is believed to contribute to cachexia, a severe form of muscle wasting and fatigue seen in cancer patients [63]. Pro-inflammatory cytokines can stimulate the central nervous system (CNS) and trigger the hypothalamic-pituitary-adrenal (HPA) axis to initiate catabolism of adipose and muscle tissue [53]. To further reduce muscle integrity, inflammatory cytokines such as IL-6 and IL-1β may limit protein synthesis and induce protein degradation [53]. Other cytokines (e.g., tumor necrosis factor-alpha [TNF-ɑ]) act directly on muscle tissue to reduce specific force [64], which may contribute to feelings of weakness. Cancer growth can also lead to low interleukin-15 (IL-15) levels, the cytokine responsible for regulating skeletal muscle tissue transcription and cachexia in mice [65]. Interestingly, mice that received an intracerebroventricular (ICV) injection of pro-inflammatory cytokines demonstrated anorexia, lethargy, and catabolism of tissue, suggesting that increased inflammatory cytokines may induce fatigue and muscle atrophy [53]. Additionally, cancer-induced inflammatory activity can require an additional 100–200 kcal expenditure per day [64], a substantial metabolic demand [66], potentially one that results in weakness. Therefore, chronic inflammation may lead to fatigue, one of the most distressing symptoms among cancer survivors, via deterioration of skeletal muscle tissue and increased cellular energy demands.

The Role of Cellular Bioenergetic Health in Post-cancer Symptoms

Mitochondria are responsible for cell survival through adenosine triphosphate (ATP; i.e., cellular energy) production and cell death via critical signaling mechanisms [67]. Cancer cells utilize altered versions of these mechanisms to proliferate and evade apoptosis, or programmed cell death [67]. Thus, treatments often target mitochondria to reduce the bioenergetic health of cancer cells [68]. Unfortunately, anticancer therapeutics can inadvertently damage healthy tissue [69]. Long-term damage to healthy cells may lead to decreased cellular energy output [70]. Evidence suggests reduced cellular energy due to cancer treatment is associated with symptoms of fatigue [52].

Therapeutic Impacts on Mitochondria

In healthy cells, mitochondria produce 90% of all cellular energy in a process called oxidative phosphorylation, wherein mitochondria convert glucose from food into usable compounds called ATP [71]. Oxidative phosphorylation and glycolysis are two mechanisms used to produce ATP [72]. The availability of oxygen, inflammation, and momentary energy requirements are important cues that determine which process the cell will utilize [73]. While glycolysis is faster than oxidative phosphorylation and helpful for addressing excess energy demands (e.g., during exercise), it results in the production of 2 ATP per molecule of glucose [72]. When compared to oxidative phosphorylation, which yields 36 ATP per molecule of glucose, glycolysis is an inefficient process [74]. ATP is needed for cognition, muscle contraction, cell maintenance, cellular communication, and protein synthesis [75]. Insufficient ATP production is associated with physical disability and symptoms of fatigue and muscle weakness [76, 77].

Mitochondria are particularly sensitive to inflammatory signals in the peripheral nervous system [52]. In response to signs of immune activity, mitochondria release unstable free radicals called reactive oxygen species (ROS). ROS are used to “sound the alarm” and recruit white blood cells to help attack invaders [78]. However, if the inflammation persists, as it often does in cancer patients, excess ROS will ironically lead to mitochondrial DNA and protein degradation [68], making inflammation reduction more difficult [79]. Chemotherapy can increase inflammation and ROS, which can reduce the efficacy of the mitochondrial electron transport [80]. For instance, the chemotherapy drug doxorubicin appears to impair mitochondria in the hippocampus and interfere with mitochondrial respiration in both skeletal and cardiac muscles [70, 81]. Cisplatin, another form of chemotherapy, can cross the blood-brain barrier and reduce spare mitochondrial capacity [82]. Spare mitochondrial capacity is thought to demonstrate how well cells can meet increased energy demands during exertion or stress [83]. Reductions in spare mitochondrial capacity in the brain have been observed in Alzheimer's patients [83], as well as cancer patients with cognitive deficits [82]. Indeed, higher-level cognition requires a lot of energy, and limited ATP production may contribute to feelings of "cancer brain" or brain fog, as both cancer and brain cells fight for resources [84].

Hyperglycemia

Recent research also suggests that tumors are capable of reprogramming hepatic glucose management to prioritize tumor growth [85]. This means that cancer patients may struggle to compensate during exertion because their tumor has suppressed gluconeogenesis in the liver [56]. Humans typically store about a day's worth of glucose in glycogen molecules and a week's worth of glucose in the liver and adipose tissue [72]. These glycogen molecules can be converted to ATP. Cancer growth alone can dysregulate this delicate system by siphoning glucose away from healthy cells and reducing available glycogen [61, 86]. However, glucose management may be permanently altered in some cancer survivors. Chronic inflammation can interfere with the liver's ability to regulate glucose as glucose-sensitive neurons in the hypothalamus create a response loop that impacts hepatic gluconeogenesis and results in hyperglycemia [56]. Hypometabolism of glucose in the basal ganglia and frontal cortex has also been associated with cancer-related fatigue [53]. In the 1960s, researchers discovered glucose-sensing neurons in the hypothalamus [87]. These neurons are sensitive to cancer-induced alterations in glucose availability [56]. Glucose-sensing neurons in the brainstem and hypothalamus can influence sleeping and eating behaviors and physiologically increase hepatic gluconeogenesis [56]. Neurons flooded with glucose may make it difficult for patients to practice some of the most critical healthful behaviors needed to improve posttreatment symptoms [55, 56]. Commonly recommended behaviors such as maintaining a consistent sleep schedule, following a healthy diet, exercising, and living a low-stress life may be physiologically difficult for cancer survivors because of these changes in the brain [88, 89]. Altered feeding behaviors may potentially limit caloric intake necessary for proper mitochondrial function, and disturbed sleep schedules may increase inflammation and fatigue [56]. These behaviors may perpetuate a cycle of inflammation and mitochondrial dysfunction in cancer survivors for decades.

A major limitation within posttreatment quality-of-life literature is that many of the negative symptoms that are most often studied (e.g., depression, anxiety, fatigue) are strongly interrelated. It is still unknown whether symptoms like fatigue and depression increase cellular dysfunction, cellular alterations cause post-cancer symptoms, or if they interact in a bidirectional manner. Determining the biological mechanisms uniquely related to depression or fatigue may be difficult as the presence of either symptom doubles one's risk of having the other [102]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), lack of energy is a symptom of major depressive disorder [103]. To study one symptom independent of all others may be difficult; however, it is important to recognize the interrelated mechanisms behind symptoms such as depression, fatigue, and anxiety. Many of the pathological observations related to cancer-related fatigue and depression are seen in rodent models. Future research in human cancer survivors is necessary to confirm these initial findings.

Psychosocial Interventions and Biological Outcomes in Cancer

Thus far, we reviewed evidence linking psychosocial factors to cancer incidence, progression, and the biological mechanisms that impact survivors' quality of life. Over the past few decades, the importance of utilizing psychosocial interventions alongside biological therapeutics has become evident [90]. Evidence suggests that integrating mind and body techniques cannot only reduce mental signs of stress but also improve biomarkers of stress [90–92]. Research suggests dynamic patient care can help patients feel healthier, and this idea coincides with a recent scientific movement toward caring for the "whole patient" [93]. In 2008, the Institute of Medicine (IOM) recommended that a new standard of quality cancer care must integrate psychosocial aspects in routine cancer from diagnosis through survivorship [94]. Researchers have demonstrated the impact common psychosocial interventions such as meditation, cognitive behavioral therapy, and guided imagery can have on stress hormones like cortisol, norepinephrine, and epinephrine [95]. Relaxation training psychoeducation, coping skills training (e.g., problem-solving, setting goals), and cognitive-behavioral elements (e.g., cognitive restructuring) can be used to decrease stress, lessen perceived symptom severity, and alter metabolic pathways to improve health [96].

As mentioned previously, a common and distressing symptom associated with cancer treatment is fatigue. Pharmacological interventions for fatigue are very limited [97]. Evidence suggests that yoga interventions can improve fatigue and alter molecular signaling pathways associated with inflammation [51]. Thirty-two breast cancer survivors with persistent cancer-related fatigue were randomly assigned to either a 12-week Iyengar yoga intervention ($n = 16$) or a health education control group ($n = 16$). The yoga group showed reduced activity of NF-κB (i.e., the signaling pathway that plays a central regulatory role in pro-inflammatory gene expression) and cAMP response element-binding protein (CREB) family transcription factors, as well as increased glucocorticoid receptor (GR) activity, compared to the control group. Levels of soluble tumor necrosis factor receptor type II (sTNF-RII) remained stable in the yoga group and increased in the health education group. There was no evidence of change in C-reactive protein (CRP), interleukin 6 (IL-6), or diurnal cortisol. In a separate randomized controlled trial utilizing a much larger sample of breast cancer survivors ($n = 200$), participants were randomly assigned to either 12 weeks of 90-minute twice-weekly hatha yoga classes or a wait-list control group [98]. The researchers found a decrease in pro-inflammatory markers (IL-6 and IL-β) at 3 months post-intervention, particularly among those who continued practicing yoga after the intervention concluded [98]. Taken together, these findings add to the growing body of literature on the anti-inflammatory effects of mind-body interventions.

Interventions that reduce chronic disease risk factors (i.e., blood pressure, chronic inflammation, and cortisol) may be particularly important for older cancer survivors as this population is at an increased risk for chronic diseases compounded with cancer-related treatment effects [99]. Another study demonstrated the efficacy of a 12-week Tai Chi Chih (i.e., a mind-body exercise) intervention [100]. Sixty-three senior female cancer survivors with physical functioning limitations who were, on average, 67 years old were randomly assigned to either a Tai Chi Chih intervention or a control group [100]. The Tai Chi Chih group exhibited reduced cortisol levels compared to the control group, but there were no significant effects on immunological variables (i.e., inflammatory cytokines) [100].

A randomized clinical trial of a 9-week psychosocial telephone counseling intervention proved to be beneficial for cancer survivors [101]. The telephone counseling intervention covered topics related to managing stress and emotions, health and wellness, and managing relationship and sexuality concerns. During the sessions, patients' stressors were identified, and counselors provided psychoeducation on problem-solving, social support, thought-changing, and role-playing communication strategies to address each patient's personal issues. One hundred and fifteen cervical cancer survivors were randomly assigned to telephone counseling, and 89 were assigned to usual care. There were no significant differences in cytokines between telephone counseling versus usual care groups. However, patients with a longitudinal decrease in plasma IL-10, a counter-regulatory cytokine associated with the chronic stress response, also showed an increase in quality of life [101]. As a result, the evidence suggests that some psychosocial interventions appear to impact both mental health and biomarkers of illness positively.

Finally, several limitations exist in the current psychosocial intervention literature. For example, most studies that assess biological outcomes after psychosocial interventions evaluate exclusively female breast cancer survivors (an estimated 75%) [96]. In fact, only 8.3% of psychosocial therapy trials utilizing PNI outcomes included individuals with cancers other than breast or prostate cancer [96]. Further research is needed to determine whether interventions are similarly efficacious for different populations of cancer survivors. Additionally, few intervention studies utilize a comprehensive measurement approach that evaluates outcomes of all three PNI (psychosocial, neuroendocrine, and immunological) subsystems. Such research is needed in order to test hypotheses regarding how variables may change or explain known associations within the literature. Testing these hypotheses may lead to better interventions due to a more complex understanding of how the three subsystems may be interrelated and adapting current interventions in order to maximize benefits. Finally, because both direct and indirect links between biobehavioral factors and processes associated with tumor progression are now well-documented in basic studies, researchers testing psychosocial interventions should include tumor-related biological outcome measures (e.g., tumor invasion, metastasis, and inflammation) in both the tumor microenvironment and in the periphery when at all possible [104]. This approach would greatly inform our overall understanding of how and whether psychosocial interventions affect actual disease progression (e.g., evidence of intervention impact on disease progression, operationalized as changes in angiogenesis and apoptosis levels after a 12-week physical exercise intervention among female breast cancer patients) [105].

Conclusions and Limitations

Throughout this chapter, we have discussed how psychological factors may be associated with biological mechanisms that promote cancer incidence and progression, as well as quality-of-life difficulties during cancer survivorship. Much of the research in this area has focused on the role of well-known stress relevant biological pathways (e.g., inflammation, catecholamines); however, novel research indicates that related biomarkers, such as cellular bioenergetics, also appear promising as research and intervention targets.

While the mechanisms and interventions explored here are promising, this area of research is limited in various ways. For example, within the cancer survivorship quality-of-life literature, many of the symptoms that are most frequently studied (e.g., fatigue, depression, anxiety) are strongly interrelated. As a result, we are not yet able to understand how, and under what conditions, cancer survivors develop some symptoms that impact quality of life, but not others. Additionally, the biological mechanisms discussed as explaining the association between psychological factors and cancer risk and survivorship difficulties (e.g., inflammation, cellular bioenergetics, cortisol) have strong potential for bidirectional associations. As an example, it is plausible that poor cellular bioenergetic health leads to low physical activity and fatigue. Yet, low physical activity may also promote poor cellular bioenergetic health. Longitudinal studies that include measurement of psychological factors, quality-of-life difficulties, and biological markers are needed to disentangle how such associations develop and potentially change over time. Finally, the vast majority of psychosocial intervention research has focused on breast cancer survivors. Although such work has been highly valuable for moving the field forward, research with survivors of other forms of cancer is clearly needed. Understanding how to improve the quality of life of cancer survivors is critical.

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10

Psychosocial Interventions in Cancer

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Introduction

Cancer survivors face significant disease- and treatment-related changes that can be distressing and lead to long-term physical and psychosocial dysfunction and quality-of-life deficits. At all points in the cancer experience, from diagnosis to long-term survivorship, there may be physical, emotional, interpersonal, and existential or spiritual difficulties. People vary in their ability to cope with the stressors that occur with diagnosis and treatment and the ongoing challenges of late and long-term treatment effects. Psychological responses range from normal feelings of vulnerability, sadness, and fear to problems that can become disabling, such as clinical levels of depression or anxiety, interpersonal dysfunction, social isolation, and existential or spiritual crisis. Distress may be experienced as a reaction to the disease, disruptions in quality of life, uncertainty about the future, and fears about long-term impairment and risk. Importantly, not all psychological reactions are negative, and many cancer survivors report finding some benefit in their experience such as a finding meaning, new appreciation of life, improved self-esteem and sense of mastery, and closer relationships with loved ones [1].

Psychosocial distress associated with cancer exists on a continuum ranging from normal adjustment issues to clinically significant symptoms that meet full diagnostic criteria for a mental disorder. The National Comprehensive Cancer Network (NCCN) published the first distress screening and management guidelines for patients in the oncology setting in 1997 and were most recently updated in 2019 [2]. These guidelines aim to address that the majority of cancer patients experience some form of distress at some point along the cancer experience [3]. Distress screening enhances the ability of hospitals and cancer centers to identify those in need. Screening alone does not treat distress, however, and referrals and implementation of supportive care resources for those who screen positive for distress are lacking [4–6]. It must be considered that patients in high need may require more than one referral or are best cared for through a multidisci-

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plinary approach, which may be difficult to coordinate through screening measures, such as the NCCN distress screening. Other screening measures, such as the Hospital Anxiety and Depression Scale or the Psychological Distress Inventory, offer alternative methods of capturing and reporting those who may be in most need presenting in the clinic [7]. There are multilevel factors that affect institutional capacity for responding to positive distress screening including the need for multidisciplinary referrals to address identified problems [8]. Other evidence suggests many individuals may refuse to complete distress screeners or refuse additional support regardless of distress, and other screening instruments may be used [9, 10]. Nevertheless, patient-centered care principles highlight the importance of treating the "whole person," and it is critical to identify those in need of support. Evidence-based psychosocial interventions are important for addressing cancer survivors' distress and promoting adaptive coping in the long term.

Importantly, the benchmark for intervening with patients is not the clinical diagnosis of a mental disorder but more often is related to the level of interference or impairment they are experiencing and desire for support. At one end of the spectrum, individuals express "normal" adjustment reactions and experience transient feelings of distress such as anxious thoughts and depressive symptoms. Although there may be some impairment in functional domains, ongoing emotional reactions are not severe enough to significantly impair functioning, and patients demonstrate adequate coping skills and support resources. At the other end of the spectrum, individuals experience symptoms that are severe and frequent enough to meet diagnostic criteria for a debilitating mental health disorder such as major depressive disorder or an anxiety disorder. Between both ends of the continuum lay adjustment disorders and subclinical symptoms of mental health conditions. Up to 52% of cancer patients report high levels of distress, and between 24 and 47% of survivors indicate clinically significant psychiatric disorders [3, 11, 12]. Estimates indicate that during treatment, up to 27% of individuals with cancer report depression and 14% meet diagnostic criteria for current major depressive disorder, and 48% report clinically relevant symptoms of anxiety and 18% meet criteria for an anxiety disorder [13, 14]. Posttreatment cancer survivors experience greater rates of major depressive episodes, severe distress, suicidal ideation, and serious mental illness at up to two times that of their cancer-free counterparts [15]. Other common syndromes include persistent depressive disorder (previously dysthymia) and subsyndromal depression (also called minor depression or subclinical depression). Mental health disorders are often accompanied by upsetting symptoms such as sleep disturbances, fatigue, and pain [16–18]. These symptoms may co-occur and exist in clusters as a mix of psychological, physical, or cognitive symptoms that often present together, such as fatigue, depression, sleep disturbance, and pain which together predict quality of life of patients with cancer [19]. The psychological and emotional reactions to cancer are considered briefly below.

The impact of cancer on psychological and emotional well-being is highly variable and often multifactorial. Cancer site and stage, treatment course, prognostic medical factors, and the burden of side effects and/or long-term physical impact will predict many of the challenges individuals face and are among the strongest predictors of emotional reactions. Psychosocial outcomes also vary among subgroups based on demographics and the occurrence of protective factors such as having a strong support network and well-honed coping skills. For example, depression is more common in younger-aged survivors and in those with poorly controlled pain, physical impairment or discomfort, limited social support, and more advanced-stage disease [20, 21]. Among young adult survivors of cancer (18–38 years old), rates of mental illness are up to four times those of cancer survivors ages 50–64 [15]. Those with a premorbid history of depression or anxiety or who present with current and ongoing symptoms at the time of diagnosis are also at increased risk for experiencing adjustment difficulties and more severe emotional reactions

[20, 22]. Non-cancer stressors, either preexisting or concurrent, may compound cancer-related stress and further overwhelm the survivor and increase supportive care needs.

Despite this, the majority of cancer survivors adjust relatively well. Although the normative reaction to a cancer diagnosis is typically that of alarm and fear and coping with side effects may be quite difficult at times, most patients never meet full diagnostic criteria for a mental health disorder. This should not undermine the need to address emotional difficulties and support needs of cancer survivors. Even mild symptoms of distress can lead to impairment if untreated with clinically significant outcomes. For example, avoidant behaviors may affect cancer treatment through missed medical visits or treatment nonadherence [23, 24]. It is important to highlight the continuum within which emotional well-being and psychological distress occurs and to approach clinical care with this variability in mind.

Psychosocial interventions for cancer survivors generally aim to reduce emotional distress, enhance coping skills, and improve quality of life. Additional aims may include improvements in treatment engagement or adherence, assistance with practical issues, and bolstering health behaviors such as diet and exercise [25]. The design may be for individuals or group- or couples-based. Intervention components typically involve an emotionally supportive context to address fears and anxieties, the provision of information about the disease and treatment and intervention approach, cognitive and behavioral coping strategies, and relaxation training. Psychosocial interventions may be best utilized by targeting the specific needs and stressors of individuals at different levels of psychological functioning and at each phase of the cancer experience.

The goal of this chapter is to review the psychosocial responses of cancer survivors across the cancer continuum, from diagnosis to long-term survivorship, and describe interventions that may be used at each stage of the cancer experience to best meet the emotional and supportive care needs of survivors with a targeted approach.

Psychosocial Responses in Cancer Survivors

Diagnosis

The initial diagnosis of cancer is often a traumatic and distressing experience. Normative emotional reactions include feelings of disbelief, guilt, anger, denial, panic, fear, and despair. Cancers caused by poor health behaviors may be particularly distressing, shameful, or stigmatizing, as is seen among smokers who develop lung cancer. The spectrum of emotional reactions ranges from depressive symptoms to clinically significant symptoms of adjustment disorder or major depressive disorder, categorized by impairing distress. Whether real or perceived, facing the threat of life limiting illness or long-term impairment is a jarring experience. It is very normal for patients to struggle with feelings of uncertainty and fear for the future. Concurrently, decisions about treatment options and preparing for impending procedures, typically within a short time frame, often add to stress levels with little time afforded to patients to adjust and garner resources for support and coping.

Survivors may feel additional distress in anticipation of treatment-related changes and inherent uncertainty about the future including the degree of life disruption and impact on loved ones. For example, young adults often struggle with forced disruptions in educational pursuits and career disruption, which may impact long-term financial well-being and life trajectories. Older individuals may need to depend on the care and support of their children, and these role changes may be distressing, particularly if they worry about being a burden. The social context is critical in determining the emotional impact on patients. This period of time may be more difficult for those who are un-partnered, in an emotionally unsupportive relationship, or who lack an adequate support network. Social isolation is associated with poorer immune function and physical and mental health outcomes across cancer types and stages [26, 27]. Cumulatively, the sudden emotional cascade and anticipated life changes that come with a new cancer diagnosis may be quite stressful and overwhelming for many patients and their loved ones.

Although a cancer diagnosis is naturally quite distressing at first, initial emotional responses are often relatively brief, extending over several days to weeks [28]. Nevertheless, individuals may still benefit from interventions designed to enhance adjustment and coping skills and prepare them for the challenges ahead. Relevant tasks that can be experienced as stressful include disclosure to loved ones and planning for expectable life changes such as time away from work or childcare needs, which may require sharing the news with colleagues and employers, asking for help, and financial planning. Research points to the efficacy of relaxation techniques, education, and skills training in preventing and relieving anxiety and depression and promoting quality of life in newly diagnosed survivors [29, 30]. It is critical to provide newly diagnosed patients information about what to expect based on the medical circumstance and where to find resources if and when difficulties arise. It may also be important to introduce supportive interventions to begin skills building to manage stress and anxiety and prepare for the future.

Treatment Decision and Pretreatment Preparation

With a new diagnosis of cancer comes a cascade of medical decisions and treatment planning for upcoming medical care. It is common for survivors to feel overwhelmed and stressed with treatment decision-making as many will be uninformed about their disease and treatment options and may have difficulty understanding guidelines or risk/benefit ratios, particularly when there is uncertainty about treatment efficacy or risk of complication. In some instances, treatment options may be relatively equivalent, and the decision, therefore, should depend on individual values, priorities, and preferences in relation to expected posttreatment side effects and quality of life impact. It can be difficult to predict the impact late and long-term effects will have on quality of life, and many survivors underestimate the degree to which they are bothered by side effects when they occur [31]. The challenges of treatment decision-making and preparation may be exacerbated for those with inadequate medical care or poor communication with their oncology team, particularly for subgroups with limited language proficiency and poor health literacy. Internet searches are the most common method for finding information related to cancer for oneself or a loved one and can lead to misinformation [32]. Whether sought out or unsolicited, survivors often hear anecdotal cancer information from social networks that can also be misleading and confusing.

Targets of intervention during the pretreatment time period focus on providing support for treatment decision-making and treatment preparedness (e.g., stress management and relaxation techniques prior to surgery). Interventions to assist in the treatment decision-making typically involve decision aids with the objective that patients will make informed, values-based decisions with careful consideration of risk-benefit tradeoffs (pros/cons of treatment options) and consistency with personal priorities and goals [33, 34]. Decision aids may be used to guide decisions when there is equipoise among treatment options such as the case with localized prostate cancer deciding among active surveillance, radical prostatectomy, or radiotherapy or breast cancer patients determining surgical and reconstruction options [35, 36]. Alternatively, decision aids may be used to support decisions about concomitant care such as young adults considering fertility preservation prior to gonadotoxic treatments [37, 38].

Psychosocial interventions designed to be delivered prior to the start of treatment have mostly been conducted among breast and prostate cancer survivors prior to the start of chemotherapy or surgery and typically involve relaxation training (e.g., progressive muscle relaxation techniques, guided imagery) and stress management to prepare survivors for their treatment(s). Those designed to prepare individuals for cancer treatment have been shown to be effective in reducing anxiety and depression and improving satisfaction with cancer care, with evidence suggesting that even brief interventions (e.g., one session, 15–20 min long, remote delivery) may be beneficial [28, 29, 39–41]. Reviews of the literature have suggested positive effects on disease-specific and general quality of life, including reduced posttreatment side effects such as nausea and vomiting and less psychological distress [20].

Active Treatment

The active treatment phase poses additional stressors that often impact psychosocial well-being and quality of life. Treatments almost inevitably have some side effects that may include one or a combination of symptoms such as pain, nausea and vomiting, insomnia, fatigue, bodily changes or disfigurement, urinary or bowel incontinence, and sexual dysfunction. The sequelae of side effects vary between early and more advanced-stage disease and extent of treatment received. Advances in screening and early detection have led to more individuals diagnosed with early-stage disease with treatments that have fewer or less intense side effects. Survivors living with advanced disease face additional physical (e.g., pain, functional limitations) and emotional (e.g., fear of dying, end-of-life issues) consequences that further impact quality of life. Additional stressors during this time may include negotiating changes in occupational and family roles, managing household and childcare responsibilities, worrying about finances, and interference with educational or career advancement. Even for those who do not experience chronic or debilitating side effects, significant change in functioning or altered independence may still be highly distressing, particularly if survivors experience changes that threaten identity and sense of self. There may be downstream physiological changes as well including decreased immune function associated with negative psychosocial outcomes and cognitive function [42].

Some of the most common concerns reported by cancer survivors during treatment are related to feelings of uncertainty and a diminished sense of control and predictability. Again, the specific nature of these concerns often depends on medical factors including disease stage and treatment course, and the general impact on daily living and expectations about the future. Uncertainty may be related to treatment efficacy or anticipated side effects and, particularly among those with more advanced-stage disease or with poor prognostic indicators, include worries about long-term quality of life and fears about death and dying. Undergoing medical treatments involves a certain degree of losing control and autonomy over one’s body and can create a sense of feeling “medicalized” or disconnected from the body. It may lead to a feeling of reduced autonomy and self-efficacy related to their physical condition and health outcomes, particularly if they feel uninvolved in decision-making about treatments and medical care. Lack of social support or feel disconnected from social networks due to illness contributes to psychosocial distress. Many patients experience a loss of daily routines and disrupted work and social activities during treatment. They may be limited in social activities that can lead to reduced time spent with loved ones, distancing of relationships, and social isolation. High levels of cancer-related distress are associated with interpersonal dysfunction including reduced support-seeking behaviors and lowered perceptions of support. For example, treatment for head and neck cancer often results in facial disfigurement and functional limitations (e.g., problems with speech, breathing, and/or eating) that are associated with embarrassment, lowered self-esteem, body image concerns, and social isolation [30, 31]. Cancer-related changes can disrupt interpersonal relationships and lead to inadequate levels of social support, which may continue posttreatment.

Psychosocial interventions in cancer survivors undergoing treatment have shown positive effects on physical and emotional well-being. Evidence suggests that relaxation training, psychoeducation, supportive or supportive-expressive therapy, and cognitive behavioral therapy have all been found to be effective in preventing or relieving anxiety and depression; evidence is strongest for relaxation training in reducing anxiety [29]. This is reviewed in more detail in later sections of this chapter.

Advanced-Stage Disease

As suggested, individuals experiencing progressing or advanced cancer with poorer treatment outcomes report the greatest levels of psychological distress and decrements in quality of life. Aside from the emotional difficulty of coping with end-of-life concerns, advanced-stage cancer survivors often experience more significant physical side effects, such as pain, nausea and vomiting, urinary incontinence, fatigue and difficulties breathing, eating and/or swallowing, and declining functional abilities that lead to further decreases in quality of life and emotional well-being. As the degree of debilitation advances and patients are unable to manage their self-care, the caregiver burden may become too great and discussions about assisted care may be required. For those who are in the hospital, additional concerns include bed sores, difficulty sleeping, disruptive or unfamiliar environments (e.g., nurses checking in periodically through the night), as well as the added stress of spending time with and interacting with family members and loved ones outside the comfort of one's home or familiar environment. Stresses are compounded by the need to negotiate difficult choices around end-of-life treatments and care, coping with anticipatory grief, as well as the emotional reactions of children and other family members, and concern about the patient's legacy in both psychological and practical terms. At the end of life, as physical well-being declines, patients may experience a more profound loss of control over their body and reduced dignity and self-esteem. If care is transferred to an inpatient medical setting for an extended period of time, survivors may experience a loss of relationships, both with friends and family as well as spiritual relationships, that lead to a perceived loss of support and greater social isolation [43, 44].

Existential fears will naturally occur among patients coping with progressive disease and anticipated death that further challenge psychological well-being and interpersonal functioning at the end of life. Aspects of existential and spiritual concerns refer to survivors' sense of peace, purpose and connection to others, and their beliefs about the meaning of life. Religiosity and strong spiritual beliefs can be protective in guiding patients toward greater acceptance about the eventuality of death and beliefs about an afterlife, or, alternatively, the experience may cause a spiritual crisis and increased distress (e.g., feeling abandoned by one's God). Those who experience significant threats to their existential and spiritual well-being are at increased risk for feelings of despair and hopelessness, feeling like a burden to others, loss of their sense of dignity and will to live and desire for death [44, 45]. They may feel overwhelmed by suffering and unable to cope with the situation. Research suggests that "feeling like a burden to others" is significantly associated with depression, hopelessness, greater fatigue, and lower quality of life [45]. Alternatively, those who are able to find a sense of meaning and peace of mind in their cancer experience may be better equipped for handling end-of-life concerns, adjusting to changes, and optimizing quality of life to the extent possible. The degree to which survivors are able to cope with existential and spiritual concerns is related to cancer-related adjustment overall and perceptions of total health and well-being. Interventions tailored for terminal cancer patients must address the realistic concerns that occur at this time including fears about disease progression, death, and dying, progressing functional limitations, and worrying about loved ones; and focus on skills building for relaxation, coping with cancer worries, and activity pacing [22, 46].

Posttreatment Survivorship

As the number of cancer survivors continues to grow, there is increasing recognition of the need to manage their unique medical and psychosocial needs within a long-term care approach. Posttreatment cancer survivorship is now characterized as a chronic condition requiring specific and targeted efforts to address the long-term issues and late effects survivors experience [47]. This paradigm is a departure from how cancer care was historically conceptualized, as an acute and time-limited course of treatment that is managed by oncology specialists. In contrast, due to factors that are unique to cancer care, individualized patient profiles, long-term and late effects, and need for ongoing surveillance, it must be recognized that survivors face a number of distinct psychosocial challenges that persist well past the acute phase of disease and active treatment.

In the posttreatment survivorship phase, psychological distress may result from a number of cancer-specific concerns that persist well past the acute phases of illness, irrespective of being in remission or "cured" of disease. Negotiating the transition back to "normal" life is often a primary challenge. This involves resuming daily activities and relationships, including intimate and sexual relationships, discussing changes in life plans, implementing health behavior changes, coping with long-standing or permanent disease and treatment effects, and managing fears about disease recurrence. For young adult survivors, cancer often interrupts educational and career pursuits, and survivors may feel derailed from their expected life trajectory. This transition involves coming to an understanding of how cancer has affected personal and interpersonal life narratives such as finding meaning in the cancer experience, finding closure, and negotiating any changes in existential beliefs and life purpose. Many survivors need to actively integrate this new aspect of their identity as a "cancer survivor" into their self-concept while learning to accept changes that persist beyond the end of treatment (e.g., cognitive declines, new outlook on life) and adjusting to the prospect that they may be unable to return to their precancer "normal" self. Fear of recurrence is one of the universal psychosocial challenges at this time and is identified as a root cause of posttreatment psychological distress [48]. The challenges survivors face may be quite personal, and others in their social network may fail to recognize the continued difficulties they experience. Some may expect survivors to "go back to normal" after cancer and fail to recognize continued support needs. At high levels of distress, survivors may avoid medical care or resist long-term surveillance or be unmotivated to comply with risk-reduction behaviors (e.g., physical activity, smoking cessation) as a way of avoiding reminders of cancer and to manage distress.

Sexual health, in particular, is often cited as a particularly challenging domain of survivorship. Without intervention, sexual side effects often persist or worsen in survivorship and can lead to significant impairment in personal well-being and relationships. Despite reporting posttreatment levels of vitality, physical well-being, and levels of general quality of life that are comparable to or above age-matched normative levels, men often indicate distress related to sexual dysfunction [49, 50]. Functional impairment and body image concerns all contribute to sexual impairment. For younger survivors, treatment-related infertility risk is cited as among the most distressing aspects of cancer survivorship with long-term effects on psychosocial well-being, particularly if there are barriers and challenges to achieving family-building goals.

There is a clear rationale for continued psychosocial support after the active treatment. Psychological distress should be assessed, monitored, and treated promptly at all stages of cancer, including the survivorship phases.

Distress management in the survivorship phase of cancer care:

- Need for routine screening to assess psychological distress and psychosocial needs.
- Screening should identify the level and nature of the distress.
- Referrals for psychosocial interventions should be specific to the survivorship needs.

Benefit Finding Importantly, many cancer survivors report beneficial effects of cancer and psychological growth as well. It is a common finding that survivors feel stronger and more able to handle future life challenges after having survived their cancer experience. Cancer caregivers also report benefit finding in relation to meaningful experiences created while caring for their loved ones [42]. For patients, positive psychological consequences reported in the literature include better interpersonal relationships, including quality of marital relationships, changes in values and priorities, greater appreciation of life, and improved quality of life [51–53]. Such positive changes are associated with altered attitudes about personal health and death and may occur up to months or years after diagnosis and treatment. Notably, both positive and negative effects of cancer may – and often do – occur, representing multiple domains of physical and emotional well-being and quality of life [51, 52], suggesting that psychological assessment and intervention may be required even among those who indicate some benefit or positive outcome of cancer.

Critical Transition Period

The transition from active treatment to the posttreatment phase of the cancer continuum is often a time of change and uncertainty for many cancer survivors. The first few months may be filled with mixed emotions. For those that are disease free, there is a relief to be finished with the demands of treatment and welcome the resolution of side effects. At the same time, survivors may feel uneasy with the decreased contact with their providers and safety net of the medical team. It is common to have feelings of hesitation in celebrating being cancer-free. As individuals move from frequent to more infrequent medical visits, they no longer receive the reassurance of frequent check-ins with providers and the reassurance those interactions provide and as a result feel an increased sense of vulnerability. Likewise, there may be great uncertainty about recommended health behaviors (e.g., “Now what do I do?”). Settling into a “new normal” can be challenging and stressful, particularly if late/long-term effects are debilitating or cause functional limitations. Close relationships may be affected. Partners may adjust in different ways and that incongruence is associated with increased distress in both survivors and their partners and cause interpersonal dysfunction. Unrealistic expectations for physical recovery, whether self-imposed or received from others, may exacerbate adjustment difficulties and lead to disappointment and distress. Friends and family members may expect that survivors will be able to resume all of their activities at precancer levels of functioning once treatment is over. Survivors may also expect this from themselves and may be surprised and distressed by physical and emotional limitations following treatment.

Rationale for posttreatment psychosocial assessment and referral:

- Provides opportunity for education and early intervention
- Extends continuum for cancer care
- Facilitates reentry transition
- Facilitates referral for specialized survivorship services

Thus, the critical transition from active treatment to posttreatment survivorship is a unique time period for survivors characterized by paradoxical feelings of both positive and negative emotional reactions. Interventions that have targeted survivors immediately following the end of primary treatment have suggested that relatively simple interventions may help to reduce common adjustment difficulties. These have included videotape interventions depicting issues related to reentry transitions and one-time individual sessions with a cancer educator to prepare and set realistic expectations [29, 54].

Short-Term Survivorship (<1-Year Posttreatment)

In the first year following treatment, many survivors feel “lost in transition.” The transition from “sick role” to “well role” is frequently more difficult than survivors expect and navigating the practical issues related to reentry into social and professional networks can be difficult. Many of the physical and emotional difficulties noted may become more apparent as survivors take on more and more of their precancer activities and responsibilities. For example, cognitive changes (e.g., attention or memory problems; “chemo brain”) may become more distressing if they interfere with work-related activities and job performance. The emotional aftermath of the cancer experience may only begin to sink in after some time has passed, and many survivors may struggle with a new onset of fears and worries akin to post-traumatic stress. While some may meet full diagnostic criteria for a post-traumatic stress disorder, many more will experience subclinical levels of symptoms that still warrant attention.

Although many studies have described the quality of life of cancer survivors in the first year following primary treatment, this research has largely focused on a few cancers (i.e., breast and prostate), and generalizations to other cancer types that involve different treatment regimens are limited. As treatments are constantly evolving, becoming more complex and, at times, more toxic, caution should also be taken regarding interpretation and applicability of older reports. Nevertheless, there have been many psychosocial interventions targeting this stage of the cancer experience. Interventions typically aim to increase physical and emotional well-being and quality of life by providing psychoeducation related to the expected occurrence and time course of late and long-term effects, improving coping and stress management, and increasing social support.

Aftereffects of Cancer

Aftereffects refer to any long-term or late effects of cancer and its treatment and may range from very mild to serious in terms of their effects on physical and emotional well-being and quality of life (see Table 10.1) [55]. The occurrence of aftereffects and how long they last is often difficult to predict and varies across disease and treatment types and relevant individual characteristics.

Table 10.1 Aftereffects of cancer

IOM Report: Defining Long-Term and Late Effects of Cancer Treatment
Long-term effects refer to any side effects or complications of treatment that begin during treatment and continue beyond the end of treatment; also known as persistent effects
Late effects refer specifically to unrecognized toxicities that are absent or subclinical at the end of treatment and become manifest later because of any of the following factors: developmental processes, the failure of compensatory mechanisms with the passage of time, or organ senescence. Late effects may appear months to years after the completion of treatment

From Aziz and Rowland (2003) [55]

Long-term and late effects impact a range of physical and emotional domains and may have practical implications for survivors related to accomplishing day-to-day life activities, employment and job performance, and obtaining or maintaining health insurance [55]. Common long-term and late effects are listed in Table 10.2.

Table 10.2 Long-term and late effects of cancer

Aftereffects of surgery include
Scarring at the incision site and internally
Lymphedema or swelling of the arms or legs
Problems with movement or activity
Nutritional problems if part of the bowel is removed
Cognitive problems such as memory loss and difficulty concentration
Changes in sexual function and fertility
Pain that may be acute (sudden) long-term or chronic
Emotional effects that may be related to feeling self-conscious about physical changes
Aftereffects of chemotherapy include
Fatigue
Sexual problems
Early or premature menopause
Infertility
Reduced lung capacity with difficulty breathing
Kidney and urinary problems
Neuropathy or numbness, tingling and other sensations in certain areas of the body, especially the hands and feet
Muscle weakness
Cognitive problems such as memory loss or inability to concentrate
Osteoporosis
Changes in texture and appearance of hair and nails
Secondary cancers
Aftereffects of radiation include
Cataracts, if treated near the eyes, cranial-spinal or if given total body irradiation (TBI)
Permanent hair loss if the scalp is radiated over certain dose levels
Dental decay, tooth loss, receding gums if radiated near the mouth
Loss of tears and the ability to produce saliva if lacrimal or salivary glands in the face are radiated or there has been TBI
Problems with thyroid and adrenal glands if the neck is radiated
Slowed or halted bone growth in children if bone is radiated
Effects on the pituitary gland and multiple hormonal effects if the hypothalamic-pituitary region is radiated

(continued)

Table 10.2 (continued)

Decreased range of motion in the treated area
Skin sensitivity to sun exposure in area of skin that is radiated
Problems with the bowel system if the abdomen is radiated
Secondary cancers in the areas radiated
Infertility, if ovaries, testes, cranial-spinal area or TBI is directly radiated
Emotional aftereffects following cancer treatment may include
Anger
Sadness, depression, or loneliness
Anxiety
Post-traumatic stress
Health worries and fear of recurrence
Sense of loss for what might have been
Uncertainty and vulnerability (e.g., “my body let me down”)
Uncertainty about the future; feeling unable to plan for the future
Concerns about pain, fatigue, or physical side effects
Concerns about body image
Concerns about the future or having a new orientation to time and future
Existential or spiritual concerns (e.g., “Why me?”; “Why now?”)
Concerns about death and dying
Search for meaning and purpose; appreciation of life
Social aftereffects may include
Loss of support; isolation
Alienation or stigma
Altered social relationships, including intimate relationships and those with family members, friends, and peers
Comparisons with peers or other cancer survivors
Practical aftereffects may include
Job performance; difficulty working due to physical or emotional aftereffects
Problems getting health or life insurance coverage
Challenges communicating concerns to your healthcare team
Financial stressors
Employment discrimination

- *Long-term effects* develop during treatment and are persistent or chronic side effects that continue for months or even years past the end of treatment. Common long-term effects include physical (e.g., anemia, fatigue, and neuropathy) and emotional (e.g., depressive symptoms) domains of well-being. Many long-term effects improve or resolve with time, whereas others are permanent such as limb loss, muscular weakness, or nerve damage. The prevalence of long-term effects is associated with cancer and treatment type and is influenced by the health and well-being of the individual including premorbid physical and psychological condition.
- *Late effects* refer to any disease- or treatment-related difficulties that are absent or subclinical at the end of treatment but manifest anywhere from months to years later. The increasing complexity of treatment regimens has led to increased prevalence of late effects, which are often dose and modality specific. The increased risk of a second cancer is the most life-threatening late effect, but other disabling conditions occur and need to be monitored for and addressed through medical and psychosocial interventions. Other common late effects include chronic fatigue and neuropathy, cognitive dysfunction, and declines in cardiovascular health [56, 57]. Female cancer survivors may experience premature menopause, and both male and female survivors may experience infertility.

The risk of long-term and late effects depends on the tissue exposed as well as the age and health condition of the patient at the time of treatment [56]. Many older survivors have comorbid medical conditions that may exacerbate treatment-related effects or complicate recovery of premorbid functioning. Tissues at risk for late toxicity include bone/soft tissues, cardiovascular, dental, endocrine, gastrointestinal, hepatic, hematological, immune system, neurocognitive, and nervous system tissue [55–57]. There is an ongoing need to monitor for and prevent late effects and promote healthy lifestyles. Some aftereffects may be expected given the nature of disease and treatment; brain and spine tumors, for example, increase the risk of neurologic deficits [58]; survivors of head and neck cancer are at increased risk for impaired eating, communication, and musculoskeletal functions of the neck and shoulder [59]; individuals with bone cancers are more likely to experience mobility problems due to amputations or limb-sparing procedures [60]; and gonadotoxic therapies (e.g., alkylating chemotherapy, surgery or radiation affecting reproductive organs or hormone regulation) will impact fertility [61]. Beyond general predictions, the degree of risk of late/long-term effects can be difficult to calculate. Many of the aftereffects mentioned in this section extend well into long-term survivorship phases (>5 years post-treatment) [47].

Aftereffects of cancer treatment have the capacity to impact all domains of life including physical/medical, psychological, social, existential, and spiritual aspects of identity and well-being. Some aftereffects may be easily identified because they are visible or have direct effects on function and well-being and are well known and researched. Other effects, however, can be subtle and not readily apparent to the untrained observer (e.g., postural changes due to osteoporosis) or are not directly observable and only detectable through diagnostic testing (e.g., infertility, hypothyroidism). Likewise, emotional difficulties are often difficult to pinpoint and may go unrecognized or be misunderstood by survivors or by their loved ones. Important considerations in dealing with aftereffects of cancer treatment, particularly with respect to emotional and psychological effects, include premorbid mental health functioning, personal and interpersonal resources, and coping strategies. Psychosocial interventions in the first year after treatment typically address concerns related to survivorship transition and coping with residual side effects of treatment and research suggests that participation is associated with a number of benefits to physical and emotional well-being.

Long-Term Survivorship (>5 Years Posttreatment)

Prolonged challenges associated with the cancer experience and permanent impairment in functioning or well-being may manifest as new or exacerbated triggers of distress and dysfunction even years after the end of treatment [62]. For example, unresolved sexual dysfunction may ware on relationships over time or lead to dysfunctional patterns of interaction within couples that undermine intimacy and shared quality of life. Infertility distress may increase among young adult survivors as they approach the age of reproduction and desired family building [63]. Poor overall health and ongoing physical problems may be difficult to cope with in the long-term and lead to practical challenges affecting daily life and life planning (e.g., ability to work and job performance, problems with health insurance). Evidence suggests that despite the adoption of healthy behavior changes after diagnosis and at the end of active treatment, many longer-term survivors do not maintain behavior changes and resume unhealthy lifestyles that were present before cancer (e.g., smoking, being sedentary, being overweight or obese). Common long-term survivorship difficulties are listed in Table 10.3.

While many survivors may be able to adjust to aftereffects and manage lingering fears and concerns with time, others may find that they feel “stuck” and cope strategies are proving ineffective. This requires ongoing monitoring and interventions designed to target the specific sources of distress for survivors coping with lingering cancer effects including both physical and psychosocial areas of functioning. Some survivors may need coping skills to deal with acute but intermit-

Table 10.3 Long-term survivorship difficulties

Physical and psychosocial challenges of long-term survivorship
Adjustment to physical compromise, health worries, and sense of loss for what might have been
Body image concerns
Long-term and late effects of treatment such as fatigue and cognitive difficulties
Increased risk of poor overall health and health-related complications of treatment
Alterations in social support and perceived loss of support from loved ones as well as cancer care medical team
Interpersonal disruption and social isolation
Sexuality and fertility issues and related effects on intimate relationship functioning
Stigma of cancers associated with risk behaviors such as smoking and alcohol consumption
Fear of recurrence and concerns about future and death
Uncertainty and heightened sense of vulnerability
Existential and spiritual issues
Employment and insurance problems

tent experiences associated with cancer such as managing anxiety with annual surveillance tests. Many of the interventions developed for long-term survivors target lifestyle behavior modification to promote healthy behavior changes. Results suggest that dietary and exercise interventions are effective [64, 65], though dissemination of interventions can be difficult as survivors become more removed from cancer care [66]. Not surprisingly, home-based interventions delivered remotely and via digital platforms help to overcome barriers and promote adaptive changes in this vulnerable population of survivors.

Psychosocial Interventions in Cancer

Targets of Interventions

As a cancer diagnosis and its treatment pose significant short- and long-term challenges for survivors and their loved ones, psychosocial interventions that attempt to minimize the negative impact and promote positive adjustment and well-being are increasingly common. Interventions typically aim to improve adjustment and well-being by:

- Guiding treatment decisions and preparation
- Teaching adaptive coping skills
- Improving support-seeking behaviors and reducing social isolation
- Addressing maladaptive cognitions
- Improving communication with partners, loved ones, and providers
- Promoting adherence to recommendations and improving healthy lifestyle behaviors

Psychosocial interventions typically aim to improve adjustment and well-being through the provision of information and acquisition of intra- and interpersonal skills building. The model in Fig. 10.1 proposes that cancer survivors benefit from interventions that are tailored to their individual needs and presenting problems. For example, teaching anxiety reduction skills can provide a way to reduce anxiety, tension, and other forms of stress responses and thus help the survivor achieve a sense of mastery over disease-related

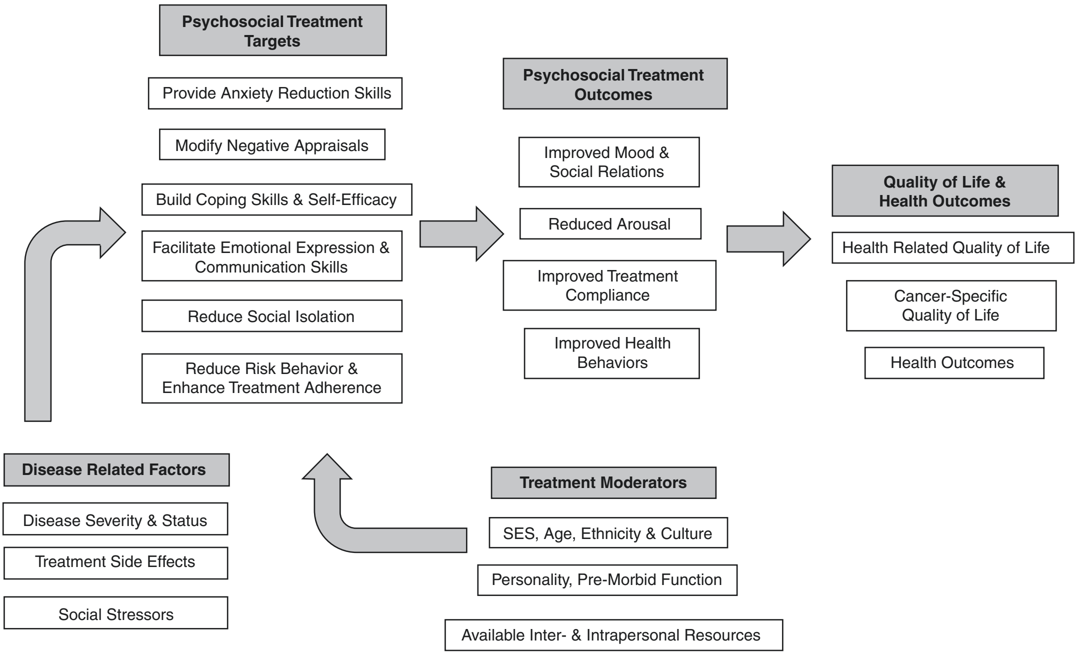

Fig. 10.1 Conceptual model of psychosocial treatment interventions

and general stressors. The use of cognitive restructuring techniques can help survivors identify links between thoughts, emotions, and somatic sensations or physiologic response and increase ability to identify and change maladaptive thought patterns and unhealthy effects on behavior. Participants in these interventions can also benefit from techniques that challenge ineffective or damaging cognitive, behavioral, and interpersonal coping strategies by increasing awareness of the use and consequences of ineffective coping strategies and patterns of behavior that do not result in desired outcomes. Therefore, attention is given to replacing inefficient and indirect ways of dealing with stressors with more effective coping including emotion and problem-focused strategies while increasing survivors' ability to adaptively express both positive and negative emotions and access supportive resources. These intervention models promote identifying and utilizing social support and providing self-management skills. Communication skills are also targeted, particularly those specific to interacting with healthcare professionals and communicating concerns and needs with spouses/partners, family, and friends. When testing psychosocial interventions, outcome measures often include a range of physical and emotional health indices as well as disease-specific and general quality of life. Another important target of intervention is the promotion of healthy lifestyle behavior changes such as diet, exercise, and smoking cessation.

Importance of health promotion following cancer treatment [66, 67]:

- Engaging in health promoting behaviors may improve health outcomes and decrease morbidity and mortality (e.g., tobacco and alcohol cessation, nutrition and diet, exercise, sun protection, cancer screening and prevention, medical surveillance).
- Engaging in health-promoting behaviors can empower active partnership with healthcare providers and may enhance perceived control over health outcomes (reference).

Fear of cancer recurrence is one of the most common occurrences and significant source of distress for cancer survivors. Psychosocial interventions targeting fear of recurrence have been shown to be efficacious, particularly those based in a cognitive behavioral framework [68]. Those shown to be most effective focus on cognitive processes such as worry, rumination, and attentional bias, rather than the content of thoughts, with the goal of altering the way in which individuals relate to their inner experiences. These interventions may be delivered in individual or group formats.

Interventions that target existential and spiritual concerns and end-of-life fears typically focus on issues of control and autonomy, identifying sources of dignity and meaning, addressing relationships challenges, and fostering acceptance and peace [44]. The goals of these interventions are largely the same as those of other interventions, aiming to improve adjustment and coping with benefit to quality of life; though physical outcomes are usually less of a focus than at other stages of the cancer experience [69, 70]. Outcome measures include assessment of self-esteem, purpose in life, optimism, and hope for the future [70]. A literature review of existential and spiritual interventions indicated that the majority of the outcome measures assessed either improved or remained stable in intervention groups and declined in control groups [45]. It appears that psychosocial interventions that target existential and spiritual concerns may be quite important for maintaining emotional well-being and optimizing quality of life even at end-of-life stages [45, 70], with limited evidence suggesting utility in improving physical outcomes [45, 69].

Finally, given the interpersonal nature of cancer, couple-based interventions have been developed with the goal of assisting dyadic processes that promote adjustment to cancer-related changes while avoiding or minimizing individual distress (patients' and partners') and relationship dysfunction. Interventions may either be at the individual- or couple-level. Individual-level interventions that include both members of the couple target individual adjustment and well-being based on the logic that a couple will adjust to cancer most effectively if each partner adjusts well [71]. Partner-assisted interventions are ones in which the goal is to teach skills to both partners to help the person with cancer adjust and cope effectively, and often the partner's role is that of a supporter [72]. Alternatively, couple-level interventions identify relationship functioning as the primary therapeutic focus and target couple-level issues and skills such as problem-solving and effective communication as the means by which individual-level adjustment is enhanced. Intervention material typically addresses cancer-related problems as well as positive relationship functioning in general. A common target of intervention for couples addresses the sexual problems that occur with disease and treatment experiences and rebuilding intimacy. The ways in which couples engage in relationship maintenance strategies (e.g., positivity, openness, assurance) after a diagnosis of cancer impact psychological and relational adjustment over time [71, 73–75], and interventions aim to leverage couples' strengths while teaching adaptive personal and interpersonal coping strategies.

Types of Interventions

There are many different types of interventions developed for cancer survivors, but common therapy components typically include an emotionally supportive context and one or a combination of education, emotional processing, skills building (e.g., to improve decision-making, coping, or communication), stress management, and relaxation training. Interventions provide an opportunity to gain knowledge about the disease and its treatment, address fears and anxieties, learn coping strategies, and, if in a group context, an opportunity to meet peers and share experiential knowledge. Benefits of psychosocial interventions are achieved through a number of therapeutic techniques based on theoretical models of stress and coping, psychological well-being, and health behavior change [28, 76, 77]. There is strong evidence to support cognitive behavioral interventions across the cancer continuum, whereby coping skills are learned from better awareness of the interrelationships among thoughts, feelings, and behaviors [78, 79]. These benefits in coping have been identified as a mechanism of intervention effects on quality of life [80]. Mindfulness-based interventions have increased in popularity and also promote better awareness of the connection between mind and body (thoughts and behaviors) and foster skills to increase control over physiologic responses and relaxation such as through meditation or guided imagery [81].

Interventions range in terms of the degree of structure and adherence to manualized or instructional approaches. Supportive interventions, often group-based, provide survivors with the opportunity to acknowledge and discuss their challenges to other survivors with similar experiences. Therapeutic processes by which participants derive benefit include self-disclosure and receiving support and validation, information exchange, and reducing social isolation [20]. Many survivors also derive esteem by participating in groups and providing support to others. Psychoeducational interventions build on this but tend to be more structured in nature, often focusing on cognitive and behavioral techniques to facilitate adjustment and skills building to foster adaptive coping and a greater sense of control over the illness experience [28, 77]. Participants are typically provided with information pertinent to their disease and its treatment and work toward building acceptance of and adjustment to cancer-related changes. Cognitive behavioral approaches emphasize skill acquisition and behavioral change through goal setting, self-monitoring, coping skills, and social skills training [28, 82]. Consensus about the efficacy of cognitive and behavioral techniques or psychoeducational methods suggests positive effects on a range of physical and emotional well-being outcomes (e.g., fatigue, pain, anxiety, depression, and general cancer distress) [17, 83–85]. Some evidence suggests that cancer survivors may benefit more from structured interventions than purely supportive ones. This may be due to the acquisition of new skills with which survivors can broadly apply to individual stressors specific to their experience and continue after the intervention has ended (e.g., cognitive restructuring, stress management, relaxation techniques) [82].

Cognitive behavioral approaches have also been combined with relaxation training and stress management techniques. Research has shown positive outcomes of a manualized cognitive behavioral stress management (CBSM) group intervention developed and tailored to meet the specific needs of several medical populations, including breast cancer [86–95], ovarian cancer [96], and localized [97–99] and advanced prostate cancer [100–104]. The intervention consists of 10 weekly group meetings that include a 90-min didactic portion and 30 min of relaxation training. Participants are taught a variety of cognitive-behavioral stress management techniques, including identification of distorted thoughts, rational thought replacement, effective coping, anger management, assertiveness training, and development of social support. Information specific to disease physiology, diagnosis, treatment, and side effects is also provided. Participants also learn and practice a variety of relaxation techniques, including progressive muscle relaxation (PMR), guided imagery, meditation, and diaphragmatic breathing, and are encouraged to practice the techniques on a daily basis. The concepts and techniques introduced in each session build upon information covered in prior sessions and are reinforced through group discussions, exercises (e.g., role-plays), and weekly homework assignments. Discussions are tailored to address the specific needs and concerns of survivors. For example, among men with prostate cancer, the intervention aims to provide an opportunity to help men accept a lowered or lack of physiologic response, normalize feelings of anxiety or depression surrounding a perceived loss of male identity, reframe intrusive or distorted thoughts of disappointment or inadequacy, and teach adaptive coping strategies to effectively communicate with sexual partners and adjust to altered sexual patterns [51, 98, 99, 105].

Individual Support and Self-Administered Interventions

Individual interventions include any form of therapy, counseling, or support that is delivered on a one-to-one basis. This may involve therapy or counseling with a qualified professional or volunteer-based support from another survivor (i.e., peer-based programs) or other types of volunteer. Psychotherapy with a professional therapist or counselor offers an opportunity to provide more attention and individualized support than group therapy, and therapeutic efforts may be targeted to the specific needs of the individual. This may be particularly important for survivors who indicate clinically significant levels of distress or meet diagnostic criteria for a mental health disorder, or in cases in which a group context provokes symptoms of distress or unwillingness to disclose information to group participants. The disadvantages, of course, include the added time and resources that individual therapy requires. Peer-based interventions may offer an alternative. It has been reported that peer support helps to increase knowledge about the cancer experience and possible coping strategies, decrease patient's sense of isolation, and provide a sense of hope to cancer survivors [106]. With regard to peer-based programs specifically, participants have indicated positive feelings toward having an opportunity to speak with someone who has shared similar experiences and seeing someone who has survived cancer [106]. In fact, among younger-aged survivors, meeting peers with similar cancer experiences is ranked as among the most important survivorship support needs [107]. There is limited empirical evidence supporting the effectiveness of volunteer-based support programs, and few well-designed randomized-controlled trials have been conducted. Although this may offer a cost-effective alternative to individual psychotherapy, disadvantages of peer-based programs include the lack of formal training of the volunteer support providers; the success of peer-based interventions may depend on their training and supervision.

Peer-based interventions represent an effort to increase the availability of psychosocial interventions by reducing costs and required resources. This may also be achieved through self-administered interventions. Self-administered interventions provide survivors with information to increase their knowledge of effective therapeutic techniques and to develop skills independently to facilitate adjustment and well-being. For example, the effect of a patient self-administered stress management intervention (SSMT) was compared to a professionally administered stress management intervention (PSMT) and a usual care control (UC) condition among cancer survivors undergoing chemotherapy [108]. The PSMT condition consisted of a single 60-min session conducted by a mental health professional in which discussion included psychoeducation regarding stress and stress management (e.g., common sources and manifestations of stress, stress management techniques to improve mental and physical well-being), guided relaxation exercises (e.g., paced abdominal breathing, abbreviated progressive muscle relaxation, relaxing mental imagery), and a brief instruction in the use of "coping self-statements" [108]. In the SSMT condition, survivors were given a package of instructional resources by a mental health professional during a 10-min session in which a booklet and prerecorded audiotapes that covered the same material and training exercises reviewed in the PSMT were provided [108]. Participation in the SSMT condition was associated with positive effects on quality of life (i.e., better physical functioning, greater vitality, fewer role limitations because of emotional problems, and better mental health) compared to the UC condition [108]. Differences between the SSMT and PSMT conditions were not directly compared, though results indicated that the SSMT intervention led to improvements in quality of life similar to previously reported PSMT intervention effects but at a much more favorable cost [108]. This type of intervention is a promising alternative for survivors with reduced access to psychosocial interventions due to disease- or treatment-related disability or other limitations (e.g., lack of transportation or childcare, insurance coverage). The efficacy and cost advantages of patient self-administered interventions warrant further investigation of techniques that require limited professional time or experience to deliver.

Group Interventions

Group interventions may provide a distinct advantage over individual interventions in several key domains. First, groups provide a setting where survivors may express their feelings to others who share similar experiences, which serve to normalize these feelings and may reduce distress merely through the normalization process and feeling understood by others [20]. Intervention participants can find others who are going through the same or similar experiences with regard to specific treatment regiments and side effects, disruptions to daily routines and functional limitations, and feelings of uncertainty. Participating in a group may buffer the social isolation that frequently occurs after a cancer diagnosis and provide valuable support during difficult times. Social support is needed for successful coping, and group interventions may provide a new and very important social connection and sense of community.

Moreover, many survivors take great pleasure in providing support to fellow group members. This has been termed the "helper-therapy principle" and suggests that many survivors gain new self-esteem by being in a position to share their experiences in ways that will help others undergoing similar difficulties (e.g., "giving back") [20]. For example, one survivor may be able to not only commiserate with fellow members over challenges but may also be able to share tips or novel ways of coping. Members benefit from the rich knowledge gained from the collective experience of the group, sometimes involving information unknown to providers or interventionists, such as creative ways of dealing with a side effect. As such, group interventions provide an opportunity for members to learn from others' experiences while also gaining a sense of accomplishment and self-esteem by helping others in similar and reciprocal ways.

Group composition appears to be an important determinant of intervention efficacy. Differential effects of interventions that include homogeneous (e.g., all distressed) versus heterogeneous (e.g., both distressed and non-distressed) participants have been evaluated, but recommendations regarding the optimal conditions under which to conduct group interventions are inconclusive. Based on theories of social comparison, some studies have shown a greater benefit for participants who report high psychosocial distress at baseline and little or no benefit for those who report low distress (i.e., distressed patients benefit from the presence of non-distressed patients) [109]. The effects of social comparison depend on many different factors (e.g., need for comparison, direction of the comparison [upward or downward], whether the individual identifies or contrasts with the comparison individual, the degree to which the individual feels change with regard to the comparison is possible) [109, 110]. Research-based group interventions are typically homogenous with regard to cancer type and often distinguish between early- and advanced-stage diseases. Further research is needed to determine moderators of intervention efficacy (e.g., disease severity, baseline distress) to better inform theory and clinical practice.

Interventions for Couples and Families

Undoubtedly, the impact of cancer is not limited to the individual patient. Instead, the entire family is often affected. Each family member will have an emotional response and must also adjust to changes in roles and responsibilities and overall family functioning and well-being. Partners, in particular, must cope with worries and fears about the potential loss of their partner and their ability to provide emotional and practical support. Family members routinely provide personal care and help with logistical needs, such as driving to and from appointments, and may be the primary source of support for the cancer survivor. Taking on these responsibilities may be stressful and distressing for caregivers and affected family members. Financial concerns related to medical bills, changes in employment or income, and insurance status may also arise, adding to the stress and burden of cancer. Although spouses/partners and family members are often negatively affected, they typically fail to receive the respite and support they need and access to therapy may be limited.

All phases of the cancer experience have challenges that can be distressing to survivors and partners individually and taxing to the relationship as a whole. Through active treatment and posttreatment transition to survivorship, partners may take a more direct caretaker role. After the end of treatment, as survivors regain their strength and resume precancer activities and responsibilities, couples must navigate the transition in roles and relationship functioning again. Common stressors include changes in role functions, communication difficulties, and sexual dysfunction [71, 73, 75, 111]. Relationship distress may continue even after individual distress is alleviated [71]. Importantly, the effects of cancer may also be positive, such as increased intimacy and marital satisfaction [112]. Nevertheless, despite some indication of overall benefit, many couples will experience some difficulty adjusting to cancer-related changes in their relationship, particularly those who face more advanced-stage disease, more significant side effects or physical dysfunction, greater disruption to daily living, or worse prognostic factors.

Couple-based psychosocial interventions are effective for improving partners' individual psychological well-being and relationship functioning. Specifically, interventions have shown positive effects on communication and marital functioning, distress, appraisal of illness, appraisal of caregiving, feelings of uncertainty and hopelessness, and general and disease-specific quality of life [71, 113–117]. Partners are most often included in dyadic interventions in one of two ways: as a support to the patient learning intervention content and coping skills or by actively intervening on the couple as a unit [117]. Several theories have been identified to explain how couples cope with cancer, including relationship-focused coping, transactional model of stress, and systemic transactional model of dyadic coping [118]. Additionally, self-regulatory theory has been used to explore couples coping with risk or diagnosis of cancer. This theory posits that an individual is likely to respond to health-related threats based on how the individual affectively and cognitively processes threat-related information, so within a couple, each individual will respond and create a complex overall couple response to such information [119]. The majority of couple-based interventions have included heterosexual couples coping with breast and prostate cancers, and interpretations may not generalize to other cancers or couple types. Localized prostate cancer, for example, has a high survival rate, and couples are more likely to focus on treatment-related side effects and long-term adjustment issues, whereas couples coping with lung or pancreatic cancer will most likely have to face end-of-life concerns and open communication about grief and loss. Couples' concerns and demands on the relationship will differ depending on cancer site and stage. Individual and relationship moderators of psychosocial interventions are discussed in more detail below, though gender has been found to play a role in couple responses to the cancer experience with women often experiencing greater levels of distress than men regardless of role (e.g., patient or partner of patient [120].

Caregiver Interventions

It is well recognized that informal family caregivers face their own stresses and psychological burden associated with the physical and emotional toll that comes with providing care to a patient with cancer. Family caregivers may include partners, adult children, or other loved ones that are able to provide support and care. These individuals typically receive little preparation, training, or support to learn and perform their caregiving role. Often in a very short amount of time, they must navigate role transitions with the patient, along with the added responsibilities of managing patient needs, while coping with uncertainty, fears, and other difficult emotions that arise when a partner or loved one faces a cancer diagnosis. "Caregiver burden" is conceptualized as a multidimensional biopsychosocial reaction that results when care demands exceed caregivers' personal, physical, emotional, social, and financial resources given the other multiple roles they fulfill [121]. In most instances, a cancer diagnosis occurs unexpectedly, and both patients and their loved ones are unprepared for the challenges ahead. Those that take on caregiving roles often feel overwhelmed by the added responsibilities, life changes, and emotional difficulties and struggle to continue self-care behaviors. Caregivers have been shown to report high levels of distress, and caregiver burden is associated with increased anxiety and depression over time [122, 123]. Caregiver burden is also associated with physical health complications including sleep difficulties and fatigue, lowered immune functioning, poor health-related behaviors, and greater morbidity [124, 125]. Conversely, there is some evidence for the potential rewards of providing care, including gaining meaning in life and increased appreciation of others [126, 127]. Nevertheless, the psychological and physical symptoms associated with caring for a patient with cancer place caregivers at greater vulnerability for experiencing negative outcomes.

Given these risks, caregiver-focused distress screening is warranted and has been shown to be feasible and perceived favorably by caregivers [128]. A number of systematic reviews of psychosocial interventions for informal caregivers have been conducted [129–135]. Common components of caregiver interventions include psychoeducation, skills training, and therapeutic counseling, commonly based in a cognitive behavioral theoretical framework. Strategies used in cognitive behavioral interventions include cognitive restructuring, coping skills training, problem-solving techniques, behavioral activation, the use of structured homework, and relaxation techniques for stress and anxiety management [134, 136]. Interventions may be delivered to caregivers alone or jointly to patients and caregivers. Psychosocial interventions targeting caregivers have been shown to significantly reduce perceived burden of providing care to the patient with cancer, improved coping ability, increased self-efficacy, improved physical well-being, and improved quality of life. Notably, some evidence suggests the magnitude of effects may only be small to medium, and robustness of findings limited [135], which may depend on baseline caregiver needs and levels of distress, intervention fidelity, and therapeutic approach. Most intervention studies have been conducted with primarily female caregivers, and further work is needed to successfully implement interventions into practice. Widespread programs do exist, representing varied ways of addressing caregivers' needs across settings e.g., [137].

Modes of Delivery

An important consideration regarding the delivery of psychosocial interventions to cancer populations concerns their availability and accessibility. There are barriers that sometimes prevent cancer survivors from attending in-person intervention sessions such as debilitating side effects, geographic distance, and access to transportation, as well as work- and family-related responsibilities (e.g., need for childcare) [108, 138–142]. Additionally, many survivors may prefer not to return to the hospital, which may be a trigger for cancer-related distress [143]. Telehealth and telemedicine options have certainly become more commonplace in recent years, and many survivors may prefer interventions that are delivered remotely via digital health platforms. Home-based interventions that utilize digital platforms or rely on mailed materials may offer greater hope of reaching those that would otherwise be unable or unlikely to participate.

There are several advantages to remote/home-based verse in-person interventions. The modality of delivery is relatively flexible. For example, psychoeducational material may be delivered synchronously (e.g., real-time telephone calls or chat rooms) or asynchronously (e.g., materials that are mailed or emailed). There is also a greater variety of facilitation options including increased scheduling convenience, which may translate to increased access for individuals who would otherwise be unable or unlikely to attend. Depending on the use of technology, remote interventions may require fewer resources and costs than in-person interventions [140, 141].

Digital platforms include the internet, smartphone application (apps), and telephone or telehealth options (e.g., video conferencing). Evidence supports the efficacy of digital interventions across a range of outcome variables. Internet-based psychoeducational interventions have shown significant benefits for survivors of cancer, including decreased depression and fatigue and increased health-related quality of life and cognitive function [144, 145]. For example, breast cancer survivors have demonstrated significant improvements in depression, cancer-related trauma, and perceived stress following a web-based psychoeducational support group (12-week intervention) [142], as well as significant improvements in exercise behaviors and weight gain following a telephone-based physical activity intervention even during adjuvant treatment phases that included chemotherapy and/or radiation [146].

App-based interventions may assist in targeting and engaging populations previously underrepresented in hospital-based psycho-oncology research. Apps may be refined for specific, targeted outcomes, like psychosocial (e.g., fear of recurrence) or physical symptoms (e.g., fatigue), adherence to treatment, and promotion of health behaviors (e.g., exercise and weight loss) [147–150]. Findings suggest that technology-based interventions may be effective in improving disease-specific and general quality-of-life outcomes among patients undergoing active treatment and into survivorship. Technology may be used in combination with more traditional types of interventions to optimize delivery and access, such as using an app, website, or telephone, to compliment and expand in-person intervention support. Additional research is needed to assess the role of ever-changing technology in the delivery and use of psychosocial interventions in cancer populations.

There are some disadvantages and limitations to consider with remote interventions utilizing digital platforms or technology. The most obvious is that individuals must have access to and knowledge of the technology that is required to participate in the intervention including devices (e.g., smartphone, computer) and Internet/Wi-Fi access, as needed. This is particularly relevant to older and rural populations who may not be as familiar with or comfortable using more advanced technology (e.g., "web cams") or have reliable Internet access. Technological mishaps may be frustrating for intervention participants and disruptive to group processes and cohesion. Intervention facilitators should be aware of potential difficulties and prepared to adjust to whatever problems may arise during the course of the session. The use of mobile phones and internet to deliver an intervention may add additional concerns regarding confidentiality and privacy. For example, group-based interventions via video conference calls carry the inherent risk that non-group members may overhear group discussions or see participants' faces, or group members may allow non-group members to view postings by participants or see photographs of other members. Participants should be reminded of the limitations of confidentiality and that their postings should be treated as potentially public documents. Despite these limitations and given the barriers to dissemination of in-person interventions, there is a distinct need for remote and home-based interventions. Preliminary evidence indicates that home-based interventions are feasible, affordable, and acceptable to survivors and may be beneficial across disease-specific and general quality-of-life outcomes. Remote technology interventions provide an efficient means of reaching survivors who may otherwise be physically and/or socially isolated or lack the self-efficacy to report problems and seek support.

Interventions Across the Cancer Continuum

Pretreatment Interventions

The number of interventions that have targeted survivors in the pretreatment phase of their cancer experience is limited. Psychosocial interventions have been used to prepare survivors for the likely sequelae of physical and functional side effects and emotional reactions following treatment, and evidence suggests they may be effective in preserving quality of life over the course of treatment. A review of pretreatment interventions suggests that several different types (e.g., psychoeducation, behavioral, coping skills training, relaxation, and guided imagery) administered prior to the start of chemotherapy demonstrated positive effects on treatment side effects (e.g., nausea, vomiting), emotional distress and depression, functional limitations due to disease and/or treatment, and better overall quality of life [108].

Psychoeducation interventions may be used to reduce fear and uncertainty. Reviews suggest that psychoeducation that focuses on what to expect posttreatment and ways to cope with disease- and treatment-related stressors are beneficial. For example, a 90-min "coping preparation" intervention for survivors about to start chemotherapy included a tour of the oncology clinic, provision of videotaped and written materials about coping with the effects of treatment, and a discussion session with a therapist and was combined with a relaxation training intervention. Compared to relaxation training alone and a standard treatment control condition, the combined coping preparation plus relaxation training intervention resulted in less anticipatory nausea, less depression, and less interference in daily life from disease- and treatment-related effects [29, 151]. Similarly, a psychoeducation intervention consisting of only a brief (15–20 min) meeting with a counselor delivered at the time of the initial treatment consultation with the medical oncologist and designed to orient the survivors with the facility and prepare them for their treatment (i.e., included a tour of the oncology clinic and treatment procedure rooms, description of clinic procedures, provision of contact information for clinic services and local and national support services, and a question and answer session) demonstrated positive effects on anxiety and depressive symptoms and satisfaction with medical care compared to usual care alone [151].

Interventions administered prior to the start of treatment that attempt to prepare survivors to cope with treatment-related challenges and side effects may have a beneficial impact on physical and psychosocial outcomes. Behavioral interventions that consist of relaxation training (e.g., progressive muscle relaxation and guided imagery techniques) prior to the start of chemotherapy resulted in fewer treatment-related side effects (e.g., nausea, vomiting), less psychological distress, and better overall quality of life compared to standard treatment control conditions [29, 152]. Likewise, relaxation and stress management interventions administered prior to surgery significantly improved postoperative mood and quality of life, and some evidence suggests that benefits may extend beyond the perioperative period. For example, a preoperative interview with either a 30-min psychotherapeutic intervention or chat with a consultant surgeon trained in listening and counseling skills was effective in improving adaptive coping strategies and reducing body image distress, depression, and anxiety compared to standard care alone among breast cancer survivors at 3 months post-surgery (some effects continued up to 12 months post-surgery) [153]. The psychotherapeutic intervention was superior to the chat with a surgeon condition only among participants who reported severe stressful life events, highlighting the increased need for distress screening and targeted intervention for at-risk survivors [153].

Findings support the utility of cognitive behavioral and relaxation techniques, specifically, to enhance stress management and adaptive coping skills and suggest that interventions do not necessarily have to be extensive in nature (i.e., one to two sessions). Further research is needed to determine the specific timing of optimal intervention design (e.g., time-limited prior to treatment versus ongoing throughout treatment course) and to identify those survivors most likely to benefit from different treatment components (e.g., relaxation training versus cognitive stress management techniques). Although pretreatment interventions among cancer survivors are limited, interventions conducted prior to treatment in other disease populations further support their utility. For example, the provision of stress management and relaxation techniques prior to surgery in various non-cancer patient populations has been associated with less pain and use of analgesic medication, lowered blood pressure, less distress, and better quality of life in following surgery [154].

Interventions Conducted During and Immediately Following Treatment

The vast majority of psychosocial interventions in cancer survivors have been conducted either during active treatment or in the first year following the termination of primary treatment. Reviews of the literature have suggested positive effects on a range of outcomes, including psychosocial and behavioral well-being, and general and disease-specific quality of life [155]. These are reviewed below.

Emotional and Physical Well-Being and Quality of Life

Reviews of the literature support the efficacy of psychosocial interventions among cancer survivors during and immediately following active treatment, particularly regarding their effects on emotional well-being. Emotional well-being outcomes have included distress, anxiety and depression, anger, self-esteem, optimism, and self-efficacy. Interventions promote better understanding of illness, self-efficacy, having a more positive outlook, benefit finding, and hope for the future. Important physical outcomes include pain, sleep disruption or insomnia, vigor, and fatigue. Group-based cognitive behavioral interventions appear to be efficacious in improving emotional well-being and quality of life in cancer survivors in the posttreatment period, while improvements in physical functioning may be less prominent [30]. Cognitive behavioral interventions, specifically, have been related to short-term effects on anxiety and depression and both short- and long-term effects on depression and quality of life [29]. Group interventions that utilize cognitive behavioral approaches have considerable potential to be incorporated as a routine part of clinical care offered to survivors finishing treatment to promote positive adjustment to cancer survivorship, and remote delivery should be considered to increase accessibility and convenience for participants. Similarly, stress management and relaxation training are effective and feasible intervention components to improve coping, emotional well-being, and quality of life among survivors undergoing active treatment and in the transition to posttreatment survivorship. The majority of psychosocial interventions for cancer survivors focus on dimensions of psychological distress and health-related quality of life; greater attention should be paid to mechanisms of action (i.e., psychological and physiological processes that promote positive outcomes) [156]. Although cognitive behavioral and stress management approaches are suggested as viable and effective interventions, further research is needed to improve long-term benefit.

Immune Function

Psychoneuroimmunology is an area of growing interest that focuses on the complex interplay of illness, immunity, and psychosocial factors. Stress is one factor that has been identified as playing a key role in the development, progression, and fight against cancer [157]. Immune function is a primary pathway through which the impact of stress and other negative psychosocial factors impact patient health and well-being. A variety of physiological and biological markers may be measured to assess immune function, such as levels of immune cells (e.g., lymphocytes, natural killer cells, T-cell activity), inflammatory factors (e.g., cortisol, interleukin (IL)-2, IL-6, IL-10, C-reactive protein, cytokines), and expression of disease and metastasis-related genes or receptors [157, 158]. Negative psychosocial factors, such as chronic stress, distress, depression, poor social support, disrupted sleep, and perceived social isolation, have been associated with negative changes in the immunity of patients with cancer, such as dysregulated cortisol slopes, increased inflammation, decreased white blood cell counts, and damaging oxidative cellular stress [157, 159–161]. Furthermore, negative PNI changes, like these, have been linked with worsened patient morbidity, mortality, and disease prognosis.

Behavioral and psychosocial interventions intend to alter such emotional and psychosocial states, in turn facilitating changes in immune function, and ultimately improving clinical outcomes. Psychosocial interventions include individual therapies (e.g., expressive writing, cognitive-behavioral therapy, massage, relaxation and visualization training, psychoeducation, hypnosis) and group programs (e.g., cognitive behavioral stress management, mindfulness-based stress reduction, Qigong, yoga, body-mind-spirit) [162]. Recent reports suggest interventions based in cognitive behavioral therapy are most effective in improving immune outcomes [163], which may be mediated by components of mindfulness that act on downregulating sympathetic nervous system activation caused by stress [164]. Patients who received group interventions have improved short-term (e.g., 1 year) survival, compared to individual interventions or controls. However, results are mixed, often report small effect sizes, and vary by stage and disease type, thus warranting further research in this area [158, 165–168]. PNI pathways in the body show promise and warrant further attention as outcomes in psychosocial interventions due to their involvement in important clinical indicators, like survival.

Survival

Very few psychosocial or behavioral intervention studies conducted in cancer have examined survival as an outcome, and conclusions regarding improvement in survival time following participation in an intervention are preliminary. Although some studies have reported beneficial effects on survival time (e.g., supportive-expressive group therapy [169–172], psychosocial behavioral intervention [173, 174], psychoeducational intervention [175], intervention to improve medication compliance [176]), other studies have found no significant survival benefit of participation involving various forms of psychotherapeutic intervention [171, 177, 178]. Efficacious studies have been conducted in several cancer populations, including breast and malignant melanoma, with follow-up times of up to 10 years post-intervention [87]. Common factors among those interventions that demonstrated significant effects on survival have been identified [179] and include (1) group compositions that were homogenous with respect to cancer type and stage and (2) interventions that included an educational component, stress management, and coping skills training [179]. However, in a meta-analysis of the effect of psychosocial interventions on survival time in cancer, neither randomized or nonrandomized studies indicated a significant effect [179]. The authors highlighted several methodological limitations in making comparisons across studies due to significant variability with respect to cancer types and stage, intervention components, and follow-up times [179].

Several psychosocial factors have been linked to the development and progression of cancer and have been shown to be important considerations in cancer care, including helplessness/hopelessness coping style and social isolation. It is plausible that interventions that alter modifiable risk factors may significantly impact prognosis and survival. For example, high levels of perceived stress have been shown to have suppressive effects on immune function, and this relationship may be modulate by social support [180]. Psychosocial interventions that aim to reduce perceptions of stress, improve physical and emotional well-being, and achieve optimal immune function may very well influence relevant disease-related factors related to prognosis and survival. Conclusions regarding the benefit of psychosocial interventions on survival should be interpreted with caution, but theory and empirical evidence provide rationale for further investigation.

Mixed Findings

While there have been many reviews that have strongly supported the benefit of psychosocial interventions on emotional and physical well-being, adjustment to disease- and treatment-related side effects, and quality of life, others have offered only tentative recommendations or have cited insufficient evidence with which to make recommendations for or against the use of interventions. Meta-analyses have cited several problems in how results are reported in the literature such as low quality of methodology and inconsistent findings regarding intervention efficacy [181–183]. One reason for inconsistent findings is the inclusion of survivors who are not in need of psychosocial support and lack of individualized and targeted intervention strategies. Reviewers have recommended that large-scale studies should screen survivors for distress prior to enrollment [178]. Additionally, few interventions have reported mechanisms of change associated with positive outcomes.

Taken together, evidence suggests that psychosocial interventions need to be employed with greater awareness of moderating factors associated with emotional distress and intervention efficacy as well as mechanisms of change associated with active verse inactive intervention components. To this end, intervention components may be developed with greater specificity to target cancer populations and subpopulations characterized by different sociodemographic and health-related factors and psychosocial needs. A greater understanding of factors that are associated with increased risk of poor adjustment and active therapeutic mechanisms will result in refinements to interventions that enhance efficacy and inform underlying theory.

What Works for Whom?

Sociodemographic Factors

Age Evidence suggests that younger survivors are more likely to experience emotional distress (e.g., depression and anxiety) in response to cancer and its treatment than older survivors, particularly among women [28]. This may be due to younger survivors feeling more unprepared to cope with a serious threat to their health and mortality, particularly if other responsibilities (e.g., parenting of younger children) are a concern. Conversely, older survivors (>65 years) may already be coping with age-related declines in physical health or may have peers that have faced similar (or worse) health challenges and therefore better equipped to negotiate cancer-related changes. For example, despite experiencing significant treatment-related disruptions to physical well-being, localized prostate cancer survivors often report above average levels of emotional well-being compared to age-matched normative populations [184].

Socioeconomic Status Disparities in quality of life among cancer survivors may be explained in part by differences in socioeconomic status (SES). High-income survivors are not only more likely to survive cancer but have greater access to resources and report higher levels of quality of life than low-income survivors [47]. Cancer diagnosis and treatment may exacerbate socioeconomic difficulties, or socioeconomic concerns may arise from cancer treatment such as financial stress related to costs of care, access to health insurance, and the ability to continue or return to work or school. Individuals characterized by lower SES may be in greater need of psychosocial interventions designed to address stress management and active coping skills to access resources and meet global needs of daily living such as dependable access to food and shelter. Some evidence suggests that survivors who report lower SES may benefit more from interventions than those who report higher SES, but this likely depends on the type of intervention and targets of therapy [185].

Ethnicity and Cultural Backgrounds Ethnic minorities are more likely to experience greater difficulty adjusting to cancer and greater decrements in quality of life, as well as worse health outcomes, including more frequent recurrence, shorter disease-free survival, and higher mortality rates [186–188]. Immigration status and language barriers pose additional challenges in accessing care and getting cancer needs met [189]. Despite this, few interventions have been tailored to meet the specific needs of ethnic minorities with different cultural backgrounds, and limited evidence has evaluated the extent to which ethnic and cultural differences are associated with intervention efficacy [91, 190, 102]. Furthermore, strategies to achieve cultural appropriateness within psychosocial interventions for ethnic minorities have largely focused on recruitment and retention efforts and have not focused enough on ensuring that sociocultural concepts are incorporated into content of the intervention [191]. Although some efforts are underway [192, 193], cultural adaptation of evidence-based interventions for ethnic and cultural subgroups is a priority area in psycho-oncology.

Medical Factors

Not surprisingly, more advanced disease is associated with greater likelihood of psychological distress and worse physical functioning and overall quality of life. As such, there is an increased need for effective psychosocial interventions in this patient population. Support-expressive therapies and cognitive behavioral therapy have been shown to be effective in preventing or relieving depression and anxiety among survivors with metastatic disease; relaxation techniques, alone or in combination with education/skills training, may be more effective in preventing or relieving depression and anxiety among survivors in the terminal phase of their disease [46].

Physical and Emotional Well-Being

Cancer survivors who report significant distress and/or disability throughout the cancer continuum are likely to be in need of psychosocial interventions, and limited evidence suggests that intervention efficacy may vary depending on baseline levels of physical and emotional well-being [194]. Furthermore, interventions designed for cancer survivors experiencing heightened levels of psychological distress have demonstrated immediate and sustained intervention effects [22, 29]. Finally, as the stress of cancer often exacerbates prior psychiatric symptoms or mental health disorders, identifying those who may be at increased risk for clinically significant symptoms based on their mental health history may also be important.

Perceived Stress

The degree to which cancer survivors appraise their situation as being unpredictable, uncontrollable, or overwhelming has significant implications for their emotional well-being [172, 195, 196]. Perceived stress has been shown to be a significant moderator of intervention effects on emotional well-being such that those with higher levels of perceived stress at baseline report significantly greater improvements in emotional well-being following participation than those with lower levels of perceived stress at baseline [197]. Similarly, greater severity of lifetime stressful events has been associated with greater benefit from interventions including improvements in adaptive coping skills and emotional well-being (e.g., depression, anxiety, body image distress) [153]. As perceptions of stress and stress management skills have been significantly related to lowered emotional well-being, physical functioning, and lowered quality of life, findings suggest an increased need for screening and targeted interventions for survivors with high levels of perceived stress.

Social Support

Higher levels of social support are associated with better general and disease-specific quality of life, and, conversely, social constraints (e.g., avoidance of cancer-related discussions) are associated with worse emotional well-being and quality of life [198, 199]. Cancer survivors with less social support and fewer interpersonal resources with which to cope are at increased risk for experiencing emotional difficulties and decrements in quality of life and are more likely to benefit from psychosocial interventions. Social isolation, living alone, and being unmarried or unpartnered negatively affect psychosocial outcomes and mortality [200]. Among breast cancer survivors, lack of personal resources (i.e., low self-esteem, low body image, low perceived control, and high illness uncertainty), low partner-specific emotional support, and lack of physician informational support have been shown to be associated with intervention efficacy, independent of socioeconomic status, and disease stage [201]. Similar findings have been reported among male cancer survivors and suggest that single men, compared to single women and married or partnered men and women, may be particularly vulnerable to psychosocial and health-related morbidity due to low levels of support [200, 202]. It remains unclear whether men would also benefit from emotional support interventions despite reluctance to admit as much, and evidence suggests the importance of considering social support as a moderator of intervention effects. Young adult survivors are also at higher risk for support deficits given their unique stage of social development and lower chance of knowing same-aged peers with similar cancer histories and report peer support as a primary unmet need in survivorship.

Coping Styles

Research suggests that different coping styles are differentially related to adjustment and well-being. Generally speaking, greater optimism and active coping styles relate to more positive adjustment [203, 204]. Approach, problem-focused, and emotion-focused coping strategies (e.g., seeking social support) are associated with better physical and emotional well-being, whereas avoidant coping (e.g., disengagement, cognitive avoidance) is associated with worse outcomes [52, 205–207]. Approach coping has been related to better self-esteem, positive affect, and lower depression and anxiety symptoms, whereas avoidant coping relates to worse psychological adjustment and physical functioning [207]. Among a mixed sample of male cancer survivors, avoidant coping was associated with greater severity of sleep disruption and more interference with daily functioning; increased depression was identified as a significant mediator of the relationship between avoidant coping and sleep disruption [208]. Women with gynecologic cancer undergoing extensive chemotherapy who reported greater use of avoidant coping were also more likely to report poorer physical and emotional well-being and greater anxiety, depression, fatigue, and total mood disturbance; those using active coping reported less distress, better social well-being, and closer relationships with their doctors [209]. Evidence also suggests that negative effects associated with avoidant coping may be more pronounced among survivors with advanced-stage disease and/or extensive treatment regimens [210]. Alternatively, emotion-focused coping may be more effective among survivors with advanced cancer than problem-focused coping [206]. Findings are mixed regarding the effects of religious or spiritual coping, though evidence suggest that this type of coping may be particularly relevant in advanced-stage disease and during end-of-life care [43, 44]. It has been postulated that avoidance and denial coping may be beneficial to some individuals, particularly those who may not have adequate intra- or interpersonal resources with which to acknowledge and accept the full extent of disease- and treatment-related challenges [206]. The effectiveness of these coping strategies among subgroups characterized by different psychosocial needs requires further evaluation.

Accessibility of Care

As described in this chapter, there are a wide variety of formats, delivery modalities, and content provided in psychosocial interventions for cancer patients. An additional area of interest includes accessibility of such interventions and care: if we develop effective interventions, how do we get them to those in need? A key step to providing accessible care is to first identify those in need, and we previously discussed the need for distress screening before, during, and after cancer with appropriate follow-up and referral. Additionally, interventions to improve care coordination, including patient navigation, case managers/coordinators, and patient-centered care approaches, are key for assisting patients and loved ones to access appropriate care, resources, and support. Cancer care coordination interventions are generally well-received and have effectiveness across several clinical outcomes, including increased appropriate healthcare utilization in urgent, primary, and end-of-life care settings, decreased costs of healthcare utilization in cancer survivors, improved psychosocial outcomes of patients, and decreased hospitalizations and emergency department visits [211]. Additional studies found encouraging improvements in satisfaction of cancer care after receiving patient navigation; however, few rigorous studies exist to characterize this relationship [212]. Such findings support additional research to investigate and integrate these interventions into cancer care settings.

Nontraditional methodological designs of research trials testing psychosocial oncology interventions, such as multiphase optimization strategy (MOST), sequential multiple assignment randomized trials (SMART), and implementation designs, may lend insights into accessibility of who, when, and how interventions should be provided. MOST designs offer a three-phase approach to identify which components of a multifaceted intervention are most “active” or effective [213, 214]. SMART designs utilize re-randomizing participants to varying lengths of intervention to assess the adaptability or benefits in variation of an intervention [213]. MOST and SMART design trial findings are limited in psychosocial oncology research; however, trials are currently underway to explore these methodologies [214–216]. Both MOST and SMART designs aim to identify potent and effective intervention components that may be later tested in traditional randomized controlled trials (RCTs), thus increasing efficiency of intervention development [213, 214]. Implementation and dissemination research designs are at the forefront of psychosocial oncology as critical steps for increasing access and integration of care. Barriers to implementation and dissemination exist at patient, provider, and healthcare system levels [8]. Recommendations for implementation of interventions include pragmatic design elements of trials, intervening at multiple levels (e.g., patient, caregiver, family members, clinical care providers, organizational settings), and conducting hybrid effectiveness-implementation study designs [217]. Ultimately, accessibility of care encompasses patient (e.g., care coordination and patient navigation), organizational (e.g., screening and identifying those in need), and methodological (e.g., methodological design and systematic implementation) approaches in the development and delivery of psychosocial interventions in the oncology setting.

Stepped Care

There are multiple ways of intervening in cancer survivorship to address psychosocial needs and distress. Regardless of the intervention approach, it is important to consider the distress continuum

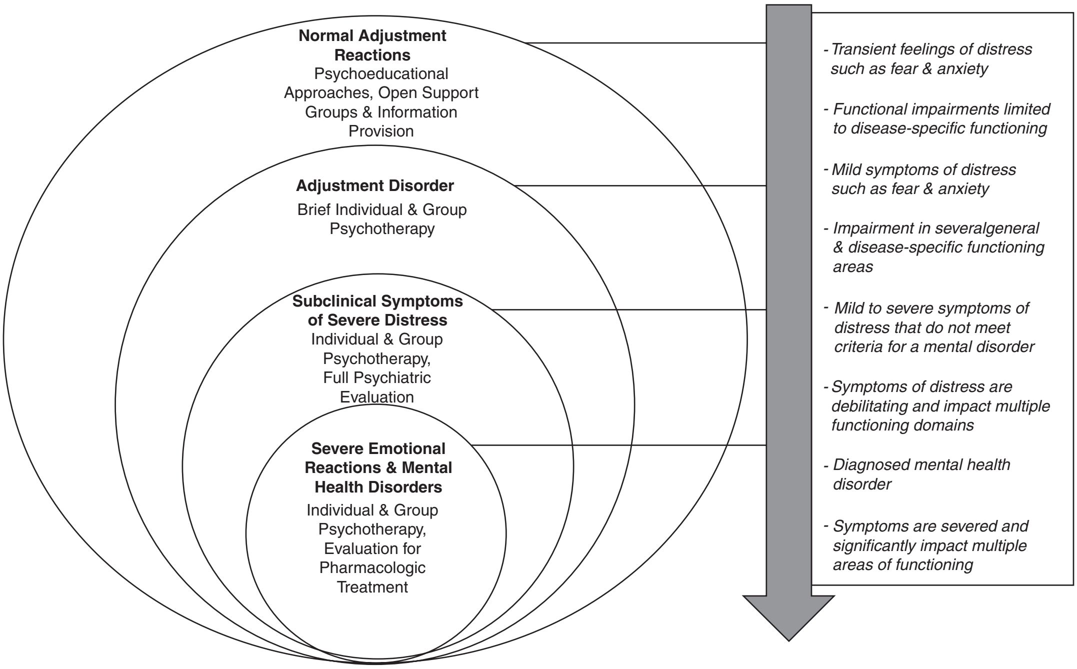

Fig. 10.2 Psychological intervention stepped approaches as a function of emotional reactions across the cancer distress continuum

among cancer survivors to determine the most optimal level of care based on their needs (see Fig. 10.2). Psychosocial intervention is not necessary for all survivors, and a stepped care model of intervention delivery is recommended. This involves a collaborative care approach in which survivors are involved in treatment planning and therapeutic resources are utilized based on systematic assessment and monitoring of survivors' psychosocial well-being. Stepped-care approaches stipulate that treatments of different intensity are provided depending on the need of the individual, thus creating an individualized treatment plan. Treatments are initially implemented that are of minimal intensity but still likely to provide benefit and progress to more intensive interventions only if survivors do not demonstrate improvement from simpler approaches or for those who can be reliably predicted to not likely benefit. An important feature of the stepped-care model is that progress and decisions regarding intervention efforts are systematically monitored and changes in outcomes of interest are carefully assessed. A "step-up" to a more comprehensive therapy is made only when there are not significant gains in the targeted outcomes. Stepped care may involve increasing intensity of a single therapeutic approach, transition to a different therapeutic approach, or using several therapeutic approaches additively. Likewise, different interventions may be applied to address different aspects of a patient's problem. Psychosocial needs also change as survivors move through their cancer experience and either transition to survivorship or face advanced disease and end-of-life concerns. Utilizing a stepped-care approach to promote adjustment and well-being at all phases of the cancer experience may enhance intervention efficacy through more stringent assessment methods and appropriateness of intervention techniques, while also conserving therapeutic resources.

The model in Fig. 10.2 proposes that treatment planning and intervention efforts must consider the distress continuum among cancer survivors to determine the most optimal level of care as the majority of individuals experience some transient levels of distress at diagnosis. For most, emotional reactions will be transient and significantly below clinical levels, and effective interventions include information provision or psychoeducational approaches that offer information on what to expect from treatment, the recovery process, available options for coping with side effects, and skills to effectively navigate the healthcare system or to communicate with loved ones. A minority but yet significant number of survivors may experience emotional reactions that warrant a more structured approach to psychological care. In such cases, brief individual and group psychotherapeutic approaches can be useful in ameliorating persistent symptoms of distress. Cancer survivors who experience subclinical manifestations of mental health disorders such as anxiety, depression, and PTSD (i.e., experience severe symptomatology but not meeting diagnostic criteria) may benefit from a full psychiatric evaluation to determine the most appropriate level of care. For these survivors, individual and group psychotherapeutic approaches can positively impact mental health and health-related quality-of-life outcomes. Among the subgroup of survivors who experience severe emotional reactions and are diagnosed with a mental health disorder, evaluation for pharmacologic treatment, in addition to individual and group psychotherapeutic approaches, is warranted.

Summary and Future Directions

Several psychosocial intervention models in cancer have shown success in reducing distress, improving quality of life, and facilitating the overall posttreatment adjustment period. Psychosocial treatment approaches have ranged from open support groups and psychoeducational programs that are based on information provision to supportive group therapy approaches and individual treatments that are structured to provide a nurturing environment to express concerns over the multiple challenges associated with cancer survivorship. Both individual- and group-based interventions based on cognitive behavioral intervention models that blend a variety of therapeutic techniques (e.g., cognitive restructuring, relaxation training) have shown success in improving health-related quality of life across multiple cancer populations. Other intervention approaches include mindfulness-based stress reduction, emotional expression, symptom management, health behavior change, and motivational interviewing. A significant amount of research has shown that effective therapy components in multimodal intervention efforts include techniques such as relaxation training (e.g., guided imagery) to lower arousal, disease information, and management, an emotionally supportive environment where participants can address fears and anxieties, behavioral and cognitive coping strategies, and social support skills training. Therapeutic processes by which participants benefit from intervention include giving and receiving information, sharing experiences, reducing social isolation, and providing survivors with coping skills that facilitate self-efficacy and sense of control over the cancer experience. Some evidence suggests that cancer survivors may benefit more from structured interventions than purely supportive ones; this may be due to learning skills with which they can more effectively cope with cancer-related changes after the intervention has ended (e.g., stress management). Interventions may also be couple- or family-based, depending on the goals of therapy and targeted outcomes, and may be administered at all phases of the cancer continuum, from post-diagnosis and treatment decision-making to end-of-life or long-term survivorship time periods. Such interventions can be delivered via several modalities including face-to-face and technology-based individual and group-based formats.

There is a large literature documenting the effectiveness of psychosocial intervention with cancer survivors. Interventions have demonstrated positive effects across a range of psychosocial and physical outcomes, including symptoms of depression and anxiety, and cancer-related fear, social functioning, and disease- and treatment-related symptoms (e.g., fatigue, nausea, pain). Although findings have been mixed with reports of nonsignificant effects as well, several reviews of the literature have concluded that the majority of psychotherapeutic interventions among cancer survivors demonstrate some improvement in psychosocial adjustment. Notably, sociodemographic factors (e.g., age, education, and socioeconomic status), premorbid psychological and physical functioning, social support, coping styles, and certain personality traits (e.g., neuroticism, interpersonal sensitivity, and social inhibition) have been associated with increased risk of adjustment difficulties following cancer diagnosis and treatment, suggesting that there may also be considerable variability in baseline functioning and response to intervention efforts.

There are also notable gaps in the literature regarding benefits of psychosocial interventions for survivors with certain demographic, disease, and treatment characteristics. This is particularly true for ethnic and racial minorities, and there is a critical gap in our understanding of whether interventions need to be specifically tailored for ethnic and racial minority groups. A significant amount of the work has also focused on more common cancers, and less is known regarding the utility of conducting psychosocial interventions among cancer survivors diagnosed with less common cancers, which are typically associated with greater treatment-related compromises, greater distress, and poorer survival rates.

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11 Altruism in Relation to Live Donor Liver Transplants for Liver Cancer

Brian I. Carr and Adil Baskiran

> Anyone who saves one life is as if he saved the entire world. (Talmud, Mishna Sanhedrin 4:5)
>
> And if anyone saves one, it is as if he had saved the lives of all humanity. (Koran Sura 5:32)

Summary

This chapter briefly reviews the history of altruism and several biological considerations, as well as national, cultural and even religious differences. Live organ liver donation is an illustration of altruism and is important in many places were medical need outstrips available cadaveric donation. The near universality of altruism propels many prospective donors, saving or extending the lives of persons suffering from liver disease. However, both altruistic donors and the transplant patients need psycho-social support, often on an ongoing basis. The examples of some donor conversations illustrate the complexity, fears and dynamics at play in so many families.

This article is divided into three sections:

A. The meanings of altruism and its concepts in general, in philosophy, in biology and history.
B. Issues concerning living organ donors from the medical literature.
C. Our experiences in a large, live-donor-based liver transplant centre in Turkey.

Meanings of Altruism

The idea of altruism in liver transplantation is the desire to donate part of the liver and thus increase the life and welfare of the individual who needs the organ. Altruism is usually regarded as a fundamental principle of transplantation. Organ transplantation is regarded as benevolent and is reasonably uncontroversial in principle, but it relies upon a supply of donated organs. The Nuffield Report provides a reason why we should continue to associate organ donation with altruism: it maintains the communal virtue of a disposition to self-sacrifice for the health needs of others. In this sense, altruism in donation is more like a form of generalized reciprocity, in which people are urged to donate partly to fulfil their desire to help others, but also because this will promote the kind of community where others would perhaps do the same for them [1, 2]. However, not all potential organ donations are

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considered ethically acceptable, such as payment for donation, although this also varies by country (section B).

Altruism is the *principle* and *moral practice* of concern for *happiness* of other *human beings*, resulting in a *quality of life* both *material* and *spiritual*. It is a traditional *virtue* in many cultures and a core aspect of various religious traditions and secular worldviews, though the concept of 'others' towards whom concern should be directed can vary among cultures and religions. Altruism can be viewed as an aspect of selflessness, which is the opposite of *selfishness*. It is an ethical theory of conduct that regards the good of others as the end of *moral* action. The term (French *altruisme,* derived from Latin *alter*, 'other') was coined in the nineteenth century by *Auguste Comte* (1798–1857), the founder of Positivism, and adopted generally as a convenient *antithesis* to *egoism.* He derived it from the Italian *altrui*, which in turn was derived from Latin *alteri*, meaning '*other people*' to designate conduct impelled by unselfish motives, inspired by the sole desire to bring about the happiness of another person, without regard to, or even at the expense of, one's own happiness [3].

Biologically, altruism can refer to an individual performing an action which is at a cost to themselves (quality of life, time, probability of survival or reproduction), which benefits another individual, without the expectation of reciprocity or compensation for that action. It may also refer to an ethical doctrine that claims that individuals are morally obliged to benefit others.

In evolutionary biology, an organism is said to behave altruistically when its behaviour benefits other organisms, at a cost to itself. So, by behaving altruistically, an organism reduces the number of offspring it is likely to produce itself but boosts the number that other organisms are likely to produce.

The opposite has also been argued that altruism is not the reason we cooperate but that we must cooperate in order to survive, and we are altruistic to others because we need them for our survival. Modern theories of cooperative behaviour suggest that acting selflessly provides a selective advantage to the altruist in the form of some kind of return benefit. Another modern perspective has been that certain types of social behaviours, including altruism, are often genetically programmed into a species to help them survive. According to the kin selection theory, altruistic individuals would prevail because the genes that they shared with kin would be passed on. Since the whole clan is included in the genetic victory of a few, the phenomenon of beneficial altruism came to be known as 'inclusive fitness' [4].

Darwin was puzzled by the consideration that natural selection should favour the ruthless. Altruists, who risk their lives for others, should therefore usually die before passing on their genes to the next generation. Yet societies value altruism, with something similar among social animals. Neuroscientists think that we have mirror neurons that lead us to feel pain when we see others suffering. So, we are hardwired for empathy and are thus moral animals [5].

Altruism in the Ancient World

In the *Nicomachean Ethics*, Aristotle (384–322 BCE) writes: 'They say that one must wish good things for a friend for his sake'. In the second book of the *Rhetoric*, Aristotle also says that loving someone entails wishing good things (or what one believes to be good things) for that person's sake and his only-not one's own, and acting, to the best of one's ability, to secure those things for him.

In identifying a set of altruistic emotions, Aristotle is concerned at least in part to distinguish them from passions that are in fact self-interested, which for Aristotle is not necessarily a negative qualification. Also, we learn from Democrates (460–370 BCE) 'The generous person is not he who looks to a return, but he who treats another well by choice'. There is a wide range of philosophical views on the obligations of humans to act altruistically. Proponents of ethical altruism maintain that individuals are morally obliged to act altruistically.

Altruism and Religion

Most religions regard altruism as an important moral value. Buddhism, Jainism, Christianity, Islam, Sikhism, Hinduism and Judaism place particular emphasis on altruistic morality.

- Buddhism: Altruism figures prominently in Buddhism. Love and compassion are important and are focused on all beings equally: love is the wish that all beings be happy, and compassion is the wish that all beings be free from suffering.
- Jainism: The fundamental principles of Jainism revolve around the concept of altruism. It preaches, *Ahimsa*, to live and let live, to not harm people and have a reverence for all life. It also considers all living things to be equal. The first Tirthankara, Rishabhdev, promoted altruism for all beings, including donation, giving oneself up for others, non-violence and compassion for all living things.
- Christianity: Altruism is central to the teachings of Jesus and Paul taught 'love seeks not its own interests'. *St Thomas Aquinas* interprets the Hebrew biblical 'Love your neighbor as yourself' (Leviticus 19:18) as meaning that love for ourselves is the exemplar of love for others and taught that Aristotle held a key in regarding the origin of friendly relations with others, as lying in our relations to ourselves and that altruism is but one possible form of love. However, an altruistic action is not always a loving action.
- Islam: The concept '*īthār*' (إيثار) (altruism) is the notion of preferring others to oneself. Altruism in Islam means to give preference to the needs of another over your own. For *Sufis*, this means devotion to others through complete forgetfulness of our own needs, and concern for others is deemed as a demand made by *Allah* or God on the human body, considered to be the property of Allah alone. Thus, *īthār* considers sacrifice for the sake of the greater good to be both important and the highest degree of nobility.
- Sikhism: Altruism is essential to the *Sikh* religion, which considers that the greatest deed any one can do is to show love, affection, sacrifice and harmony. The concept of *seva*, or *selfless service* to the community for its own sake, is an important concept in Sikhism.
- Hinduism: Selflessness, love, kindness and forgiveness are considered to be the highest acts of humanity in Hinduism. Giving alms to the poor is considered as a divine act.
- Judaism: Altruism is considered as a desired goal of creation in Judaism. An important Jewish concept is 'tikkun olam', to heal the world. It is closely allied to the concept of Tzedakah, in which charitable donors are thought to benefit as much as the recipients, and it is seen as a mandatory religious obligation. Charity is considered to be given as part of the process of seeking a just world. The antithesis between self and others is thus avoided in the ethics of Judaism, in which the fundamental motive of the moral life is in service, right now, and not the quest for happiness. This is summed up in the aphorism of the second century BCE sage Hillel (c.60 BCE-c.9 CE), who said: 'If I am not for myself, who will be? If I am only for myself, what am I? If not now, then when?' [6]. Although a person can save the life of another by sacrificing a limb, it is a choice that is encouraged and is regarded highly, but is not an obligation [7, 8].

Clinical Literature on Live Organ Donors

The shortage of deceased organ donations is a major public health concern. As supply continues to fall short of demand, patients on transplant waiting lists are dying before a suitable organ is found. In an attempt to improve this situation, medical procedures have been developed which allow a healthy, living person to donate an organ or part of an unpaired organ. Living donor transplant procedures originally required a genetic relationship between donor and recipient in order to minimize possible organ rejection. However, advances in immunosuppressants now permit non-kin live donations. Clearly, willingness to donate is significantly higher when the risk of donating is low [9]. There are large differences in organ donations by country. Thus for kidneys, *Saudi Arabia* is the highest worldwide per million population, in part due to a law that entitles the donor to compensation, a medal from the Saudi King and a discount from Saudi Airlines [10]. The '*Iranian model*' has succeeded at eliminating the waiting list for kidney donations, since paid donations of kidneys from living donors under regulated conditions are allowed. The donation is given from the recipient or, if poor, from a charitable group. This policy puts Iran in third place worldwide in terms of live kidneys per million population. However, compensated organ donation has many ethical issues and therefore is illegal in all other countries. In order to increase organ donations, some countries have agreements of collaboration, such as Scandiatransplant, which is the Nordic organ exchange organization and allows better usage of resources.

Attitudes to living donor organ donation vary hugely by country, however. In *Spain*, the attitude to live liver donations by questionnaires showed that only 44% of family members would agree to donate [11]. By contrast, 92% of *Polish* nursing students would donate if needed [12]. In another study, half of *French* adults support the altruism model of live organ donation. But a substantial minority, mostly young and more educated people, support alternative models allowing financial incentives [13]. Only a few *Romanians* held the altruism model. The free market position and compensation was the majority position (66%) [14]. In a *Greek* survey, 48% wanted to be an organ donor, and women were more prone to become donors (odds ratio 1.95), and parents were more likely to be registered as donors (odds ratio 1.84). About 63.7% of Greek Orthodox Christians wished to become donors. Interestingly, professional and education, adult children were more likely to donate (59%) an organ than their parents (37%) [15]. In a study from China, adult children were more likely to donate (59%) an organ than their parents (37%) [16]. Furthermore, it was recently reported that gender plays a major role in liver transplant successes. Among female recipients, offspring to parent live donor liver transplantation yielded inferior long-term graft and patient survival. And among offspring donors, male sex was strongly associated with inferior outcomes. They concluded that the findings have significant implications for donor selection [17].

It is becoming clear that donor care is also very important. Thus, a study of parents who donated livers to their children found that there was total agreement among the respondents that there is no choice when it comes to the question of organ donation. The findings in this study stress the importance of organizing the parental liver donation programme with as much focus on the donor as on the child [18]. In an interesting *Turkish* questionnaire study, it was found that although 88.2% of religious officials in the study stated that organ donation was appropriate according to their religion, only 1.4% agreed to donate their own organs. Participants included 59.9% who were imams and 81.2% who were Koran course educators [19]. A *Jordanian* study also emphasized the importance both of religion and of emotional support for the donors. They noted that emotional distress of living donors during the pre-donation period emphasizes the need for social and psychological support in addition to medical evaluations. In Jordan, social solidarity and religious beliefs are the most important factors that motivate donation [20]. They reported that most donors were motivated by social solidarity, and others invoked the role of their religious beliefs as the main motive. Other motives included improving the recipient's life and fear that patients would be abandoned. In a *Canadian* study on anonymous live liver donors, it was found that most donors had a university education, a middle-class income and a history of prior altruism. Half were women. Median age was 38.5 years (range 20–59). Seventy percent of the donors learned about this opportunity through public or social media. Saving a life, helping others, generativity and reciprocity for past generosity were motivators. Social, financial, healthcare and legal support in Canada were identified as facilitators. The donors identified most with the personality traits of agreeableness and conscientiousness [21]. In a *Korean* study of 10,116 living liver donors, the 10-year cumulative mortality was an amazingly low 0.9%. The most common cause of death was suicide ($n = 19$), followed by cancer ($n = 9$) and traffic accident ($n = 7$) [22]. A recent study of liver cancer patients showed that recipients of live liver donation survive longer than recipients of cadaveric livers [23]. In an Indian study of 460 donors who were evaluated for being live liver donors, 69.7% of donors did not proceed to donation. The reasons were donor-related in 63.6% and recipient-related in the rest. Donor-related reasons were donor reluctance (23.5%) and the rest were technical reasons (76.5%) relating to the donor livers [24]. Some teams, such as in Toronto, *Canada*, worked hard at the ancillary services associated with attracting and supporting live liver donors. To foster and grow live donation, they established a strong culture supporting live donation. They hired a full-time, dedicated team of individuals to support the live donor program; obtained financial support for donors through a partnership agreement with the Trillium Gift of Life Network; developed linkages with the media, community service groups and the general public; generated patient education materials; and established a website [25]. To further help live liver donors, a live donor psycho-social assessment tool (LDAT) has been developed [26, 27]. However, one study pointed out that donor resilience was an important factor, but could have been a selection criterion for donation, or contrariwise, might have been a consequence of the experience they went though [28]. Another Canadian study of anonymous liver donors found a 40% overall donor morbidity, but with no donor mortality. None expressed regret about their decision to donate, and all volunteered the opinion that donation had improved their lives [29]. There is now a considerable literature on long-term donor quality-of-life follow-up, with mostly positive assessments [30–33]. Interestingly, donor quality of life was also influenced by the outcomes in the recipient [31, 33].

Inonu University Experience with Living Liver Donors

Overall Statistics

Between 2002 and 2021, 2481 living donor liver transplants were performed. They were (85%) living donor liver transplants, with an average donor age of 31 years. Most of the patients came from the eastern provinces of the Turkey, with large families, typically with five children or more. Most of the patients (39%) had liver failure due to HBV, HCC (12%) and a variety of other liver diseases, including HCV (9%) or cryptogenic, or unknown cause (6%).

The relationships of the live liver donors to the patient comprised siblings (20%), mothers (9%), fathers (5%), sons or daughters (36.7%), nephews and nieces (6%), cousins (5%), spouse (6%), uncle or aunt (2%), bride or groom (0.6%).

Organ Donation in Turkey

Our experience is that education, socioeconomic level, culture and religion are important factors that influence people's views on organ transplantation. In Turkey, organ donation and transplantation are regulated according to a 1979 law. While 80% of the organ donors in developed countries are from cadavers and 20% are from live donors, the opposite ratio pertains in Turkey. One likely contributor to this ratio is the absence of a widespread belief in brain-death in Turkey.

Some Background on Interviews with Live Liver Donors and Families

For each recipient, about 3 prospective donors get interviewed on average, with up to 15 prospective donors, as families tend to be large.

Reasons for rejection include fatty liver (high meat diet, low exercise), small liver size for the prospective recipient size, current active hepatitis B (HBV) or hepatitis C (HCV) infection. If the recipient has HBV, then about 90% of the family will also have HBV infection. 50% of liver transplants in Turkey are for chronic HBV infection and its consequences of liver failure and/or hepatocellular carcinoma (HCC or liver cancer).

Donors are usually related to the family, being 51% females and 49% males. More females actually want to donate, but they usually have children and their families often stop them. Turkish families tend to be large with 12–16 children in religious Moslem families. The Imams tend to think that birth control is sinful. By contrast, non-religious Turkish families tend to have one to two children, as in the West. Syrians here seem to have the largest families, followed by the Kurds. However, even in Syrian or Kurdish families, there seem to be smaller numbers of children in western, as opposed to eastern Turkey. In matters of organ donation, religious factors are important here.

Donor-associated factors, post-liver transplants include depression, anger and regret. Some 10% say that if they had known of the complications, they would not have donated. Some just get angry and do not answer our questions. There are other donor anxieties or uncertainties. Many give answers related to Allah/God and religion. In our city, Malatya, patients and their families are often poor and very religious. They may not believe, but religion is important in their lives. Many donors (30%) say they have been pressured by family members to donate part of their liver. They say they don’t want to be a donor, but the family insists. Reasons include the fact that since many donors are a wife, daughter or sister, the family worries about the prospective donor’s children. Some family members may simply not like the intended recipient. The physician often gives the family an imaginary medical explanation for the donor refusal, such as poor liver size or liver disease, to avoid family fights. Of course they do not always believe him.

Sometimes there are transplant-related family problems. A woman gave her father her liver for transplant, but post-operatively, her husband got angry and decided to divorce her, due to her ugly operative scar. Sometimes, a woman donor divorces her husband as the husband opposed the donation. If we detect a disagreement in the family, we do not accept that donor.

Donor non-fatal operative complications can occur, especially biliary leaks or bleeding, but with 0 donor deaths in 2500 transplants, thus far. Biliary leaks (5%) manifest as abdominal pain, fever or ileus. Obstruction (1%) manifests as abdominal pain, vomiting, tenderness and loss of appetite. Bleeding on the cut liver surface (1–2%) manifests as abdominal pain and then fever. Most donors have untroubled minds about what has happened, go home early and have few complications; even so, psychological factors are not uncommon. These donors are mostly poor, and they receive admiration from the community. Kurds are very willing to help their large families. Syrian Arab women seem even more willing to donate than Turks or Kurds.

Examples of Four Types of Donor and Donor-Family Conversations

Type 1. Good Conversation, Good Outcome (Partial Liver Donation)

A female patient age 45 years with primary cholangitis came from Azerbaijan with her husband and 23-year-old daughter. The husband had a fatty liver and was not a suitable candidate. The daughter was tiny and weighed 50 kg., but the family did not want their only daughter to be a donor. The surgeon met privately with the daughter to discuss risks. She was both excited and frightened and asked for the family not to be told while she started pre-transplant donor testing. She was found to be a suitable donor but cried a lot. The transplant was done and was successful. She said she would never have agreed if she knew beforehand the amount of pain she would endure. Ten days later, both she and her mother left hospital. Excellent post-transplant long-term success. The Azerbaijan government pays $45,000 normally, or $55,000 with HBV present, due to the cost of HBV immunoglobulin (comparable US transplant costs: $600,000 in 2021; https://health.costhelper.com › liver-transplant).

Easy discussion with complex results. A female patient aged 60 with four adult children, who had HBV-based liver disease and came from eastern Anatolia. All four children were evaluated for being donors, but only one son was acceptable due to liver size and blood group compatibility. The surgeon discussed donation with this son, who said he was ready. Recipient and donor preparation and evaluation proceeded. The transplant was planned, and both female patient and her prospective donor son stayed in hospital the night before the planned surgery. On the day of transplant, the surgical donor team started with the donor, who had already been evaluated and signed his consent form. The donor then asked an assistant if it is a hard surgery and suddenly became fearful and shaken. He then stood up in operating room (OR) and asked the team for help due to his fear. He then walked out of the OR. The team then called the family, who did not believe what had occurred. Nobody could find the donor, till the family did, near the hospital late that afternoon. He returned to the OR, but the team could not accept him. Eventually, the son of the patient's brother was found and agreed to donate. All was cancelled while he was tested. A transplant then proceeded uneventfully. The original donor never visited his mother during that hospitalization.

Type 2. Good Conversation, But No Donation

A male patient aged 52 years had HBV and bleeding. Two sons came for evaluation as liver donors, and one son aged 26 years was found to be a suitable donor. The recipient family was prepped for the transplant. On the night before the planned transplant, the donor visited the surgeon and told him that he has a girlfriend and she did not accept that he should donate. The prospective donor decided not to donate and asked that the family not be told of his decision. The family was informed by the surgeon, who covered for the potential donor, by telling them that the donor liver tests were not normal and he would not be a suitable donor. The family was angry with the surgeon and told him to find another donor, who was not available. The patient died 1 week later. The non-donating prospective donor then visited the surgeon and thanked him for not embarrassing him to his family. He was likely pressed by the family to give unwillingly, all along.

Type 3. Bad Conversation, But Good Donor Outcome

A 20-year-old unmarried female from another Turkish city had a pregnancy-associated toxic hepatitis. She was accompanied by her boyfriend in her visit to the transplant team. She told the team that she was married in the eyes of God. The patient was very ill with hepatic coma and needed a fast transplant to survive. Her boyfriend volunteered and was found to be compatible. Our university ethics committee and psychological evaluators approved and a live donor liver transplant was done that day. Only after the transplant was the patient told the identity of her donor. However, the donor family was very unhappy about this. After 4 months, they were married officially and remain happily married for several years.

A complex story. A man loves a woman and kidnaps her (true local story). She loves him too. After 1 week, he learns that she is pregnant from another man. The pregnancy was terminated without a birth. They tell nobody about living together or their condition. After a month, they got married. All is well. One year later, they have a baby girl together. After 8 months from the birth, they learn that the baby has biliary atresia and needs a liver transplant. The man and the woman apply for divorce due to marital conflict. The court does not decide, nor does it know about the baby, which was then evaluated by paediatric gastroenterology, who agree the need for liver transplant. The wife (mother of the baby) was evaluated as a donor and found to be acceptable. However, the husband did not agree for the transplant to proceed, although he was subsequently successfully persuaded by his wife. The liver donor liver transplant was recently done uneventfully.

A very complex story. A 7-year-old male Syrian refugee child with abdominal pain and HCC (liver cancer) was staying in Istanbul. The CAT scan showed he had a large liver tumour and his family brought him to the Istanbul City municipality who in turn called the Malatya City municipality. They informed Inonu University that the Turkish government would pay for a liver transplant, if it was feasible. The child was brought to stay with our paediatrics department while being evaluated, who found his underlying liver disease was hepatitis-negative cirrhosis with HCC. No potential liver donor could be found in the immediate family. An uncle was found to be available and willing (father's brother). Our university ethics committee evaluated and approved the transplant. After the surgery, both donor and recipient were discharged from hospital within days. However, after another 5 days, the patient's liver enzymes were abnormal, and an ultrasound exam showed the presence of a portal vein thrombosis. The boy was taken back to the OR for hepatic vascular reconstruction, but the intrahepatic portal vein was found to be thrombosed, so the patient needed to be re-transplanted. The patient's condition then worsened. The Malatya municipality asked for daily reports, and a manager in the municipality office heard about this problem and asked how he could help, there being no more family donor available. Within 1 day, this unrelated manager volunteered to donate. Asked why, he said it came to him in a dream. He had never met the patient or family, but he felt a compulsion to help. The transplant team was doubtful. They put him through appropriate medical, surgical and psychological testing and blood typing. He was married and had four children of his own, ages 3–12. The transplant team asked to discuss the matter with his whole family, and they returned with him that same day. All the lab and radiology tests had meanwhile returned and were found to be both normal and compatible with his being a donor for the sick refugee child. Private conversations took place with the donor and separately, with his wife, discussing the surgical risks (2500 donor surgeries at Inonu thus far, with no donor deaths). His wife was told that without her permission, the team would not proceed. She told the team that if her husband's liver was not suitable, then the team should take hers. They were a religious family. The surgeon felt quite emotional over this generosity. The potential donor husband, age 42, was then called to interview. He was a perfect donor candidate, clinically, radiologically, ABO compatible and liver size compatible. The university ethics committee then invited the family for discussion at the municipality. They recommended a psychology evaluation, and the donor told the psychologist he wished to give his liver for God. The ethics committee reviewed the unusual circumstances with the psychologist, the police and several others. The donor told them all that he was willing to proceed, and they approved. The donor then visited the surgeon privately to discuss, and the surgeon was preparing himself for a cancellation. But the donor wished to pray in the surgeon's office and then announced that he was ready. Everything about the liver donor liver transplant went uneventfully. It is now 4 years later, and there has been no HCC recurrence. The original pathology report showed a 10 cm, well-differentiated tumour.

Type 4. Bad Conversation, Bad Outcome (No Donation)

The patient was a 52-year-old woman who had autoimmune hepatitis. She arrived with her four adult children (>18 yr.), who were all married. Seven prospective donors were evaluated (including three daughters in law), and all swore they would do anything for their mother. The youngest son was found to be a suitable donor, in terms of liver volume, biliary tract, lab values and ABO compatibility. An MRI scan was done to evaluate the biliary tract and was also normal. The prospective suitable donor returned to see the surgeon with his wife plus all his family. The wife then asked her husband to leave the room and told the surgeon that other brothers must have come and refused to donate. But the surgeon denied that. She did not accept that her husband should donate his liver. Her husband then returned to the room and asked the same questions concerning his brothers. He said, in secret, that he had only one child and did not wish to donate, but he said he was afraid his brothers would kill him if he refused to donate his liver to his/their mother. The whole extended family was called in again and told that this youngest son was not a suitable donor on medical grounds. The other siblings got angry with the surgeon, and the elder brother told the surgeon that he did not believe him. They all said the surgeon had wasted their time. The elder brother returned alone and demanded to learn the truth, and the surgeon told him that he was feeling uncomfortable with the conversation. The elder brother told the surgeon he now knew there was something strange. They all departed and nobody returned. Outcome unknown, as no other donor was available.

Conclusion

This chapter briefly reviews the history of altruism and national, cultural and religious differences. Live organ donation is an illustration of altruism. The near universality of altruism propels many prospective donors, saving or extending the lives of persons suffering from liver disease. The preceding analysis displays the deep roots of altruism and its manifestations in medical crises. But the realities of the full transplant process reveal the difficulty of achieving timely donations, since individual donors, their families and their community often struggle to balance an array of decision-related considerations. We depend on altruism for organ transplants, but the motives and reasons of donors are complex and are influenced by many factors, including socio-cultural, educational, gender and family rivalries, as in the oldest biblical narratives. Both the recipients and donors need psycho-social support, before and after the transplant procedure. From our knowledge of biology, it seems that altruistic behaviour may even be hardwired into our genes.

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Emerging Challenges in Advanced Cancer Care: Opportunities for Enhancing Patient-Centered Communication

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Introduction

As diagnostic and treatment options for cancer continue to evolve, cancer care has witnessed exciting progress. In particular, precision oncology, which uses biomarkers to identify targeted treatments for cancers, has improved outcomes in some cancers such as breast cancer, colorectal cancer, lung cancer, and acute myelogenous leukemia [1]. However, even as prognoses for some cancers and some populations have improved, cancer continues to pose enormous and life-limiting challenges to many patients. The sad reality is that many diagnosed with cancer today will face an advanced and recurrent or metastatic disease. An estimated 606,520 people diagnosed with cancer will die from the condition in 2020 [2]. While the 5-year survival rate for all cancers is estimated to be around 67%, the 5-year survival rates are much lower for cancers of the pancreas (9%), liver (18%), lung (19%), and esophagus (20%) [2]. People with advanced cancer have varied unique needs, from managing treatment-related side effects to psychological symptoms, strained social relationships, and financial burden. High-quality communication in and outside of the clinical care context is needed to identify and address the needs and priorities of patients and their loved ones. Research into how to foster patient-centered communication is of critical importance to improve cancer care and the quality of life of all those with advanced cancer.

Many of the myriad communication challenges in advanced cancer have been documented in the literature; for some, promising opportunities exist to improve and enhance patient-centered communication. To begin with, as illustrated by the term, "financial toxicities" of cancer, cancer-related costs are a major barrier to quality of life and psychosocial well-being, with negative impacts exacerbated for patients who have battled cancer for a long period of time. Patients' concerns over limited insurance coverage or surviving relatives' financial strains, as well as the lack or opaqueness of financial information, require patient-centered financial literacy interventions and improved cost communication. Another set of challenge in advanced cancer care stem from shifts in technologies and communication platforms. Increasing reliance on technology in oncology—such as the use of online health portals, telemedicine, mHealth/Apps for symptom monitoring and reporting, and Internet for

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health information—has added demand on patients to access and use technology while also offering new opportunities for patient-centered communication.

Coinciding with technologic evolution, social media has become ubiquitous. Patients and caregivers routinely access cancer-related information on social media, yet such information is often of mixed quality and accuracy. As the health information landscape is increasingly challenged by the spread of misinformation (e.g., falsehoods, myths, and unproven "miracle cures"), greater demand on digital and health literacy is placed on patients and caregivers [3–5]. This trend necessitates improved patient-centered communication to empower patients to access online cancer information and mitigate the impact of misinformation.

Moreover, patients facing advanced cancer often require significant caretaking from family members and other loved ones serving as informal caregivers [6]. Caregivers' well-being, information needs, and communication preferences are other emerging areas in advanced cancer care. Innovative interventions are poised to improve and integrate communication across patients, caregivers, and the healthcare team and to offer support for informal cancer caregivers.

Finally, while frontline therapeutics have introduced new treatments options, these new modalities may not be available or accessible to many patients. Consequently, communication challenges can ensue when some patients, upon learning about the promises of precision medicine, have unrealistic optimism or face increased confusion and uncertainty regarding their prognosis and care plans [7]. These challenges have inspired research to improve prognostic and goals of care communication as well as ways to ascertain patient values and preferences.

In addition to the key areas outlined above, a major "elephant in the room" since early 2020 is the additional challenges to care brought on by the COVID-19 pandemic. COVID-19 has upended every aspect of life, including enormous impacts on health and quality of life for those with advanced cancer. For example, concerns over virus exposure are preventing hospital visits, social isolation limits meaningful social connections, and the threat of dying without seeing loved ones has made a difficult prospect even worse. Unique health communication opportunities to support cancer patients through this crisis are beginning to be explored and implemented.

In summary, care for patients with advanced cancer is facing new and unique challenges today, bringing on new opportunities to enhance patient-centered communication. This chapter reviews critical components of each of the above-referenced issues. In each section, an overview of issues pertaining to communication will be discussed, followed by a sample of recent interventions as exemplars of opportunities to inform and improve patient-centered cancer care.

Financial Burden in Advance Cancer: Promoting Cost Conversations

People with advanced cancer often undergo intensive and costly treatments which generally undermine their financial security. Those who are underinsured, low-income, or racial and ethnic minorities are especially vulnerable to financial burden as a result of a cancer diagnosis [8]. About a third of people with advanced cancer report financial distress to be even more severe than physical or emotional distress [9]. The experience of financial burden and distress among people with advanced cancer remains under-addressed [10], despite evidence of impact on stress, quality of life, treatment decision-making, and care utilization [9, 11]. Furthermore, a longitudinal study found that patients experiencing financial hardship had, counterintuitively, over three times higher likelihood of receiving intensive and costly care [12] which can induce additional stress and suffering.

Cost conversations between patients and healthcare professionals are one critical communication opportunity to alleviate stress and help patients with advanced cancer make treatment decisions that are aligned with their goals and values. To date, patients' preferences for cost conversations far outstrip their actual occurrence. Though most cancer patients report wanting to discuss costs with their doctors and most oncologists recognize the importance of out-of-pocket costs, cost conversations remain rare [13]. For providers' part, most oncologists (84%) report considering out-of-pocket costs in treatment recommendations, yet fewer than half (43%) actually discuss costs with their patients [14]. A major barrier to cost discussion is the overall lack of transparent, accurate, accessible information about cancer costs [15, 16]. Ninety percent of surveyed physicians reported that education, web-based resources, or expert guidelines on cost-effectiveness of therapies would be useful [17]. Even with knowledge barriers addressed, providers and patients alike may feel uncomfortable about discussing treatment costs [18, 19]. Some patients worry that discussing financial challenges may cause them to receive suboptimal care [19]. Further, in general, patients lacking financial security are less likely to feel heard and understood by their healthcare providers, suggesting open, patient-centered communication about costs of care may be a key aspect of quality care in this population [20].

Key characteristics of effective cost discussion and how to implement them are beginning to be studied. Resources to support cost communication are especially salient in advanced cancer care, when trade-offs between length and quality of life tend to have significant cost ramifications and patients' preferences, values, and concerns are particularly important to ascertain [21]. In response to pressure for increased transparency in care costs (e.g., out-of-pocket costs to treatment), some health plans have developed price estimator tools for their members [22], and there is some effort to embed similar tools in the electronic health record (EHR) for physician use (https://www.cms.gov/newsroom/fact-sheets/medicare-advantage-and-part-d-drug-pricing-final-rule-cms-4180-f). The effects of these tools on cost conversations need to be measured so they can be adapted and integrated into care to support effective patient-centered cost conversations and care.

Future research efforts to support cost communication in advanced cancer may include educational tools for patients and providers, team-based care models that support patients in navigating health insurance, as well as patient-centered communication when cost conversations occur. Some newly developed tools and interventions are notable in their inclusion of cost communication: for example, one tool for people with diabetes provided a tailored list of local and national resources related to diabetes management and other social services; it was shown to significantly increase the frequency of cost conversations [23]. A primary care setting's provider training on cost communication strategies also increased the frequency of such conversations [24]. An app designed for cancer patients to support initiation of cost conversations tailored to their individual information needs and demographics has demonstrated promise in improving patients' self-efficacy and supporting cost conversations [25]. Increasing the frequency of cost conversations is an important first step. Future development and evaluation of such tools to include assessment of quality and efficacy of cost communication can help address a critical aspect of advanced cancer patients' well-being.

Information Technology in Cancer Care: Realizing Its Potential and Addressing Its Pitfalls

Rapid expansion of web-based electronic health (eHealth) and mobile health (mHealth) tools is both promising and concerning. Increased access to the internet can empower patients and caregivers to access health information and actively participate in their care. Telemedicine and patient portals can facilitate communication with healthcare providers between visits and support connections between care teams, enhancing continuity of care for advanced cancer patients [26–30]. However, there are concerns that technologies are not effectively integrated into clinical care. For example, technology may hinder effective patient-provider communication by limiting nonverbal signals such as eye contact, physical proximity, touch, or introducing frustrating delays or lags due to connectivity problems [28, 31].

Scholars have cautioned that technology ought to supplement, but not replace, in-person communication in cancer and that technology-mediated communication may not be appropriate for all patients [28, 32]. Indeed, realizing the benefit of eHealth tools requires access and technology literacy that some lack. Evidence suggests that disparities persist in the use of internet for health-related reasons. Older adults, racial/ethnic minorities, and those with lower incomes and education levels are all less likely to use technology for health-related reasons [33–35]. Individuals from these groups are also more likely to receive advanced cancer diagnoses. Potentially adding to disparities in technology use, providers may hesitate to offer eHealth-based services to patients they believe are too old or too ill to participate [36]. Narrowing these disparities requires patient-centered communication to support patients' meaningful and sustained use of potentially valuable technologies.

Palliative care is one promising context where technology (e.g., telehealth) can support advanced cancer care. The American Society of Clinical Oncology (ASCO) guidelines recommend that palliative care be delivered alongside oncology care for all advanced cancer patients [37]. Technology can help patients and caregivers connect and interact with providers, particularly when patients have limited mobility, or live in regions where access to palliative care remains low [38]. In recent systematic and scoping reviews [31] assessing the impact of video-based palliative care interactions, video consultations were found to approximate face-to-face interactions better than phones or emails. Video facilitates nonverbal communication and offers providers insight into patients' home lives, helping them respond with empathy and build rapport with patients [28, 38]. Moreover, in one qualitative study of home-based palliative care, patients described feelings of trust, closeness, and relief associated with telehealth consultations [39]. Other studies found video-based palliative care consultations to decrease anxiety for rural cancer patients [40] and to reduce hospital admissions and emergency care near the end of life by allowing remote system assessment and management [41].

Another promising use of technology in the advanced cancer context lies in symptom management: symptom monitoring devices and communication technologies can facilitate patients' and caregivers' self-management and facilitate communication of worrisome symptoms to providers. For example, the Patient Remote Intervention and Symptom Management System (PRISMS) is a smartphone app designed to track chemotherapy side effects and alert clinic nurses when symptoms exceed preset levels [42]; such tools have helped empower patients and improve patient-provider communication [43]. The use of another self-management intervention, *Webchoice*, was associated with lower symptom distress, anxiety, and depression than usual care [44]. Similar online symptom reporting systems aimed at caregivers have been associated with lower self-reported negative mood for caregivers [45] and symptom improvement for patients [46].

As reflected in the above discussion of palliative care and symptom management interventions, quality of life is a key treatment goal in caring for patients with advanced disease and/or poor prognosis. This is a domain in which technology can support assessment and clinical utilization of patient-reported outcomes on quality of life and psychological distress [44, 47–49]. Moving forward, addressing barriers to patients' adoption and the use of technology will be critical to ensuring that technologies meaningfully contribute to improved patient outcomes, including quality of life. Moreover, we need systems-based clinical trials on the effectiveness of technology-based interventions [50, 51].

Cancer Communication on Social Media: Providing Support Online and Mitigating the Impact of Misinformation

Another domain in which technologic evolutions have affected cancer care and communication occurs in the now ubiquitous social media. Patients, caregivers, and survivors routinely access information about cancer through the Internet and social networking platforms. On the one hand, social media has enabled rapid health information sharing and meaningful support for patients and caregivers, helping to meet their informational and social-emotional needs by connecting with loved ones or others with similar experiences [52]. Patients and survivors connect with other individuals who may have faced similar challenges through online communities. These connections may be useful in improving psychosocial, behavioral, and physical health outcomes [53]. Along with the increased use of social media, more cancer care interventions are being developed through the use of private Facebook pages and other social media platforms—for example, an ongoing study is examining the utility of using social media to support family caregivers caring for seriously ill cancer patients [54]. Such use of social media platforms overcomes geographic and other logistical constraints to enable critical communication among cancer caregivers.

However, the use of social media also introduces growing challenges to patient-centered communication. The online ecosystem may perpetuate the spread of and endorsement of misinformation, including cancer-related myths, falsehoods, and even unproven "miracle cures" [4, 55]. For example, an analysis of breast cancer-related Pinterest pins showed only 22% made a factual claim, whereas 51% of posts were found to have false or inaccurate claims [56]. As another example, misinformation regarding cannabidiol (CBD) and cancer is highly prevalent on the platform GoFundMe, with false claims that CBD is an effective curative therapy for cancer being widely shared and no action taken by the site to stop the spread of misinformation [57]. Unfortunately, many of the automated algorithms used by social media platforms help to create information silos, whereby individual's feeds are curated based on their previous activity, meaning that those exposed to health misinformation may not see alternative content and echo chamber effects are reinforced [5]. As a result, people can easily find information that affirms their biases or emotions and avoid information that challenges incorrect ideas. Furthermore, social media feeds are often emotionally provocative, which contributes to widespread sharing and beliefs that are resistant to rational appeals to address misinformation [58].

Addressing and mitigating the impacts of exposure to false or misleading health information is complicated and requires thoughtful attention beyond simply correcting falsehoods. Surveillance of misinformation and its impacts and development of adaptive and effective interventions to foster health and digital literacy and counter misinformation are critical starting points. Providers and healthcare systems can help patients, and caregivers evaluate the quality of cancer information and reduce the harms of exposure to misinformation [5]. One tangible effort is to reinforce health and science literacy through tools and support systems that help patients navigate the digital environment and assess the quality and trustworthiness of information they encounter. Health/cancer care organizations, clinicians, and scientific experts also have the responsibility of making credible and trustworthy cancer information more accessible. Perhaps the most effective solutions are at the broader systems level: engineering an information ecology that more effectively promotes exposure to credible content (e.g., up-ranking on search engines, providing endorsement to medical and scientific expert entities) and trustworthy sources while diminishing the impact or shareability of non-credible content. These efforts would require social media platforms to partner with researchers and practitioners in developing and implementing policies for curbing misinformation spread. Ultimately, in order to achieve patient-centered communication, we have to go back to the perspectives of the patients and "meet them where they are" by matching accurate and useful cancer information with their preferences and information needs as well as sources they trust.

Cancer Caregiving: Supporting Informal Caregivers Through Communication

Our discussion thus far has focused on the person diagnosed with cancer. However, cancer affects the whole family and social network. Furthermore, for those afflicted with advanced cancer, many responsibilities of day-to-day care and decision-making fall on informal caregivers. The physical and psychosocial-emotional toll on caregivers and disruptions in life are enormous. In 2020, an estimated 48 million US adults provided care and support for an adult facing a serious health condition. Of these individuals, 23% reported caregiving has negatively impacted their health [59]. The number of informal caregivers will continue to grow as an increasing number of individuals face multiple chronic conditions. Cancer caregivers face unique struggles and challenges: they often have to supply intense care in a short time period and are asked to preform highly technical tasks without proper knowledge or support [6]. Moreover, the experiences of cancer patients and their caregivers are often intertwined, and their physical and psychosocial-emotional well-being are often interdependent; the relationship between a cancer patient and their caregiver highlights the importance of communication—between patients and caregivers as well as among patients, caregivers, and healthcare providers—in order to improve patient-centered cancer care. Effective communication can address psychosocial needs, ensure adequate and informed supportive care, and enhance relationships and emotional well-being for both caregivers and patients.

To date, communication interventions have supported caregivers solely or family/couples (dyadic communication)—for example, singular discussions about goals of care or decision aids for treatment options. Multilevel interventions (i.e., communication efforts that target patients, caregivers, as well as the healthcare team) focusing on underserved populations are critically needed. For example, interventions should focus on integrating caregivers into the care delivery system through communication that attends to the needs of both patients and caregivers, assessing caregivers' needs and empowering them to be an active part of the cancer care [6]. However, this is still a nascent area of research and practice, and more practice-based research is needed to integrate all members invested in a patient's care to facilitate communication and improve quality of care.

Precision Oncology: Supporting Patient-Centered, Informed Decision-Making

Cutting-edge cancer research has improved treatment options and efficacy in recent years. In particular, genetics/genomics-informed treatments such as targeted therapies have provided many patients more effective treatment and life-prolonging promises. However, while precision oncology has garnered much excitement in the cancer community, for many patients afflicted with advanced illness and poor prognosis, precision oncology may be unattainable or may even promote false optimism. In some cases, genetic testing or genetically informed or molecularly targeted treatments are not available; in other cases, genetic testing may not yield helpful or conclusive results or provide actionable information to inform treatment plans. For instance, a review of patients who underwent next-generation sequencing for hereditary cancer showed that only 9% of patients had positive results for a pathogenic or likely pathogenic variant [60]. Patient-centered clinical communication is critical in order to ensure patients' informed decision-making and goal-concordant care, whether results of genetic tests are positive, negative, or inconclusive.

One key challenge to patient-centered communication in the practice precision oncology lies in helping patients and caregivers understand and manage uncertainty, such as in making treatment decisions when genetic testing results are inconclusive, or when the utility of targeted therapies is unclear. Furthermore, “tools for tailoring treatment will demand a greater tolerance of uncertainty and greater facility for calculating and interpreting probabilities,” [61]. In the case of genetic testing for breast cancer, for example, while testing is becoming more prevalent, hereditary breast cancer accounts for only a small component of breast cancer care, and oftentimes the results of genetic testing can be difficult to interpret or act upon. An estimated of 5–15% of BRAC mutations are classified as variants of uncertainty significance (VUS). For racial/ethnic minority populations such as Hispanics and African Americans, VUS rates are even higher [62, 63]. Receiving VUS results can increase patients’ and family members’ worries and stress because this result is not considered either pathogenic or benign, with no clear guidance regarding whether or how to act based on these results.

Part of helping patients manage uncertainty entails addressing their understanding of prognosis and care preferences. Unrealistic optimism of one’s prognosis is prevalent in patients with advanced diseases, so improved patient-provider communication is critically needed [7]. In fact, research indicates that many patients diagnosed with advanced stages of cancer do not accurately understand their diagnosis and that their prognostic understanding differs from their providers—for example, one study of patients’ terminal cancer found that one third believed their cancer to be curable [64]. Similar findings show that although providers believed they had discussed all the key information with their patients, some information was missing or was misunderstood by their patients. Significantly, often providers were found to neglect discussing prognosis [65]. One main reason for this discordant understanding is suboptimal patient-provider communication; for instance, providers often use vague and ambiguous language when discussing prognosis. It is important to highlight that patient-provider communication in the USA is often worse for ethnic and racial minority patients. A study reviewing communications between oncologists and patients self-identifying as Black, African American, or Afro-Caribbean found that, while prognosis and treatment goals were discussed, oncologists were often unclear and used confusing terminology and almost never used survival estimates [7].

Attending to patients’ emotions is also critical in the context of genetically informed treatment discussions. Besides the stress and emotional burdens associated with a cancer diagnosis, there are documented psychological impacts of genetic testing and return of genetic results [66–68]. Communication efforts need to ensure patients’ psychological needs are met when discussing genetics and in all treatment decisions. Patients must be informed of both the potential benefits and the limitations of treatments [69] so that unrealistic optimism can be minimized.

In implementing precision oncology, additional health literacy and numeracy demand (e.g., understanding and acting upon genetic testing results, managing uncertainty, understanding prognosis, discussing goals of treatment and preferences for end-of-life care) are being placed on patients. Explaining the science will require time and effort on the part of both providers and clinical care systems. Similarly, the implementation of genetically informed precision oncology requires that providers elicit more complex personal information (e.g., family history of cancer) from patients. To date, although precision medicine is frequently articulated in healthcare systems, public knowledge and understanding of this new field is still limited and requires the health systems’ attention. Additionally, patient concerns regarding the sharing of genetic information need to be addressed in order to enhance trust and engage patients in promising precision approaches [70]. Precision medicine has the potential to offer many benefits, but it will require strong and evidence-informed communication between patients and their providers.

Challenges of the COVID-19 Pandemic on Advanced Cancer Care

We would be remiss in writing this chapter not to discuss the significant disruptions the 2020 COVID-19 pandemic has caused for patients with advanced cancer and their loved ones. To start, many oncology clinical appointments and even scheduled treatments such as chemotherapy or radiation have been delayed or cancelled, wreaking havoc to care and adding stress. Multiple sources of data point to significant decrease in oncology office visits, increase use of telemedicine, and sharp decline in cancer screening overall in 2020 [71, 72]. Such delays in cancer screening and diagnosis are most likely to increase cancer morbidity and mortality in the near future. When in-person clinical visits do occur, concerns over virus exposure and transmission and adoption of preventive measures (e.g., mask and other PPE wearing, social distancing, inability to have physical touch for comfort or connection) can further disrupt communication by impairing patients' and providers' abilities to read and respond to important nonverbal cues. Symptom tracking and management have also been disrupted as a result of missed or ineffective clinical visits and diagnostic and monitoring tests. While absolutely necessary for community protection against the virus transmission, as the pandemic rages on, the long-term effects of these restrictions, quarantines, and overall isolation are beginning to show in cancer patients. It is important to acknowledge that these conditions will continue to impact cancer care, potentially becoming the “new normal” and deserving careful attention [73].

In addition to the disruptions and restrictions in clinical care, fear and other negative emotional impacts of the pandemic are enormous. For those who are very ill and may be near the end of life, not being able to see loved ones or have fulfilling social and emotional connections in person can be especially difficult, and some may fear dying alone. Caregivers as well as healthcare professionals struggle to support cancer patients as so many traditional means, such as in-person support groupsX, arts therapy in the clinics, prayer and faith-based gatherings, in-person counseling from psychologists, social workers, and chaplains, have all become either unattainable or difficult to carry out.

In this challenging context, achieving patient-centered communication requires multilevel and innovative approaches. New and novel ways of providing health care include telemedicine, use of video conferencing for visits and mobile Apps for symptom tracking and management. Just at the outset of the pandemic alone, according to a report from the Center for Medicare and Medicaid Services, there was a 350-fold increase in the number telehealth visits per week for Medicare beneficiaries, from an estimated 2000 telehealth visits/week in February to 1.28 million in April [74]. Indeed, as in-person medical visits became limited, many started receiving their care via telemedicine which has been greatly enhanced during the pandemic [75]. Telemedicine has rapidly expanded due to the necessity of virtual visits, though concerns about its effectiveness remain. One small silver lining is that telemedicine seems to fulfill some of the objectives of in-person outpatient visits effectively, though, as described above, it is not a replacement for in-person consultation and care [75].

Going forward, and as we begin to improve our management of the pandemic through vaccines and mitigation practices, it is important to continually acknowledge, evaluate, and address the impact of this global crisis on cancer patients, especially those who are most vulnerable due to their socioeconomic and racial/ethnic backgrounds or due to their advanced diseases.

Conclusion

Patient-centered communication is a critical aspect of cancer care. In the context of advanced cancer, and facing evolving challenges in oncology care delivery, a few critical areas warrant special interventions focusing on communication. The growing financial burden of cancer care necessitates better and more integrated cost communication between patients/caregivers and providers. The increasing reliance on technology, from access and use of online patient portals to other means of online interactions, places increasing demand on patients in order to effectively navigate their care. Ensuring patient-centered technology-mediated communication, whereby technology augments interpersonal interactions, instead of replacing or worsening them, is critical, especially for underserved segments of the population, such as those with limited English proficiency, health literacy, or technologic literacy. Outside of clinical care, patients are increasingly accessing cancer information on ubiquitous social media, meaning they are exposed to information of mixed quality and accuracy, including medical misinformation that would negatively affect their knowledge, attitudes, and behavior. Fostering trust in credible sources of cancer information and mitigating the impact of misinformation exposure present another priority in patient-centered communication. As precision oncology gains prominence in cancer care thanks to medical research advances, it is particularly important that communication efforts focused on patients with advanced diseases help them deal with uncertainty, avoid unrealistic optimism, and make informed and goal-concordant care decisions. Finally, 2020 is tragically marked by the historic COVID-19 pandemic and health disparities, and this public health crisis has undermined medicine's ability to provide optimal care for those with advanced cancer. We outlined some opportunities to ensure patients, and their needs remain central to cancer care and communication. In sum, this challenging time calls on communication scientists and practitioners to endeavor on translational work, using social science to inform patient-centered practice and affect change, even in small and incremental ways.

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Complementary Mind-Body Therapies in Cancer

Chloe Hriso, Andrew Newberg, and Daniel Monti

Introduction

The term "complementary and alternative medicine" (CAM) refers to the broad range of health systems, modalities, and practices that are not part of the conventional and politically dominant health system [1, 2]. We would also suggest that "integrative medicine" incorporates conventional medical approaches with evidence-based complementary approaches for an individualized care program designed to optimize human health and well-being. Several practices that are considered part of integrative medicine approaches in the United States include complex traditional health systems from other cultures, such as traditional Chinese medicine, as well as components of these systems that are practiced as distinct entities, such as acupuncture [3]. The originally named National Center for Complementary and Alternative Medicine (NCCAM) categorized CAM in the following domains: whole medical systems such as homeopathy and Ayurveda; mind-body medicine such as meditation and art therapy; biologically based practices such as herbs and dietary supplements; manipulative and body-based practices such as chiropractic and massage; and energy medicine such as biofield therapies and magnets [4]. But as above, even NIH has recognized the importance of integrating CAM with conventional medicine and now calls the NCCAM the National Center for Complementary and Integrative Health.

The use of integrative medicine treatments in the United States is substantial, especially among those with chronic medical problems, including cancer. Eisenberg et al. published the first national survey on the use of such approaches in 1993, which revealed that one in three respondents had used an unconventional or CAM treatment in the previous year [2]. Follow-up studies confirmed integrative medicine use rates at least that high [5, 6], and most studies suggested that people use these treatments in addition to conventional medical care. Recent data confirm that integrative medicine use continues to be particularly high among those with chronic diseases such as cancer [7]. Studies have indicated that many people do not disclose their use of such treatments to their conventional physicians, with many reporting that they perceive their doctors as unreceptive to the issue [6]. One possible explanation for the patient-physician communication gap on this topic is the limited information most physicians have about integrative medicine approaches,

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especially given its historical absence as a covered subject in conventional Western medical training. In addition, despite a recent surge of interest in complementary therapies from the medical community, including some form of integrative medicine curriculum at a growing number of medical schools [8], there is currently a limited evidence base on the topic.

The field of cancer survivorship research has been steadily growing along with the number of cancer survivors in the United States. When the National Cancer Act was passed in 1971, there were three million cancer survivors. Since that time, the number of cancer survivors has more than tripled. There are currently approximately 10.8 million survivors in the United States [9].

One of the arenas in which there has been substantial interest in the use of integrative medicine modalities is in the field of oncology, both during active treatment and in the posttreatment survivorship phase [10–13]. The use of integrative interventions is a growing area of interest in cancer survivorship research, although such approaches can be a challenging issue for oncologists, primary care physicians, and other mainstream medical professionals caring for cancer survivors, especially given that survivors are exposed to reams of information on the internet and in the media that can cause them to stray into territory that may trigger discomfort and concern from their physicians.

Motivations for the use of integrative therapies are multidimensional, including improvement of quality of life, enhancement of immune function, coping with pain, and decrease in anxiety and other psychological symptoms [14–16]. In regard to this last category, even though there is a large number of cancer survivors with high stress levels [17] and unmet psychosocial needs [18, 19], uptake of conventional supportive programs often is low [20]. Issues related to integrative medicine use may be particularly relevant to diverse groups with culturally based health beliefs, the underserved, and those who experience health disparities in the mainstream health care system [21]. As the number of cancer survivors increases, it includes more diverse groups who may be utilizing integrative medicine, so it becomes even more important to understand why particular subgroups of survivors are using such approaches, what forms they are using, and whether this is being incorporated into the rest of their care. Although at this point there has been little formal assessment of the patterns and predictors of integrative medicine use among cancer survivors from diverse ethnic groups, there are some data to suggest that its use is overall similarly high across ethnic groups, with subgroup variations in patterns of use [22]. For example, even though use of mind-body therapies is consistently high on the list of commonly used integrative medicine modalities overall, it is particularly high in some minority subgroups such as African Americans.

There are potential advantages for practitioners to be able to discuss integrative therapies with their patients and in some cases integrate it with their conventional care. One way of facilitating meaningful discussion would be for oncologists to have a positive platform from which to establish some “common ground” with patients interested in integrative medicine approaches. We previously have suggested that particular mind-body therapies with an evidence base could provide such a platform and serve as a bridge to connect potentially beneficial supportive interventions to patients, while also opening a general dialogue about integrative medicine and the needs particular patients might be attempting to address with such approaches [23]. The end result could be an improved physician-patient relationship and overall improved patient care. Mind-body therapies are a chosen platform because several have at least some positive supportive data, and many target stress reduction, which is a tangible end point that is associated with improved quality of life and better health outcomes. Moreover, such interventions generally are not practiced as an “alternative” to regular oncological care; hence, they can be integrated into the overall cancer survivorship treatment plan with relatively low risk [24].

In this chapter, we review a few mind-body therapies relevant to cancer survivors and provide a rationale for considering them as possible complementary interventions, based upon the presence of supportive data (albeit nonconclusive), an applicable theoretical framework, and relative safety. It is often stated in the literature that since integrative medicine modalities lack conclusive evidence, they should not be recommended [25]. We propose a modified perspective that also considers the potential benefits of supporting the use of certain mind-body therapies in cancer survivor subgroups, amidst a lack of absolute certainty about efficacy and mechanism of action.

Psychosocial Stress and Cancer

Given the numerous stressful challenges involved with having a cancer diagnosis [26], it is not surprising that as many as one-third of cancer survivors report high stress levels [27]. Stress can manifest in a variety of psychological symptoms, such as anxiety and depression [28, 29], intrusive cancer-related thoughts (i.e., traumatic stress symptoms), and/or physical symptoms, such as fatigue, increased pain, and impaired sleep [30–34]. Amplified stress in cancer patients has been associated with increased morbidity and mortality [19], decreased immune function [35], increased relapse [36], and decreased health-related quality of life [37, 38]. Given the known negative impact of stress on cancer patients, stress has become a priority issue in cancer treatment and research [39]. Targeting stress-related variables with psychosocial interventions has been an important emphasis in cancer care models [40]. Moreover, recent preclinical data have suggested possible direct effects of stress on tumor cell biology [41, 42], and potential indirect effects through increased oxidative stress [43, 44], underscoring the importance of addressing stress across survivor populations.

Although the conventional standard for addressing distress in cancer survivors has largely been through supportive group programs, there are significant challenges in recruiting participants to these programs, despite availability, particularly in hard-to-reach populations [45–48]. In addition, it has been well established that there are widespread health disparities that impact on cancer prevention, treatment, and survivorship and palliative care [49]. In the field of cancer survivorship research, there is an emerging body of literature acknowledging such disparities and supporting the development of interventions that are sensitive to social, cultural, and economic differences, particularly as these factors influence the quality of life [50–52]. Some of the selected findings from this research suggest that the survivorship experience varies by ethnicity, gender, and age [53, 54]. For example, population studies suggest that ethnic groups that are low utilizers of conventional supportive group interventions may be relatively high utilizers of integrative medicine [55].

As the field of cancer survivorship and health disparities grows, it will be important to access hard-to-reach and underserved populations. Therefore, there is a need to continue exploring novel interventions and options for support for the growing and diverse population of cancer survivors. Although the evidence base for a number of integrative medicine treatments is still being established, many of the mind-body therapies that have been used to support cancer patients generally are regarded as safe. We focus our discussion on a few modalities that have a promising evidence basis to serve as adjunctive interventions for supporting the psychosocial needs of cancer survivors.

Conceptual Framework

There are several theoretical models for understanding the concepts of stress, distress, coping, and stress reduction. Self-regulation is one such construct that appears to be applicable to a wide variety of psychosocial interventions. It has been shown that measuring self-regulation is reliable and may be a useful predictor of cancer patients' ability to find benefits in their cancer experience [56]. In a broader context, self-regulation theory is a framework for conceptualizing psychosocial stress, and it provides an explanation for observed therapeutic effects. Although this framework cannot be seen as complete for any intervention, we propose self-regulation theory as a common ground for considering the effects of the mind-body interventions to be discussed.

Self-regulation theory [57] provides a foundation for understanding reactions to perceptions of physical and emotional well-being. Functionally defined, self-regulation theory explains how people cope with and adapt to stressful situations such as health problems or threats (e.g., a cancer diagnosis). The model reflects two aspects of information processing: (1) the objective data, such as a laboratory result or tumor stage, and (2) subjective appraisal of that data, such as fear or anger. An essential component to this theory is the personal schema that is formed from the combined objective and subjective aspects of the health threat. The schema can be characterized as the lens through which all subsequent health-related information and cues are perceived and hence the determining factor for coping behaviors. The schema and resultant coping behaviors form a feedback loop, where one impacts the other. Hence, techniques that affect the subjective appraisal of health-related information will affect coping behaviors related to that information; likewise, techniques that modulate coping responses can affect the schema itself. The ability to negotiate subjective appraisals of health threats and resulting coping responses both directly affect stress levels [58, 59].

Mind-body therapies may affect self-regulation by either targeting the schema, the coping responses, or both. For example, some therapies teach techniques that may modify appraisals of the health-related data (e.g., mindfulness), others may provide methods to dampen or alter physiological responses to the data (e.g., biofeedback), and others may directly alter the perception of the data itself (e.g., hypnosis).

Complementary Mind-Body Therapies

The term "mind-body therapies" is a somewhat ambiguous categorization that generally refers to a collection of treatments that recognize the bidirectional nature of psyche and soma. Many of these modalities are classified as integrative medicine or CAM, mostly because they are not currently part of a dominant conventional therapeutic paradigm. Alleviating stress through various mental and physical exercises tends to be a focus of these interventions. There are numerous mind-body techniques, and below is a brief description of a few of those that may have particular relevance to cancer survivors, based upon available supportive data and relative safety.

Hypnosis

Franz Anton Mesmer (1734–1815) captivated the public in the eighteenth century when he introduced a form of hypnosis, which he called "animal magnetism." Mesmer made such an impact that his technique came to be known as "mesmerism," a word that is still sometimes used to describe a hypnotic-like trance. The word "hypnosis" (from the Greek root *hypnos,* meaning sleep) is misleading in some ways because the phenomenon to which it refers is not a form of sleep; rather, it is a complex process of attentive, receptive concentration. This state, also called a "trance," is characterized by a modified sensorium, an altered psychological state, and characteristically minimal motor functioning. In addition to achieving deep relaxation, the hypnotic treatment may include direct suggestions for specific changes in physiology and cognition [60]. Guided imagery is often an integral part of the hypnotic technique.

There are data suggesting that hypnosis may be efficacious for a variety of mental health problems [61, 62] and physical disorders that are exacerbated by stress, including pain [63]. An NIH Technology Assessment Panel [64] concluded that there was strong evidence for the use of hypnosis in alleviating chronic pain conditions, including pain associated with cancer. Hypnosis has been shown to be particularly helpful for a variety of acute and chronic cancer pain issues in children [65, 66], and there is evidence to suggest that children may have better responsiveness to hypnosis than adults [67]. Studies have demonstrated that hypnosis can be an effective means for some cancer patients to alleviate nausea and vomiting associated with chemotherapy [68]. Hypnotic effects are thought to occur through three primary mechanisms: muscle relaxation, perceptual alteration, and cognitive distraction [69]. Hence, learning new ways of perceiving an experience and developing coping strategies to negotiate the experience are important self-regulatory aspects of hypnosis.

Meditation Practices

Many common forms of meditation are extracted from traditional Eastern systems that encompass lifestyle issues beyond the meditative techniques. For example, yoga is an ancient Eastern Indian system of health that prescribes a multiphasic approach to living, including proper diet, behavior, physical exercise, and sleep hygiene. Likewise, qigong meditation practices often are derived from complex traditional Chinese medicine practices. A report from the Agency for Healthcare Research and Quality, Department of Health and Human Services [70], comprehensively reviewed and synthesized the state of research on a variety of meditation practices. Although cancer was not the focus, the report reviewed encouraging data suggesting therapeutic benefits from several meditation practices for a variety of health conditions, but the authors were unable to translate that data into firm conclusions due to the poor quality of many of the studies. In the following, we focus on a few meditation-based practices that are commonly used by cancer survivors and have at least some substantive supportive evidence for use.

Mindfulness-based stress reduction (MBSR) is a standardized, 8-week intervention that incorporates mindfulness meditation, hatha yoga practices, and other techniques, for the purposes of stress reduction and improvement of quality of life [71]. MBSR is the most studied meditation intervention, with suggested therapeutic benefits in several illness populations, including cancer [72–75]. Speca and colleagues published the first randomized, controlled study of MBSR in a mixed group of cancer patients, demonstrating significant improvements in mood disturbances and decreased stress as compared to wait-list controls [76]. These improvements were maintained at a 6-month follow-up [77] and further exemplified in a later study [78]. Another report showed that breast ($n = 33$) and prostate cancer ($n = 9$) patients who received the 8-week MBSR program had shifts in their immune profiles (reduction in Th1 pro-inflammatory to Th2 anti-inflammatory environment) associated with decreased depressive symptomology [79]. These trends continued at 1-year follow-up [80].

A primary goal of MBSR is to develop the capacity to be relaxed and aware in each moment while maintaining a nonjudgmental attitude. In this regard, thoughts and emotions are not viewed as wrong or faulty but rather as events. Together, this allows for conscious observation of both the actual experience (objective data) and the emotional response to it (subjective appraisal), which may facilitate improved self-regulation and more healthful coping strategies.

Qigong practices involve slow body movements and meditation, with or without imagery and breathing techniques. Common forms of qigong emphasize self-regulation of emotion (e.g., maintaining a peaceful, calm mood) and focused attention. In China, there was a huge resurgence in qigong after the Great Cultural Revolution in China during the mid-1970s, which has since extended to the Western world, including the United States. Yet, the majority of studies on the topic have been performed in China. A review of 50 Chinese studies on the use of qigong in cancer patients showed that although there was some indication that qigong had a positive impact on several parameters of cancer survivorship, the results cannot be considered conclusive given the poor design of most of the studies [81]. Outside of China, the majority of studies are done on healthy volunteers. One study showed that qigong practice lowered cortisol levels with concomitant changes in numbers of cytokine-secreting peripheral blood cells in a group of 19 healthy volunteers [82]. These biological indicators suggest stress reduction, which was not directly measured. Positive results from a well-designed study in patients with late-stage complex regional pain syndrome provide potential support for the consideration of qigong as a complementary intervention for the management of stress-related symptoms in cancer patients. This randomized, placebo-controlled clinical trial found that qigong training was associated with short-term pain reduction and long-term anxiety reduction [83]. Another clinical study in breast cancer survivor patients with persistent postsurgical pain showed sustained improvements in the severity of pain, stress, fatigue, and physical well-being 6 months following a 12-week qigong training program [84].

Tai Chi is characterized by a set of exercises that emphasize a series of postures and movements along with controlled breathing. Also derived from TCM, the movements are designed to balance chi, which refers to the body's energy or life force. Tai Chi is sometimes referred to as "moving meditation" because the exercises are paired with training the mind to be calm and relaxed. The variety and patterning of the movements are slow, gentle, and light, requiring focused concentration. The movements may facilitate self-regulation by their intention to foster a sense of inner and outer harmony as the movements become more fluid, yet controlled, and the mind more alert, yet peaceful [85].

There are some data to suggest cardiovascular benefits from Tai Chi, such as lowered blood pressure and heart rate [86], indirectly suggesting stress reduction and improved self-regulation. A Japanese study of older adults found significantly higher scores in health-related quality of life, particularly in the domains of physical functioning and vitality, in older adults who practiced Tai Chi as compared to age-matched national standards [87]. Although Tai Chi is common use, the data on cancer populations are limited. A recent systematic review of controlled clinical trials of **Tai Chi** as a supportive therapy for cancer patients, searched the literature using 19 databases from their respective inceptions through October 2006, without language restrictions [88]. Of the 27 potentially relevant studies, only four met the criteria of "controlled clinical trial," and all four assessed patients with breast cancer. Two of these were considered well designed, and they both reported significant differences in psychological and physiological symptoms as compared to psychosocial support control [89]**.** Hence, the data to support the use of Tai Chi are encouraging but limited and inconclusive.

Art Therapy

Art therapy facilitates self-regulation by providing concrete tasks for expressing representations in a tangible and personally meaningful manner. A recent qualitative study of women with breast cancer suggests that the process of art making and art therapy provides unique opportunities to address psychosocial needs [90]. Research with cancer survivors and with other populations supports the use of tasks that allow for the focused expression of unpleasant emotions, which can lead to a reduction in medical symptoms, such as pain, and an increased sense of well-being [91]. Although there are numerous published case and qualitative studies from the field of art therapy, including the widely reported and beneficial use of art therapy with cancer populations in both individual and group formats [92], few controlled studies exist. One particularly well-done clinical trial of an art therapy intervention with hospitalized children with post-traumatic stress disorder demonstrated that the use of specific art tasks was associated with stress reduction [93]. Recent reports in the cancer literature include the utilization of art therapy in a largely qualitative study of children with cancer, which resulted in enhanced communication and expression of emotional appraisals of the cancer experience [94]. In addition, significant reductions of anxiety were reported in a pre−/post-assessment of caregivers of persons with cancer ($n = 69$) who received a brief art therapy intervention [95]. Most recently, a controlled trial of art therapy demonstrated improved depression scores and fatigue levels in a group of cancer patients in active chemotherapy [96].

Mindfulness-Based Art Therapy

Mindfulness-based art therapy (MBAT) was developed to engender health-promoting skills and behaviors in a heterogeneous group format that can include patients with a variety of cancer types [97]. The two main components of MBAT, art therapy and MBSR, are paired with the purpose of facilitating both verbal and nonverbal information processing. Art therapy tasks are designed to meaningfully complement the MBSR curriculum, which may enhance the nonverbal process of negotiating subjective appraisals of health-related information and advance more adaptive coping. This combined intervention is new, and there are limited available data. In a recently published RCT of MBAT, 111 women with a variety of cancer diagnoses were paired by age and randomized to either an 8-week MBAT intervention group or a wait list control group. As compared to controls, the MBAT group demonstrated significant decreases in symptoms of distress and significant improvements in key aspects of health-related quality of life [98]. A recent follow-up to this study showed similar outcomes, and in addition, a subgroup from the cohort received pre- and post-intervention fMRI assessments that revealed changes in caudate activation from baseline and decreased cingulated activation in response to a stressful cue [99]. Another report of a group of prostate survivors showed improvements from the MBAT intervention consistent with the RCT of women [100].

Multimodal interventions have gained in popularity likely because of the potential for an additive therapeutic effect. A recent study of women with breast cancer used a multimodal format that included several of the elements of the MBAT intervention, showing increased emotional regulation and psychological adjustment [101]. The disadvantage of multimodal interventions from a research standpoint is the inability to distinguish the relative contribution of the components in regard to observed effects.

Music Therapy

Music therapy is an increasingly popular adjunctive intervention for supporting the psychosocial needs of cancer survivors. Music therapy may facilitate self-regulation and enhanced coping by providing a soothing stimulus to counter distressing ones, using either music alone or music combined with guided imagery. The utility of music therapy to evoke relaxation was assessed in a meta-analysis of 22 music therapy trials that had quantitative outcomes, with overall findings suggesting decreased stress-based arousal [102]. Although specific data in cancer populations are quite limited, a recent report surveyed the coping strategies of 192 cancer outpatients; 43% reported using music as a coping strategy, second only to prayer [103]. In a group of autologous stem cell transplant recipients ($n = 62$), those receiving music therapy as compared to controls had significantly lower mood disturbance [104]. In a randomized trial of cancer patients receiving radiation therapy ($N = 63$), nonsignificant trends in stress reduction were observed in the music condition as compared to controls who did not receive music [105]. Significant results were seen in a randomized clinical trial ($n = 80$) comparing terminal cancer patients receiving hospice care in their homes who were assigned to a music therapy intervention or to usual hospice care [106]. In that study, those who received repeated sessions of music therapy showed significant improvement in quality-of-life scores, while those not receiving music therapy showed decreased quality-of-life scores.

Neuro-Emotional Technique

A relative newcomer to the cancer survivorship literature, the neuro-emotional technique (NET), pairs standard psychological approaches, such as addressing cognitive distortions and desensitization procedures (e.g., relaxed breathing while visualizing distressing cues), with elements of traditional Chinese medicine, such as utilizing acupuncture pulse points [107]. This is mainly accomplished by having the patient touch particular pulse points while visualizing emotionally distressing experiences. Although there are limited data, NET may be applicable to cancer survivors as an intervention to alleviate traumatic stress symptoms. Full post-traumatic stress disorder is rather uncommon in cancer survivors, but subsyndromal traumatic stress symptoms related to the cancer illness experience can be seen in as many as one-third of survivors, causing significant impairment and distress. A recently published study of NET in 25 subjects with various types of cancer and cancer-related traumatic stress symptoms compared pre−/post-intervention changes in response to recalling a distressing cancer-related event. The results showed encouraging decreases in physiological reactivity to the distressing event and decreases in subjective ratings of distress related to the event [108]. A few other small studies suggest an anti-anxiety effect of the intervention [109]. Although there is no current evidence that the acupressure component of NET adds to the effectiveness of the psychological aspects of the technique, the combination may appeal to survivor subpopulations that are attracted to integrative medicine treatments. Improved self-regulation from NET may occur from modulating the character and intensity of subjective appraisals.

Exploring Mechanisms of Self-Regulation Through Neuroimaging

Meditation practices are among the most common mind-body therapies used by cancer patients and survivors. In the past 30 years, researchers have been able to explore the biological effects and mechanism of meditation in much greater detail, largely due to the development of more advanced imaging technologies. Initial studies measured changes in autonomic activity, such as heart rate and blood pressure, as well as electroencephalographic changes. More recent studies have explored changes in hormonal and immunological functions associated with meditation. Functional neuroimaging has opened a new window into the investigation of meditative states by exploring the neurological correlates of these experiences. A growing number of neuroimaging studies of mindfulness and other meditation practices are currently available in the literature. The neuroimaging techniques include positron emission tomography (PET) [110, 111], single photon emission computed tomography (SPECT) [112], and functional magnetic resonance imaging (fMRI) [113]. Each of these techniques provides different advantages and disadvantages in the study of meditation. In terms of the larger topic of meditation, in addition to MM, the most common other type involves purposeful attention to a particular object, image, phrase, or word. This form of meditation is designed to lead to a subjective experience of absorption with the object of focus—a dissolution of the differentiation of self and object. There is another distinction in which meditation is guided by following along with a leader who verbally directs the practitioner, either in person or on tape. Others merely practice the meditation of their own volition. We might expect that this difference between volitional and guided meditation should also be reflected in specific differences in cerebral activation. Phenomenological analysis suggests that the end result of many practices of meditation is similar, although this result might be described using different characteristics depending on the culture and individual. Therefore, it seems reasonable that while the initial neurophysiological activation occurring during any given practice may differ, there should eventually be a convergence of data.

For example, brain imaging studies suggest that willful acts and tasks that require sustained attention are initiated via activity in the prefrontal cortex (PFC), particularly in the right hemisphere [8, 9, 114–117]. The cingulate gyrus has also been shown to be involved in focusing attention, probably in conjunction with the PFC [118]. Since many meditation practices require the intense focus of attention, it seems appropriate that meditation would be associated with the activation of the PFC (particularly the right), as well as the cingulate gyrus. This notion is supported by the increased activity observed in these regions on several brain imaging studies of volitional types of meditation [111, 112]. Activation of the PFC can result in increased thalamic activity which may either activate or inhibit neuronal activity in other structures. For example, several studies have demonstrated an increase in GABA, the primary inhibitory neurotransmitter, during meditation [119]. This inhibition may help with focused attention as well as have an impact on feelings of stress and anxiety. It should also be noted that the dopaminergic system, via the basal ganglia, is believed to participate in regulating the glutamatergic system and the interactions between the prefrontal cortex and subcortical structures. A PET study utilizing 11C-raclopride to measure the dopaminergic tone during yoga nidra meditation demonstrated a significant increase in dopamine levels during the meditation practice [120]. They hypothesized that this increase may be associated with the gating of cortical-subcortical interactions that leads to an overall decrease in readiness for action that is associated with this particular type of meditation.

In addition to the complex cortical-thalamic activity, meditation might also be expected to alter activity in the limbic system given its impact on emotions. It has also been reported that stimulation of limbic structures is associated with experiences similar to those described during various meditation states [121, 122]. The results of the fMRI study by Lazar et al. support the notion of increased activity in the regions of the amygdala and hippocampus during meditation [113]. On the other hand, studies of mindfulness meditation in particular have reported enhanced PFC activity in conjunction with decreased activity in the amygdala which corresponds with diminished reactivity to emotional stimuli [123, 124]. Thus, different types of meditation practices may result in different activity levels in the limbic structures depending on whether emotional responses are enhanced or diminished.

Activity in the right lateral amygdala has been shown to modulate activity in the ventromedial portion of the hypothalamus which can result in either excitation or stimulation of the peripheral parasympathetic system [125]. Increased parasympathetic activity should be associated with the subjective sensation first of relaxation and, eventually, of a more profound quiescence. Activation of the parasympathetic system would also cause a reduction in heart rate and respiratory rate. All of these physiological responses have been observed during meditation [126]. In accord with the Indo-Tibetan tradition of self-healing, one study narrowed its analysis of MM specifically to that of mindfulness-based stress reduction; meditators experienced a notable reduction of stress levels, along with the secretion of hormones (such as cortisol) associated with stress response [127]. In fact, there are typically marked changes in autonomic nervous system activity. Several studies have demonstrated predominant parasympathetic activity during meditation associated with decreased heart rate and blood pressure, decreased respiratory rate, and decreased oxygen metabolism [128]. However, a recent study of two separate meditative techniques suggested a mutual activation of parasympathetic and sympathetic systems by demonstrating an increase in the variability of heart rate during meditation [129]. The increased variation in heart rate was hypothesized to reflect activation of both arms of the autonomic nervous system.

Thus, the physiological changes associated with practices such as meditation are varied and significant. Depending on the particular issues associated with a patient, different types of practices may be of more or less benefit. However, more studies are needed to better assess how meditation and other mind-body practices produce their clinical effects.

Conclusion

In the past decade or more, there has been an ongoing increase in both the overall number of cancer survivors and the percentage of cancer survivors utilizing integrative medicine treatments. Although it is important for oncology providers to be aware of integrative medicine approaches their patients are using, patient disclosure and communication about the topic remain problematic. Mind-body therapies could potentially serve as a positive platform from which providers could discuss integrative medicine and even link survivor subgroups to services that might at least partially address unmet psychosocial needs. This would be especially relevant for survivor subgroups that have a cultural bias toward integrative therapies. The mind-body therapies reviewed have some supportive evidence and a rationale for use in cancer survivors. Although the data on efficacy and mechanisms of action of mind-body therapies are incomplete and nonconclusive, the potential benefits of using them in survivor care plans warrant consideration.

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The Intersection Between Cancer and Caregiver Survivorship

14

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Death and Dying

Despite the pervasiveness of death in our lives, preparing for our own or a loved one's death is often extremely challenging. Our cultural background, as well as early childhood experiences with death, greatly influences our later responses [3]. In times past, the family would assist with all aspects of caring for the sick and dying, making sure they were as comfortable as possible until their death, and then prepare the body and bury the deceased. The accepted duration of mourning by a family member lasted much longer than what is expected by today's standards. For example, the generally accepted amount of paid leave from work today is three days after the loss of a family member in Western countries [3]. The mourning family members and friends are often expected to return to normal functioning within 6 months, an arbitrary time period but recognized as important by the diagnostic criteria for some disorders related to bereavement. However, if an individual returns to normal functioning too early or begins to have intimate relationships soon after a spouse's death, society looks upon this as an abnormal adjustment to the death even if it has been a prolonged caregiving period lasting years and particularly when a spouse has not had any form of intimacy or a functional relationship with their loved one secondary to the disease (e.g., Alzheimer's disease).

Advances in medicine have changed the dynamics associated with the illness process, prolonging life while distancing loved ones from death. The end-of-life process has become much less personal, and many individuals have limited exposure to the death and dying experience. In Western cultures, the medical community is much more involved in an individual's care from the onset of illness to their death. Furthermore, after a person has died, s/he is often prepared and buried by professionals rather than family as in the past [4].

The Role of Health Care Professionals in End-of-Life Care

The health care professional's (HCPs) own experiences and philosophy regarding death influence how they care for patients and families which

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may not be consistent with the patient's or family's ideas about end-of-life decisions. The HCPs often have little training or the emotional connection to the patient to provide culturally appropriate support and/or compassionate care to the person who is ill or to their family members, making communication and joint decisions regarding end of life challenging [4].

Communication and decisions about the end of life are further complicated by variation in preferences of patients or family members about how much each wants to know about the details of the diagnosis and prognosis. The patient and/or family member may believe that they cannot cope with such information and therefore choose not to ask questions or avoid such conversations. Even when HCPs do discuss end-of-life issues with patients and families, the patients and their loved ones may not hear or remember information communicated by the provider, as many patients and family members need time to process information about the diagnosis and prognosis and may be emotionally overwhelmed. It is now recommended that physicians facilitating end-of-life discussions do so over the course of several meetings as a process rather than a one-time discussion [1]. However, the constraints of our health care system mean putting this into practice in place is nearly impossible.

When a loved one is diagnosed with cancer, this may be the first time the patient or family caregiver has considered death. Unlike other traumatic events that take a person's life immediately, cancer often allows the patient and family time to prepare, some more than others. The quality of that time depends on several factors, such as the symptoms of cancer, side effects of treatment, patient's and caregiver's personality and relationship, prior experience with loss, support from family and friends, spirituality, prior psychological functioning, and interactions with health care professionals.

We know that details regarding the goals of care, life-sustaining options, where and how a person will spend their final days of life, and funeral arrangements are infrequently discussed until the final months or weeks of life. Wright and colleagues found that only 37% of patients had discussed end-of-life preferences with their physician [5]. Of those patients who did have a discussion, the QoL was better and the cost of health care less when compared to those who did not have the discussion with their medical team [5]. Another study demonstrated that discussions with physicians regarding end-of-life care resulted in an earlier referral to hospice, less aggressive care, and better QoL [6].

When curative treatment is no longer an option, symptom management becomes critical to maintain the best QoL. The most common symptoms experienced at the end of life include pain, delirium, dyspnea, fever, hemorrhage, and, in the final days, a rattle [5, 7, 8]. The most feared symptom reported by patients is unmanaged pain. Pain management is often difficult secondary to fears of addiction by the patient, family, or health care providers. However, close monitoring of opioid prescriptions by physicians or specialists in pain management can result in a better QoL for patients. There have been recent efforts to understand how to better communicate the risks and benefits of opioids for pain management among cancer patients by their providers. The consensus is that better communication strategies are needed to educate patients about the risks and benefits of opioids to manage cancer pain [9]. In the final months of life, particularly if a patient enters hospice, management of pain with opioids becomes more acceptable by patients, families, and health care professionals. At that point, the primary concern may be that pain management could hasten death; however, there is little evidence supporting this fear [10, 11].

As noted above, when an individual is dying, several issues should be discussed including nutrition, symptom management, the location where the individual would like to die, and circumstances under which the person would like to be resuscitated. Resuscitation often includes all interventions that provide cardiovascular, respiratory, and metabolic support necessary to maintain and sustain life. Both the patient and family need to understand the advantages and disadvantages of resuscitation in order to make the most appropriate decision. Unfortunately, many dying patients have not made choices in advance or communicated their wishes to their families or health care team. As a result, the families are left with difficult decisions. Often, aggressive treatment is performed due to this lack of communication between patients, families, and health care providers. These aggressive treatments have been associated with poorer QOL for the patient and worse post-loss adjustment for the surviving loved ones [5, 8].

Palliative sedation is another challenging topic for patients, families, and health care professionals. Few reports or studies have been conducted regarding the use of palliative sedation for psychosocial symptoms (e.g., anxiety, psychotic symptoms). Four palliative care programs in Israel, South Africa, and Spain reported the use of palliative sedation [12–15]. In addition, a retrospective study of 1207 patients admitted to the palliative care unit at MD Anderson found that palliative sedation was used in 15% of patients. The most common indications were delirium (82%) and dyspnea (6%). Sedation in these circumstances is often used on a temporary basis and was reversible in 23% of patients [15].

Palliative Care and Hospice

Palliative care may be used for a number of illnesses, including cancer, and is particularly beneficial at the end of life. According to the World Health Organization, palliative care may be defined as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and treatment of pain and other problems, physical, psychosocial, and spiritual." [16] Palliative care has several goals: (1) provide relief from pain and other distressing symptoms; (2) affirm life and regard dying as a normal process; (3) intend neither to hasten nor postpone death; (4) integrate the psychological and spiritual aspects of patient care; (5) offer a support system to help patients live as actively as possible until death; (6) offer a support system to help the family cope during the patient's illness and in their own bereavement; (7) use a team approach to address the needs of patients and their families, including bereavement counseling, if indicated; (8) enhance QOL, and try to positively influence the course of illness; and (9) apply early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy.

The term, "hospice" refers to programs that provide special care for people who are near the end of life and for their families, either at home, in freestanding facilities, or within hospitals. Although palliative care may also include care in a hospice setting, a referral to hospice occurs when the medical team has determined that a patient may no longer benefit from traditional medical treatments and the patient is expected to have less than 6 months of life. Hospice is interdisciplinary and targets physical, emotional, social, and spiritual discomfort during the last phase of life. In 2007, people with cancer made up approximately 43% of these admissions to hospice [17]. The duration in hospice is often quite short with a median length of stay in hospice of just 21.3 days [17]. Although the reasons for late referrals are not known, it is thought that advanced care discussions between the patient and health care provider are not being initiated by patients, families, or health care professionals early enough.

Care During the Final Hours

Although the signs of approaching death may appear obvious to health care professionals, family members lack that knowledge since death has become more institutionalized. Many family members may have never observed the death of a loved one. Educating family members about the signs of approaching death can help them understand changes in their loved one. For example, in the final days to hours of life, patients often experience a decreased desire to eat or drink, as evidenced by clenched teeth or turning away from offered food and fluids [15]. This behavior may be difficult for family members to accept because of the meaning of food in our society and the inference that the patient is "starving." Family members should be advised that forcing food or fluids can lead to aspiration. Reframing would include teaching the family to provide ice chips or a moistened oral applicator to keep a patient's mouth and lips moist [15]. The sensitivity and communication of the health care providers with the patient and family are critical in the final weeks and days of life. Poor relationships and conflict between patients and families and the health care providers can lead to short- and long-term psychological and health consequences for the grieving family members who misinterpret the apparent indifference of the health team to nutritional issues.

It is important for health care professionals to explore with families any fears associated with the time of death and any cultural or religious rituals that may be important to them [17]. Such rituals might include placement of the body (e.g., the head of the bed facing Mecca for an Islamic patient) or having only same-sex caregivers or family members wash the body (as practiced in many orthodox religions) [18]. When death occurs, expressions of grief by those at the bedside vary greatly, dictated in part by culture and in part by their preparation for the death. Chaplains or other religious or spiritual leaders should be consulted as early as possible if the patient and family is interested in this type of assistance [18]. However, previous discussions with the patient and/or family are critical as prior conflict with the church and/or religious leaders may result in increased distress for the patient.

Grief and Bereavement of the Family Caregiver

The patient's QoL toward the end of life and the medical team's communication and behaviors can have lasting effects on the family caregiver. If the relationship between the patient and/or family and medical team is poor, then early cessation of treatment, lack of access to hospice care, and conflict regarding end-of-life decisions (e.g., DNR) may result. The guilt that caregivers experience may be long-lasting if s/he decides to stop life support before they have exhausted all options. Health care professionals who have more experience with end-of-life circumstances may not always understand the family's perspective when the health care team knows that the chances for extending life are minimal. The health care team has a responsibility to offer respect for the decisions of the patient and family. Patients and families also have the responsibility to discuss issues such as power of attorney and living wills prior to death or before the patient is unable to make decisions due to mental status changes.

A substantial body of research exists regarding the possible consequences of caregiving and bereavement on psychological well-being and health of family members. Caregiver stress or burden has been demonstrated to be associated with a caregiver's increased risk of depression, perceived stress, poorer QoL, increased risk of health conditions including cardiovascular disease, obesity, hypertension, diabetes, high cholesterol, and even mortality [1, 2, 4, 5, 8, 12–21].

When cancer caregivers were compared to age-matched controls, caregivers reported higher levels of emotional distress than controls [22]. Furthermore, the prevalence of medical comorbidities such as hypertension and heart disease was reported to be higher in cancer caregivers when compared to an age-matched control group during the caregiving period [22]. After adjusting for age, gender, income, and the care recipient's cancer severity, the caregiver's health morbidity at 5 years after the care recipient's cancer diagnosis was significantly related to levels of caregiving stress reported 3 years earlier [22]. However, no study has followed cancer caregivers through the caregiving and bereavement period as has been done with caregivers of those with dementia [23].

If the prevalence of psychological morbidity of *cancer* caregivers is as high as caregivers of those diagnosed with dementia during caregiving and bereavement (approximately 50%), it is estimated that over 6 million current cancer caregivers may be at risk for increased psychological and health morbidity and possibly mortality.

Stress, depression, and prolonged grief are all treatable conditions; therefore, the ability to reduce these symptoms, improve QoL, and decrease health morbidity and mortality could be significant.

It appears that caregiving in general may affect psychological functioning and health, but there are differences across caregivers. The groundbreaking research by Schulz and colleagues (1999) found in a cohort of individuals providing care for loved ones with dementia that, at the 4-year follow-up, those who reported high levels of strain during caregiving had a mortality risk that was 63% higher than their non-caregiving controls [24]. Since this seminal paper, Christakis and colleagues (2006) have also found an increased risk of mortality after the hospitalization of a spouse (which may reflect increased perceived stress) [25].

In contrast, some researchers have not found evidence for this link between psychological morbidity during caregiving and mortality. In a recent study, the risk of mortality was found to be *lower* in caregivers of those with osteoporosis fractures when compared to non-caregivers at the 3-year follow-up [26]. Interestingly, those participants who reported higher levels of perceived stress had increased risk of mortality, independent of their role as a caregiver [26]. Another study which compared caregivers to non-caregivers also found that as age increased, the risk of health problems became similar to that of non-caregiving controls [26]. As a result, further research is warranted to determine if the psychological consequences of caregiving are associated with increased risk of health morbidity and mortality in the context of cancer caregiving.

It appears that the type of caregiving (e.g., dementia vs. fracture) is not the only consideration. Other difficulties with post-loss adjustment are critical factors that may affect the association between psychological morbidity during caregiving and mortality [24–26]. Several methodological problems exist with prior research attempting to link caregiving with mortality including problems with recruitment and retention of both caregivers and controls. In prior research, recruitment and retention have been low (e.g., 10–20% of those approached for participation enrolled). In addition, there is a great disconnect between caregiving and bereavement literatures. This disconnect in research literature makes it difficult to identify how caregiving and subsequent bereavement impact the long-term physical and mental health consequences on the caregivers.

The absence of studies finding a link between psychological morbidity and mortality may be secondary to the time frame of assessment. Generally, psychological symptoms are assessed only cross-sectionally or for a short period of follow-up. Furthermore, inconsistent findings have been reported with post-loss adjustment of caregivers of care recipients diagnosed with dementia. High levels of stress, burden, and competing responsibilities during caregiving have also been associated with negative post-loss psychological outcomes [27, 28]. Conversely, other studies have found that caregivers who spent more time caregiving and had higher levels of distress in that caregiving role actually experienced significant declines in depressive symptoms at 3 months and 1 year after the loss of their loved ones [27, 28].

Decades of research by Bonnano and his colleagues have resulted in four patterns of loss: (1) resilience: the ability of adults in otherwise normal circumstances who are exposed to an isolated and potentially highly disruptive event, such as the death of a close relation or a violent or life-threatening situation, to maintain relatively stable, healthy levels of psychological and physical functioning as well as the capacity for generative experiences and positive emotions; (2) recovery: when normal functioning temporarily gives way to the threshold or subthreshold psychopathology, usually for a period of at least several months, and then gradually returns to pre-event levels; (3) chronic dysfunction: prolonged suffering and inability to function, usually lasting several years or longer; and (4) delayed grief or trauma: when adjustment seems normal but then distress increase months later [29]. Although Bonnano's theory can guide the research concerning caregivers of those diagnosed with cancer, Bonnano's research has focused on sudden and traumatic loss and has not included the period prior to the loss of the loved one (caregiving) [29].

Bernard has applied trajectory analyses to the study of psychological functioning after the loss of a loved one diagnosed with cancer and has included both the caregiving and bereavement period [8]. The results of his work found that two trajectories emerged: (1) relief model, which predicts that caregiver stress or strain will abate and ease the bereavement process, and (2) complicated bereavement model, which suggests that caregiver stress diminishes the psychological resources needed to cope during the bereavement process [29]. Interestingly, these trajectories were supported in spousal caregivers, but not in adult female children of breast cancer patients who were caregiving [8]. Furthermore, Bernard only followed the caregivers for 90 days after the loss of their loved one; therefore, other trajectory groups, particularly those associated with prolonged or delayed grief syndrome, may have not emerged [30].

Much of the previous research concerning predictors of caregiver outcomes have been conducted with those caring for loved ones diagnosed with dementia. Predictors of psychological morbidity during caregiving have included cognitive impairment, lack of anticipatory grief, younger age, female gender, lower education, poorer physical health, greater interference with life, and lower levels of caregiver mastery, poorer patient functional status, lower perceived control, greater number of hours spent caregiving, care recipient behavioral disturbances, and poorer quality of the patient-caregiver relationship [14, 31]. In regard to post-loss adjustment, prior research has found that caregivers with higher levels of pre-loss depressive symptoms and burden, a positive caregiving experience, and a cognitively impaired care recipient were more likely to report clinical levels of complicated grief [32].

Of the studies that have been conducted concerning *cancer* caregivers, similar findings were reported as those found in dementia caregivers. Predictors of depression during caregiving included high levels of caregiver burden, longer duration of caregiving and impact on other activities, mastery of caregiving tasks and neuroticism, previous health problems, lower levels of social support, avoidant coping, anxious attachment, and marital dissatisfaction [32]. Predictors of post-loss depressive symptoms, in cancer caregivers, have been found to include pessimism, pre-bereavement depressive symptoms, low levels of social support; and longer duration of caregiving [28].

Caregiving, Bereavement, and Health: Potential Biobehavioral Mediators

The two biobehavioral mediators that have been hypothesized to be one potential pathway linking caregiver stress and/or depression with mortality are health behaviors and/or immune system dysregulation [33, 34]. They may result in the worsening of preexisting illnesses or increase vulnerability to new health problems, including cardiovascular disease, some types of cancer (e.g., head and neck, pancreatic, stomach, lung), and diabetes. However, more recently other factors such as hostility, alcohol use, and caregiver stress have also been shown to be predictive of intermediate endpoints of cardiovascular disease [33].

Family members caring for loved ones with dementia have previously reported sleeping less, engaging in less regular exercise, and gaining weight when compared to their precaregiving behavior [35]. Caregivers report engaging less in preventative health care, such as mammograms or prostate exams, while providing care for a loved one [8]. Furthermore, caregivers have been found to use a greater amount of substances including alcohol and tobacco and consume foods high in saturated fat than non-caregiving controls [36–53].

In regard to health care utilization, Schulz and colleagues reported that caregivers engage in fewer preventative health behaviors during the caregiving period [37]. The National Alliance for Caregiving found that 72% of caregivers reported that they had not gone to the doctor as often when compared to before they were caregiving. Fifty-five percent of caregivers reported that they had missed doctor's appointments while caregiving [54]. Rural caregivers compared to urban caregivers have reported even lower rates of physician visits during caregiving [54]. Finally, caregivers are less likely to fill their own prescriptions than are non-caregivers [54].

In contrast, other studies have found that caregivers of dementia care recipients utilized more health services than their non-caregiver counterparts. These dementia caregivers demonstrated an increased number of physician visits, increased prescription drug use, and a higher incidence of inpatient hospitalizations [54]. Schubert and colleagues found that higher health care utilization was associated with depressive symptoms while others have reported that a greater number of stressors were associated with more frequent use of health care services [55]. Finally, the role of health care utilization in care recipients at the end of life has been found to be critical for the caregiver's health. Two recent studies found that higher rates of mortality were observed in those caregivers whose loved ones did not utilize hospice care [56, 57]. Gender differences in survival were observed in wives who used hospice support whereas only a trend was observed in male spouses [56, 57].

The second pathway that has been hypothesized linking psychological factors and health morbidity has been immune system dysregulation [58, 59]. As early as the 1990s, a meta-analysis was performed and confirmed the role of stress on immune system functioning [60] Two other meta-analyses followed with the same conclusions. A series of papers has provided evidence for the link between stress and immunity specifically in caregivers [61, 62]. Lasting effects of caregiver stress on immune system dysregulation have been reported up to one year after the end of caregiving [62]. A plethora of studies have also demonstrated that depressive symptoms are associated with immune system dysregulation and increased risk of mortality in those with chronic disease as well as in the general population [63–70]. Prolonged grief syndrome has also been associated with long-term immune system dysregulation and increased risk of mortality [71, 72].

The link between immune system dysregulation and health is well-documented. A plethora of studies have demonstrated an association between elevations in pro-inflammatory cytokines (e.g., IL-1α, IL-6, and TNF-α) with the development of cardiovascular disease [73–75]. Similarly, the development of diabetes and kidney disease has also been found to be associated with elevations in pro-inflammatory cytokines such as IL-6 and TNF-α [74, 75]. Dranoff has explained the importance of cytokines in cancer pathogenesis [76]. High levels of IL-6 and IL-10 in serum have been associated with poorer prognoses across cancer types [77–79]. Respiratory diseases, such as allergies and asthma, rheumatoid arthritis, alcohol dependence, and hyper- and hypothyroidism have also long been associated with changes in cytokines, particularly IL-1-ß, TNF-α, and IL-6 [80].

Despite decades of research regarding the link between psychological factors and immunity and a separate literature that has demonstrated the link between immunity and health outcomes, little evidence exists for the *mediation* of immune system dysregulation linking these psychological pathways with health outcomes. Possible explanations for this inability to link all three of these factors may be as follows: (1) chronic levels of psychological morbidity were not assessed and analyzed, which is what is likely to have a profound effect on health, and (2) immune system markers that have been found to be associated with these psychological factors were in the normal range (when compared to controls) and as a result may not have an impact on health.

Caregiving has the potential to cause chronic levels of stress, and thus, strategies to reduce this stress, prevent depression, and decrease short- and long-term effects on health are warranted. Interventions have begun to be developed and tested to improve end of life QoL for patients, These interventions, in turn, can reduce caregiver stress and its associated long-term health consequences. These newer interventions have begun to address the patient and caregiver as a unit (dyad), and interventions for the dyad may have a significant impact on the psychological functioning and health of the caregiver.

Interventions to Improve Quality of Life at the End of Life

With advances in modern medicine, it can be easy to focus on the eradication of disease and lose sight of the patient's experience of the illness. However, the patient's QOL as s/he copes with the disease process, especially at the end of life, is an important focus of care. Quality of life is understood to be multifaceted and includes physical, emotional, social, spiritual, and material [81, 82]. As such, assessment of disease-related QoL has been designed to reflect its multidimensional nature (e.g., European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EOTRC-QLQ), Functional Assessment of Cancer Therapy (FACT). In earlier QoL work, however, some researchers assessed QoL in a more restricted manner, assessing primarily emotional functioning (e.g., depression, anxiety). Thus, earlier studies discussed will have fewer comprehensive measures of QoL, whereas later studies will include assessments of QOL measuring multiple domains.

A growing body of research has focused on understanding ways to enhance QoL, particularly at the end of life. Health care providers face many unique challenges, and enhancements to QoL can be difficult to achieve. Several of these interventions have been primarily psychosocial and administered by mental health professionals (e.g., social workers, psychologists, nurses with psychological training); however, several interventions have also been medical in nature and administered by physicians and/or nurses [83, 84]. Whereas many of these interventions have impacted physical symptoms, such as pain, they have generally yielded little impact on QOL. Thus, the primary focus of this discussion will be on interventions with a significant psychosocial focus.

In the first randomized controlled trial reported in the literature, a 2-week intervention, which was intended primarily to educate newly diagnosed advanced cancer patients, was compared to a no-treatment control group through the use of experimenter-derived measures [85]. The intervention had a positive impact on the patient's self-concept, hospital adjustment, and knowledge about cancer from pre-treatment to immediately following the intervention.

Shortly thereafter, Spiegel and colleagues published results from a longitudinal study examining the effect of their group interventions on various aspects of functioning in women with metastatic breast cancer [86, 87]. Women participated for up to 3 years in a weekly supportive intervention. Those who received the intervention exhibited significantly less distress, less fatigue, and fewer maladaptive coping responses, as well reporting reduced pain sensation and suffering over time than did those in the control group. However, a later replication of this intervention, which included a multidimensional measure of QoL (EORTC QLQ-C30), found no effect of the intervention on Qo, but mood was improved and perception of pain was decreased [88]. In a similar study, comparing supportive-expressive group therapy to a control group receiving relaxation therapy, some benefit was observed. Participants in the intervention experienced less hopelessness, improved social functioning, and reduced intrusive and depressive symptoms [89].

Linn and colleagues conducted a randomized controlled trial with stage IV, primarily lung cancer patients, to test an intervention that was delivered over the course of multiple brief sessions per week by a therapist with expertise in death and dying [90]. Although no differences were found at 1-month follow-up, the treatment group was found to have lower levels of depression and alienation as well as more self-esteem and life satisfaction than the control group at 3 to 12 months. At 9 to 12 months, participants in the treatment group reported a greater internal locus of control [90].

As research in interventions to improve QoL for end-of-life cancer patients has grown, the interventions have become more multidimensional. This may be in part because of a recognition of the diverse nature of QoL. In a randomized controlled trial of lung cancer patients by McCorkle and colleagues (1989), two specialized home interventions (i.e., visits by a member of an interdisciplinary team or visits by an oncology nurse with advanced training) reported a 6-week delay in the amount of distress and dependence the patient experienced, in comparison to a standard office care control group [91]. A more recent randomized controlled trial examining the effects of a relatively brief intervention designed to target the multidimensional nature of QOL across 8 sessions found the treatment provided a buffer for advanced cancer patients. The treatment group did not experience the decrease in QOL experienced by the control group [92].

In a randomized controlled trial comparing the use of psychopharmacology alone to combined psychopharmacology treatments – one with social support provided by volunteers and one with structured psychotherapy – the researchers found that patients receiving the combined treatment did not have a worsening of QOL over time, as measured by the Functional Living Index-Cancer (FLIC) and experienced decreased depression and anxiety [93]. In contrast, the patients receiving psychopharmacology alone did worse with one exception (i.e., they experienced a reduction in anticipatory and posttreatment nausea and emesis) [93].

These findings reflect unique challenges of conducting intervention research with patients at the end of life, and questions remain about how to design optimal interventions to improve QOL. The interventions have varied considerably in their content, providers, and length of intervention. The early QOL findings of Spiegel and colleagues with women with metastatic breast cancer were not supported by later clinical trials [86–89]. The multidimensional interventions show some promise in improving QOL, and brief interventions may have a positive impact [92].

Future research in this area would likely benefit from exploring whether briefer interventions have benefit. Many patients at the end of life view time as precious and focus on spending time with loved ones, potentially making lengthy interventions less practical and too burdensome. These patients may benefit from more flexible interventions that are tailored to their preferences and allow greater options for how treatment is delivered (e.g., telephone calls or web-based visits instead of face-to-face visits). Although much research needs to be done still, web-based caregiver interventions show some promise in positively impacting psychosocial outcomes among caregivers [94].

Interventions Targeting Caregiver Quality of Life

Although patients at the end of life face several unique challenges, the caregivers can experience a myriad of concerns, which include determining how to provide emotional and instrumental support as well as coping with the anticipated loss of a loved one. In addition to patients having significant concerns about their family's adjustment, caregivers can experience increased levels of psychological distress, such as anxiety and depression, especially when they are unable to balance their caregiving responsibilities with engaging in activities of interest to them [95–98]. Perhaps even more troubling is that some caregivers are reluctant to seek support from loved ones or professionals [99].

A large amount of research has examined caregiver interventions with only a small proportion of studies focused on *end of life* caregiving [100]. Although researchers have assessed the utility of various interventions (e.g., psychoeducational, skills based, supportive), none of the interventions has had a consistent impact on caregiver and patient outcomes, making it difficult to determine the type of intervention to best suit their needs. A discussion of these different interventions as well as associated outcomes follows. The focus will initially be on single modality interventions (e.g., supportive care), followed by multimodal treatments, which are designed to target symptom management as well as various psychosocial concerns (e.g., effective coping, social support). A summary will then follow, which includes a discussion of future directions.

One of the first randomized controlled trials with caregivers of patients at the end of life examined the effect of a weekly supportive treatment for caregivers. This intervention took place over 6 months and found no advantage for the treatment group over the control group [101]. Subsequent supportive interventions have had a limited impact as well. In a randomized controlled trial comparing usual hospice care in all cases, with one arm adding three supportive visits and another arm adding coping skills sessions. In each case, the researchers found no benefit for the supportive intervention on caregiver outcome [102]. Only participants in the third group had significantly improved caregiver QoL, reduced burden of patient symptoms, and reduced caregiver burden when compared to the other two groups [102].

The only study to show any benefit of a single modality, supportive intervention was a study examining family-focused grief therapy, which began during palliative care and continued into bereavement [89]. They found that caregivers experienced a reduction in distress at 13 months after the patient's death but only for the families who were highly distressed at the initiation of the study. In another randomized controlled trial comparing standard home-based palliative care (SHPC) plus 2-session psychoeducation to SHPC alone, a more positive caregiver experience over the long term in the psychoeducation group was found [103]. However, perceived competence, self-efficacy, and anxiety did not differ between groups.

Multimodal interventions, which often have some degree of psychoeducational emphasis, have also been developed. In a study by McCorkle and colleagues (1998), a weekly psychoeducational home care intervention was compared to the same type of treatment but with one arm adding a skills training [104]. The researchers found only a slight advantage for the group that included skills training (i.e., less depression and paranoid ideation) and did not find a significant group by time interaction [104].

In another study examining the impact of a supportive, psychoeducational family intervention, a decrease in psychological distress in both patients and caregivers in the intervention group was observed but only for a limited period of time [105]. An examination of the influence of a brief, three-session skills training plus psychoeducational intervention found caregivers experienced an increase in self-efficacy by helping the patient manage pain; however, there was no effect of the treatment on patient pain [106]. A more recent randomized controlled trial comparing psychoeducation with a secondary supportive focus to usual, multidisciplinary treatment found no difference in caregiver outcomes between groups [107].

Couples Therapy at the End of Life

Research examining the effectiveness of couples' interventions targeting the spouses or significant others of cancer patients at the end of life is a relatively new endeavor. Mohr and colleagues (2003) conducted one of the first studies examining the impact of couple's therapy on nine couples. In this small sample, they found significant reductions in the patient's worry about dying as well as the partner's worry about the patients' demise [108]. They also found an improvement in relationship quality. Another intervention, emotionally focused couple therapy has also shown some promise for improving marital function and decreasing symptoms of depression in both caregivers and patients [109].

In summary, caregivers of patients with cancer who are at the end of life are at risk for psychological distress, and it is not clear how to best support them. Neither single- nor multimodal interventions offer clear advantages. Research on couple's therapy, however, indicates that this type of intervention shows some promise in improving psychosocial outcomes. Future work in this area is desperately needed and should be theory-driven and include outcome measures that are relevant to end of life in both patients and caregivers, such as QOL, pain management, and psychological distress.

Summary

The intersection between the end of life in the context of cancer and caregiver survivorship is beginning to receive the attention of researchers. There is an increasing focus on the psychological and health consequences that families can experience as a result of caregiving and/or bereavement. Interventions and research concerning predictors of the short- and long-term effects of caregiving have been studied extensively in caregivers of dementia. However, there is a relative paucity of research concerning cancer caregivers, including formal and informal. Much work needs to be done to determine which medical and psychological interventions improve QoL for patients at the end of life and their surviving family members. Some work indicates that the patients and caregivers cannot always be treated separately and interventions developed for the dyad may be most effective; however, research in this area is still greatly needed to better understand the effects of the patient and caregiver functioning on one another particularly at the end of life (e.g., actor-partner independence).

Additionally, training of health care professionals who interface with patients and families could be enhanced, and practice guidelines across medical disciplines could be developed that include recommendations for appropriate and timely referral to palliative care and hospice. Clinicians and researchers may also want to consider the economic toll on society that caregiving and/or problems with bereavement may have on a large percentage of the population.

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Controversies in Psycho-Oncology

15

Aishwarya Rajesh and Michael Stefanek

> No great advance has ever been made in science, politics, or religion, without controversy.
>
> —Lyman Beecher

> No doubt science cannot admit of compromises, and can only bring out the complete truth. Hence there must be controversy, and the strife may be, and sometimes must be, sharp. But must it even then be personal? Does it help science to attack the man as well as the statement? On the contrary, has not science the noble privilege of carrying on its controversies without personal quarrels?
>
> —Rudolf Virchow

Science is saturated with controversy. Some of this “controversy” is more junk political controversy than science, such as the “debates” over climate change. Some controversy is politically or religiously driven such as the battles over evolution versus creationism or whether homosexuality is defined at birth or caused by environmental factors. If we consider issues less tainted by politics or religion, in a perfect scientific world, our knowledge would be smoothly cumulative, with each reported finding building upon prior findings until we have a pure body of knowledge ready for application in the real world. Unfortunately, this is not the case. We have varying research designs, some more rigorous than others, meta-analyses that result in attempting to summarize a series of studies that differ significantly in any number of ways (subject sample, design, measures), reviewers of articles that differ in their opinions of the value of any given submission of research findings, and, yes, even scientists who fudge data or, more benignly, are driven by their own unrecognized biases to find what they are looking for.

Behavioral science and psycho-oncology in particular are no less susceptible to controversy than any other scientific field. Certainly, such controversy need not be accompanied by personal attacks or acute sensitivity to criticisms of our own scientific work. Indeed, it is our role as scientists to most aggressively attack our own theories and welcome work that challenges the assumptions behind and the results of our own findings. By supporting such challenges, we can increase the chances that our current controversies will be viewed as more settled matters of scientific fact in the future.

In this chapter, I do not assume that any of the work reported involves incompetence or an attempt to mislead the field of psycho-oncology. I hope that the criticism or questioning included in this chapter is viewed as important to the credibility and integrity of the field of behavioral sci-

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ence and psycho-oncology. As perhaps a scientist or clinician engaged in psycho-oncology reading this chapter, I hope you agree that we owe it to ourselves and all those involved in cancer care, including patients and family members themselves, to take the role of healthy skeptic and closely examine the scientific foundations of our clinical practices and policies.

My selections in this chapter include critiques of work involving (1) psychosocial screening of cancer patients, (2) the benefit of psychosocial interventions to decrease emotional distress among cancer patients, (3) the role of positive psychology in cancer care, (4) the role of support groups in increasing survival among cancer patients, and (5) the relatively new field of "integrative cancer care." Some of these topics are covered tangentially or directly in other chapters of this text. I encourage you to review this chapter in the context of these related contributions to arrive at your own tentative conclusions about the state of the science in these areas.

Finally, my intent in writing this chapter, given the scope of coverage across these four designated controversial areas, is not to provide an exhaustive review of each area. Rather, I attempt to summarize findings, discuss concerns that give rise to my view that this is a controversial area, provide my opinion on the state of the science, and provide solid references for readers who wish to pursue these areas in greater depth.

Screening for Emotional Distress in Cancer Patients

The argument to screen cancer patients for emotional distress seems like a straightforward one. Who could argue against the need to identify such distress among patients facing a potentially life-threatening illness? After all, depression, anxiety, and distress are common following the diagnosis of cancer [1], with overall prevalence in unselected cancer patients greater than 30% [2, 3]. Clearly, psychosocial needs require attention due to their direct and indirect effects on health and quality of life. In addition, there is evidence that such distress is not easily recognized among oncologists [4], nurses [5], or general practitioners [6] and that errors may involve both false positives and false negatives. One meta-analysis of studies assessing clinical accuracy among general practitioners found that they had considerable difficulty accurately identifying distress and mild depression. Out of 100 consecutive presentations, a typical general practitioner making a single assessment would correctly identify 19 out of 39 people with distress, missing 20, with 13 false positives [6]. Thus, it seems to make intuitive sense that in order to provide optimal care to cancer patients, using some type of screening questionnaire and initiating formal screening programs to identify cancer patients experiencing high levels of emotional distress is warranted.

Perhaps it is appropriate at this point to review briefly what we mean by screening and the major tenets involved in "successful" screening. The most well known are those by Wilson and Junger [7] and these are as follows:

- The condition screened for should be an important health problem.
- There should be an accepted treatment for patients with the disease.
- Facilities for treatment and diagnosis should be available.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition should be adequately understood.
- There should be an agreed-upon policy about whom to treat as patients.
- The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case finding should be a continuing process and not a once and for all project.

While these tenets have been set out to focus upon medical screening, they apply to screening for general emotional distress, depression, or even overall quality of life as well. For instance, issues such as which questionnaires provide solid sensitivity and specificity is key, as are other issues such as the length of questionnaires (burden to patients), whether in any given site appropriate treatment is available and cost-effective, whether such treatment is acceptable to providers, patients, etc. Thus, it is the case not simply of determining that clinical encounters by health care providers do or do not address issues of emotional distress but also of providing evidence that formal screening of patients is superior in identifying distress relative to not screening *and that such screening leads to superior treatment—the successful conversion of screening tests into screening programs with established benefit to patients.*

To frame the issue clearly, we know that health care providers, including oncologists, often underdiagnose and undertreat emotional distress, including depression [8]. We also know that few health care providers systematically utilize any screening instruments, even ultrashort measures, to assess emotional distress [9]. The idea of using brief, easy-to-use case finding instruments to detect such distress has wide appeal in psycho-oncology. For instance, several organizations, including the National Comprehensive Cancer Network and the Canadian Strategy for Cancer Control, have established guidelines supporting the practice of brief screening of cancer patients to attempt to detect emotional distress, endorsed by some as the "6th vital sign" for patients with cancer [10, 11]. However, despite the understandable drive to decrease emotional distress, anxiety, and depression among cancer patients, the idea of using screening as an effective way to do so has not been systematically examined. Indeed, the guidelines noted above have been based upon expert opinion rather than a systematic review of the evidence.

There are a host of studies that have assessed the accuracy of short, easily administered screening tools to identify patients with cancer who have high levels of distress. In one of the earlier analyses of "ultrashort" (less than 15 items) methods of detecting cancer-related mood disorders, Mitchell [12] identified 38 such reports involving a total of 6414 unique patients, including 19 studies that assessed the Distress Thermometer [13], a single-item measure asking patients to self-report their level of emotional distress on a 0–10 scale to the question "How distressed have you been over the last week on a scale of 0–10?" This is the main distress scale recommended by the National Comprehensive Cancer Network [14]. This review estimated that 12 of 20 probable cases detected by ultrashort methods actually would have significant distress defined by an acceptable standard. Most troubling perhaps was that in the case of depression, when a patient screened positive on an ultrashort method, only 7 in every 20 "positives" were actually depressed. However, such instruments fared much better in "ruling out" depression. Of 20 patients screening negative, 19 could be correctly ruled out, with only one case of depression missed. Based upon the above, it appears that ultrashort methods are best at ruling *out* depression, anxiety, and distress, but poorer if used to confidently rule *in* depression, anxiety, and distress. Overall, findings indicated that ultrashort methods were modestly effective in screening for mood disorders and questioned their value as a stand-alone measure to diagnose depression, anxiety, or distress in cancer patients.

There have been a number of other reports that have reviewed the use of screening instruments for emotional distress among cancer patients [15–17] since the report noted above by Mitchell [12]. These reviews focus specifically upon the ability of selected instruments to identify cancer-related distress or upon the psychometric properties of existing tools currently used for screening purposes, with the idea of encouraging screening programs to use those with strong psychometric properties. There are a number of instruments that meet such standards, although issues such as acceptability and cost-effectiveness are not addressed, and many of the cancer-specific scales require further validation with clinical interviews before they can be recommended [15, 16].

A key addition to the evidence base for screening and its impact on psychological well-being is a thorough review by Bidstrup et al. [17]. This review described and discussed the findings of randomized clinical trials of screening on psychological outcomes. A meta-analysis was not possible, due to the heterogeneity of the designs across studies and differences in the intervention content, site of cancer among patients in the studies reviewed, and the outcome measures applied. Only seven randomized trials were found. In this case, a randomized trial involved assignment to an intervention group that received a questionnaire to assess distress with results provided to staff or assignment to a control group that either received normal care or whose questionnaire data was not made available to staff. A distress management plan was included in four of the seven studies (e.g., contact by a social worker), while three studies provided no plan on how the staff should act on the basis of the screening results. Three of these studies showed an effect, three showed no effect, and one showed an effect only for patients reporting depression at baseline. This review was the first such overview to address the issue not just of the psychometric properties of the screening instruments, acceptability, and feasibility but also whether such screening really made a difference in the psychological outcomes of patients screened versus not screened. As noted, while many methodological differences make comparisons across studies challenging at best, the results do not provide evidence of a clear benefit for screening of cancer patients.

In addition to the valuable contribution of Bidstrup et al. [17], a recent review [18] evaluating the potential benefits of depression screening for cancer patients assessed: (1) the accuracy of depression screening tools, (2) the effectiveness of depression treatment, and (3) the effect of depression screening on depression outcomes. This review included studies that (1) compared a depression screening instrument to a valid major depression disorder criterion standard, (2) compared depression treatment with placebo or usual care in a randomized controlled trial, or (3) assessed the effect of screening interventions on depression outcomes in a randomized controlled trial. While there were 19 eligible studies on screening accuracy, there were only one depression treatment randomized control trial and one randomized controlled trial on the effects of screening on depression outcomes. Examining the 19 trials on screening accuracy, many had small sample sizes, while the single treatment trial reduced depressive symptoms moderately (effect size = 0.37). Only one study assessed the effects of depression screening on actual depression outcomes and found no significant improvements.

As with screening for general emotional distress, screening for depression is only useful to the degree that it leads to improved outcomes above and beyond usual care or other existing programs not including formal screening. The results reported above support the position that psychosocial screening of cancer patients does not provide benefit to patients in terms of improved psychosocial outcomes and speak to the lack of data rigorously examining this important question related to cancer patient care.

More recent work has continued to demonstrate challenges associated with the use of screening as an effective way to achieve the ultimate goal of managing emotional distress in cancer patients. Findings indicate that moving from completion of a psychosocial distress measure to a referral being made to the actual delivery of psychosocial services may result in significant attrition (36%) [19]. The successful treatment of distress would of course impact this number even more significantly. This adds to concerns about the benefit of screening above and beyond what might be achieved in terms of patient outcomes without a formal screening program [20, 21].

Recent reviews of psychosocial screening converge by concluding that the effectiveness of screening as standard practice is not supported [22, 23]. A recent Cochrane review [23] notes a host of issues making claims for the benefit of routine psychosocial screening suspect, including methodological issues across studies and the need for more uniformity in reported outcomes.

Conclusion

An Institute of Medicine report [24] and clinical guidelines from the National Comprehensive Cancer Network [10] have advocated the use of screening for emotional distress, including depression, for standard cancer care. However, none of these recommendation statements provide a systematic review of the benefits of such screening, but rather are based upon expert opinion, concern for patients suffering from emotional distress, and an emphasis on work relegated to psychometric properties of screening instruments, feasibility, and acceptability. However, despite calls for the benefit of such standard screening [25], there are clearly questions as to whether such screening of patients adds value to standard care in terms of positively impacting the emotional distress cancer patients face with their cancer diagnosis and treatment. It appears that screening, while offering a seemingly simple solution for early successful treatment of emotional distress, has yet to demonstrate a clear benefit over standard approaches such as simply offering patients the chance to discuss their concerns, regardless of formal screening programs. A screening program is the widespread distribution of a screening test and includes a support system post-screening across a health care system. This effort in developing and maintaining a screening program should not be underestimated and the evidence supporting such a program should be daunting. Given the brief review of the findings to date noted above, the data hardly provide a strong evidence base at this time to warrant such largescale intervention. Despite the above, it should be noted that much work has been done examining the psychometric properties of various instruments, including many "ultrashort" questionnaires. Such brief measures likely increase the chances that clinicians will find screening acceptable and decrease the cost (time to complete, review, score) to both patients and health care providers—all necessary steps in the process to assess the cost-benefits of screening.

Where to go now? In line with the recommendations of Bidstrup et al. [17], future randomized trials need to compare the validity of different screening approaches, minimize the cost of false positives and false negatives, and, most critically, evaluate the benefits of screening *linked* to standard treatments. Standardized outcome measures need to be utilized and theory-driven management/treatment plans need to be tested. Studies to date have failed to provide sufficient details on the treatment plans implemented, acceptability of the treatment plan developed, and staff training issues. At this time, without evidence from future trials, it is premature to suggest the utilization of programs to systematically screen for emotional distress among cancer patients. However, arguing for the continuation of the status quo within which patient distress can be too often ignored or addressed in an unsystematic, hit-or-miss fashion is also unacceptable. The controversy should not involve whether to provide psychological services and support to cancer patients struggling with a disease and often treatment with significant impact on quality and quantity of life. Rather, the controversy is whether cancer patients are best served by routine screening for psychological distress or if resources may be better applied to strengthening support services for cancer patients seeking such services within and outside of the oncology setting proper.

Psychological Interventions for Emotional Distress Among Cancer Patients

Surveys going back decades present data indicating that emotional distress is common following the diagnosis of cancer and extending throughout treatment [2, 26]. The distress, anxiety, and depression accompanying the diagnosis impact quality of life and even satisfaction with and adherence to treatment regimens [27, 28]. This has led not surprisingly to a call for psychosocial interventions for cancer patients, with the a priori assumption, quite reasonable, that such interventions should certainly prove no less beneficial than such interventions for individuals without cancer. However, it does behoove us to demonstrate that what we provide to patients is acceptable and of benefit to them. Without such a demonstration, the credibility of our interventions and our ability to procure resources for interventions will necessarily (and understandably) be compromised.

With the field of psychosocial oncology no longer in its infancy, it should come as no surprise that a host of psychological intervention studies have been published, and even several narrative reviews and meta-analyses completed [29, 30]. Perhaps what is surprising is that this area of psycho-oncology has made it to the list of controversial topics. Why is that the case?

One critical issue surrounding the evaluation of the scientific literature related to psychological interventions is a definitional one. That is, what do we mean by "psychological intervention" as this term relates to cancer care? In a "meta-review," Hodges et al. [31] determined how the term "psychological intervention" had been defined and used to group and compare such interventions in the context of cancer care. The authors report that they were unable to find any explicit definition of the term in over 60 narrative reviews and meta-analyses. Obviously, such a glaring problem presents a challenge in attempting to cleanly summarize research findings and utilize such findings to inform clinical practice. For the purposes of this chapter, the definition will follow the one most closely adhered to during the Society of Behavioral Medicines (Annual Meeting, 2005) "Great Debate" on this topic [32]. For this purpose, psychological intervention was defined as an interpersonal process (i.e., a relationship between a trained professional and the client or clients, if the relationship involves a group process) intended to bring about changes in behavior, feelings, cognitions, or attitudes. It includes what would be generally considered "psychological" interventions, such as cognitive-behavior therapy, psychosocial support groups, and individual or group counseling, utilizing a measure or measures of emotional distress as an outcome (e.g., global distress, depression, anxiety) in adult cancer populations. To be clear, this excludes pharmacological interventions and non-psychological interventions (e.g., medically based nurse home visits, peer support without a professional facilitator, massage, music therapy, nutritional or physical activity interventions, prayer). It also excludes interventions that focus on outcomes such as pain, increased survival, fatigue, and sexual problems secondary to disease or treatment.

Early meta-analyses of the effect of psychosocial interventions on measures of emotional distress or quality of life were promising [29, 30]. In the first such meta-analysis reported [29], 45 published randomized trials reporting 62 treatment–control comparisons were identified. Measures included not only emotional adjustment but also functional adjustment (e.g., socializing, return to work), treatment-and-disease-related symptoms (nausea, vomiting, pain, etc.), and medical outcomes (e.g., physician ratings of disease progression). Given our definition noted above, focusing on emotional adjustment, Meyer and Mark [29] found a small but significant benefit of psychosocial interventions (effect size $d = 0.24$, 95% CI = 0.17–0.32). Limitations of the meta-analysis include small sample sizes that prevented examining interaction effects in many of the studies (e.g., assessing benefit by type of intervention) and overrepresentation of white women across studies. In addition, many types of "psychosocial" interventions were included in the meta-analysis, including music therapy, informational and educational treatments, and social support interventions by nonprofessionals. Finally, little discussion was provided by the authors of the quality of the studies reviewed and how such quality impacted inclusion or weighing of the meta-analytic results. Of interest is the authors' conclusion that interventions benefit patients and that more studies assessing the effect of psychosocial interventions on cancer patients would be an inefficient use of resources. This is a conclusion that certainly appeared premature then and arguably one that continues to be premature.

The second early meta-analysis assessing psychosocial interventions on quality of life [30] reported on 37 published, controlled (i.e., presence of a control group, not necessarily randomized) studies among adult cancer patients. The quality of life measures included those assessing emotional adjustment or functional adjustment and could be either global or disease specific. The measures could also include either self-report ratings or ratings by another observer (most frequently, the health care provider). Overall, the findings were generally synchronous with those of Meyer and Mark [29], supporting the hypothesis that psychosocial interventions had a positive impact on cancer patients, consistent with a small to moderate effect size. While this analysis did include patient education programs, most studies (84%) focused upon interventions consistent with the definition we have adopted. However, again, little data was provided about the methodological quality of the studies included in the meta-analysis and how such quality was utilized for the conclusions presented. In addition, there was little data presented on demographic variables that might be significant, although the authors did note that breast cancer patients were overrepresented in the studies assessed. The authors did find that interventions of longer duration (>11 weeks) were more likely to be of benefit in decreasing emotional distress. Finally, and perhaps most critically, the selected studies varied significantly in experimental design, treatment conditions, and outcome measures.

As a result of some of the weaknesses of these early meta-analyses raised above, the Society of Behavioral Medicine convened a "Great Debate" at its annual conference in 2005 [32]. The proposition considered in the debate was that "psychological interventions for distress in cancer patients are ineffective and unaccepted by patients." This debate prompted a series of stimulating papers that served to promote differing viewpoints on the state of the science, but with some ultimate concurrence on the research needed to drive progress in this area [33–38].

The "con" position in this debate [34, 35, 37], based on the phrasing above, is that psychological interventions are indeed effective. The basic position of the "con" side noted that a plethora of studies had addressed this topic, and given the large number of such studies, single studies should not lead us to conclude that psychological interventions, in general, are not beneficial to cancer patients. Data to support the "con" position were drawn from two meta-analyses not reviewed above [39, 40], noting an overall small to medium and clinically significant effect of psychosocial interventions on emotional distress. As the debate raged, other key points of the "con" side emerged [34, 35, 37], focusing upon results from both qualitative reviews [41, 42] and the quantitative meta-analyses above [39, 40] and selected randomized controlled trials. The summary of the data reviewed indicated that while the qualitative reviews were quite tentative in supporting the benefit of psychosocial interventions, results were more definitively positive based upon the quantitative reviews. The latter found effect sizes in the small to medium range, with more benefit for outcomes specific to emotional distress and anxiety than for depression. An important point made from these meta-analyses was that more of an effect was found under conditions when (1) the studies were methodologically superior and (2) interventions were delivered to those most in need, i.e., patients reporting high levels of distress preintervention. In addition to utilizing the reviews to support the position that interventions were of benefit, a review of the highest-quality randomized clinical trials published within 5 years of the debate was completed [43–47]. These trials were selected using the Consolidated Standards of Reporting Trials (CONSORT) criteria [48] in combination with evaluative criteria established for empirically based therapies by Chambless and Hollon [49]. The "con" position held that these five studies provided sufficient detail to judge the degree to which they adhered to the criteria for a rigorous empirically supported treatment. Their summary point was that four of these five interventions, focusing on cognitive-behavioral approaches, showed statistically significant beneficial effects on psychological distress outcomes when compared to a no-treatment comparison group. One study showed a beneficial effect for patients displaying higher levels of distress preintervention [43]. Two of the studies [45, 46] evidence small effect sizes, while the Nezu et al. trial [43] reported a large effect size. Two of the studies [44, 47] did not publish effect sizes. Overall, these findings from what was considered the most rigorous investigations of psychosocial interventions led the "con" position to support the stance that cognitive-behavioral interventions for cancer patients are indeed efficacious. Moreover, data from Nezu et al. [43] are consistent with the position that such interventions are beneficial for those cancer patients presenting with high levels of baseline distress.

The "pro" position in this debate held the position that psychological interventions are not effective [33, 36, 38]. The main tenet of this position held that while dozens of studies have been conducted examining the efficacy of psychosocial interventions and several reviews of this literature, the result of both present conflicting and inconsistent conclusions. Much of this confusion is a result of the poor quality of the studies examining intervention impact, which leaves the field in a rather murky, inconclusive scientific state. The strategy for the "pro" position was to assess a 10-year period of reviews of the psychosocial intervention literature and focus on reviews that minimize bias by using a systematic and comprehensive search strategy while controlling for the effects of lesser quality studies on results. This was done utilizing guidelines offered by the QUORUM statement checklist [48] and the Cochrane group [50]. This process resulted in one review [51] which was clearly superior based upon the aforementioned guidelines. This review identified 129 potentially relevant trials, with only 34 trials deemed of sufficient methodological quality to fully review for efficacy, based on the Cochrane Collaboration guidelines. Across these trials, there were few statistically significant differences favoring interventions on measures of distress (anxiety, depression, global distress), with only about 25% of tests across the various outcome measure of emotional distress reaching statistical significance. Thus, based on this high-quality review of the efficacy of psychosocial intervention, results would support the "pro" position that interventions are ineffective in reducing the distress of cancer patients.

In the rebuttal to the "pro" positions findings, Manne and Andrykowksi [37] contended that finding 25% of the analyses of individual outcome variables is not an indication of lack of benefit. Rather, they noted that no comparisons were statistically significant in the direction favoring the control group, a finding that would be expected if indeed there was no treatment effect. In addition, the issue was taken with the use of the singular, albeit rigorous, review utilized by the "pro" position [51], and the argument was made that the dismissal of other meta-analyses was unreasonable. It was noted that such meta-analyses, although including flawed studies, generally supported the benefit of psychosocial interventions.

As the final rebuttal accorded the "pro" side (supporting the position that psychosocial interventions are ineffective), Coyne and Lepore [38] made the following points: (1) the "con" side relied on reviews that included nonrandomized trials to prove efficacy while the one exception [51] did not provide evidence for efficacy, and (2) four of the five intervention studies selected by the "con" side failed to provide an analysis of treatment × time interaction needed to demonstrate efficacy. That is, while the "pro" side agreed that the studies selected as the "best" by the "con" side did indeed show main treatment effects for an outcome related to emotional distress, they argued that this is potentially misleading as an indicator of efficacy. Rather, what is most critical is whether the change over time is different between groups (group × treatment interaction). Finally, they argued that the fifth trial selected by the "con" side as evidence of efficacy [43] did not provide enough evidence of efficacy as a stand-alone study to overwhelm the body of data not supporting the benefit of psychosocial intervention. Their stance remained that the data to date fail to provide even a modest case for the efficacy of psychosocial interventions to reduce distress among cancer patients.

Several studies have shifted focus toward identifying individual-level variables and intervention-related characteristics as moderators of treatment outcomes. This academic pursuit has helped limit ecological bias, promote more diverse representation of participants, increase the specificity of intervention efficacy, and highlight the importance of culturally sensitive psychosocial interventions. Furthermore, recent meta-analytic reviews have primarily examined studies incorporating systematic randomized control trials (RCTs) while also accounting for the quality of included studies. Such RCT-based study designs have been characterized by clearly defined protocols for the delivery of treatment. Thus, the overall quality of such meta-analyses has improved allowing for robust inferences to be made. For instance, Kalter et al. [52] conducted a meta-analysis of individual patient data from 22 RCTs. In this study, 19 RCTs evaluated transdiagnostic skill-based approaches such as relaxation training, cognitive restructuring, and activity planning. The remaining two RCTs evaluated experiential insight-based approaches such as self-awareness and self-acceptance. Notably, the authors found that skills-based interventions conferred unique benefits to women with breast cancer treated with chemotherapy and to patients less than 50 years of age. Across both types of interventions (i.e., skills-based and insight-based), intervention effects were significantly larger for patients who were single or living alone, patients who received chemotherapy, and those who had higher psychological distress at baseline. Overall, it has been posited that the principal mechanisms of change associated with these various psychotherapy approaches are a reduction in cancer-related thoughts and feelings, an increase in self-efficacy and self-concept, as well as a better understanding of cancer pain [53, 54].

In recent years, face-to-face psychotherapy interventions have extended to other platforms such as telephone-based and web-based interventions, allowing for improved access to care. A meta-analytic review of 20 RCTs by Agboola et al. [55] highlighted the potential of such telehealth interventions in improving psychological outcomes in cancer patients. However, of the 20 RCTs reviewed in their study, only 2 telehealth interventions were modeled as psychological interventions (i.e., interventions involving a psychotherapy relationship between a trained professional and the client(s)). Of these, one demonstrated equal efficacy for both face-to-face and telehealth intervention models, with participants reporting lower distress levels relative to a waitlist control at a 3-month follow-up [56]. The second study demonstrated the scope of providing treatment options that were culturally adapted [57]. This latter study was conducted in Latinas with breast cancer and their supportive partners and incorporated aspects of interpersonal therapy with cancer education. It showed that culturally tailored, telephone-delivered interventions that provide emotional and psychoeducational support were moderately effective in diminishing depressive tendencies in patients and their partners (range of effect size $d = 0.30$ to 0.37). Overall, emerging intervention models leverage the portability and accessibility of telehealth to provide services to underrepresented, racially diverse populations. Furthermore, they allow for more efficient monitoring of psychological outcomes using computerized adaptive testing and repeated assessments (e.g., [56, 58, 59]).

Collectively, across both face-to-face and telehealth treatments, meta-analytical evidence suggests positive psychological outcomes even when interventions are brief (i.e., less than or equal to 12 weeks [52, 56, 57]), countering previous findings. There is convergent evidence that baseline distress predicts the degree of benefit accrued from psychosocial interventions, consistent with earlier studies. There is still a dearth of literature examining the moderating role of individual-level variables and specific mediators of treatment efficacy, as well as problems with generalizability due to small sample sizes. It is plausible that technology-based interventions may circumvent these difficulties and provide a more organized narrative of whether and in what contexts psychological interventions reduce emotional distress in cancer populations.

So where does this leave us? More recent work has not served to clarify this controversy, with mixed findings of single studies [60, 61] and reviews continuing to note significant limitations in the scientific literature [62–64]. It is at best unsettling to appreciate that after dozens of intervention studies and several systematic reviews and meta-analyses, the data linking psychosocial interventions to decreased emotional distress, anxiety, and depression remains equivocal. It does speak to our failure to systematically build a cumulative science in this important area of cancer care. In the midst of this confusion, there are some directions for research to move, clarified by the "great debate" and the thoughtful work produced by this discourse.

First, there is some data to indicate that our reviews are getting better with time [65], and it should be noted that several reviews and meta-analyses were completed before the advent or major dissemination of CONSORT [66]. Thus, moving forward, there is hope for more rigor in our clinical trials and more quality systematic reviews. It is hoped that the time of nonsystematic, uncritical analyses of this field (and others) is behind us, or at least moving in that direction.

Second, in terms of future trials, there is a need to clearly identify the type of treatment and to consider utilizing consistent outcome measures across trials so we are not comparing "apples and oranges" when the time is ripe for a review or meta-analysis. There is indeed suggestive data that interventions, if effective, are much more likely to be effective for those cancer patients demonstrating a clear need—that is, patients reporting high levels of emotional distress, anxiety, or depression at the time of entry into a psychosocial intervention. In addition, as we define our targeted populations for intervention trials, we should note that we have little information on the benefit of interventions for low-income, ethnically diverse populations, and some evidence that men are underrepresented in such trials historically.

Finally, while not specific to studies related to psychosocial interventions and cancer, increased attention to the methodology utilized in our systematic reviews and meta-analyses is needed. Such reviews and meta-analyses make life easier for researchers and clinicians alike but come with the risk of oversimplifying complex issues. As researchers, we do need to move beyond simply linking to conclusions and need to appraise each trial separately while looking at the consistency of the results. It is humbling to note that meta-analyses have very inconsistently predicted the results of subsequent large randomized trials [67]. Part of this involves our need to move away from interventions with small sample sizes that raise significant issues relative to confirmatory bias and other concerns relative to randomization [68, 69].

In summary, significant resources have been utilized with good intent to conduct studies to help cancer patients decrease their level of emotional distress secondary to diagnosis and treatment. As individual studies suffer from small sample size or lack of methodological rigor, subsequent meta-analyses and systematic reviews suffer in their ability to derive a solid take-home message based upon these inadequately designed single studies. As a result, the quality of this work has not allowed us to derive an unqualified answer to the question of whether interventions work, what interventions, and with whom.

The Role of "Positive Psychology" in Cancer Care

A generation ago, the field of psycho-oncology was working diligently to demonstrate empirically that cancer was indeed a stressful time period, from diagnosis through survival or end of life care. It was not until the early 1980s that research began to document the prevalence of emotional distress among diagnosed cancer patients [3, 70]. Psychiatrists, psychologists, social workers, and other mental health professionals were working within a biomedical system that had yet to formally endorse the concept of "quality of life" as a research domain, and had not allocated institutional resources for such professional groups to be major players in the ongoing care of cancer patients. Thus, the evolution of psycho-oncology care necessitated a focus on demonstrating high levels of distress among cancer patients so that appropriate services could be provided and reimbursed. From a historical perspective, it is interesting to note that discussions of patients benefitting in any way from cancer would very likely not have been embraced by the field of psycho-oncology, and such attention may have been adamantly opposed by those striving to ensure cancer patients received adequate psychosocial care.

The flip side of the above is the "tyranny of optimism" spawned by lay publications in the early-mid 1980s which essentially told cancer patients that thinking positively and having the right attitude would cure cancer [71, 72]. In the late 1980s, a study by David Spiegel and colleagues supported the notion that psychosocial support groups could increase survival among women with metastatic breast cancer [73], and this study was unfortunately utilized by many in the alternative medicine community to promote the belief that cancer was a case of "mind over matter." As a practicing psychologist in a major cancer center at that time, on more than one occasion, I was clearly instructed by well-intentioned family members not to allow their relative with cancer to address the possibility of cancer progression or issues surrounding the possibility of death and dying during our counseling sessions. The fear was that such "negative" thinking would both demoralize the patient and lead to his or her physical demise. This mandate to "think positively" due to the belief that such thinking is key to survival has been appropriately labeled the "tyranny of optimism" [74] and represents a very real danger of unquestioned acceptance of "positive psychology."

It is in some ways comforting that the idea of "positive psychology," including concepts such as "posttraumatic growth" and "benefit finding" has made its way into this chapter, signaling that it is indeed undergoing empirical scrutiny. The lines of research in this area have included the conceptualization of positive psychology constructs, methodological considerations, and implications for practice. The recent attention given this exciting area in the research literature warrants its inclusion in this chapter as an ongoing psycho-oncology controversy.

A number of constructs have historically dotted the health psychology literature as "positive psychology" constructs, including "fighting spirit" [75], the related concepts of benefit finding and posttraumatic growth [76], and optimism [77]. Since "fighting spirit" has essentially been dismissed as a construct of prognostic value [78, 79], this brief review will focus upon optimism, benefit-finding, and posttraumatic growth related to coping with cancer and health outcomes.

Interest in optimism as a personality characteristic linked to psychological adjustment and health outcomes has increased over the past several decades, examining whether dispositional optimism (a generalized expectation that good things will happen) is linked to health. Much of this work has indeed found a protective effect for optimism when examining such outcomes as pain reports [80] or rehospitalization following coronary bypass surgery [81].

A review of this association between optimism and physical health was recently completed, with results generally supporting this optimism–health connection [77]. This meta-analysis found 84 studies that met the criteria of including measures of dispositional optimism, physical health outcomes, effect size estimates (or the provision of statistics allowing transformation to an effect size), and sample size information. Overall, the mean effect size denoting the relationship between optimism and health was 0.17 (95% CI = 0.15–0.20; $p < 0.001$), indicating a positive but fairly small effect for optimism. However, further analyses provided additionally interesting results. When analyzing studies utilizing subjective measures (primarily self-report measures of health) of physical health versus objective measures, the mean effect size for objective measures was significantly smaller than that for subjective measures. Although both were statistically significant overall, the mean effect size for subjective measures was nearly twice as large as the mean effect size for objective measures. Thus, these analyses indicated that the measurement mode of the health outcome assessed moderated the relationship between optimism and good health.

While this meta-analysis and other studies have linked optimism to positive health or health behaviors in a number of health domains [82, 83], there is not a wealth of data from the cancer domain. However, one such study [84] investigated the relationship between pretreatment levels of optimism and survival in patients with non-small cell lung cancer. One hundred and seventy-nine patients (n = 179) completed the Life Orientation Test (LOT) [85] at pretreatment, a standard questionnaire assessing dispositional optimism. There were no evidence that optimism was related to survival in this sample of patients with lung cancer and no statistical trend in that direction. This study arguably surpasses others in this research arena, given the use of a reliable, valid measure of optimism, a reasonably large sample compared to other investigations, a single type of cancer (non-small cell lung cancer) with no evidence of metastatic disease at the time of pretreatment questionnaire administration, and adjustment for a number of potential confounders in the data analysis.

A second study involving cancer patients investigated the hypothesis that head and neck cancer patients who were pessimistic had a greater probability of dying within 1 year of diagnosis than optimistic patients [86]. This prospective observational study also used the LOT [85] at baseline and tracked survival over 1 year. With a total of 96 subjects, they reported support of their hypothesis. However, the odds ratio for dying within 1 year for pessimistic patients was only 1.12 (95% CI = 1.01–1.24), raising the issue of the clinical significance of such an isolated finding. It is likely that, given the small sample size, this small difference in the odds ratio was driven by only a few study subjects.

In sum, studies to date in cancer have not warranted the seemingly strong belief that optimism does indeed make a difference in health outcomes related to cancer.

It should be noted that dispositional optimism is of interest theoretically and clearly shows promise linking to health behaviors and health outcomes. However, defined as *dispositional* optimism, it has generally been conceptualized as more of a personality trait than a "state" measure. Thus, it is unclear how further work would lead to an intervention strategy that would change such a trait and impact survival, other than providing clinicians an awareness that differing levels of such optimism might impact intervention success.

A "positive psychology" variable with potential relevance to a psychosocial intervention is benefit finding or posttraumatic growth. These are clearly related concepts and integral to the "positive psychology" movement. This concept refers to finding benefit or experiencing personal growth in some way as a function of stress or trauma, in this case, the diagnosis and/or treatment of cancer. This benefit or growth might take the form of a greater sense of personal resilience, appreciation of one's ability to cope, enhanced relationships with family or friends, or greater appreciation of life. It may also take the form of more discrete behavior change, such as smoking cessation and eating healthier. These two constructs (benefit finding and posttraumatic growth), when measured separately, have been found to be positively correlated [87], and both have been plagued by definitional challenges, measurement issues, and the lack of studies utilizing prospective designs [88, 89]. There has been recent attention focused upon determining how different concepts linked with positive psychology are related [90] and predictors of benefit finding among cancer patients [91]. However, without a clear conceptual distinction at this time between benefit finding and posttraumatic growth, the discussion below embraces both constructs examining the data linking them to positive adaptation or health outcomes.

One recent meta-analysis reviewing benefit and posttraumatic growth examined the relationship of these constructs to both psychological outcomes and physical health [76]. Results from cross-sectional studies (n = 87) found benefit finding linked to less depression and more positive well-being, but no relationship of benefit finding to quality of life measures and subjective health reports. Interesting moderator analyses found that the links of benefit finding to the outcomes above were affected by how much time had elapsed since the stressor, the measure used to assess benefit finding, and racial composition. Other reviews focusing upon cancer and benefit finding or posttraumatic growth have found inconsistent links between benefit finding and outcomes. This is true when outcomes have included both psychosocial adaptation measures and health outcomes [92], and reviews converge in noting the inconclusive data to date [93, 94].

Coyne [89] notes that such inconsistent results may be due to several factors. There may be a nonlinear relationship between benefit finding and adjustment or health outcomes, moderators unmeasured to date may be operating, or there may be something about the use of this strategy that increases emotional distress in some fashion [93], an intriguing possibility given that some studies have found that benefit finding has a negative impact on psychological outcomes [92].

More recent work has made it clear that claims continue to exceed evidence in this research domain [89] and the often touted notion that such positive psychology interventions strengthen the immune system in ways that impact cancer lacks support. A recent systematic review of positive psychology interventions in breast cancer [95] included no limitations on studies selected based upon study design or outcome measures, and found significant issues impacting research quality, including small sample sizes, wide variability in outcome measures utilized, lack of control groups, and overall extremely poor research quality. Moreover, a review examining positive psychology applications across medical conditions [96] found work in this area involving primarily correlational studies and noted a clear shortage of high-quality research.

Given the above, we are once more in position to call for more clarity of the core concepts of "positive psychology" prior to extensive development of interventions to enhance benefit finding and promote posttraumatic growth, a position endorsed by both Tennen and Affleck [94] and Gorin [97]. If we move away for the moment from intervention studies, where might we move to promote a cumulative science in this area and determine the value of intervention development?

Aspinwall and Tedeschi [98] warn against "throwing the baby out with the bathwater" and suggest several critical directions the field might go prior to any such "tossing of the baby." First, given some supportive work linking these concepts in domains outside of cancer, it makes sense not to give up on the study of optimism or benefit finding, but rather devote more work to the pathways involved in these health domains. Second, such preintervention work should not focus solely on physical health or survival, but rather include as important outcomes those involving quality of life and psychological distress. This relationship has indeed been challenging to pin down consistently even outside of the cancer domain and may relate to our fundamental lack of knowledge about benefit finding or the posttraumatic growth process. For example, the finding by Helgeson et al. [76] that outcomes are impacted by the amount of time since the stressor may clearly impact findings related to psychosocial outcome variables and should be considered in future work. Finally, the inclusion of positive psychology measures in a more standard fashion as we assess psychological and physical health outcomes among cancer patients would be welcome so that findings might spur additional hypotheses and directions for research.

In sum, the recommendation to return to more of a focus on theory development, measurement development and testing, and more observational prospective research designs will lead to a more solid conceptual understanding of the role of "positive psychology" variables in cancer outcomes related to physical health and psychosocial adjustment [94, 97].

Finally, it will our responsibility to temper the enthusiasm that this area of research produces among mental health clinicians and the media and continue to be cautious as we discuss findings that link "being positive" with outcomes, particularly survival. We need only look back to the Spiegel et al. study [73] linking support group participation with increased survival to appreciate the stir such findings might create and the challenges faced in revising beliefs when such findings are placed in a more cautious framework [99].

Support Groups and Survival in Cancer

This area of controversy has a history dating back over two decades, beginning with two studies [73, 100] with results widely interpreted as showing increased survival among cancer patients participating in group psychotherapy. This work by Spiegel et al. [73] and Fawzy et al. [100] reported that, in the case of metastatic breast cancer [73] and malignant melanoma [100], participation in a support group with other cancer patients significantly extends survival relative to a control group of patients not participating in such an intervention. These studies impacted the psychosocial and even biomedical oncology community at the time and helped to establish the belief by some in the professional community that psychological factors could directly impact the progression of cancer and survival from the disease. These studies and much media attention helped to promote this belief in both the professional and lay communities, with a not insignificant proportion of women attending support groups noting that they did so in part to extend survival [101]. While several thorough reviews have exhaustively challenged these findings and those of others purporting to show life-extending benefits of support group interventions [99, 102], this belief in the power of support groups to extend life among cancer patients and the promotion of this belief manages to linger [103].

Given the importance of these two studies, a brief overview of each is provided. Spiegel [73] reported the effects on survival of a 1-year structured professionally led group intervention delivered to metastatic breast cancer patients (n = 50) versus a control group (n = 36). Very generally, this "supportive-expressive" therapy approach focused upon group members discussing coping with cancer and expressing their feelings about their experience. More specifically, the content involved redefining life priorities, managing side effects of treatment and the illness, self-hypnosis for pain management, and building emotional bonds with group members. Interestingly, the study was not designed to assess survival, but was done due to the media publicity that was being accorded to the idea of "mind over matter" in disease by such alternative practitioners as Bernie Siegel, publishing books for lay consumption [71, 72]. The study found the mean time from randomization to death was approximately twice as long in the intervention group (36.6 months) compared to the no-treatment control group (18.9 months).

Fawzy et al. [100] reported on the survival of patients with malignant melanoma shortly after diagnosis and initial surgery who participated in a 6-week, 90-min structured group intervention (n=34) versus a control group (n=34). This intervention included education about melanoma and health behaviors, stress management—teaching and discussing of coping strategies—and support provided to and from other group members. Consistent with the Spiegel study [73], this intervention was also professionally led. At 6- and 10-year follow-up, risk of recurrence was significantly reduced (6-year follow-up only), as was risk of death (both 6- and 10-year follow-ups) in patients assigned to the intervention arm.

The first meta-analysis of the effects of psychosocial interventions on survival time in cancer patients [104] was completed well over a decade following the work of Spiegel [73] and Fawzy [100] and included other trials examining this same issue. This meta-analysis reviewed both randomized trials (n = 8) and nonrandomized studies (n = 6) of the impact of psychosocial intervention on survival among cancer patients. For inclusion in the analysis, intervention variables needed to involve some type or combination of education, social support, psychotherapy, skills training, etc. The summary of this review supported no overall treatment effect by the randomized trials or the nonrandomized trials. Indeed, the only primary study for group therapy for breast cancer which found a significant effect favoring intervention was the trial described above by Spiegel et al. [73]. Reviewing this meta-analysis and acknowledged by the authors, this review suffered from the "apples and oranges" problem often experienced in meta-analytic attempts, i.e., significant differences across studies in cancer site, intervention, and settings, making it challenging at best to derive firm conclusions overall. This meta-analysis suffered from a small number of diverse studies, with missing data (e.g., cancer treatment) that may well have impacted individual study findings. A very conservative summation by the authors noted that conclusions about whether psychosocial interventions can increase survival were premature, driven perhaps by the finding that individual interventions (versus group) were found to be more effective.

Given the influence and lasting impact the original Spiegel study has had on the field of psycho-oncology, it is interesting to look at the replication study completed by the same investigator [105] and a replication effort by an independent investigator [106].

Goodwin [106] reported a replication of the Spiegel et al. study [73], randomly assigning 235 women with metastatic breast cancer to weekly supportive-expressive therapy or no-treatment control groups, although all participants received educational materials. Of note is that interventionists in this study received training by Spiegel to ensure the integrity of the intervention content, including performance reviews and feedback. The intervention did not increase survival, with median survival in the intervention group reported as 17.9 months versus 17.6 months in the control group. Multivariate analyses incorporating a number of important variables (e.g., presence or absence of progesterone and estrogen receptors linked to differential survival, nodal stage at diagnosis, age at diagnosis) identified no significant effect of the intervention on survival and no significant interactions with treatment and study center, marital status, or baseline mood disturbance.

Spiegel also designed a study [105] to replicate his earlier findings that group therapy extended the survival time of women with metastatic breast cancer. With a much larger sample size than his original study, 125 ($n = 125$), metastatic breast cancer patients were randomly assigned to a supportive-expressive group therapy condition ($n = 64$) or a control condition ($n = 61$) which received educational material. The content, length, and duration of the intervention mirrored the original investigation [73]. The earlier finding that survival was extended with supportive-expressive therapy was not replicated. Overall mortality after 14 years was 86%, with a median survival time of 32.8 months. No statistically significant effect of support group intervention was found on survival, with median survival times for the intervention group (30.7 months) not significantly different than the 33.3 months for the control condition.

In addition to these more recent studies, interested readers are referred to an extensive recent review of the psychotherapy and survival in cancer literature [99], which includes discussions of research design, interpretation of results, and reporting of clinical trials, all issues that have not been sufficiently appreciated in this body of scientific work.

Since the extensive systematic narrative review noted above [99], Andersen et al. [107] reported on a randomized trial of breast cancer patients with local progression who received psychosocial intervention and achieved longer recurrence-free and survival intervals over a median follow-up of 11 years compared with women randomized to no intervention. While the belief in the impact of such psychosocial intervention on the survival of cancer patients had decreased following the negative findings of the replicated works described previously [73, 100] and the extensive critical review noted above [99], this work resurrected the subdued optimism among believers in the power of such interventions. In reviewing the study and findings, this renewed optimism seems unwarranted.

Briefly, this trial randomly assigned newly diagnosed regional breast cancer patients ($n = 227$) to an intervention-with-assessment arm or assessment-only arm, measuring psychological, social, immune, and health benefits of the intervention. The intervention included professionally led groups focusing upon relaxation training, coping skills training, and strategies to improve health behaviors and adherence to treatment. Patients in the intervention arm were exposed to 39 h of psychosocial intervention (26 sessions) over 12 months. Reported results demonstrated longer recurrence-free and survival intervals over a median follow-up of 11 years compared to the women receiving no such intervention.

However, a critique of this trial [102] noted that in this trial, survival was not a primary endpoint, the observation period was not specified beforehand, and the analyses presented were post hoc, not allowing for a straightforward interpretation of the outcome. A key concern impacting the validity of the findings was that there were no differences in unadjusted rates of recurrence or survival between the intervention and assessment-only groups. Overall, while the trial demonstrated that participants in the intervention were satisfied with their group experience and found the groups cohesive with some modest impact on health behaviors, mood, and some selected immunological measures, it did not demonstrate decreased recurrence or improved survival.

In a follow-up study [108], the authors assessed survival among those patients who recurred, numbers that included 29 patients from the intervention group and 33 patients from the assessment-only group. Ten ($n = 10$) of the 29 patients in the intervention group survived (34%), while 8 of the 33 in the assessment-only group survived (25%). While the authors propose that this 59% reduction in the risk of dying from breast cancer is statistically significant, it is challenging to appreciate the magnitude as being clinically significant when viewed in absolute terms. In addition, the results were not statistically significant in simple analyses, but only in multivariate analyses in which the strategy for selection of covariates was not concretely specified [109].

Clearly, evidence supporting the role of support groups on survival is lacking, and more recent studies shed additional doubt on the rationale for such interventions focused on increased survival as an outcome. A number of investigators have recently addressed the role of psychological factors that may be impacted by interventions such as support groups (e.g., psychological distress) in cancer incidence or mortality. This work [110–115] examining cancer incidence, cancer-specific mortality, or all-cause mortality either suffer from significant limitations (e.g., psychological distress measured at baseline only; issues with recall bias, etc.) or report no association between psychological factors and incidence of cancer [111, 112] or very small risk ratios related to cancer mortality [113, 114], potentially confounded by other factors.

In sum, it appears that the belief that psychosocial interventions positively impact survival among cancer patients extends beyond the data. The earlier study by Spiegel [73] was not replicated by the same investigator [105] and a second independent study [106], both replications utilizing the same diagnostic group (metastatic breast cancer patients) and intervention content (supportive-expressive group therapy). Other trials reporting positive results of psychosocial interventions on survival have significant design or analysis flaws, or do not account for outstanding confounding factors (e.g., more medical attention by those participating in the active psychosocial treatment) [99]. Little headway on changing the beliefs of many that interventions were effective positively impacting survival among cancer patients, [116, 117], the evidence appears clear: No randomized trial designed with survival as a primary endpoint and in which psychotherapy was not confounded with medical care has yielded a positive effect [99].

So where do we go from here? As noted by Stefanek and McDonald [118], researchers need to appreciate the complexity and biology of the many diseases called “cancer” and work in an interdisciplinary fashion with those expert in disease and treatment issues that may impact on survival. It seems appropriate to take a step back from large clinical trials at least until we understand much more about the basic and biobehavioral science that links psychological variables to biological changes that have the potential to impact cancer progression. There are cellular and molecular studies that have identified biological processes that could potentially mediate cancer progression [119]. Chronic depression, social support, and chronic stress may influence multiple aspects of tumor growth and metastasis through neuroendocrine regulation (adrenaline, glucocorticoids, dopamine, estrogen, etc.). Work in this area may highlight how behavioral or pharmacological interventions might impact neuroendocrine effects on tumors and slow progression or increase survival [120, 121]. Exciting approaches have used results from more basic molecular and biological studies identifying signaling pathways that influence cancer growth and metastasis as a way to build our basic knowledge base. More specifically, such work explores the impact of stress on certain types of programmed cell death and considers how psychosocial factors may play a role in the avoidance of such cell death by cancer cells [122]. Such basic and translational work allows a body of knowledge to be built that may lead to more efficient, model-driven psychosocial interventions to impact cancer progression. More generally, work needs to consider the hallmarks of cancer that comprise the multistep development of human tumors [123, 124] such as the tumors ability to evade growth suppressors, resist cell death, or induce angiogenesis and determine which of such processes are impacted by psychosocial variables prior to resorting to clinical trials uninformed by this critically important basic knowledge of tumor growth and tumor microenvironment nurturance.

Once such knowledge is gained, and if such knowledge does indeed lead to interventions that may impact tumor growth and metastasis and subsequently survival, there are other important considerations to consider in order to build a cumulative scientific base. First, too many such studies have suffered from small sample size issues. Fox [117] and Piantadosi [69] have both noted challenges with such small trials, including the fact that studies with low power are more likely to produce false positives. Second, in addition to measuring biological changes that may impact survival, it will be crucial to continue to monitor issues such as treatment adherence, changes in health behaviors, confounding by increased medical attention provided to intervention groups that may explain changes due to "psychosocial" variables. Third, careful selection of tumor types is warranted, perhaps focusing on those that are hormonally sensitive such as breast cancer or others potentially immunogenic, such as melanoma. Targeting early-stage tumors may be most productive, since the natural course of more advanced tumors, refractory to chemotherapy, or other medical treatments may dwarf the impact of psychological interventions.

If/as we move to testing psychosocial interventions based upon solid basic and translational biobehavioral work, the quality of such studies needs significant improvement. A systematic approach to the reporting of trials to ensure complete transparency in the design, conduct, analysis, and interpretation of results is sorely needed and sorely absent from the great majority of previous work [99].

Finally, the issue of individual differences has not been extensively explored in this area of research. In this era of "personalized medicine," we do not know what key areas of such differences have physiological relevance, an area that might be informed by the more basic research noted above [120–122]. The role of each individual's genetic and experiential background may well be critical. Related to the role of individual differences, we know very little about the role of socioeconomic status, education, gender, race, and other such variables and how such variables may interact with the impact of standard psychosocial interventions. These individual variables may be important in their own right, rather than "noise" in the system in need of statistical control.

In closing this section, we should remember that there are upper limits to human longevity influenced by both nature and nurture. Quality of life and psychological distress are both worthy clinical endpoints. The role of psychological intervention to impact these important aspects of our lives is an important one, independent of the issue of increased survival.

Integrative Oncology

Despite efforts by promoters of integrative medicine to provide some distance from complementary and alternative medicine, this term is arguably interchangeable with what many have and do refer to as "cancer complementary and alternative medicine." More formally, integrative care or integrative oncology has been defined as a "patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments" [125]. This definition does not exclude the utilization of such therapies to directly impact clinical outcomes and disease progression or prevention, although most of the focus is on disease side effects or side effects of cancer treatment.

Two recent reports have focused upon the use of such alternative approaches within NCI-designated cancer centers and conclude that a majority of them provide services to patients and increasingly provide information on integrative oncology services on their websites [126, 127]. From these data, it appears at first glance that there is an increasing and significant number of major cancer centers promoting and offering a wide range of services such as healing touch, acupuncture, Qigong, along with more mainstream therapies such as dance therapy, yoga, and nutritional consultations—all also included under the terms "integrative therapy" in these studies. There are several issues with the studies noted and the use of such "integrative therapies" in major cancer centers [128]. First, there are concerns about the precise definitions of categories of such therapies and the overinclusion of categories labeled "integrative" with activities such as yoga, nutritional consultation and massage lumped with interventions such as healing touch, Qigong, and Reiki. Several of the interventions are not alternative at all, but rather already part of mainstream medical practice. Including these mainstream treatments in the definition serves to twist the data to make it seem as if complementary and alternative medicine is sweeping across the nation's cancer centers. Second, there is little evidence for many of the interventions reported and at best results are mixed or suffer from small sample sizes, the use of multiple outcomes, or report "trends" in outcomes vs. statistically significant differences. These studies also note the need for further research [129, 130]. One study reported detrimental effects on dyadic adjustment and relationship quality as a function of a couple-based mindfulness intervention [131]. Given the above, there are ethical concerns related to the routine use of such therapies with cancer patients, including a lack of transparency related to patient decision-making prior to initiation of any integrative cancer (or more standard) care interventions. Patients should be aware of the supportive evidence (or not) for interventions that may impact their quality of life. Major cancer centers need to be mindful of who is "minding the store" and providing interventions that may or may not be "evidence-based." There should not be two standards of evidence—one used only when the outcomes are more focused upon disease cure or prevention and one when the outcomes are more focused upon quality of life and emotional distress.

In sum, the myth lies in the evidence that such integrative therapies are indeed skyrocketing across major cancer centers and that many of the interventions have what could be considered an "evidence-based" foundation. The interventions promoted, if indeed they have a solid scientific basis to support their use, need to be compared not to "usual care" but to any active treatment to determine what works and how powerful the intervention might be. Finally, such work has historically been less than rigorous (e.g., sample size issues). Thus, much more work lies ahead before we begin the process of promoting the varied interventions currently under the label of "integrative cancer care " [128].

Conclusion

This chapter has included critiques of work involving (1) psychosocial screening of cancer patients, (2) the benefit of psychosocial interventions to decrease emotional distress among cancer patients, (3) the role of positive psychology in cancer care, (4) the role of support groups in increasing survival among cancer patients, and (5) integrative cancer care. As noted in the introduction to this chapter, I encourage you to read other entries in this excellent text that summarize perhaps different perspectives on these areas of psycho-oncology and derive your own working hypotheses about the state of the science in each of these selected controversial areas.

My thanks are extended to the coeditors of this text for including a chapter on current controversies. There is indeed a very important role for the "healthy skeptic" in behavioral oncology [132]. Our field would be better served by more focus on post-publication critiques of our work. Relying solely on a handful of overworked volunteer reviewers, no matter how dedicated to the role, to determine the merit of work published, with no further formal comment by others most interested in a given topic, does not serve our field, or science, well. This self-evaluation, even if dominated by self-criticism, provides a more transparent and broad review, and likely would lead to superior replication attempts.

Finally, this selection of controversies was intended to focus on science, not the researchers involved in the work critiqued. I certainly did not intend to suggest incompetence or deliberate attempts on the part of any investigator to mislead the scientific field. However, I would remind us all that we should ourselves challenge our own hypotheses most strongly, and it would serve us all well and the science we engage in to be open to debate and criticism of our work. To end on a more philosophical point:

> In a controversy, the instant we feel anger we have already ceased striving for the truth and have begun striving for ourselves
>
> —Buddha

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16

Resources for Cancer Patients

Carolyn Messner and Maria Lorena Tan Wang

Setting the Stage

> A little help, rationally directed and purposefully focused at a strategic time is more effective than more extensive help given at a period of less emotional accessibility. [15]

> In cancer care, the goal of all intervention is to help individuals maximize their existing resources, strengths, and strategies as well as acquire any needed additions so that they experience the greatest sense of well-being of which they are capable. When they are able to do so to the degree that they can experience a sense of calm and strength in the midst of threat, they have achieved a still point. [10]

The Art and Science of Resource Referral

A few weeks ago, Norma, a 70-year-old, single woman called in crisis, not knowing what to do and where to turn. Norma is a member of a weekly, patient support group. She has attended this group for 2 years. She is a Holocaust survivor and had been a teacher until her cancer recurrence 4 years ago. She is a wise and courageous woman who values life and has undergone radical surgeries and treatments so that she could live. Her first encounter with cancer was at the age of 40, when she was diagnosed with breast cancer. At that time, she had a radical mastectomy followed by extensive radiation treatments. A side effect of her radiation treatments was severe damage to the skin in her chest area. Although this was a common occurrence at that time, current radiation treatments no longer have these side effects. The skin in Norma's chest area is paper-thin and scarred. Four years ago, Norma developed metastatic breast cancer in her other breast and had a mastectomy, followed by chemotherapy.

Norma's current crisis was precipitated by a visit she made to a free local skin cancer screening clinic. She had a mole on her hand that "looked suspicious," and she had wanted to have it checked by a dermatologist for possible skin cancer. Although she was relieved to learn that the mole was not cancer, the dermatologist had examined Norma's body for possible skin cancers. The dermatologist had expressed concern about the radiated skin on her chest. He felt that she might have extensive skin cancer in this area and wanted to do a biopsy of the skin tissue to determine if Norma had skin cancer. Norma was terrified of having a biopsy since the skin tissue in that area of her chest was so thin and would probably not heal. She was also frightened that if she did nothing, she would then have an exten-

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sive area of skin cancer in her chest area which could not be surgically removed, because the skin no longer had the capacity to heal.

When she called for help, she was clearly in a state of crisis. She anticipated that the cancer would spread, if untreated, and could eventually be life-threatening. Her balance of coping had been disrupted. She described her inability to think logically and coherently about what to do. Her health care professional suggested an immediate second opinion consultation with a leading cancer center in her city. Since her income is fixed, she was concerned about the cost. The oncology social worker offered to call the cancer center and clarify the cost. In the process, she learned that the office accepted Medicare assignments and that, if Norma wished, she could have an appointment the following day.

The social worker called Norma and told her what she had learned. Norma felt that a second opinion would be helpful to her and proceeded to call and secure the appointment for the following day. She then called back, much relieved. She talked with her social worker about some of the possible options and together, they made a list of the questions she needed to have answered. Her oncology social worker wondered about her going alone to such an important appointment. Norma realized that she had a close friend who could accompany her. Norma and her social worker again reviewed the possibilities and that if this dermatologist was not helpful, they would work together to find another doctor, until she felt satisfied. As she talked, Norma sounded calmer and more in control. Her social worker suggested that Norma and her friend go out after the appointment for some coffee so that she could process the appointment with her friend.

Norma called the following day after her appointment. She no longer felt in crisis. The dermatologist said that Norma did not have skin cancer. He felt that she might develop skin cancer in the future due to the extensive radiation treatments. He did not recommend a biopsy but rather wished to follow her every 3 months. He carefully told her how to care for the skin on her chest and also described the treatment he would recommend, should she ever develop skin cancer. He answered all her questions and spent time alleviating her distress. She felt able to cope with the possibilities and more in control and had arranged to see the dermatologist again in 3 months. After the appointment, she and her friend had gone out to dinner to relax and celebrate the good news and Norma's renewed sense of mastery.

Norma is the archetypal cancer patient – scarred by her cancer but not overpowered, and wanting to find moments of solace, tranquility, and joy in her life. Her scars are not visible to the passerby as her cancer surgeries are covered by her clothing.

A possibility of recurrence can create a crisis for a cancer patient. Oncology health care professionals who work with cancer patients need a thorough understanding of the crisis intervention approach and the challenges people impacted by cancer face in order to be effective in-service delivery and resource referrals for this population.

Types of Resources: Helping Our Patients and Their Loved Ones Utilize Resources

The majority of oncology patients and their caregivers who contact health care professionals or our institutions for resource information, like Norma, feel overwhelmed or anxious and are often in a state of crisis. They turn to their health care professionals for solutions to their particular problems. The problem often has many components, and it is the art and science of the practitioner [17] to assess the level of distress [8] and come up with a resource outcome treatment plan. The Institute of Medicine Report, *Cancer Care For The Whole Patient: Meeting Psychosocial Health Needs* (2008), clearly raised the bar of expectations that treatment of cancer patients includes the full range of psychosocial health services. The types of resources which those living with cancer and survivors often require are as follows:

- Information on a specific type of cancer, treatment decisions, side effect and pain manage-

ment, sexuality and fertility, survivorship care plans, palliative care, and hospice.
- Practical help, financial and co-payment assistance, legal support, transportation, home care, child care, elder care, housing/lodging, wigs, hair care, prostheses.
- Psychosocial and psychospiritual support and counseling, support groups, methods to cope with the anxiety, uncertainty, and distress of cancer, mind/body techniques.
- Facts about the workplace and cancer, reasonable accommodation, Family and Medical Leave Act (FMLA), Americans with Disability Act (ADA), COBRA.
- Health insurance – private and government, including Medicare and Medicaid.
- Disability updates – short-term disability (STD), long-term disability (LTD), social security disability insurance (SSD).
- Government programs, federal, local, and state assistance, Supplemental Security Income (SSI), Medicaid, and veteran's benefits.
- End-of-life planning, including living will, health care proxy, advance directives, power of attorney, will, permanency planning for children, funeral arrangements, and spiritual issues.

This extensive typology requires specialized knowledge of resources by health care professionals and how to access strategic information that our patients and their loved ones require [1–7, 11, 14, 16, 18]. The skill of the health care professional in communicating to patients and their caregivers about needed resources impacts their follow-up. Sometimes, our referrals are reactive to a patient situation, but increasingly, our referrals are proactive based on team assessment prior to crisis. Information and resource referrals are provided upfront to patients to empower and facilitate their coping [21].

Health care professionals have considerable expertise, but their compassionate communication skills significantly impact patients' successful utilization and access to resources [9]. As in the case of Norma, follow-up with patients on a resource referral suggested is essential to ensure the efficacy of the patient's benefit from a referral. Many of us spend our careers gathering resource information on how to connect our patients to needed resources. Patients depend upon their practitioners' network, guidance, roadmaps, and social capital to help them navigate their cancer experience and reduce cancer health disparities in accessing needed help [7, 19, 20].

Resource Guide

This section of the article includes a suggested compendium guide of useful resources for cancer patients. Many provide free services. It would take many volumes to compile all the resources currently available. This resource roadmap is intended as a point of access for health care professionals as well as patients for resources to address myriad problems patients and survivors confront. It is by no means exhaustive. Each organization listed is able to provide specific services, many of which are free. However, their staff of health care professionals will tailor additional resources to fit the patient, survivor, caregiver, or bereaved person's particular needs. The listing does not include the many nonprofit cancer-specific organizations that focus on a particular type of cancer. The organizations listed are able to provide additional referrals to resources for all cancer types.

As you become familiar with these resources and their particular focus, it will facilitate matching each specific resource to the need or problem presented. For those who do not have Internet access in their homes, local libraries can be of assistance in providing access to information on the websites listed. Many of these organizations have toll-free numbers staffed by information specialists to answer questions, guide patients, serve as patient navigators, and mail educational materials.

Collaboration brings together the strengths of each organization and profession to make the best use of their resources. When institutions and their staff partner together successfully, patients and families benefit due to their increased access to a broader range of resources, services, and programs [19]. Working together and pooling resources can energize people and result in innovative ways of tackling problems that might have seemed unsolvable. Interprofessional commitment and partnerships may also serve to counteract the compassion fatigue of practitioners and enable novel help for patients [13].

Resources

American Cancer Society combines an unyielding passion with nearly a century of experience to save lives and end suffering from cancer. As a global grassroots force of millions of dedicated volunteers, we fight for every birthday threatened by every cancer in every community. We save lives by helping people stay well by preventing cancer or detecting it early; by helping people get well by being there for them during and after a cancer diagnosis; by finding cures through investment in groundbreaking discovery; and by fighting back by rallying lawmakers to pass laws to defeat cancer and by rallying communities worldwide to join the fight. As the nation's largest nongovernmental investor in cancer research, contributing more than $4.9 billion since 1946, we turn what we know about cancer into what we do. The American Cancer Society is proud to have contributed to the work that has resulted in a 29% drop in the overall cancer death rate in the United States. That drop equates to 2.9 million fewer cancer deaths between 1991 and 2017. To learn more about us or to get help, call us anytime, day or night, at 1-800-227-2345 or visit www.cancer.org.

American Psychosocial Oncology Society (APOS) is a nonprofit 501(c) 3 professional membership organization that provides a connection point for the professionals and patient advocates that support people affected by cancer. APOS members include physicians, mental health professionals, social workers, nurses, and clergy, among many others, dedicated to treating the human side of cancer. Our mission is to advance the science and practice of psychosocial oncology so that all people with cancer and their loved ones have access to psychosocial services as a part of quality cancer care. Among the programs offered is the APOS toll-free helpline, which assists cancer patients, their caregivers, and advocacy organizations to obtain a local referral to help manage distress. APOS also offers online education in psychosocial oncology and distress management, as well as practical handbooks on adult, pediatric, geriatric, and palliative care. Please visit www.apos-society.org.

American Society of Clinical Oncology (ASCO) is the world's leading professional organization representing physicians of all oncology subspecialties who care for people with cancer. ASCO's more than 45,000 members from the United States and abroad set the standard for patient care worldwide and lead the fight for more effective cancer treatments, increased funding for clinical and translational research, and, ultimately, cures for the many different types of cancer that strike an estimated 10 million people worldwide each year. ASCO publishes the *Journal of Clinical Oncology* (*JCO*), the preeminent, peer-reviewed, medical journal on clinical cancer research, and produces Cancer.Net, an award-winning website providing oncologist-vetted cancer information to help patients and families make informed health-care decisions. For more information about ASCO patient resources, please visit www.cancer.net or call 1-888-651-3038.

The Association for Molecular Pathology (AMP) is a not-for-profit scientific society that advances the clinical practice, science, and excellence of molecular and genomic laboratory medicine through education, innovation, and advocacy to enable the highest quality health care. Our education and innovation efforts work together to provide pathways for the translation of scientific discoveries into diagnostic tests and services, while our advocacy efforts focus on issues that impact patient access to molecular testing. www.amp.org or outreach.amp.org or call 1-301-634-7939.

Association of Clinicians for the Underserved (ACU) is a nonprofit, transdisciplinary organization of clinicians, advocates, and health care organizations united in a common mission to improve the health of America's underserved populations and to enhance the development and support of the health care clinicians serving these populations. Membership in ACU is open to any person or organization in support of its mission. Our members are united by their common dedication to improving access to high-quality medical, behavioral, pharmaceutical, and oral health care for our nation's underserved communities. Learn more at https://clinicians.org/. Or call 1-844-422-8247. Email: acu@clinicians.org.

Association of Oncology Social Work (AOSW) is a nonprofit, international organization dedicated to the enhancement of psychosocial services to people with cancer, their families, and their caregivers. Created in 1984 by social workers and other professionals interested in oncology, AOSW has become the world's largest professional organization entirely dedicated to the psychosocial care of people affected by cancer. For more information contact: AOSW, 111 W. Jackson Blvd, Suite 1412, Chicago, IL 60604; phone: 1-847-686-2233; fax: 847-686-2253; website: www.aosw.org.

Black Women's Health Imperative is a not-for-profit, education, advocacy, research, and leadership development organization that focuses on health issues that disproportionately affect Black women. The Imperative instituted aggressive national programs in health policy, education, research, knowledge, and leadership development and communications to save and extend the lives of Black women. Presently, the organization continues to be dedicated to promoting physical, mental, and spiritual health and well-being for the nation's 19.5 million African American women and girls. For more information about the Imperative, please visit www.bwhi.org or call 202-787-5931.

Cancer*Care* is a national nonprofit, 501 c (3) organization that provides free, professional support services to anyone affected by cancer: people with cancer, caregivers, children, loved ones, and the bereaved. Cancer*Care* programs – including case management, counseling, support groups, educational workshops, publications, and financial assistance, and practical help – are provided by professional oncology social workers and are completely free of charge.

For more information, visit www.cancercare.org or call 1-800-813-HOPE (4673).

Cancer*Care Co-payment Assistance Foundation* is a not-for-profit organization established in 2008 to address the needs of individuals who cannot afford their insurance co-payments to cover the cost of medications for treating cancer. The Foundation is proud to be affiliated with Cancer*Care*, a national not-for-profit organization that has provided free professional support services including counseling, education, financial assistance, and practical help to people with cancer and their loved ones since 1944. For more information, visit www.cancercarecopay.org, or call 1-866-55-COPAY (866-552-6729) or email: information@cancercarecopay.org.

Cancer Patient Education Network (CPEN) is comprised of health care professionals who share experiences and best practices in all aspects of cancer patient education. The organization's overall mission is to promote and provide models of excellence in the areas of patient, family, and community education across the continuum of care. For additional information, visit https://www.cancerpatienteducation.org/ or email info@cancerpatienteducation.org.

Cancer Support Community, as the largest professionally led nonprofit network of cancer support worldwide, is dedicated to ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by the community. Cancer Support Community is here to provide relevant and highly personalized support when and where it is needed most because community is stronger than cancer. Because no cancer care plan is complete without emotional and social support, the Cancer Support Community has a vibrant network of community-based centers and online services run by trained and licensed professionals. For more information, visit www.cancersupportcommunity.org, or call 1-888-793-WELL (9355).

Caregiver Action Network is the nation's leading family caregiver organization working to improve the quality of life for the more than 90 million Americans who care for loved ones with chronic conditions, disabilities, disease, or the frailties of old age. CAN serves a broad spectrum of family caregivers. CAN is a nonprofit organization providing education, peer support, and resources to family caregivers across the country free of charge. Website: www.caregiveraction.org or call 855-227-3640.

Joe's House is a nonprofit organization that provides an online nationwide accommodation directory that helps cancer patients and their families find lodging near treatment centers. The website, www.joeshouse.org, lists thousands of places to stay across the country near hospitals and treatment centers that offer a discount for traveling patients and their loved ones. Lodging options include hospitality houses, hotels, motels, apartments, private homes, and more. Users of the site may search by city or by proximity to a hospital. Information about each lodging facility includes how to make a reservation, rate information, amenities, distance to the hospital, and more. Many facilities offer online booking capabilities. Website: www.joeshouse.org. Toll free line: 877-563-7468 (877 JOESHOU).

Latinas Contra Cancer (LCC) is a leading service and advocacy organization for Latinos around issues of cancer. Their mission is to create an inclusive health care system for Latinos around issues of cancer. LCC provides cancer awareness education, survivor support, patient navigation and Spanish language psychosocial support services for patients and their families, a bilingual website for information and resource links, and special services of bras, wigs, and prostheses. Their major educational programs are Cancer Education Bingos (similar to "Loteria") to teach facts and dispel cancer myths or misinformation common in the Latino community. They provide Train the Trainer programs to teach agencies and their promotoras (community health educators) how to use our bingos. For more information, please check our website www.latinascontracancer.org or call 1-888 LCC-8110 (1-888-522-8110).

The LGBT Cancer Project is our country's first and leading lesbian, gay, bisexual, and transgendered cancer survivor support and advocacy nonprofit organization. The LGBT Cancer Project is committed to improving the health of LGBT cancer survivors through direct and support service, patient navigation, education, and advocacy. The LGBT Cancer Project volunteers include oncologists, social workers, and psychologists. Many of us are cancer survivors or family members of cancer survivors. All of us are united with you in our fight against cancer and in support of equal and appropriate access to health care for our LGBT community. For more information, visit our website at https://www.lgbtcancer.org/.

Livestrong Founded in 1997 by cancer survivor and champion cyclist Lance Armstrong and based in Austin, Texas, Livestrong's mission is "Which everyday cancer problem will we fix today?" Livestrong's priority is helping cancer survivors and their loved ones from day one. They believe in putting the survivor first, and that is why they created tools and resources to help ease the challenges of a cancer diagnosis. Known for the iconic yellow wristband, Livestrong's mission is to inspire and empower anyone affected by cancer. For more information, call 1-855-220-7777, or visit www.livestrong.org.

Multinational Association of Supportive Care in Cancer (MASCC) is an international, multidisciplinary organization dedicated to research and education in all aspects of supportive care for people with cancer regardless of the state of their disease. It operates in collaboration with the International Society for Oral Oncology. Founded in 1990, MASCC now includes members from more than 70 countries. MASCC aims to promote professional expertise of supportive care through research and international scientific exchange of ideas. MASCC provides different practice resources such as MASCC Guidelines, MASCC Assessment Tools, clinical apps, pain management center and much more. To find out more information about MASCC, visit our web site: https://www.mascc.org/

National Association of Social Workers is the largest membership organization of professional social workers in the world, with 120,000 members. NASW works to enhance the professional growth and development of its members, to create and maintain professional standards, and to advance sound social policies. For more information, please visit: www.socialworkers.org or call 1-202-408-8600.

National Center for Frontier Communities (NCFC) is the only national organization dedicated to frontier communities – the smallest and most geographically isolated communities in the United States. NCFC serves as a central point of contact for referral, information exchange, and networking among geographically separated communities. Frontiers communities differ in many ways, but all of them are small and far from larger population centers. NCFC gives a voice to people and programs in frontier communities and raises awareness of frontier issues to policymakers, agencies, and the public. Their programs and services are designed to help bring vitality to the Frontier Communities from better access to food to other matters of advocacy. For more information, visit: www.frontierus.org or call 1-575-597-0039.

National Coalition for Cancer Survivorship (NCCS) advocates for quality cancer care for all people touched by cancer. Founded by and for cancer survivors in 1986, NCCS created the widely accepted definition of survivorship and considers someone a cancer survivor from the time of diagnosis through the balance of life. Its free publications and resources include the award-winning *Cancer Survival Toolbox*®, a self-learning audio program created by leading cancer organizations to help people develop essential skills to meet the challenges of their illness. For more information about NCCS, its advocacy, and patient materials, please visit www.canceradvocacy.org or call 1-877-NCCS-YES (1-877-622-7937).

National Comprehensive Cancer Network® (NCCN®) – *NCCN Guidelines for Patients*®, a not-for-profit alliance of 30 of the world's leading cancer centers, is devoted to patient care, research, and education. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. As the arbiter of high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers. The primary goal of all NCCN initiatives is to improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives. For more information, visit www.nccn.org/patients.

NeedyMeds is a national nonprofit organization founded in 1997 whose mission is to educate and empower those seeking affordable health care. The resources listed on the website, www.needymeds.org, include pharmaceutical patient assistance programs, programs that offer financial assistance based on diagnosis, free/low-cost/sliding-scale clinics, application assistance programs, drug coupons, camps, retreats, scholarships based on diagnosis, disease-specific pages, and government programs. NeedyMeds also offers a free drug discount card that can save people up to 80% off the costs of medications. All of the information is free, easy to access, updated regularly, and anonymous. Please call 1-800-503-6897.

Research Advocacy Network was founded in 2003 to bring together participants in the research process. Our mission is to develop a network of advocates and researchers who can influence medical research from initial concept to patient care through collaboration, education, and mutual support. The patient advocacy movement has changed the face of research. Through their efforts, research advocates have begun to help shape the design, conduct, and dissemination of medical research. As the involvement of advocates in research grows, there is a need to educate more advocates and integrate them fully into the research community. Our services include research engagement programs, advocate training, both onsite and online, patient education materials, tools for advocates, and models of patient advocate involvement in research activities. For more information, call 1-877-276-2187 or visit our website at https://researchadvocacy.org/.

Scott Hamilton CARES Foundation is dedicated to changing the future of cancer by funding advanced, innovative research that treats the cancer while sparing the patient. CARES stands for Cancer Alliance for Research, Education, and Survivorship. We seek to be a neutral convener between organizations, researchers, academic scientists, drug developers, and others to accelerate the advancement of less toxic treatments for isolated cancers and tumors. Please visit our website at www.scottcares.org or call 1-844-SCOTT84. (844-726-8884).

Sisters Network® INC. – A National African American Breast Cancer Survivorship Organization – is committed to increasing local and national attention to the devastating impact that breast cancer has in the African American community. Founded in 1994, it is the leading voice and only national African American breast cancer survivorship organization in the United States. The organization's purpose is to save lives and provide a broader scope of knowledge that addresses the breast cancer survivorship crisis affecting African American women in the country. For more information, please visit: www.sistersnetworkinc.org or call 866-781-1808.

Triage Cancer is a national, nonprofit organization that provides education on the practical and legal issues that may impact individuals diagnosed with cancer and their caregivers, through free events, materials, and resources. For more information, please visit: www.triagecancer.org or call 1-424-258-4628.

Vital Options is an international cancer communications organization whose mission is to become a global health foundation focused on health education, supporting the financial needs of qualified patients and their families and give patients and caregivers a voice. Founded over 30 years ago as an innovative leader in patient advocacy, Vital Options has expanded to include direct support of patients, their caregivers, and their families across all chronic and life-threatening illnesses. With its innovative programs such as *Vital Connections*, their online caring community in which you will be able to connect to other members for inspiration, motivation, and support. For more information, go to www.vitaloptions.org.

Conclusion: Lessons Learned

It is always prudent to call a resource before referring a patient to check that their number or website has not changed, the resource can assist the person you are referring, and their services are free. Patients, survivors, caregivers, and the bereaved always appreciate our taking this extra step when making a referral as well as our follow-up with them to see if the needed service was received or there is still a need for additional help. Key components of successful usage of the many cancer resources available include maintaining frank and open communication, establishing realistic and achievable expectations and goals, keeping at your fingertips a network of resources and interprofessional colleagues to contact for help, and guiding your patients on how best to work with the resource referral you have made.

Given the changing needs of cancer patients, it is the innovative health care professional and institution that will be able to meet the future needs of this population by increasing access to cancer resources [12]. It takes a village to meet their needs. We cannot do this work alone – it is our collaborative work together, interprofessional practice, partnerships, and evolving understanding of resources that enables us to stay the course and provide the highest-quality care.

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Adolescent and Young Adult Cancer Survivors

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A diagnosis of cancer during adolescence and young adulthood (AYA) can result in various medical and psychosocial needs unique to this age group [8, 44]. One recent study on AYA survivors found that over 80% of survivors had at least one unmet need [9, 47]. AYAs often report these unmet needs in the form of supportive care and psychosocial issues. Unmet needs arise from deficiencies in a variety of areas, including support surrounding medical care, sexual health, interpersonal relationships, school, and employment [117].

Survivors of cancer diagnosed in adolescence or young adulthood have different experiences than those diagnosed as children or older adults. For example, a key feature among adolescents is the intersection of the cancer experience with a period of rapid biological and psychosocial development. Specific and relevant developmental areas for this group include autonomy and independence, peer pressure, social and sexual maturation, fertility, and finances [10]. Moreover, adverse and late effects of treatment can physically impact survivors, as well as cause short- and long-term effects on their self-image and well-being [1, 40]. Young adults also present with unique challenges, including those related to new marriage/partnership, educational or occupational pursuits, finances, or child-rearing. Prior reviews of the literature have highlighted the need for further exploration and clarification of outcomes within the AYA cancer survivorship population – especially because in much of the extant literature, this specific age group has been typically assessed in combination with younger and/or older ages [29]. In this chapter, we aim to identify relevant psychosocial outcomes, specific needs, and existing psychosocial interventions pertaining to AYA cancer survivors. We also examine physical and psychosocial well-being, survivorship care, underserved groups, and relevant interventions for AYA survivors.

Physical Well-Being and Symptoms

Physical well-being is an individual's functional/physical activities, health behaviors, and knowledge of health and/or disease [80]. Symptoms also

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include strength/fatigue, sleep/rest, overall physical health, diet, fertility, and pain. These symptoms are known to impact overall well-being and, for cancer survivors, can be significantly impacted by treatment side effects or late effects [40].

One large-scale health-based registry comparing AYAs with and without a cancer history found that AYA survivors had poorer health behaviors compared with same-age controls [106]. Current smoking was significantly greater among AYA survivors (26%) compared to controls (18%), although there was no difference in binge drinking rates (14% vs. 15%). More AYA survivors reported no leisure-time physical activity in the past month (31% vs. 24%). Another national health survey found that compared to female healthy controls, female survivors reported poorer physical health and were more likely to meet criteria for lifetime and current medical conditions, greater health-related disabilities, and greater functional limitations [64].

Psychosexual, fertility, and body image sequelae were found among male and female AYAs [5, 33, 50, 62]. Keim-Malpass and colleagues [51] reported relevance and gender-specific effects of sexual sequelae of diagnosis/treatment (e.g., functioning, fertility, gender norms). AYAs reported significantly lower health-related quality of life compared to those diagnosed at younger ages, leukemia or sarcoma survivors, or healthy controls [81].

Psychosocial Well-Being

This section describes outcomes related to psychological distress and unmet needs, mental health symptoms such as anxiety and depression, fears of recurrence and cancer worry, and strategies for coping with treatment. Psychosocial well-being also includes roles and relationships, psychosexual function and fertility care, education and employment, and cancer-related disclosure and how these might be impacted by the experience of cancer and cancer survivorship.

AYA survivors reported that cancer reduced feelings of control over life, finances, work plans, social relationships, and relationship or family planning, and increased concern in these areas [5, 16, 21]. However, AYAs also endorsed a positive impact of cancer in the following areas: improved relationships, future planning/goals, and health competence [5].

Unmet emotional and psychological needs were reported as major concerns for AYAs in the posttreatment period ([73, 96]; Overall, AYA survivors reported ≥14 days of poor mental health in the past 30 days (20% vs. 10%) compared to healthy controls (20% vs. 10%; [106]). There are also reports of unmet needs in terms of fears of cancer recurrence, cancer-related worry, and untreated depression [2]. AYAs described the need for greater family and peer support throughout their cancer journey [21, 123], more opportunities to meet other AYA survivors [124], and the perception of interpersonal social support as promoting healthy psychosocial adjustment at various treatment stages [108, 125]. Unfortunately, existing literature also demonstrates that many survivors do not seek help for these unmet needs, and some have difficulties accessing aid [47]. Disease and treatment features also affect psychosocial outcomes and treatment-seeking [120, 123].

Lang et al. [60] found that distress and anxiety were higher among AYA survivors when compared to healthy peers. In contrast, another study found survivors to be well-adjusted, with stress and social support as significant predictors of post-traumatic growth [96]. Social support was found to be a significant predictor of psychosocial growth [64]. Perceived support from parents and peers was found to be related to self-esteem and cancer-related worry [110], with higher quality of perceived support related to higher self-esteem among survivors.

However, a recent study showed that more perceived support does not always correlate with higher reported self-esteem [69]. They found that higher perceived support was significantly correlated with lower self-esteem. Furthermore, lower self-esteem was then significantly associated with a higher cancer-related worry among some AYAs [69]. This contradiction of previous assumptions serves as further reasoning for more in-depth exploration into cognitive interventions and support that target peer and parent relationships, self-esteem, and cancer-related worry in AYA cancer survivors, ultimately improving psychosocial development [69]. Recent research suggests that cancer-related worry could be further complicated by covariates such as self-esteem [69]. Self-esteem has been found to correlate with an AYA survivor's physical self-perception [119]. Research has also shown that helping AYA survivors feel more confident and competent could positively affect their self-esteem [119]. Among AYA survivors, higher self-esteem has been found to be directly correlated to better interpersonal relationships, family life, and academic support [110].

Anxiety and fear have been generally found more commonly after completion of treatment compared to depressive symptoms [121]. In a large survey study, more than half of AYAs who needed mental health services did not receive them, and emotional problems interfering with social activities were associated with unmet service and information needs [49]. Additionally, 75% of AYA survivors reported the desire for a support group [49, 66]. Overall, higher psychosocial stress increased the likelihood of obtaining psychosocial treatment and psychotropic medication, and AYAs diagnosed with a second malignancy were more likely to receive psychosocial treatment.

Fear of cancer recurrence, which is the fear, worry, or concern related to the possibility that cancer will come back or progress [105], has been found to be positively correlated with poorer physical health and high levels of psychological distress. A related concept is cancer-related worry, which are the feelings of anxiousness concerning the uncertainty about the future and potential adverse events that might arise from long-lasting implications of the cancer [68]. Both fear of recurrence and cancer-related worry have been found to be higher among female AYA survivors and those survivors who received more intensive cancer treatments.

Individuals diagnosed with cancer between the ages of 15 and 20 were nearly twice as likely to use antidepressant medication as individuals diagnosed before age five, and AYA survivors frequently reported symptoms of post-traumatic stress, anxiety, and depression, as well as fears of recurrence [25, 26, 31, 50, 66]. Depression in AYAs can also lead to higher levels of fatigue and disrupted sleep, which in turn results in overall worse mental health functioning [22].

Psychological coping with cancer at each phase presents new challenges: diagnosis phase (i.e., information, relational interactions, and perceptions), treatment phase (i.e., taking action, control, adaptation, situation self), and posttreatment/remission/palliative phase (i.e., normalcy) [72]. AYAs report a lack of survivorship preparation (especially from healthcare providers), late effects that pervade their entire lives, and a lack of posttreatment understanding from social networks [47]. Employment of various coping strategies can benefit AYA cancer survivors when transitioning to different life stages and processing the distress that stems from the cancer experience. Belpame et al. [6] identified five coping strategies AYA cancer survivors developed during treatment and frequently used during their daily lives. These included: focusing on the present moment, abstaining from discussing their cancer experience, recalling and preserving positive memories, positively redefining cancer's impact, and consolidating and maintaining a sense of togetherness. Krasne [58] found that AYA breast cancer survivors frequently report using social support from partners or family members as their most helpful coping strategy. Frequent engagement of healthy coping strategies can influence the maintenance of a positive outlook to improve coping with the long-term physical and psychological ramifications from their previous illness [6]. Additionally, behavioral and pharmacologic interventions are potential facilitators that help cancer survivors cope with emotional distress [121].

Research has also shown a gender difference in survivors: female survivors are more likely to experience worse depression [99]. Controlling for treatment status, predictors of depression include physical and daily living needs, as well as health system and information needs [28]. Female AYAs have been found to score significantly worse than healthy peers on mental health outcomes and were more likely than peers to meet criteria for serious psychological distress [84], and also have reported experiencing persistent struggles, such as post-traumatic stress symptoms and anxiety [50].

The relationship between stress (negative relationship), social support (positive relationship), and post-traumatic growth may be moderated by the level of physical activity; the relationship with social support and psychological growth was stronger for individuals with lower levels of physical activity [64].

Cancer diagnosis is a potential moderator of being in school or employment at follow-up, with ALL and non-Hodgkin's Lymphoma diagnoses less likely to be in one of these groups compared with other diagnoses [5, 82]. AYAs experiencing cancer-related education or work interruption reported significantly more distress [120]. AYAs more than 2 years posttreatment reported worsened psychosocial well-being and functioning and decreased positive attitude toward care [16]. A registry-based study found that 35% of survivors working or in school full-time pre-diagnosis believed that cancer had a negative impact on their plans, and greater than 50% reported problems with work or school post-diagnosis [82]. Acute Lymphocytic Leukemia (ALL) and Non-Hodgkin's Lymphoma survivors were less likely than other cancers to be working or in school 15 to 35 months post-diagnosis [82]. When examining time since treatment, AYAs greater than 2 years posttreatment were found to have greater adjustment in vocational environments compared to AYAs on active treatment [16].

In social settings, AYA survivors must decide if, when, and how to disclose their survivor status to others. Disclosure is associated with numerous psychological and physical benefits [3]. Learning how to confess this personal piece of information is an individual journey for each survivor. Disclosure entails a delicate balance of revealing cancer-related information in a way that will provide survivors access to support if needed, but will not compromise their abilities, character, or potential for advancement in their formative years [89]. Many survivors express that disclosing their cancer experience is dependent on the context and environment of the given situation. For example, AYA survivors are cautious in their approach to workplace/school disclosure. Social support is vital to disclosure, as those who feel supported by their peers or colleagues are more likely to disclose.

Psychosexual, fertility, and body image sequelae were found among male and female AYAs [5, 33, 50, 62]. Keim-Malpass and colleagues [51] reported relevance and gender-specific effects of sexual sequelae of diagnosis/treatment (e.g., functioning, fertility, gender norms). AYAs reported significantly lower health-related quality of life compared to those diagnosed at younger ages, leukemia or sarcoma survivors, or healthy controls [81].

After one or more years posttreatment for acute leukemia, no significant difference in psychosexual dysfunction was found between those treated with a bone marrow transplant (BMT) and chemotherapy only [76]. By gender, however, females overall reported decreased sexual drive, and female BMT survivors had lower frequency of sexual behaviors than all other groups. Masculinity and self-image have been found to be simultaneously impacted among testicular cancer survivors, who perceived social challenges: feeling different, viewing their differences as "damaged goods," struggles with cancer-related disclosure, and feelings of embarrassment that directly lead to treatment and medical care delays [17].

Among breast cancer survivors, treatment decisions were greatly motivated and determined by survival chances; however, fertility options, services, and empowerment were either inadequate or provided too late during and posttreatment [33, 62]. Women reported persistent struggle regarding fertility concerns [50]. Both female and male AYAs who had received bone marrow transplant or chemotherapy reported poorer body image, and women reported lower frequency of sexual behaviors, decreased sexual drive, and less satisfaction posttreatment than physically healthy controls [76]. Overall, AYA's experiences transitioning off-treatment are challenging, complex, and long-lasting [51, 72, 73].

Survivorship Care

Survivorship care is comprised of essential components of care that facilitates access to comprehensive and coordinated care. The IOM has collaboratively defined this to include: prevention of relapse, new cancers or late effects, surveillance/follow-up care of cancer, and assessment of medical and psychosocial late effects. This also includes intervention for consequences of cancer treatment, coordination between providers, health insurance access, financial toxicity, and treatment-related informational needs. Jones et al. [47] note that the transition to life posttreatment can be quite difficult as AYA survivors rarely receive preparation for what this process entails.

Survivorship, as defined by the National Cancer Institute, includes multifaceted aspects of the physical, psychosocial, and economic issues of cancer, beyond diagnosis and treatment [81]. Survivorship themes in the relevant qualitative literature include feelings about cancer survivorship, work/education participation or outcomes, "being [neither] sick nor healthy," attitudes toward healthcare and intervention modalities, pain/fatigue, sexual functioning and fertility, risk behaviors (e.g., smoking, physical activity), and physical status and health [39, 62, 91, 108].

AYA informational needs include information regarding aspects of cancer care that AYAs describe as important, helpful, or particularly lacking in the current healthcare system or survivorship culture. This includes needs at diagnosis, during treatment, and posttreatment. The content of these three areas of need includes disease/treatment information and education regarding issues such as follow-up care, psychosocial resources, or fertility preservation. The primary theme noted within this domain was the need for care and resources to be targeted to the age-specific and unique needs of the AYA population [125]. Numerous studies emphasized that age-appropriate information and affordable care are critical to providing long-term support to AYAs diagnosed with cancer [55, 70, 71, 123, 124]. The need for flexibility in treatment scheduling to allow for work and family demands was frequently endorsed [90, 91]. A consistent theme was a desire to gain support from peer survivors or peer support groups, who were familiar with the unique challenges of managing cancer at a young age [39, 73, 108]. Informational needs regarding fertility were emphasized [73]. Many women felt they were insufficiently informed regarding health promotion, fertility concerns, and fertility-related treatment effects, although they acknowledged the complexity of addressing this topic in the midst of survival and treatment-related concerns during active treatment [33, 62, 73]. Older AYAs also described the need for care providers to foster greater autonomy in care decisions as they age.

The importance of providing AYAs with relevant information as they transition to survivorship is consistent with the broader literature in cancer survivorship. AYAs desire information concerning possible late and long-term side-effects of treatment, their capacity to pursue family and work-related goals in the future, the transition to survivorship and what to expect, guidance on which health professionals to seek out for various issues, as well as access to supportive care to manage challenges in reintegrating to school and work roles [39, 66, 82]. A multi-center examination of this issue with a survey of 523 AYAs approximately 1 year from treatment for a variety of cancer diagnoses found that more than 50% reported unmet information needs, primarily around the potential for recurrence and secondary cancers, as well as long-term side effects [49]. Another study found that AYA survivors desired better educational and occupational support services after completing treatment [73]. Further analysis revealed that those who were male, older, non-white, of poorer overall health, with more treatment-related side effects (i.e., >3), and who perceived that their quality of medical care had been poorer were more likely to report unmet needs. Additionally, AYAs reporting poorer physical or mental health also reported greater unmet service and information needs. AYAs with more years elapsed since treatment also tended to report a worse attitude toward their ongoing medical care.

Health services and healthcare access are defined generally as availability and access to interventions, medical and survivorship resources, medical appointments, screening, and/or follow-ups, as well as healthcare utilization and psychosocial care needs for survivors and families. This additionally can include the delivery of medical information, services, or interventions. Among AYAs, common health services and access needs included fertility preservation and information, cost and location barriers, insurance delays, lack of existing services, and communication with healthcare providers.

Overall, AYAs desire better communication regarding, and access to, fertility preservation options [62, 70, 71, 123]. As noted above, some survivors perceived that such options were provided too late during their treatment, while others reported being provided inadequate information (or time) to make a sound decision, forcing them to make rushed treatment decisions, such as choosing between delayed treatment and infertility risks [33, 62]. A minority of survivors noted that providers did not discuss fertility options at all, and felt they were not included in a decision that should have been their own [62]. AYAs that were provided with only written fertility information described it as not useful, or useful only to prompt dialogue with providers. Speaking with a fertility specialist was desirable, and women expressed desire to have open and honest discussions with providers regarding fertility [62].

Providers and patients agreed on the importance of having adequate health insurance and follow-up plans [124]. Availability of state-of-the-art, age-specific treatment and adequate health insurance were the most highly ranked healthcare needs among emerging adult survivors [123]. In a population-based study, survivors who reported poorer overall health reported greater cost barriers. AYA survivors reported going without care as a result of higher costs than non-cancer controls, and cost barriers were particularly high for 20–29-year-old survivors, and for female survivors [55]. After completion of cancer treatment, survivors are often persistently faced with delayed treatment bills, high health insurance premiums, and long waits for qualify for life insurance due to having a “pre-existing condition” [51].

Posttreatment financial concerns and financial toxicity can greatly affect AYA survivors’ independence. In addition, cancer patients and survivors are more likely to experience financial toxicity than those without cancer. As many AYAs must take time off from work or school for cancer care, they may lose insurance benefits and can experience a difficult time re-entering the workforce or re-enrolling in school. Because of treatment bills and continuing follow-up and healthcare costs, AYAs may become entirely financially dependent on their parents during the posttreatment phase [70, 71]. AYAs in their 20s or younger and/or less physically active AYAs were more likely to encounter cost barriers compared with older and/or more physically active AYAs.

Generally, studies reported that older AYAs were more likely to follow up with oncological care on the recommended schedule. Similarly, females were generally more likely to comply with recommended oncological follow-up (but also experience greater cost barriers) compared to men. However, males were more likely to experience unmet service needs. Hispanic and non-Hispanic Black survivors were less likely to participate in studies compared with other racial/ethnic groups, and non-white AYA survivors were more likely to experience unmet service needs. Additionally, geographic location also creates barriers for this population. For example, patients living in rural communities, compared to urban areas, have limited access to specialized cancer care resources and services, often resulting in delayed diagnoses [70, 71].

Cancer Care among Underserved Groups

Research exploring health disparities among AYA cancer patients and survivors and the unique needs of AYAs across ethnic, racial, sexual, and gender identities is in its infancy. However, the importance of developing this area of research has become increasingly clear. The next section will present what we know about ethnic/racial and sexual/gender-expansive adult cancer survivors broadly and then present the limited knowledge of needs and disparities among these AYAs.

Race and Ethnicity

Racial and ethnic disparities exist across the cancer continuum, beginning at diagnosis and continuing through survivorship. Prior research has demonstrated that compared to other racial/ethnic groups, Hispanic/Latino adult survivors reported lower health-related quality of life and higher symptom burden following cancer, were more likely to report suboptimal physical and social well-being, and report greater unmet needs [74, 97]. Studies among Black adult patients and survivors have discovered that pain severity since diagnosis is predicted by the Black race, with Black patients reporting significantly worse pain than their White counterparts [34]. Additionally, Black survivors and survivors residing in high-Black-segregated counties report significantly lower HRQOL than White survivors and those not residing in such counties [37]. This could be due to economic hardship, which has been reported as one of the negative outcomes of cancer faced disproportionately by Black survivors [85]. Studies of Black and Hispanic/Latino survivors have reported that these cancer populations face a multitude of barriers to care. Language and acculturation barriers are evident and have been found to be related to lower self-efficacy in patient-provider communication – a variable tied to survivor outcomes in past studies [74]. Other studies have found that the likelihood of prescription medication adherence after cancer is lower among these populations, though the exact reason for this is unclear [116]. Finally, Black and Hispanic/Latino survivors have reported more negative opinions about the reproductive counseling they received after cancer [53]. Despite these barriers, studies have also demonstrated benefits unique to ethnic groups that are important for consideration and incorporation into interventions targeting these groups. For example, one study discovered that spiritual well-being and spirituality-based coping were higher among this group than others [97].

Research among Black and Hispanic AYA survivors is minimal but is developing in research and focus on healthcare. Existing studies have demonstrated that outcomes for survivors who self-identified as a race other than White report fair/poor health, more poor mental health days, and activity limited days significantly more than their White survivor counterparts [56]. Furthermore, AYA survivors identifying as part of a racial/ethnic underserved population are more likely to report unmet information needs relating to their cancer returning and cancer treatments [49]. Studies have demonstrated that survivors from underserved racial/ethnic populations report the highest total mood disturbance compared to White survivors [126], with Latino survivors scoring higher in depressive symptoms and lower in quality of life compared to non-Latino AYA survivors [93]. Race/ethnicity has also been found to be a predictor of emotional health-related quality of life [77]. Despite the increasing attention to these disparities in cancer research, barriers to reaching these groups remain, with studies reporting that Hispanics and non-Hispanic Black survivors are often less likely to participate in cancer survivor-related research, which suggests the importance of the use of cancer registries for recruitment rather than recruitment through clinics [38]. Given the nascency of the AYA cancer survivor field, future research is needed to establish the unique needs of underserved racial and ethnic populations, to tailor cancer care in a way that monitors and addresses these needs adequately.

Sexual Orientation and Gender Identity

The scarcity of research exploring disparities among and unique needs of all cancer survivors diverse in sexual orientation and gender identity has become a gap of increasing focus in the cancer research community, with calls from the American Society of Clinical Oncology [35] and the Association of Community Cancer Centers [86] to expand this area of research to improve cultural competency. This area of research has expanded rapidly since these calls in 2017; however, many significant gaps still remain, especially among AYAs. Among the general sexual and gender minoritized survivor population, studies have demonstrated significantly worse outcomes compared to heterosexual and cisgender cancer populations. These outcomes have included higher odds of poor physical, mental, and emotional quality of life, greater difficulties concentrating, and higher levels of distress, anxiety, and depression among sexual minority survivors compared to heterosexual survivors [12, 32]. One study reported that survivors who were sexual minority women demonstrated up to 2.3 times the odds of reporting fair or poor health compared to survivors who were heterosexual women [13].

Many of these outcomes can be tied to barriers to care, discrimination, and the under-preparedness of cancer centers to meet sexual minority survivors' needs. Research has demonstrated more access deficits among sexual minority women survivors than heterosexual women survivors, with these deficits being associated with poorer physical and psychological outcomes [12]. Studies report that sexual minority patients are less likely to be insured than heterosexual patients [43], in addition to a multitude of additional barriers to care [11]. Discriminatory attitudes from care providers are commonly mentioned among sexual minority survivors, as well as inequalities and gaps within cancer care and support for this population [41]. Studies have found that sexual minority survivors report lower satisfaction with cancer care compared to heterosexual survivors, even after controlling for demographic and clinical variables associated with care [45].

Studies have also reported unique perspectives and needs among this population, with research suggesting that sexual minority survivors have different perspectives of cancer care and cancer-related needs than heterosexual survivors [41]. For example, many sexual and gender minority patients and survivors report a lack of social support and isolation during cancer treatment above that of heterosexual patients and survivors [4, 14]. The ways in which negative psychological outcomes after cancer can be addressed in this population is also unique, with a study finding the presence of psychosocial resources as a mediator of the relationship between minority stress and psychological distress, through enhancement of resilience [48].

Disclosure may impact the quality of care received during treatment and survivorship for sexual minority survivors. Routine documentation of sexual orientation and gender identity in healthcare is predicted to significantly reduce LGBTQ disparities in satisfaction with care and outcomes after cancer and has been recommended by the Institute of Medicine. However, in a study exploring the attitudes toward this disclosure among adult patients and providers, it was discovered that while only 11% of sexual minority and heterosexual patients reported being offended by this question, over 80% of providers reported feeling that collecting this data would offend patients, demonstrating a large discrepancy between provider attitudes toward sexual and gender minority identity disclosure and the perception of patients [65]. Among sexual minority patients, issues regarding sexual identity disclosure in the cancer context are commonly reported [4].

Finally, discrimination has been demonstrated to impact the physical and psychological outcomes of cancer. One study found that sexual and gender minority cancer survivors were more likely to think that disclosing their sexual and/or gender identity to their provider affected the care they received [14]. Studies have also reported associations between discrimination exposure and sexual minority stress with rates of psychological distress and cancer-related treatment side effects among sexual minority patients and survivors [30, 48].

To date, there has yet to be a study of cancer survivors that included assessments of gender minority status or focused specifically on gender minorities [52]; however, studies have demonstrated the importance of knowledge acquisition in this area to adequately fulfill the needs of gender diverse survivors. For example, cisgender models used when addressing changes to the body that result from biomedical treatment for cancer have been found as wholly inadequate to account for transgender and gender-nonconforming people's experiences of cancer treatments and access to and mobilization of related knowledge [107].

Research specific to AYA sexual and gender minority survivors is extremely limited, acting as a major gap in the cancer care literature [20]. Existing studies suggest that AYA cancer survivors who are sexual minorities experience twice the odds of anxiety, with social support being significantly associated with lower odds of anxiety [23]. The unique outcomes associated with cancer and fertility has also been assessed in AYA cancer survivors, with studies finding that among LGBTQ survivors, despite reporting similar information regarding fertility loss to heterosexual survivors, survivors report fertility concerns as having less of an effect on romantic relationships, are more flexible with the idea of raising non-biological children or not becoming a parent, and report less distress due to fertility loss information [95]. Another study has also supported this, finding that AYA survivors with non-heterosexual identification were more likely to report being voluntarily childless [59]. Research examining the unique experiences, barriers, and needs related to cancer care among sexual and gender-expansive survivors is direly needed to improve cultural competency and patient and survivor outcomes.

Psychosocial Interventions

While promising, most evidenced-based interventions to improve psychosocial well-being and address unmet needs in AYA survivorship are currently in a bourgeoning stage. The quality of data available to describe the development, evaluation, and dissemination of these interventions is notably inconsistent, but the cross-cutting themes, research, and sample interventions that are highlighted here will illustrate the growing evidence base for interventions that are feasible and tailored to AYA survivors' needs.

The specific targets of available interventions largely align with AYAs' expressed interests in increasing physical activity, nutrition and weight loss, relaxation, emotional support, and informational support [90]. A recent metanalysis of AYA survivorship interventions indicates small but statistically significant treatment effects for improving physical and functional health, mental and cognitive health, academics, cancer knowledge, and general quality of life. Interventions did not significantly improve AYAs' social/relational well-being, which is an area of concern [127].

While it seems clear that AYAs benefit more from psychosocial intervention when they are off-treatment than on-treatment for cancer, more evidence is needed about which AYAs will benefit and from which interventions [115]. Integrating psychosocial care with other aspects of cancer care, using an interdisciplinary approach, can facilitate AYAs' receiving maximal benefit from psychotherapy [109].

In tailoring and developing interventions for AYAs, clinicians should emphasize individual autonomy, choice, and decision-making, respect privacy, provide multiple sessions, and facilitate interaction with peers [90, 109] as well as incorporate digital intervention, assess for cultural differences, and obtain feedback directly from AYAs [83]. AYAs most highly value intervention that is flexible and convenient, as late effects of treatment such as fatigue and amotivation may constitute barriers to participation [90]. Efforts to tailor intervention should also consider AYAs' age relative to the broad range of 18–39, which may constitute as many as three distinct developmental phases with differing likelihood to benefit from intervention [127].

In a critical review of psychosocial interventions tailored to AYA survivors, authors noted the variability of measures used to assess the effectiveness of interventions [115]. Outcome measures can encompass quality of life, psychopathology, social support, and stress and coping – making it difficult to compare across interventions, assess mechanisms of effect, and identify promising new targets for intervention. More, and larger, randomized controlled trials and multi-site studies are warranted in order to represent the diverse and often complex intervention needs of survivors (Phillips & Davis 2015). In particular, follow-up measurement is needed to assess long-term outcomes of interventions [115]. Currently, there are no psychometrically validated patient-reported outcome (PRO) measures specifically for AYA cancer patients and survivors, which are identified as a which are a gold standard for capturing disease-related experiences.

Interventions Providing Informational Support and Psychoeducation

Survivorship Care Planning

Facilitating self-management of health after the end of cancer treatment, with attention to developmental age, is a priority for AYA survivors. The collaborative development of, and adherence to, a survivorship care plan (SCP) is intended to increase health self-efficacy and mitigate any gaps in care [19, 57]. Interventions to develop and promote SCP have shown adequate feasibility and acceptability to AYAs, but limited evidence of benefit in improving general health knowledge and care outcomes [100].

Recent intervention work has effectively incorporated digital approaches including tailored text messaging, applications, and websites to enhance self-management. A controlled trial of a Web-based SCP focused on fertility concerns led to improvements in health knowledge and infertility concerns, but no significant improvement in targeted psychosexual and physical symptoms [104]. Future research should investigate mechanisms underlying the lack of benefit of survivorship care planning, and their limited engagement despite positive feedback from AYAs [54]. Effectiveness may improve when SCPs are tailored to age groups within the AYA age range, address the heterogeneity of treatment outcomes and ongoing symptoms, are flexible, consider ethnic/racial disparities, and incorporate family caregivers when feasible [57].

Behavioral Health

The research and sample interventions highlighted here reflect some of the supportive care programs most requested by AYAs in enhancing behavioral health (and thereby long-term health outcomes), including sleep, nutrition, and physical activity.

Insomnia and sleep disruption are common among AYA survivors, and tailoring evidence-based cognitive-behavioral therapy for insomnia (CBTi) has been shown to be both feasible and efficacious in this population [130]. This example of successfully tailoring an established biobehavioral treatment for AYA survivors can be used to adapt other evidence-based interventions. Specifically, successful adaptation included psychoeducation about sleep disruption following cancer treatment, psychological and physical barriers to restful sleep after cancer, providing AYA-specific information about circadian rhythms and alcohol consumption, featuring images of AYAs on study materials, and soliciting support for sleep hygiene from family and roommates [129].

A recent systematic review of four studies of interventions for diet and metabolic health in AYA survivors shows promising results, with significant improvements in dietary quality or body composition [102]. The majority of these interventions aimed to increase self-efficacy about diet and nutrition in survivorship. Authors noted promising outcomes across therapy modalities, such as in-person counseling, phone sessions, and digital approaches, as well as a dearth of rigorous outcome studies on this population. In addition to further dissemination and study of interventions, they recommend the incorporation of social support and more individualized tailoring to AYAs' individual dietary needs [102].

AYA survivors' fatigue, deconditioning and sedentary activity related to treatment for cancer contribute to significantly reduced physical activity as compared to same-age peers (Munsie et al. 2019) [78]. Exercise interventions have been shown to be safe and effective in significantly increasing the number of minutes of physical activity, as well as the number of steps, per week in AYA survivors [78, 128]. The use of technology such as accelerometers may improve the accuracy of tracking and acceptability among AYA survivors [78]. Physical activity intervention may have further benefits in improving quality of life, although further and more rigorous study is needed [128].

Addressing psychosexual symptoms and fertility-related distress in AYAs is an acknowledged gap in survivorship care, and comprehensive care for AYA survivors entails attending to both reproductive and sexual health after cancer [88]. Recent interventions have aimed to increase health literacy, improve access to multidisciplinary care, enhance self-management, and promote informed decision-making.

Assessing and increasing reproductive health literacy facilitates access and communication between AYA survivors and clinicians and can contribute to greater satisfaction with health decision-making [79]. Assessing developmental age, cancer history, and family support are necessary for determining the timing and content of discussions about fertility, psychosexual symptoms, and sexual health. Interventions that work on multiple levels – such as preparing educational materials for a patient, training clinicians in 'difficult conversations,' and involving family caregivers, will be most effective in increasing health literacy when implemented synergistically [79]. Implementation science research featuring a cohort of both oncofertility care providers and AYA survivors reached consensus on a stepwise system encompassing screening, referral, and fertility counseling [27]. However, while educational interventions may improve health literacy and improve communication between AYAs and providers, they are generally inadequate to significantly reduce fertility-related distress or general distress [111].

Ongoing research takes a two-pronged approach to simultaneously assessing predictors of sexual dysfunction and fertility-related distress as well as providing web-based psychoeducation intervention to AYA survivors of childhood cancer [63]. In order to mitigate decision uncertainty and fertility-related distress which is compounded by the many and complex options for family-building in survivorship, a novel Web-based decision aid is being tested longitudinally for its effect in reducing decisional conflict and improving psychological functioning in female YA survivors (Benedict et al. 2019 [7]).

Digital Health Interventions

Digital health interventions include those delivered through the Internet, eHealth (electronic health), mHealth (mobile health), social media, wearable devices, and telehealth [24]. Digital means can be used to provide informational support about cancer, to promote communication between patients and providers, and to assess health status over time. AYAs report preferences for mobile health applications based on their confidence with technology, flexible availability, and perception of confidentiality and privacy in accessing informational and social support that they may feel hesitant about requesting in-person [61].

Digital health interventions to improve behavioral health and reduce emotional distress consistently show feasibility and acceptability among AYAs, who may enjoy using wearable technology to self-monitor their health behaviors [122]. However, research on the efficacy of these interventions is moving at a notably slower pace than technological advancement itself [24, 67, 92, 114].

Preliminary evidence suggests that the most efficacious interventions to reduce psychological distress are personalized and presented in a format that promotes engagement, such as groups or gaming; effective interventions in behavioral health promote active and frequent self-monitoring [92]. Web-based interventions which take a cognitive-behavioral approach have been effective in reducing fears of recurrence and improving sleep health, and a Web-based self-compassion writing exercise intervention was effective in reducing body image distress [103]. Baseline motivation to change health behaviors, and better self-perception of health, can predict greater engagement with digital applications [87].

Barriers to the adoption of digital health interventions include technical glitches [87] as well as the gaps between clinical services and digital health tools, the risk that AYAs' privacy and health data will be compromised, and difficulty identifying which technologies are worth investing in [118]. To optimize users' experiences and facilitate engagement, digital interventions should be developed in a staged fashion, incorporating stakeholders such as AYA focus groups and their healthcare providers, as well as multidisciplinary experts in digital technology and evidence-based psychosocial intervention [24, 118].

Group Therapy

Facilitating social interactions is of key importance in interventions for AYA survivors, both to ameliorate disruptions in social relationships that were incurred by cancer, and to offer peer support for cancer-related distress [127, 99]. When consulted, AYAs keenly request that interventions provide peer support [91]. Group-based cognitive behavioral therapy may impart skills for coping with cancer survivorship, such as problem-solving and communication, and allow the opportunity to practice them with peers. A pilot study of a principle-driven group therapy intervention for AYAs in treatment for cancer successfully conducted sessions to impart skills in behavioral activation, cognitive restructuring, and attunement to physiological sensations, although clinical outcomes are not yet available [36]. Ongoing research indicates that offering cognitive-behavioral group therapy through videoconferencing over the Internet offers additional advantages in flexibility and access, without compromising group cohesion, quality of participation, or alliance between AYA survivors and their therapists [98, 99].

Cognitive-Behavioral, Mindfulness, Acceptance, and Meaning-Based Therapeutic Interventions

The exemplars described here portray the potential impact of therapeutic intervention for improving a range of important outcomes in AYA survivorship, using skills-based approaches which are evidence-based.

Cognitive-Behavioral Therapy

Two recent randomized controlled trials of interventions to reduce psychological distress and improve skills in goal-setting, stress management, and emotion regulation among AYA cancer survivors highlight the usefulness of tailored cognitive-behavioral therapy for this population. The novel intervention Goal-Focused Emotion-Regulation Therapy (GET), developed for AYA survivors of testicular cancer, is currently investigating the impact of imparting skills in self-regulation, goal navigation, and emotion regulation skills, on psychological and biobehavioral outcomes (Hoyt et al. 2020 [42]). The Promoting Resilience in Stress Management (PRISM) intervention, which aimed to build skills in cognitive reframing, meaning-making, and goal-setting, was shown to significantly increase resilience and cancer-specific quality of life among a sample of AYAs with cancer (Rosenberg et al. 2018 [94]). Both interventions capitalize on skills and techniques drawn from cognitive-behavioral therapy, tailored to the clinical and developmental concerns of AYA survivors, and their brief and manualized nature offers promise for dissemination once they are demonstrated to be effective.

An intervention to address post-traumatic stress and anxiety in AYA survivors of childhood cancer, Onco-STEP, also utilizes principles from evidence-based cognitive-behavioral therapy to facilitate adaptive cognitive processing of traumatic cancer-related experiences and build coping skills for fears related to cancer [101]. This ten-session intervention was found to significantly reduce post-traumatic stress, anxiety, and fear of cancer recurrence post-intervention and at three-month follow up. Randomized controlled trial in the future will indicate whether this intervention may be adaptable to other populations as well [101].

Mindfulness and Self-Compassion

Building mindfulness skills is an evidence-based way to become more aware and non-judgmental of thoughts, feelings, and physical sensations that may lead to worry and rumination [112]. For AYAs who are vulnerable to elevated risk for depression and anxiety following cancer, mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) may be adapted to include psychoeducation about cancer, such as fear of recurrence and self-care [112]. A randomized waitlist-controlled trial of mindfulness-based stress reduction (MBSR), which takes a mind-body approach to reducing stress with tools from mindfulness meditation and Hatha yoga, in young adults with cancer found good feasibility and acceptability as well as improvements in physical, social, and emotional functioning immediately after completing an eight-week MBSR course [113]. The majority of YAs who declined to participate in this trial noted that they would be interested in an online version, which should be taken into consideration for future intervention [112, 113].

A feasibility study of a brief, group-based videoconference intervention to increase mindful self-compassion found the intervention to be feasible and acceptable, as well as effective in improving body image, mindfulness, and self-compassion, reducing anxiety, depression, and social isolation. The intervention aimed to increase mindfulness to reduce worrying and rumination, to improve self-kindness to reduce critical self-judgment, and to highlight common humanity and social connectedness in sharing the cancer experience with other young adults. Future randomized controlled trials will further assess the efficacy of the intervention [15].

Future Directions

The development and dissemination of interventions tailored to AYA survivors are in the early stages, and further research is needed to identify prospective targets for intervention, key mechanisms of action, and optimal means of delivery to this dynamic age group. As at other stages in the cancer care continuum, it is clear that intervention content should be tailored to AYAs' unique developmental, social, and psychological needs. Following the successful adaptations of cognitive-behavioral and mindfulness-based therapies, interventions which have been found effective for others affected by cancer (e.g., meaning-centered psychotherapy) may be tailored to AYA populations. Means of delivery of interventions should be flexible and convenient, with respect to AYAs' competing priorities such as work and family that may change over time as a survivor [91].

Future interventions may be further tailored to AYAs' individual health needs and their cancer history, such as the type of cancer they have or the specific late effects of the treatment they received. For example, cognitive concerns after cancer treatment are a critical area of unmet need among AYA survivors, with insufficient tailored interventions available [46]. A novel intervention promoting problem-solving, memory, and positive thinking was rated most highly by the survivors of brain tumors with the most cognitive impairment and most intensive treatment history, indicating the potential benefit of targeting the most symptomatic AYAs for intervention [75]. Additional benefits may be gained from targeting cultural and personal identity, such as in a recent pilot study for Latino AYA survivors and their families using a *photonovela* to increase cancer knowledge and promote communication with providers [18].

Research to understand the efficacy and effectiveness of intervention should adopt consistent outcome measures and utilize heterogenous and representative samples. Disparities in access to intervention persist, and tailored intervention may address AYAs' cultural and personal identity. Interventions should seek to equalize assessment and access to care in survivorship, particularly for populations that face disparities and discrimination in medical settings such as ethnic and racial minority survivors, those who live in rural areas, and those with low-income households or financial toxicity due to cancer. Digital health intervention may provide ease of access, but research and development will need to be targeted to these populations to identify and reduce barriers to adoption.

Overall, the range of presented quality of life concerns (physical, psychological, social) emphasize the AYAs' experience as described and reported as challenging, complex, and nuanced. Due to the unique developmental challenges of AYAs, this group is positioned to experience different outcomes from childhood or older adult survivor counterparts and is underrepresented in the literature. AYAs require age-appropriate and flexible care and informational needs that garner autonomy geared toward long-term survivorship. Importantly, more research is needed with racial and ethnic as well as sexual and gender minoritized groups. Intervention work with AYAs is also in a nascent but developing stage and further focused and randomized clinical trials are not only desperately needed, but hopefully will be forthcoming and improve long-term outcomes and survivorship.

While this highlights future directions for survivorship, the short- and long-term impact of cancer starts at diagnosis. At diagnosis and the start of treatment, multidisciplinary healthcare providers and interventions should provide AYAs and families with greater resources about fertility (particularly for women), sexual functioning, late effects of treatment, social networks for survivors, disclosure, re-entering school/work, and attaining revised educational/career goals; key issues identified during survivorship. These issues are developmental and not static; they should be established and adjusted over time since treatment and AYAs' developmental stage. They should be reflected in follow-up care, survivorship care planning, continuing educational interventions (e.g., consultations, education pamphlets/programs), and direct provider training. This is a unique population that engenders multifaceted variables contributing to posttreatment outcomes. As such they require equally multifaceted care and consideration in research and clinical practice.

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Cancer Fatalism: Attitudes Toward Screening and Care

18

Miri Cohen

Fatalism and Cancer: Attitudes Toward Screening and Care

Introduction

During the last 20 years, interest in fatalism has emerged among health care researchers [1, 2]. This interest was generated by the search for efficient targets for intervention to increase healthy behaviors and screening attendance among underserved social groups [3–7]. Studies have shown that fatalistic beliefs are related to lower adherence to medical examinations and lifestyle regimens needed in the management of chronic diseases such as cardiovascular disease [8], diabetes [9], and HIV [10] and to attitudes toward health behaviors such as practicing safe sex [11, 12], smoking [13, 14], and screening for the early detection of several types of cancer [1, 3, 5–7].

Definitions of Fatalism

Although definitions vary, fatalism is usually conceptualized as a belief that events are predetermined and that human beings are unable to change their outcomes [15]. Fatalism refers to two similar but not identical beliefs: the belief that events are beyond personal control and the belief that a person cannot change the outcome of events. Fatalism is incompatible with free will, and individuals with a strong belief in fatalism believe that very little or nothing can be done to change the course of events determined by external forces [16].

Fatalism may or may not be based on belief in God. Believers tend to accept that God has control over every detail of life, whereas nonreligious fatalism may be expressed in the belief that things happen by chance or luck [17–21]. In a modern society, which stresses free will and self-actualization, fatalism often attains a negative connotation [5] and is viewed as related to pessimism, hopelessness, and despair [3, 22].

Cancer Fatalism

Studies have defined cancer fatalism as the perception that encountering cancer is a certain death sentence and that sooner or later, the individual with cancer will die [3, 23–25]. Less attention has been given to another aspect of cancer fatalism, which is the belief that health is a matter of God's will, fate, or luck and beyond an individual's control [15, 18, 26]. It is often accompanied by an assurance that "it will not happen to me" or by the pessimistic conviction of an individual that he or she will encounter cancer sooner or later, regardless of personal actions.

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These beliefs have often been found to be related to perceptions that screening for early detection of cancer is not necessary because if the end outcome is death, it does not matter when the cancer is detected [1, 3, 7, 27–29]. These beliefs may also encourage refusal or nonadherence to cancer treatment or a healthy lifestyle due to the same reasoning—that these factors will not change one's personal fate [30–34].

Thus, cancer fatalism can act as a barrier to screening [1, 2, 18, 21, 23, 26, 28, 35–47], can be a cause for delay in seeking medical help once symptoms appear [30–33, 48, 49], or can be a cause of refusing to receive all or certain treatments for cancer [50]. However, it is important to bear in mind that similar to other health attitudes, fatalistic beliefs held by individuals vary along a continuum from extreme fatalistic beliefs to a strong belief in personal actions as determinants of one's health [17, 18, 23]. Accordingly, their effects on individuals' perceptions vary [21, 23, 35, 37, 38].

This chapter addresses empirical data on cancer fatalism—its relationship to ethnicity and socioeconomic status (SES), screening behaviors, delay in seeking help, and coping with cancer once diagnosed. Finally, based on the review of existing empirical knowledge, a multidimensional conceptualization of the concept of fatalism is suggested.

Cancer Fatalism in Diverse Population Groups

Most of the studies on cancer fatalism have been conducted in the United States, exploring the attitudes of its multicultural groups, especially Caucasians, African Americans, and Latinx or Hispanics [1, 2, 26, 28, 37–45, 47, 51–54]. Several studies have been conducted in Israel, which explored fatalistic beliefs related to cancer among Jewish and Arab interviewees [21, 25, 35–37, 55–58]. Studies assessing cancer fatalism have also been conducted in South Asian countries [59, 60] and among indigenous people in Australia, New Zealand, and Canada [61]. Despite the large advances in medical treatment and cure rates, cancer fatalism is a widespread belief in Western countries [62]. In a study based on a random sample of 6369 Americans, 27% of the participants agreed there is "not much people can do to lower their chances of getting cancer." [34].

Several studies have been conducted by Powe and her colleagues, a central research team in this study area [1, 2, 32, 43, 49, 51, 63–65], and by other researchers [6, 24, 39, 41, 45, 47, 66] on attitudes of African Americans toward cancer. However, most of the studies assessed levels of cancer fatalism among African Americans alone, without a comparison to Caucasians or other ethnic groups [2, 32, 39, 43, 45, 63, 64, 66]. Few studies have compared fatalism among different groups [1, 6, 41, 47, 67]. In one of the first studies, 192 older persons, mostly African Americans, were asked to complete Powe's Fatalism Inventory (PFI) [1]. This inventory was developed to assess perceptions of cancer fatalism using 15 yes-or-no items that assess fear, pessimism, inevitability of death, and predetermination [1, 23]. The study found higher levels of cancer fatalism among African Americans [1]. In a study of 190 young men, significantly higher cancer fatalism was found among African Americans than Caucasians. However, the overall scores of fatalism were very low (3.0 for Caucasians and 4.5 for African Americans, on a possible scale of 0–15) [68]. In a comparison between African Americans and Hispanic men [67], moderate fatalism was reported for both groups, but it was higher for Hispanic men as compared to African Americans (6.6 and 4.8, respectively). However, the study did not control for the higher education level of the African American participants [67]. Another study reported that Latina women reported higher levels of fatalism as compared to African American women [69]. Another study found higher levels of fatalism in African Americans compared to Caucasians [46], but it did not control for the main demographic variables.

In a study that focused on African Americans only, substantially higher levels of cancer fatalism were reported for the older African American women compared to younger women [63].

However, in another study of women aged 28–78, cancer fatalism scores were similar in the younger and older participants (4.4 and 5.6, respectively) [43]. These low scores are especially interesting because 361 of the women were from primary care centers in the southeastern United States. The authors noted that these centers serve an underserved population, with about 66% at or below the poverty level and 75% uninsured or on Medicaid. In a study on breast cancer knowledge and perceptions among African Americans, only 16% of 179 women agreed that a "woman's chance of surviving breast cancer is very low, even if it is found early." [64] Several other studies focused on correlates of fatalism, but did not provide details on fatalism scores [6, 19, 32, 40].

Another group of studies examined cancer fatalism in the Latinx and Hispanic population [26, 28, 42, 44, 69–74]. Several of these studies found higher levels of cancer fatalism among Latina women compared to Caucasian women [26, 69, 71–73]. A large-scale study with a random sample, although conducted in 1992, compared Latina and Caucasian women regarding various health perceptions and beliefs [72]. It found that a higher proportion of Latinas believed that having cancer is like receiving a death sentence (46% vs. 26%, respectively), that cancer is God's punishment (7% vs. 2%), that there is very little one can do to prevent contracting cancer (26% vs. 18%), and that it is uncomfortable to touch someone with cancer (13% vs. 8%).

In another study with 803 Latina women and 422 Caucasian women, the Latina women, especially those born outside the United States, expressed more fatalistic beliefs regarding cervical cancer [26]. A study among Latina women revealed moderate levels of fatalism (mean of 2.4 on a scale of 1–5), with higher scores among less-acculturated women. However, the scale was a combined fatalism and fear measure, consisting of five items, including perceived risk, fear of cancer, and lack of control over developing cancer [48]. In a qualitative study of 29 rural Latina women, many of them believed in fate or God as the cause of breast cancer; however, the report did not mention whether participants discussed beliefs regarding the possibility of a cure for cancer [70].

Several studies assessed cancer fatalism among Jewish and Arab women in Israel [35, 37, 38, 56–58]. Baron et al. [56] assessed cancer fatalism using two items representing fatalistic beliefs in external forces as a cause of cancer (God and fate) in a random sample of 1550 women recruited from one of four major health care services in Israel. The sample included four culturally distinct groups: ultra-Orthodox Jewish women, Arab women, Jewish women who were secular to moderately religious, and recent Jewish immigrants. The authors found moderate fatalistic perception in the non-ultra-Orthodox Jewish women (mean of 2.5, range 1–5) and higher fatalistic perceptions in ultra-Orthodox Jewish women (3.7) and Arab women (4.5). Differences were significant for the Arab group only compared to the other groups. Azaiza and Cohen [35] conducted a qualitative study with Arab women in Israel in which the women expressed fatalistic beliefs regarding their chances of contracting cancer; they perceived that life and death were in the hands of Allah (God). Thus, cancer might be a punishment for bad deeds, a test for believers, or a way of atonement. Interestingly, these beliefs were expressed by the participants together with notions regarding biomedical knowledge of causes of cancer such as genetic predisposition, lifestyle, or environmental causes such as radiation from electrical appliances and cellular networks. Some of the participants in the focus groups said they believed that cancer is a death sentence and that medical interventions only postpone the inevitable death. This fatalistic view was strengthened by witnessing cancer survivors from their own surroundings who had later died from cancer. It should be noted that some of the participants who expressed the belief that cancer is a test from God, although admitting their belief in an external force that causes cancer, believed that God places the outcome of the disease in individual's hands. Thus, they perceived a substantial level of control over the outcome.

In another study, a comparison was made between Palestinian women residing in Israel and the Palestinian Authority (*N* = 697) [37, 38].

Cancer fatalism was assessed using a two-item perceived cancer fatalism scale, which is a part of the Arab Culture-Specific Barriers scale [21]. The scale was developed based on focus groups' content analysis and further validated in a quantitative study using content, criterion, and divergent, convergent, and construct validity. The Israeli Arab women expressed lower cancer fatalism than the participants from the Palestinian Authority. The authors noted that although some of the differences may be explained by disparities in SES and sociopolitical status, the results may represent differences in location along the traditional Westernizing continuum. They also noted that although the two groups had similar cultural origins, they represented different phases of Westernization, which might have affected their perceptions of cancer [37].

The existing empirical data on fatalistic beliefs among ethnic groups should be regarded with caution. Many of these studies reported statistical differences between ethnic groups as compared to Caucasians or other mainstream groups. However, this review shows that the overall levels of fatalism, when reported, were mild to moderate in most studies. Another misconception may arise from studies reporting on correlates of fatalism in specific ethnic groups, but not reporting the actual scores obtained for fatalism. These data may lead to a simplistic conclusion that cancer fatalism is mainly a cultural characteristic [23, 29, 75].

Moreover, several scholars argued that higher cancer fatalism in ethnic groups should be analyzed in relation to social and structural factors that characterize many individuals who belong to ethnic groups [23, 29, 75]. For example, lower SES and lower education were found to be consistently related to higher cancer fatalism [18, 34, 47, 69, 74]. In addition, lesser knowledge about cancer causes and cancer treatments, lower acculturation, and language barriers [29, 44, 72] were also found related to higher fatalistic perceptions of cancer. Relevant to this discussion, Pasick [76] argued that caution is needed regarding an overgeneralized view of fatalism as a cultural component and attested that fatalism should be understood in its socioeconomic context. Poverty, racism, discrimination, and inadequate access to health care services may be mistakenly interpreted as fatalism [29, 74, 77]. Moreover, ethnic groups living in Western countries or even those residing in their original countries are going through modernization processes that affect their knowledge, perceptions, beliefs about diseases and medical treatments, and health behaviors [35, 78–81]. Thus, conclusions from studies regarding health perceptions or beliefs should be reached with a deep understanding of the dynamic and changing nature of health perceptions and the complexity of research.

Cancer Fatalism and Screening for Early Detection of Cancer

Cancer fatalism has often been reported to be related to lower performance of various health behaviors [15, 34, 59, 62, 82]. Analysis of data from 6369 respondents revealed that individuals with high fatalistic beliefs led less healthy lifestyles: they performed less regular exercise, were less likely to eat fruits and vegetables, and smoked more [34]. Other studies reported that higher fatalistic perceptions of cancer were related to a lower rate of attending screenings for breast cancer [39–41, 53, 58], colorectal cancer [2, 26, 51, 52, 54], and cervical cancer [26, 44, 60].

Mixed results on the associations between fatalism and screenings were obtained in studies that controlled for possibly confounding or intervening variables in their data analysis [18, 26, 28, 37, 38, 41, 44, 46, 47, 74]. When adjusted for demographic variables, some of the studies demonstrated significant links between fatalism and screening attendance. For example, in a study with Chinese, Malay, and Indian women, adherence to mammography, clinical breast examination, breast self-examination, and Pap smears was predicted by fatalism (measured by the FATE [18], a seven-item scale consisting of fatalistic attitudes toward health in general, medical screen testing, and individual responsibility for well-being). However, the authors did not describe the demographic variables for which the regression model was adjusted [18]. In a study of more than 1200 Latina and Caucasian participants, adjusting for confounding variables, fatalistic beliefs predicted attendance of cervical cancer screening [26]. Similar results were obtained by Harmon et al. [44] in a study of 566 Latina women and in other studies [28, 41]. Several studies reported that higher education and higher cancer knowledge were related to lower cancer fatalism [66, 73, 83, 84]. However, education served as a moderator between online information seeking and fatalism, such that for less-educated participants, more exposure to information about cancer via medical and health websites led to an increased level of cancer fatalism, whereas among more-educated participants, greater exposure lowered cancer fatalism [85].

In contrast, several studies found no or marginal associations between fatalism and screening attendance after adjusting for demographic variables [46, 47, 85–87]. For example, Russel et al. [46] reported that in a multivariate logistic regression, fatalism did not predict mammography attendance in a sample of 175 African American and Caucasian women. In Mayo et al.'s [47] study of 135 African American women aged 70 or older, the association between fatalism and mammography attendance stopped being significant in a multivariate regression analysis when adjusted for age, education, and doctors' recommendation. Also, in a study using a stratified cluster sampling to recruit 1364 women aged 50–70 years from six ethnic groups, fatalism did not predict mammography screening in a logistic regression model [6].

Higher cancer fatalism (measured by two items assessing belief in cancer as a fatal disease) in Palestinian women residing in the Palestinian Authority was also found to be associated with lower attendance of mammography. This association remained significant after adjusting for demographic characteristics, health beliefs, and situational barriers [37]. In addition, situational barriers related to the sociopolitical situation were correlated with attendance of mammography and clinical breast examinations, but did not predict their attendance in a multivariate logistic regression, whereas cancer fatalism remained a significant predictor [38]. Baron et al. [56] assessed the effect of fatalistic perceptions (using two items from the PFI [1]) on mammography attendance among 1500 women in Israel. Similarly, adjusting for possible demographic confounders, they found a significant association between fatalistic beliefs in external forces as a cause of cancer and attendance of mammography as reported by claims records among Arab women and ultra-Orthodox Jewish women, but not among Jewish veterans or new immigrants [56]. In addition, a recent study found that among Muslim women and ultra-Orthodox Jewish women, cancer fatalism was a significant predictor of undergoing mammography, after controlling for background variables [58].

However, comparison between results of the studies reviewed is difficult due to principal variability in definitions and measurement tools of fatalism, size and type of samples, age ranges, and methodology used. Of special concern is the divergence in defining adherence to screenings. Most of the studies relied on self-reporting [42] or face-to-face interviews [18, 37, 38, 47, 63], and only a few used claims records to assess adherence to screening [56]. Most studies defined adherence to mammography, clinical breast examinations [18, 36, 37, 47, 56], or Pap smear tests [44] as ever attended or never attended, whereas others assessed frequency [41], being on time with screenings [88] or frequency of more than four mammograms per 10 years [6], at least one mammography in the last 5 years [45] or compliance with overall screening guidelines [40]. Flynn [19] calculated clinical breast examination adherence as the total number of clinical breast exam tests reported divided by the maximum number that a woman of her age should have if she complied with screening guidelines. This wide diversity is probably responsible to some extent for the mixed results and difficulty in coming to conclusions regarding the relationships between cancer fatalism and adherence. Also, many questions should still be investigated, such as whether the nature and direction of these relationships differ for different screening methods, different types of cancers, or among different ethnic groups and what factors moderate or mediate the associations between cancer fatalism and screening behaviors.

Cancer Fatalism and Delay in Diagnosis

Delay in seeking medical care when or after symptoms are identified often leads to a later stage at diagnosis and lower survival rates [89]. Studies reported that delay in seeking help is not a rare situation. The estimated rate of delay ranges in different studies from 16% to 30% [90]. Norsaadah et al. [91] reported a 2-month delay of 72% and a 6-month delay of 45% among Malay women. Higher rates of delay were related to lower income [90, 92], lower education [32, 49, 90, 92], lack of a regular health provider or health insurance [90, 92], and belonging to ethnic groups [90, 93–95]. Also, delay in seeking help was found to be associated with less knowledge about cancer and greater misconceptions of symptoms [90].

Only a few studies assessed delay in diagnosis in relation to cancer fatalism. Gullatte et al. [30, 49] studied 129 African American women aged 30 to 84 years who were diagnosed with breast cancer after self-detecting a symptom. Time elapsed from the onset of symptoms to seeking medical care was 5.5 months on average. Religiosity, spirituality, and fatalism did not predict length in delay or stage at diagnosis, whereas lower education and being unmarried were significant predictors of delay. In addition, women who talked about their breast symptoms only to God were more likely to delay seeking medical care. In contrast, women who told a person about their breast symptoms were more likely to seek medical care sooner [30, 49].

Using medical records, Weinman et al. [33] reported that of 2694 cancer patients with advanced and early-stage breast cancer, 7% (195 women) refused provider advice to further examine symptoms or abnormal results. These women tended to be at a more advanced stage of breast cancer at diagnosis, were older, and had high parity. The most frequent reasons the women gave (as documented in the medical records) for their initial refusal were related to fatalism, avoidance or denial, fear of mammography pain or discomfort, and fear of surgery.

In a very small-scale study that assessed 11 women with locally advanced breast cancer and 11 women with early-stage cancer, semistructured interviews identified that late diagnosis was associated with not being aware of screening guidelines, denial, fatalism, and reliance on alternative therapies. Also, the spouses of the women in the late diagnosis group tended to be more passive about their wives' medical care and also expressed fatalistic thinking and denial [48].

Burgess and colleagues [31] conducted interviews with 46 women newly diagnosed with breast cancer. Of them, 31 had waited 12 weeks or more between noticing symptoms and approaching their physicians. Women who delayed seeking medical care differed from nondelayers in their fatalistic beliefs about the consequences of cancer treatment and perceptions of other priorities taking precedence over personal health. In a qualitative review of 32 papers, Smith et al. [30] found that fear, of either embarrassment or pain, suffering, or death from cancer, was among the main reasons for the delay, in addition to not recognizing or misconceiving the symptoms.

The few studies that focused on the role of fatalism in delay in seeking help are not sufficient to draw conclusions. Gaining more knowledge on the nature of this relationship is necessary for planning future interventions among women at risk of delay in seeking medical care.

Cancer Fatalism and Cancer Survivors

Although numerous studies were conducted to assess cognitive, emotional, and behavioral aspects of coping with and adjustment among cancer survivors, relatively few studies focused on fatalistic beliefs of cancer survivors and the impact of the beliefs on the process of adjustment [96–100]. Therefore, very little is known about perceptions of fatalism among cancer survivors and their effects on psychological reactions, adherence to treatment, and other relevant issues.

One of the very few studies on fatalism among cancer survivors was conducted by Sheppard et al. [96] This study involved a small sample of 26 African American breast cancer survivors aged 42 to 73 years and at different stages of breast cancer. Cancer fatalism was assessed using the PFI [1]. The authors reported that 80% of the sample had at least one type of fatalistic belief, but the overall score of fatalism was low. Interestingly, many of the women said they believed that contracting cancer was a matter of fate, but a low rate of positive answers was given to items that referred to cancer as causing an inevitable or imminent death. For example, none of them said they believed that "if someone gets breast cancer, their time to die is soon" or "if someone has breast cancer, it is already too late to get treated for it."

An intriguing but unanswered question in this regard is whether fatalistic perceptions change in individuals once they are diagnosed with cancer [97, 98]. An indirect insight into the process of change may be gained from the contrast that exists regarding fatalistic beliefs of healthy women and those of cancer survivors, as depicted in qualitative studies. For example, as previously reported, healthy Arab participants in focus groups reported many fatalistic beliefs regarding the causes and the fatal outcome of breast cancer [35]. In contrast, in a qualitative study using in-depth interviews with 40 Arab breast cancer survivors who were about a year post-treatment and without evident signs of disease, all the women were optimistic about the outcome of their disease and confident that they would defeat it, with God's help [99].

Another qualitative study with 16 Chinese individuals with colorectal cancer revealed that most participants perceived their cancer as a predetermined destiny. This belief was followed by passive acceptance alternating with a focus on positive aspects. However, the authors identified a flow in fatalistic beliefs that was strongest at early diagnosis and lowered as treatment progressed. Upon treatment completion, fatalism reemerged regarding disease recurrence [100].

Fatalism in cancer survivors was also studied from a different perspective, as a coping style [101, 102]. Although scholars in the area of coping usually differentiate between cognitive perceptions (e.g., optimism or fatalism) and coping strategies [103], Greer and colleagues [101, 102, 104] combined cognitive perceptions and coping responses into a single construct termed coping styles (also referred to as adjustment styles) [102]. They constructed a profile of five coping responses: fighting spirit, hopelessness and helplessness, anxious preoccupation, fatalism, and avoidance [101, 102, 104]. Fatalism was described as "a perception that no control can be exerted over the situation and the consequences of lack of control can and should be accepted with equanimity." [101, p.13] As a result, the attitude of women with a fatalistic coping style toward cancer is one of passive acceptance [101]. Studies using this typology of coping styles reported that higher use of fatalism was associated with lower adjustment and higher emotional distress. The same was found for cancer survivors using coping styles of hopelessness or helplessness and anxious preoccupation in contrast to the use of fighting spirit [13, 105, 106]. Also, an intervention study using cognitive behavior therapy showed a significant decrease in anxiety and depression concomitant with an increase in fighting spirit and a decrease in the less adaptive coping strategies [104]. However, in a sample that included 101 women with advanced breast cancer, no association was found between emotional distress and using fatalism as a coping style [107]. One study assessed 353 women treated for primary breast cancer within 1 year of diagnosis for emotional distress, anxiety and depression, adjustment, and coping style [108]. The authors combined fighting spirit with fatalism to create a coping style termed "positive reappraisal." The multivariate analysis conducted suggested an association between this combined coping style and lower fatigue.

Greer and his group [101, 102, 104] conducted longitudinal studies in which cancer survivors were followed for long periods to assess the role of coping styles in survival. They reported that survivors who responded with fighting spirit or denial were significantly more likely to be alive and free of recurrence 5, 10, and 15 years after diagnosis than survivors with fatalistic or helpless responses [102, 109]. These results were obtained after controlling for demographic and disease-related variables. When the prognostic factors were examined individually, psychological response was the most significant factor in predicting death from any cause, death from cancer, and first recurrence.

A similar view of fatalism as a means of coping was suggested by Sharf et al. [50] The authors proposed that fatalism may be used by cancer survivors as a mode of coping with the uncertainty imposed by cancer diagnosis. Similarly, other researchers referred to fatalism as a means of coping with self-blame [110].

The extent and nature of fatalistic views in cancer survivors and their effect on psychological and physical health are still mostly unknown and understudied. The distinct ways of conceptualization of fatalism in cancer survivors in the few existing studies hinder reaching conclusions and point to the necessity of expanding the research in this area.

Understanding Cancer Fatalism as a Multidimensional Construct

The mixed results on cancer fatalism and its consequences [1, 2, 39, 40, 44, 47, 52, 53, 111] described in this chapter point to the complexity of the structure of fatalism and emphasize the need to consider interrelations among cultural, structural, and individual factors.

I propose a multidimensional conceptualization of cancer fatalism derived from our preliminary research [112]. The construct comprises four dimensions: fatalistic beliefs and their extent, fatalistic causal attributions of cancer, antecedents of fatalistic beliefs, and outcomes of fatalistic beliefs (Fig. 18.1). For these purposes, fatalistic beliefs consist of the extent to which individuals believe that cancer occurrence is out of their control and that death is inevitable, casual attributions are the perceptions of causality underlying the fatalistic beliefs, antecedents are the socioeconomic and environmental factors that may affect fatalistic beliefs, and the outcomes are the health behaviors of individuals.

Extent of Cancer Fatalism

This dimension refers to the extent to which individuals believe that the occurrence or outcome of cancer is predetermined and beyond personal control or behavior and that a cancer diagnosis is the equivalent of a death sentence. These two aspects of the cancer fatalistic beliefs accord with previous definitions of cancer fatalism [18, 26, 32, 33, 55, 113]. However, these two fatalistic beliefs are often interchangeably addressed in the literature as cancer fatalism [34]. Yet some evidence points to the different nature of these constructs. For example, several qualitative studies showed that although participants believed they had no control over developing cancer (occurrence fatalism), most did not express fatalistic attitudes concerning their chances of surviving cancer (outcome fatalism) [114]. Therefore, individuals may believe that contracting cancer is not in their personal control but may also believe that treatment can be effective. Also, when fatalism was studied in relation to culture or ethnicity, often no distinctions between the dimensions were made [29]. However, some evidence exists as to the different nature of the constructs. For example, in a study of Latina women, 54% believed they had no control over developing cancer, yet most did not express fatalistic attitudes concerning the chances of surviving breast, uterine, or cervical cancer [71]. Note that attributions of causality and cancer fatalism intensity may be related to background factors, such as education, economic status, health literacy, and access to health services [34, 41, 44].

Fatalistic Causal Attributions of Cancer

Based on prior conceptualizations [18, 34] and preliminary findings [112], I define four types of fatalistic causal attributions of cancer, each

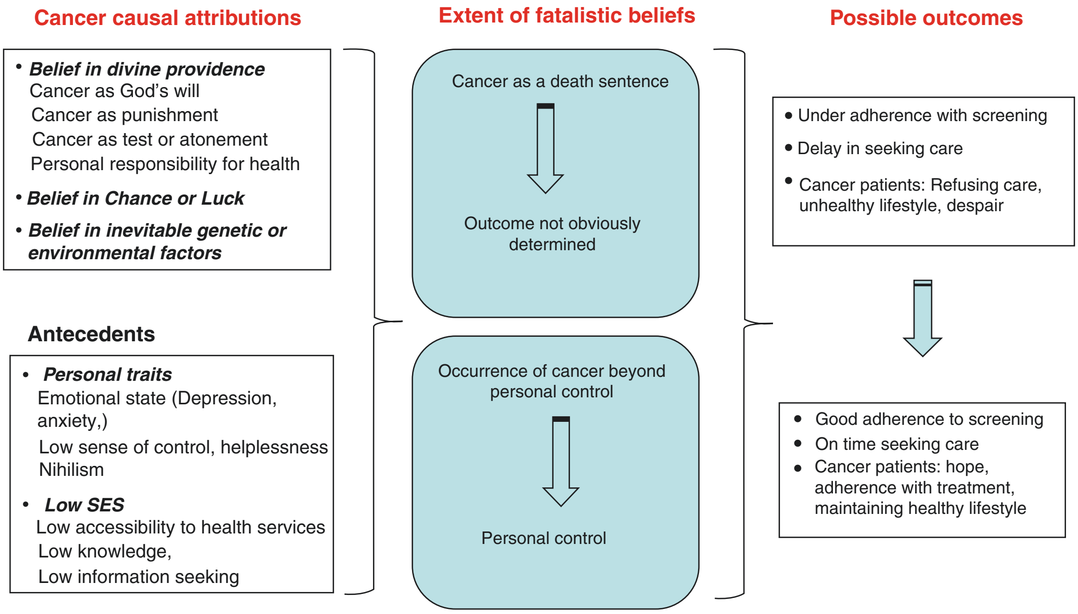

Fig. 18.1 A multi-dimensional model of fatalism

of which leads to perceptions of cancer or its outcomes as predetermined: belief in divine providence, belief in chance or luck, and belief in the inevitability of environmental or genetic factors.

Belief in Divine Providence The three main monotheistic religions—Christianity, Judaism, and Islam—share the belief that major life occurrences are in God's hands and beyond our personal control [15, 35, 57, 115]. Nevertheless, contracting cancer and other diseases is believed not to be arbitrary but rather God's response to an individual's deeds or behaviors. A cancer diagnosis may be punishment for unfaithful or unacceptable behaviors, or it may be a test of an individual's faith in God [35], similar to Job's story. A young Arab woman said in a focus group: "God tests our patience, the same as what happened to Job. God tried him with all kinds of diseases and disasters to test how strong his belief was. God strikes those He loves, as He wishes to test them." [35, p. 37] Women in the focus groups also raised the idea that cancer may be God's act to stimulate atonement or change in a person's attitudes and way of life [35].

Although the main religions convey the belief that everything is in God's hands, they also state that a person's body is a gift given to the individual to take care of until the time comes to give it back; thus, the individual has a personal responsibility to preserve their health [35, 116]. In contrast to passive acceptance and neglect of personal health often reported to be related to fatalism [1], these religious perceptions of fatalism encourage the individuals to actively act to preserve or promote their health [39, 115]. Of course, it cannot be ruled out that religious beliefs may be used as an excuse for a passive attitude toward health [15].

A distinction should be made between attributing to God a diagnosis of cancer or the view that death is inevitable. In a study described earlier in the chapter, breast cancer survivors who participated in in-depth individual interviews [99] expressed a strong belief in self-responsibility stemming from their wish to overcome the disease for their own sake and for their families, but it was also rooted in religious writings and their belief that it was God's will. Also, healthy participants in focus groups expressed strong beliefs that cancer is an incurable fatal disease [35, 55]. However, in another study, these beliefs were countered by more optimistic voices [78]. Also, in focus groups with Hispanic participants, most participants reported that their religious beliefs encouraged them to use health services, including cancer screening tests [117–119].

This view of religious-related fatalism can provide an explanation for the unanswered paradox regarding the relationships between fatalism, religion, and health: on one hand, fatalism was reported to be more prevalent among ethnic minorities, who are often considered to be more religious [15, 117], whereas on the other hand, religiousness was reported to be related to a healthier lifestyle and better health indexes [118, 120, 121]. In addition, several studies revealed that different perceptions may coexist in specific population groups [15]. For example, in focus groups and qualitative studies with religious Arab women [35, 56] and ultra-Orthodox Jewish women [57], women differed in the degree of their perceptions of health as a completely uncontrolled fate or a factor within their responsibility, although governed by God.

Belief in Chance or Luck The belief that cancer is a matter of chance or mere luck, and not guided by higher forces or controllable by an individual's behavior, is also widespread [18, 34]. Powe and Johnson [3] connected it to a sense of nihilism common in modern Western society. Several scholars have suggested that the attribution of cancer to luck or chance is in part due to the nature of cancer research, which is difficult to communicate to the lay public [34, 113]. A mass of findings regarding the causes of cancer is frequently communicated to the public by the media [114]. These findings are often conflicting and cause confusion and mistrust [113]. An example is the previously strongly disseminated knowledge that high-fiber diets have cancer-preventing properties, which scientists concede is now unclear based on newer results of studies [62]. A national survey found that 47% of the American public believed that "it seems like almost everything causes cancer" and 71% agreed that "there are so many recommendations about preventing cancer, it's hard to know which ones to follow." [34] Therefore, they react with fatalistic beliefs in the lack of control over cancer occurrence.

Belief in Inevitable Genetic or Environmental Factors A comparatively new aspect of fatalism—genetic fatalism—was recently presented [110]. Research in this area appeared following the identification of familial risk of specific types of cancer such as breast, ovarian, or colorectal cancer. About 27 years ago, breast cancer mutations in the BRACA1 and BRACA 2 genes were identified as increasing susceptibility to breast and ovarian cancer [122]. The identification of these specific mutations has increased the sense of genetic fatalism in first-degree relatives of people with breast or ovarian cancer [110, 123].

Previous studies concluded that people often respond in fatalistic ways when they hear about genetic causes of disease [124]. This reaction has been explained by misconceptions people often have regarding the role of genes in disease susceptibility. Walter et al. [124] argued that once a disease is perceived to be caused solely by genes, the individuals' reaction may be one of lack of control and fatalism. One of the few similar studies involved parents of neonates who had received a positive screening test result informing them that their child was at risk of hypercholesterolemia, an inherited predisposition to heart disease [116]. Parents who regarded this condition as a genetic problem perceived the situation as uncontrollable and, hence, more threatening.

Very few studies assessed fatalistic perceptions in persons with familial history of cancer or diagnosed as carriers of identified mutations of susceptibility [44, 125–127]. The existing studies were mainly conducted with women who had first-degree relatives with breast cancer, and in almost all of these studies, fatalism was measured indirectly or was not the primary focus of the study. For example, it was reported that women at high risk often overestimate their lifetime risk of developing breast cancer [128, 129] and experience higher levels of anxiety and depression than matched controls [125, 130–133], although several studies did not find higher distress among high-risk individuals [134–136].

Fatalistic beliefs were examined by Ryan et al. [126] using focus groups with 29 first-degree relatives of cancer survivors. The authors noted that some of the women reported fatalistic beliefs regarding their risk of contracting breast cancer. Harmon [44] reported that individuals who reported a family history of cancer were more likely to endorse fatalistic beliefs. Cohen et al. [125] assessed cognitive perceptions, coping strategies, and emotional distress in 80 adult daughters of breast cancer survivors as predictors of levels of stress hormones and immune cytotoxic functions. To examine cognitive perceptions, the participants were asked to grade their sense of control over contracting breast cancer. They expressed a lower sense of control over contracting breast cancer than the participants in the control group. In addition, lower levels of perceived control were associated with higher psychological distress, higher levels of stress hormones, lower natural killer activity, and lower secretion of cytotoxic cytokines (interleukin [IL]-2, IL-12, interferon gamma). These immune functions take part in immune defense against viruses, infections, and cancerous cells. Of special interest was the relationship between lower sense of control and lower IL-2-induced natural killer activity against breast cancer target cells [125]. Higher perceived control over contracting breast cancer predicted higher adherence to screenings for early detection of breast cancer [125].

Another study used focus groups with first-degree relatives of ovarian cancer survivors. The participants in this study expressed an increased sense of vulnerability. They perceived that vulnerability to cancer was much higher than for other diseases in their family such as heart disease or other cancers. They felt fatalistic and helpless about ovarian cancer because they believed there were no lifestyle risk factors that they could control by living a healthy lifestyle [127].

A view of high susceptibility and a sense of inevitability about contracting cancer among individuals at high risk of breast cancer may affect health behaviors in two directions. It may reinforce a sense of lack of power to affect the inevitable fate; thus, health behaviors or screenings may be perceived as not needed and thus avoided. In contrast, the sense of vulnerability may encourage them to engage more in health behaviors, screening, or even prophylactic action. Informing individuals at high risk about the meaning of genetic predisposition and that cancer cannot be caused solely by genetics may reduce their sense of fatalism [124] and encourage active involvement in prevention or early detection efforts, thus increasing chances for survival.

Causal attributions of cancer to environmental factors is represented by the notion that in the modern age, individuals tend to consider themselves surrounded by environmental risk factors for cancer [35]. Individuals believe they cannot influence or change the environment, nor can they protect themselves from factors that can cause cancer occurrence or affect its outcome [18, 34, 35]. This concept is based on widely disseminated scientific information stating that exposure to a wide variety of factors, such as radiation, natural and artificial substances in the environment or food, certain drugs, hormones, bacteria, and more, is responsible for at least two-thirds of cancer incidence [18, 21, 34, 35].

Antecedents of Cancer Fatalism

Cancer fatalism may develop as a result of socioeconomic conditions and education or other environmental factors. According to the studies that found associations between cancer fatalism and level of knowledge or education [34], the lack of knowledge of options of treatment and cure or of the impact of early detection on survival may indeed foster fatalism [27, 44, 72]. Peek et al. [39] cited one woman as saying, “I didn’t know that it was a possibility to live after you had breast cancer or had been found having breast cancer. Everybody I know who had breast cancer [has] died. I [wasn’t aware] of anything different.” (p. 1851)

Higher fatalism was often found among individuals from ethnic minority groups in Western countries or ethnic groups in their original countries [1, 2, 38, 49, 51, 63, 67, 72]. Thus, fatalism was often referred to as a cultural belief. However, it may also emerge from social structures that are characteristic of disadvantaged groups [23, 29, 75, 76]. Low socioeconomic circumstances may reinforce beliefs that death is inevitable when facing cancer independent of culture. Poor people have lower access to health services, they may not have health insurance or regular health providers [29], and even if they have health insurance, they often cannot provide themselves with the cure opportunities that people with higher incomes have. Also, studies have reported that physicians impart less information and recommend less screening and checkups for individuals from minority groups or disadvantaged individuals [80, 137]. As a result, individuals witness around them more cases of cancer that were not cured, and this may reinforce the fatalistic belief that death is an inevitable outcome of cancer [35, 62].

Another issue that needs consideration relates to the complex relationships between different psychological factors (e.g., self-efficacy, helplessness, hopelessness, sense of control, fear, anxiety, depression) and fatalism. Very little empirical knowledge exists regarding the nature of these relationships and whether these factors act as antecedents to fatalism or outcomes of fatalism or are perhaps coincidently related. Considerably little attention has been given in fatalism research to the role of personal traits or psychological characteristics of individuals in the development of fatalism. Although most studies stress the cultural and ethnic connection of fatalism, it may develop due to personal characteristics at least partially independently from the cultural perspective. Several studies found high fatalism to be related to low self-efficacy [46, 138, 139], with the underlying notion that when an individual perceive themselves as ineffective, they will believe that events in life are out of their control [45, 46, 138]. Also, external health locus of control was mentioned to be related to higher fatalism [140] and lower performance of good health behaviors [78, 81]. However, external locus of control may also imply higher adherence to physicians' recommendations [140] or higher belief in God, which might be related to healthier lifestyle and performance of health behaviors [121].

Several other personal traits may be related but not studied yet in relation to fatalism. For example, helplessness is a personal trait that develops following early and later life experiences. It provides the person with a sense of lack of resources and power to affect life circumstances, including health. Helplessness was often found to be related to lower utilization of health behaviors and worse health outcomes [141]. This personal attitude may, as a result, reinforce a fatalistic view that life happens to the individual without an option of exerting personal control over it. However, the nature of the relationships between perceived helplessness and fatalism is yet to be explored.

Emotions studied in relation to fatalism were mostly specific cancer-related or screening-related emotions, such as fear, anxiety, and embarrassment [19, 41], often referring to negative emotions as an outcome of fatalism [23, 142]. No attention has been paid to emotional states such as anxiety or depression. Examining these emotional states may provide an additional way to study fatalism from an individualized perspective. Depression is defined by categories of symptoms: emotional, cognitive, and behavioral symptoms (DSM-5) [143]. Cognitive symptoms of depression consist of lack of motivation for action, perceptions of hopelessness, and lack of sense of meaning. These cognitions may be translated into fatalism when a depressed individual is asked about his or her beliefs. Moreover, depressed individuals engage much less in good health behaviors and screening, due to difficulty in making decisions, planning, and acting.

Based on clinical interviews [144], about 18–30% of the adult population in the United States is reported to be distressed, and 12-month and lifetime prevalence of major depressive disorder is 5.3% and 13.2%, respectively. Rates of depression are even higher among older adults and individuals with low income and low-level education

[145]. Thus, it may be that in studies examining fatalism among these groups, the results are confined to depression. Also, higher trait anxiety or higher cancer-specific anxiety may result in higher scores of fatalism.

Outcomes of Cancer Fatalism

In accordance with the review earlier in this chapter, cancer fatalism may cause unwillingness or refusal to attend screenings [23]. It is believed that if the end outcome is already known, early detection will not change the inevitable course of the disease. Thus, individuals may logically decide that it is more worthwhile to avoid screenings [18] and thus avoid negative emotions of fear and anxiety that arise when focusing on cancer or taking steps toward screening. In addition, as reviewed above, high cancer fatalism, especially the outcome of delay or refusal of treatment, may cause feelings of hopelessness and despair and may discourage people from maintaining the healthy lifestyle that is essential for quality of life and to reduce risk of recurrence. On the other hand, it is possible that the perception that death is inevitable may be the only significant cause of adverse health behaviors, whereas the perception that getting cancer is uncontrollable can encourage early detection adherence. So, as described earlier, the perception of divine providence as a major factor can prevent healthy behaviors, but the specific perception that the individual can affect the results of cancer is also part of religious beliefs. To the same extent, the perception of cancer as an event of chance or fate or caused by genes or environment can also be associated, but not necessarily, with negative health behaviors.

The lack of clear distinctions between different aspects of fatalism and the lack of conceptualization of the causal attributions of cancer have so far not allowed a thorough understanding of the links between fatalism and health behaviors. These gaps may also explain some of the limitations of the measurement tools, which may also be responsible for the mixed and contradictory findings in fatalism literature [7]. Gaining greater understanding of the distinct dimensions of fatalism will allow the building of a multidimensional construct of fatalism. This construct may be further used to understand the fine differences among its dimensions, their specific antecedents, and their unique effects on preventive behaviors, screening adherence, and the adjustment of cancer survivors to their illness. It will also provide tools for studying specific populations, such as individuals at high risk or individuals who delay seeking medical treatment.

A more finely tuned knowledge of different dimensions of fatalism is also essential for tailoring interventions to overcome barriers of fatalism. Because delivering preventive health care information may not be enough to increase adherence to screening, a few studies measured the effect of interventions tailored to target specific fatalistic beliefs on change in health behaviors [4, 36, 54]. For example, Azaiza and Cohen [36] used a tailored intervention with Arab women to lower specific barriers to attending mammography and clinical breast examinations. Using scripts, the interviewers reframed notions of cancer as an inevitable fate and that the notion of personal ability to control the outcomes once cancer is detected early was in their control, stressing that this notion coincides with the scripture writings of Islam and Christianity. For example, the belief that cancer is a punishment from God was reframed as a motivating notion that cancer may be a test from God. The results showed that almost 48% of the intervention group and 12.5% of the control group scheduled or attended a clinical examination and 38.5% of women in the intervention group and 21.4% of the control group attended or scheduled a mammography postintervention. In another study with African American women, biblical passages about the importance of staying healthy were provided and discussed in an intervention aimed at increasing attendance at colorectal cancer screenings [52]. The selected biblical passages were used to empower participants to take control of their health [52]. In this study, 539 African American men and women 50 years of age or older participated. The intervention group had a significantly greater proportion of those receiving a colonoscopy within 3 months after the educational session than the control group.

Further controlled studies are needed to assess the effect of challenging the different types of fatalism among healthy participants to increase screening and good health behaviors and among cancer survivors to promote adaptive coping and well-being.

Discussion and Conclusions

This chapter provides a review of various aspects of cancer fatalism, including its prevalence in different population groups and correlates of fatalism with sociodemographic variables. An effort has been made to critically review the role of fatalism in screening behaviors and delay in seeking help. The effect of cancer fatalism on cancer survivors' adjustment and well-being was also addressed. In addition, the relatively new concept of genetic fatalism and the few studies related to the concept were reviewed. Finally, a conceptualization of fatalism as a multidimensional construct has been suggested.

This chapter demonstrates the complexity of the concept of fatalism, consisting of different dimensions that each may have a unique effect on health behaviors. Also, its various correlates and confounders call for caution in drawing conclusions from cross-sectional and correlative studies.

Most studies that assessed fatalism in ethnic groups have not addressed the dynamic nature of culture. Traditional societies are steadily going through a process of Westernization, incorporating cultural beliefs regarding health and illness with modern biomedical knowledge [79]. Thus, fatalism should be studied in this context of change.

It is suggested that further studies examine multidimensional aspects of fatalism based on new or refined tools. In addition, attention should be given to psychological confounders of fatalism, such as depression and trait anxiety, and their interaction with coping styles such as emotional control or use of denial or avoidance. Special caution should be paid to pitfalls of overgeneralization and simplistic linking of fatalism to specific ethnic groups.

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Cancer and the Aging Population

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Introduction

Geriatric oncology focuses on the care of older adults with cancer. Cancer predominantly affects adults aged 65 years and older, and the majority of newly diagnosed cancers and cancer-related mortality (i.e., ~70% of all cancer deaths) occur in this age group [1, 2]. Their increasing numbers, their varying levels of fitness, and their high prevalence of vulnerabilities and frailty justify further research and guideline development in the evaluation and management of older adults with cancer [3–5].

Considerations Prior to Cancer-Directed Management

Older adults with cancer present with differing tumor pathologies and biologies, diverse comorbidities and overall health, and a wide range of fitness and functional abilities. As a result, they have varied physical, psychosocial, and economic needs. The prognosis of older adults with cancer is inextricably intertwined with the presence of geriatric syndromes, such as frailty, which are associated with greater adverse events from cancer treatments [6, 7]. Frailty is defined as a clinically identifiable state of older adults characterized by an increased susceptibility to adverse changes in health which results from multi-organ declines in physiologic reserve and functional status [8, 9]. Frailty is usually associated with the loss of muscle mass and bone density, depression, functional decline, hospitalization, and increased mortality [8, 10, 11]. Although there is no gold standard for the detection of frailty, multiple frailty tools have been developed and utilized such as the Fried Frailty Phenotype and the Deficit Accumulation Model of Frailty [12, 13]. Geriatric assessment (GA) serves as a useful tool to identify and quantify frailty in older adults with cancer [13].

Oncologists have traditionally employed the Karnofsky performance status score (KPS) and the Eastern Cooperative Oncology Group (ECOG) performance status scale to evaluate

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functional status [14]. These scales, however, may not accurately reflect the underlying health status of an older patient, and they were validated primarily in clinical trials that excluded those with functional impairment or high levels of comorbidity [15]. In order to provide evidence-based treatment plans for older patients with cancer, researchers have developed an assessment approach, known as the GA, which can capture the specific characteristics and fragility of this population. GA is a multidisciplinary, multidimensional systematic process to evaluate the influence of age-related factors that may affect health status in older adults [16]. Recent studies have demonstrated that GA can provide more information on the functional status of older patients with cancer than the standard oncology performance measures such as KPS [17, 18].

GA consists of a compilation of reliable and validated tools that assess age-related conditions that are important in determining the physiologic age of older patients. These conditions include functional status, cognition, comorbidities, physical performance, medication review, psychosocial health, social support, and nutritional status [16, 19]. The psychological health domain relies on validated instruments to assess depression, distress, and anxiety in older adults such as the Geriatric Depression Scale, Distress Thermometer, and Generalized Anxiety Disorder Scale (GAD-7) [20–22]. Studies have demonstrated a high prevalence of psychological impairment in older adults with cancer [19, 23]. Furthermore, depression is a significant predictor of unplanned hospitalization, functional decline, and lower survival in this population [24, 25].

Although beneficial, GA may be difficult to conduct within the time constraints of busy clinical practices in limited resource settings [26, 27]. Therefore, a two-step approach has been recommended, in which high-risk groups are first identified using screening tools that differentiate relatively fit patients from those who are vulnerable or frail. A full GA can then be conducted for these patients. Multiple geriatric screening tools have been developed and are increasingly implemented in daily practice, such as the Geriatric 8 (G8), Senior Adult Oncology Program, abbreviated Comprehensive Geriatric Assessment, and Vulnerable Elders Survey-13 (VES-13) [28–30]. Abnormal results on these tools are associated with functional decline, greater chemotherapy toxicities, and/or lower survival in older adults with cancer [31–33].

Cancer-Directed Therapies

Patients diagnosed with cancer experience a decline in overall health status due to cancer and side effects from cancer therapies [34]. These declines are even more pronounced in older adults due to coexisting age-related conditions that predispose them to short-term and long-term disability. Older adults may experience, for example, accelerated sarcopenia, increased adiposity, bone loss, and declines in cardiorespiratory performance simply due to age [35, 36]. These factors may increase their risk of adverse events from cancer therapies. Additionally, older patients with cancer are susceptible to cognitive decline and psychological distress, including depression and anxiety [35]. Therefore, it is important to consider the particular needs of older patients with cancer, how therapies might affect them, and whether supportive care interventions (e.g., exercise) are available that could be implemented before and during treatment [34]. Here, we briefly review the main therapeutic options that may be offered to older patients with cancer.

Systemic Therapies

Chemotherapy

Toxicity from chemotherapy is an important consideration when selecting treatments for older adults with cancer. Several factors associated with aging such as comorbidities, functional impairment, falls, and psychological issues may influence treatment tolerance in older adults. Studies have shown that older adults experience a higher rate of chemotherapy toxicity than their younger counterparts [36, 37]. These toxicities can lead to hospitalizations, treatment discontinuation, and decreased quality of life. Clearly, it is important to describe chemotherapy toxicity, counsel patients on the risks, and provide supportive care to optimize their ability to tolerate chemotherapy prior to initiating treatment. Two risk calculators have been developed using the GA and clinical variables to evaluate the risk of chemotherapy toxicity in older adults: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) [38] and the Cancer Aging Research Group (CARG) [37] toxicity tools. Among older adults with cancer, both the CRASH and CARG tools are more predictive of severe chemotherapy-related adverse events than oncologist-rated KPS and ECOG performance status scales [37–42]. In a study of 199 older patients, the CARG toxicity tool identified the need for additional support (e.g., follow-up visits or testing, social work referral) in 38.5% [43].

Targeted Therapies

Therapeutic measures aimed at molecular targets have revolutionized the treatment of many cancers in recent years. Older adults, however, have generally not been participants in the clinical trials of these newer treatments, leading to limited data on the efficacy, safety, and dosing of targeted therapies in this age group [44]. In limited studies, targeted therapies have been shown to be an effective option, albeit associated with more adverse events in older adults [45]. Bevacizumab, a vascular endothelial growth factor inhibitor, has been studied in combination with chemotherapy in older adults (median age 76 years) with untreated metastatic colorectal cancer (AVEX). The study showed improvement in median progression-free survival by 4 months (median PFS 9.1 vs 5.1 months, $p = 0.001$) [46]. Advanced age, however, is associated with bevacizumab-associated hypertension [46, 47]. Further problems with targeted therapies in older adults include issues of polypharmacy and drug interactions between targeted agents and other prescribed and over-the-counter medications, specifically those metabolized by CYP450 agents [48, 49]. No risk calculators exist for targeted therapies, although a GA-based algorithm has been proposed to guide the incorporation of CKD4/6 inhibitors (i.e., palbociclib and abemaciclib) in the management of ER+/HER2-negative advanced breast cancer in older women [49]. Finally, there is a need to understand of effects of these agents on health-related quality of life and functional status.

Immunotherapy

Immunotherapy agents, such as immune checkpoint inhibitors, are increasingly used to treat many types of cancers. Immunotherapy is also generally better tolerated than chemotherapy in older adults, and it is often considered in older adults who are perceived to be unable to tolerate cytotoxic chemotherapy [50]. Although studies suggest that the safety profile of immunotherapy is comparable for older and younger patients, older patients may not have the functional reserve to recover from immunotherapy-related adverse events. In a retrospective study of older adults ≥70 with advanced lung cancer, those who were treated with immune checkpoint inhibitors had relatively high rates of ICI discontinuation, use of glucocorticoids, and hospitalization [51]. Further work is needed to understand the efficacy and tolerability of immune checkpoint inhibitors and to assist with the selection of older adults for immunotherapy in the setting of immunosenescence, comorbidities, and geriatric syndromes.

Surgery

Older adults are at increased risk for serious postoperative complications, such as functional decline and death [52, 53]. Therefore, it is important to consider a multidisciplinary approach when evaluating older patients for surgery. A novel risk stratification for older adults undergoing free-flap reconstruction for head and neck surgeries showed that the variables with worse outcomes included age ≥80 years, moderate or severe comorbidities, BMI of <25, and frailty [54]. In addition, geriatric comanagement of care for older patients undergoing cancer-related surgical treatment was found to improve postoperative mortality [55]. Together, these studies suggest that GA is an important component of the preoperative risk assessment of older adults undergoing cancer-directed surgery.

Radiation

Radiation therapy is commonly included in the treatment of older adults. GA can help predict the toxicities and tolerability of radiation, resulting in changes in up to 49% of patients' initial treatment plans [56]. Certain considerations in older adults, especially those with comorbidities, such as whether dementia might make it difficult for patients to achieve maneuvers like breath holding or lying flat, are particularly important in radiation therapy planning. If a patient will have difficulty with transportation, a hypofractionated course of radiation could be considered, although this choice would need to be weighed against the risks of a higher radiation dose per session [57].

Cellular Therapies

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is a life-prolonging and potentially curative therapy for patients with hematologic malignancies; it is being used with increasing frequency in older adults. Autologous HSCT in older adults can be a safe and effective therapy for multiple myeloma and lymphoma, although retrospective studies have shown that older adults may have a higher risk of mucositis and cardiac arrhythmias and a longer time for bone marrow recovery [58]. Allogeneic HSCT is an option for selected older adults. Several studies have demonstrated that age alone is not the best predictor of toxicity and outcomes in older adults undergoing HSCT. Comorbidities and functional status, as measured by GA, serve as better predictors of how older adults tolerate HSCT and can identify the presence of geriatric syndromes and comorbidities. Use of GA can thus help optimize the health of older patients who are undergoing either an autologous or allogeneic HSCT [59].

Chimeric Antigen Receptor T-Cell (CAR T) Therapy

CAR T-cell therapy has produced favorable results in patients with relapsed/refractory aggressive lymphomas after multiple lines of therapy. Two anti-CD19 CAR T-cell therapies have been approved by the United States Food and Drug Administration (FDA): tisagenlecleucel and axicabtagene ciloleucel for adults with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma who are ineligible for stem cell transplant. Brexucabtagene autoleucel, a CAR-T cell therapy, is the first FDA-approved cell-based gene therapy for the treatment of mantle cell lymphoma. CAR T-cell therapy has the potential to provide durable remissions in older adults, who comprise the majority of those diagnosed with aggressive lymphomas. In the phase II portion of ZUMA-1, 24 patients ≥65 years were treated with axicabtagene ciloleucel with a 92% overall response rate in subgroup analysis, compared with 79% in patients <65 years [60]. In the JULIET phase II portion, 25 patients (out of 111 total patients) age ≥65 received tisagenlecleucel. Subgroup analysis showed an overall response rate of 59% in adults ≥65 years, compared with 49% in patients <65 years [61]. In a real-world study of older adults with lymphoma, the use of CAR T-cell therapy was shown to benefit patients who otherwise would be excluded from clinical trials [62]. In addition, CAR T-cell therapy has been associated with reduced healthcare costs during the 6 months after treatment vs. the 6 months prior to treatment, including a 50% reduction in the total number of ED visits [62]. Based on available data, CAR T-cell therapy can be a viable treatment option that is well-tolerated by older adults.

Clinical Trials

Older adults have been underrepresented in pivotal cancer clinical trials [63]. Even when they are enrolled in clinical trials, the selected older adults are not representative of the average older patient treated in clinical practice—they have better performance status, fewer functional impairments, and fewer comorbid conditions [64]. In a study of 302 phase 3 clinical trials, significant age disparities were found between trial participants and incident disease populations across trials; these disparities appear to be increasing over time. Ludmir et al. pointed out that the median age among those who participated in clinical trials was on average 6.49 years younger than the population median age (95% CI −7.17 to −5.81 years; $p < 0.001$) [63]. Industry-funded trials have greater age disparities than non-industry-funded trials [63].

Several barriers inhibit clinical trial participation by older adults. System barriers include stringent eligibility criteria, trial availability, and informed consent language. Provider barriers include time demands, lack of resources and personnel, reluctance to enroll older adults due to concern for increased risk of toxicity, and general concern about patient age. Patient barriers include patient knowledge, time, transportation and financial issues, patient concerns about investigational drugs, and emotional burden [64]. Despite these barriers, older patients enrolled in clinical trials are no less likely than their younger counterparts to complete the study. Among 12,367 patients enrolled on the American College of Surgeons Oncology Group (ACOSOG) Z901101 Alliance trials, although only 36% of the entire cohort were age ≥65, there was no association between age and trial completion [65].

To better inform the management of older adults with cancer, it is imperative that they be better represented in clinical trials. Trials should be designed specifically to accommodate older adult participation, which would require broader eligibility criteria, availability of treatment modifications, incorporation of older adult-specific endpoint, and novel methods for data capturing that are feasible and convenient for older adults.

Supportive Care in Older Adults

Supportive care, also known as palliative care, is complementary to the traditional oncologic care of older adults with cancer and can be beneficial at any stage of illness. It focuses on optimizing symptom management and quality of life, which helps patients to live as well as possible for as long as possible. Palliative care has been shown in multiple studies, including randomized clinical trials, to assist in medical decision making, clarification of treatment goals, management of symptoms, psychological health, functional status, and the building of rapport. The National Comprehensive Cancer Network has recommended that patients with advanced cancer should receive dedicated palliative care services concurrently with their oncologic care, starting early in their disease course (preferably within 8 weeks of diagnosis) [66]. Palliative care services can also provide additional support to established outpatient cancer care programs for older adults, who are at increased risk for experiencing a high symptom burden and may have unmet physical or psychosocial needs. GA can guide supportive care interventions by the interdisciplinary team [67]. Two randomized clinical trials, presented at the American Society of Clinical Oncology Annual Meeting 2020, showed that providing guidance to oncologists with GA-based interventions decreased grade 3–5 treatment-related toxicity when compared to usual oncologic care [68, 69]. In addition, the INTEGRATE study from Australia showed that integrated oncogeriatric measurement improved overall health-related quality of life and reduced unplanned hospitalizations and treatment discontinuation [70]. Optimizing supportive management of geriatric syndromes can help prevent common complications, including febrile neutropenia, nausea, poor bone health, cytopenias, depressed mood, fatigue, and insomnia [71]. Therefore, supportive care should be incorporated in the management of older adults with cancer.

Financial Considerations

The number of therapeutic options for cancer has exploded in the past several years with the development of new classes of drugs and health services. Advances in treatment, however, are associated with an increase in healthcare utilization and costs associated with cancer and its treatment. Many patients and families experience financial burdens as a consequence [72]. The median monthly cost of chemotherapy has increased sharply over the past several decades [73, 74]. Some patients may have difficulty obtaining oral medications as a result of high cost. Not all states have parity laws that require insurance companies to pay for oral chemotherapy as there are for intravenous chemotherapy, and often, oral therapy is viewed as a "prescription drug benefit," which leads to increased out-of-pocket responsibility [75]. Financial burden is a major contributor to stress, anxiety, and emotional strain. Some cancer types may be more vulnerable than others. A study conducted by Knight et al. demonstrated that out of 106 patients surveyed, 58 (54%) met the definition of financial toxicity, which is described as the objective financial burden and subjective financial distress of cancer care. The authors concluded that compared to patients with other forms of cancer, patients with acute leukemia represent a subset of people who are more susceptible to financial distress [76, 77]. Patients who are affected by financial toxicity are less likely to adhere to treatment schedules, appointments, and mental healthcare [77]. Therefore, healthcare providers should be aware of the costs of drugs, tests, and treatments that they offer. It is crucial that conversations occur at the time of diagnosis regarding cancer cost and treatment value and availability of and access to resources. Such discussions will ensure high-value care, decrease the burden of financial toxicity, and ultimately improve morbidity and mortality. Utilization of a standardized model of identification and intervention is necessary on a multidisciplinary level (physicians, pharmacists, social workers, nurses, and financial counselors) to identify at-risk patients.

Social Support Considerations: Multidisciplinary Team-Based Care and the Role of Caregivers

A diagnosis of cancer can cause significant distress that adds to the burden that older patients may already face. Older age comes with a host of losses, which include the loss of loved ones, independence, cognition, and physical function. Strong social supports are needed to provide emotional strength and help navigate the complexities of diagnosis and treatment [78]. A patient's social support system is usually made up of family members and other relatives and friends who can help patients attend appointments, procedures, diagnostic studies, and treatments. While most cancer treatment is comprehensive and interdisciplinary, the psychosocial needs of patients are sometimes neglected. Studies have demonstrated that increased and unmet social support needs were associated with decreased mental and physical quality of life. The need for social support can vary among patient populations, with some requiring more social support than others, such as divorced or single individuals and patients with multiple comorbidities [79, 80]. Conversely, social interactions between patients and their friends or close relatives have been shown to be associated with improved quality of life and survival [81]. Healthcare providers need to be aware of the social aspects of cancer care and ensure that isolated patients are connected with a social network. Many older adults and their caregivers report a lack of access to information, services, and supports [82]. A person-centered approach that promotes and implements GA and the involvement of an interdisciplinary team at the initial visit can help meet the complex needs of older patients.

Cancer Survivorship of an Aging Population

The National Coalition for Cancer Survivorship defines a cancer survivor as any person who has been diagnosed with cancer, from the time of diagnosis to the end of life. The number of cancer survivors across the United States continues to grow, which can be explained by increased survival rates due to advances in cancer diagnosis and treatment, as well as an increased number of cancer cases diagnosed in an aging population. As of January 2019, approximately 16.9 million

Americans were alive with a history of cancer, with a projected increase to more than 22 million by January 2030. Nearly 64% of cancer survivors are age 65 or older, although the age distribution depends on the cancer type [83].

Cancer survivorship in older adults is complicated by the presence of multiple comorbidities, an increased propensity to experience therapy-related side effects, and the need for extra social support. In addition, there are significant differences in cancer therapy and survivorship among different racial/ethnic groups, which highlights the health disparities seen in survivorship care. Studies show that Black cancer survivors have worse posttreatment functional status and inadequate disease surveillance compared to White cancer survivors [84–86]. Side effects and toxicities related to cancer treatment can be acute or chronic, and they can affect the quality of life and functional status of patients with cancer. Survivors of cancers diagnosed at a young age may have long-term concerns, such as infertility, sexual dysfunction, cardiovascular and neurologic sequelae, and secondary cancers. These are best addressed using an interdisciplinary approach, which includes the institution of palliative, rehabilitation, and psychosocial support services.

The best practices for survivorship care are continuously evolving. A survivorship care plan should be tailored using a patient-centered approach with interdisciplinary team involvement to meet the medical, psychological, and social needs that are unique to each older cancer survivor. The Alliance for Quality Psychosocial Cancer Care has provided a comprehensive resource guide that can be used by healthcare providers to provide quality care to cancer survivors. With the ever-increasing numbers of older patients with cancer, it is imperative that we have age-specific interventions for these patients [87].

Conclusion

As this chapter illustrates, the care of older adults with cancer is complex and requires an interdisciplinary approach. Older adults' comorbidities, functional status, and geriatric syndromes have significant effects and implications for treatment tolerance, anticipated adverse effects, patient-reported outcomes, and survival. GA-based interventions in three randomized, prospective studies have been shown to increase quality of life, decrease unplanned hospitalizations, and decrease chemotherapy-related adverse events. Various parts of the GA can be done incrementally with each oncology visit, and older adults with cancer can be comanaged by an interdisciplinary team that consists of geriatricians and supportive care team members. In addition, it is important to increase the enrollment of older adults in cancer clinical trials to better inform the management of this vulnerable population. As the expected proportion of older cancer patients continues to rise, it is important that healthcare professionals be familiar with the holistic evaluation of older adults using GA-based tools and interventions in order to improve the quality of life and outcomes of these individuals.

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Mindfulness-Based Interventions for Patients with Cancer

20

Laura S. Porter and Tina M. Gremore

Cancer patients' lives are often marked by complex emotional and physical experiences that may include anxiety, depression, post-traumatic stress, fatigue, pain, changes in quality of life, and post-traumatic growth. To assist in diminishing this distress and to facilitate positive adaptation in patients with cancer, there has been increasing interest in mindfulness-based interventions (MBIs). In this chapter, we describe the philosophical underpinnings and key elements of mindfulness, review research on MBIs for cancer-related populations and outcomes, and discuss opportunities and future directions for research on mindfulness as it relates to cancer.

Definition and Principles of Mindfulness

According to Jon Kabat-Zinn, founder of the widely disseminated Mindfulness-Based Stress Reduction (MBSR) program, the definition of mindfulness is paying attention on purpose to the current moment, with acceptance [1]. Mindfulness involves the focused practice of increasing awareness of all aspects of one's experience, including thoughts, feelings, physical sensations, and external stimuli, such as sounds or sights, in a receptive, non-judgmental manner. Perhaps one of the most important aspects of mindfulness is the cultivation of meta-awareness or being aware of the current focus of attention. Meta-awareness, or awareness of awareness, allows the mindfulness practitioner to not only increase information received from all aspects of one's experience but also cultivate the knowledge that a choice exists with regard to where attention is focused.

Another key element of mindfulness is acceptance of one's experience. Cancer patients and survivors often experience a range of aversive physical symptoms (e.g., pain, fatigue), thoughts (e.g., worries about cancer progression or recurrence), and emotions (e.g., fear, sadness, anxiety) that they tend to either ruminate on or try to push away and avoid. Mindfulness practice can help individuals to accept their situations and body responses, thoughts, and emotions the way they are without additional suffering. This can lead to decreases in maladaptive coping strategies, such as rumination and catastrophizing, and increases in more adaptive coping strategies which in turn are associated with decreased negative emotions and enhanced QOL [2].

An additional key element of mindfulness is the cultivation of equanimity or nonreactivity. Through practicing mindfulness meditation, individuals learn to simply observe their experiences, without having to change them or react to them. They also learn to recognize their tendencies

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toward habitual ways of responding that may be ineffective. This can lead to deliberate choices to engage in alternative, more adaptive coping strategies.

Content and Format of Mindfulness Interventions

The traditional format of mindfulness interventions in medical settings follows that of the Mindfulness-Based Stress Reduction (MBSR) program developed by Jon Kabat-Zinn. MBSR is the most standardized mindfulness intervention and is the focus of much of the research in cancer populations. In this model, participants attend eight weekly group 2.5 hour classes and a full-day (7–8 hour) retreat. Classes include didactic instruction in the principles of mindfulness, experiential practice with mindfulness meditation and mindful hatha yoga, and group discussion. Participants are instructed to practice meditation and yoga exercises 45–60 minutes per day outside of class. In addition, participants are often required to attend an orientation session which provides information on the nature of MBSR and a brief experience of mindfulness practice, assesses the individual's fit for the program, and elicits a commitment from participants to engage in active participation in the program including class attendance and home practice. Delivery of MBSR is by certified MBSR teachers who undergo intensive preparation and training including attending several 5–10 day mindfulness meditation retreats and completing a teacher training program which includes several multi-day residential training courses. MBSR teachers are expected to have an ongoing daily mindfulness meditation and yoga practice. Thus, MBSR is a time-intensive commitment for participants and teachers alike.

While the MBSR program is the most ubiquitously researched mindfulness approach, other mindfulness-based programs are also prevalent in research with cancer populations. Additional mindfulness-based therapies include mindfulness-based cognitive therapy (MBCT), mindfulness-based cancer recovery (MBCR), mindfulness-based art therapy (MBAT), and acceptance and commitment therapy (ACT). Using MSBR as its foundation, MBCT focuses primarily on mindfulness practices, such as mindful breathing, body scan, hatha yoga, and other meditations. MBCT also includes a more explicit focus on cognition and the relationship between thinking and mood and was originally intended to treat depression and prevent relapse [3]. MBCR is one of the most widely evaluated cancer-specific adaptations of MSBR. Also based on the MBSR program, MBCR involves eight 90-minute group classes, plus a 6-hour workshop between weeks 6 and 7. As with MBSR, the focus is on mindfulness meditation, yoga practice, and sustaining mindful awareness in day-to-day life. MBCR also includes cancer-specific reading assignments and reflective exercises that are tailored to the unique challenges of cancer [4]. MBAT consists of eight 2.5 hour weekly sessions that follows a similar structure to the MSBR curriculum except that MBAT integrates art therapy exercises as a way to teach and enhance mindfulness and does not include an additional full-day retreat [5, 6]. ACT promotes increasing present moment awareness, psychological flexibility, accepting the cancer diagnosis, as well as thoughts, feelings, and symptoms, clarifying individuals' values, and committing values-based actions in the context of coping with cancer-related symptoms [7, 8].

The literature on MBIs for patients with cancer has been well-synthesized between 2005–2015 in meta-analyses, literature reviews, and book chapters [9]. The goal of this chapter is to summarize contributions to the literature within the past 5 years (2015–2020). We have organized the review of the literature into the following sections: (1) reviews and meta-analyses of MBIs for cancer; (2) studies focused on patients with advanced cancer; and (3) studies using eHealth interventions. Our goal in reviewing the most recent literature is to identify the outcome variables for which MBIs have good empirical evidence, while also highlighting important limitations in generalizability and opportunities for future research directions.

Reviews and Meta-Analyses of MBIs for Cancer

Studies Including Multiple Cancer Types

Two recent reviews and meta-analyses examined the effects of MBIs on psychological and physical outcomes in cancer patients and survivors [10, 11]. Each review identified 29 randomized clinical trials (RCTs), and the studies included in the reviews were largely overlapping. In addition to examining overall intervention effects, the meta-analyses examined the possible moderating role of a number of patient, cancer, and intervention characteristics. Also explored were associations between potential MBI mechanisms (mindfulness skills, self-compassion, and rumination) and the effects of MBIs on psychological distress.

Overview of Studies. The majority of the reviewed studies were conducted with female breast cancer patients: 15 of 29 studies reviewed by Xunlin and colleagues [10] and 13 of 29 studies reviewed by Cillessen and colleagues [11] were conducted exclusively with breast cancer patients. In studies involving patients with mixed cancers, breast cancer was often the most common diagnosis. Overall, 86% of participants were female [11]. Few studies focused exclusively on other cancers: two studies focused on prostate cancer, two on colorectal cancer, and one on lung cancer. Few studies included patients with metastatic disease. The most common MBI tested was MBSR. Other MBIs included mindfulness-based cognitive therapy (MBCT), mindfulness-based art therapy (MBAT), mindfulness-based cancer recovery (MBCR), and acceptance and commitment therapy (ACT). Two-thirds of the studies compared MBIs to usual care or wait-list control.

Main Effects of MBI. Findings of the meta-analyses indicated that MBIs had statistically significant effects on a variety of outcomes. Participants who received MBIs reported significantly lower anxiety, depression, stress, fatigue, fear of recurrence and pain, and greater post-traumatic growth and mindfulness than those in the control conditions. The effect sizes were generally small to moderate. Xunlin and colleagues [10] reported moderate effects for anxiety, depression, fatigue, and stress, while Cillessen and colleagues [11] reported small effect sizes for anxiety, depression, and fatigue, as well as for fears of cancer recurrence, sleep disturbances, and pain. Xunlin and colleagues [10] found large effect sizes for post-traumatic growth and mindfulness. All outcomes were examined immediately post intervention.

Subgroup Analyses. Both meta-analyses examined patient gender and type of cancer as potential moderators. Results from Xunlin and colleagues [10] indicated a significant impact of gender on anxiety and depression, whereby MBIs had significant effects in studies with female and mixed gender patients, but no effects for studies with only male patients. In subgroup analyses of type of cancer, MBIs significantly reduced anxiety among participants with breast cancer and mixed cancers but not among participants with prostate cancer. However, given that only two studies were conducted with all-male patients, these findings should be interpreted with caution. In contrast, Cillessen and colleagues [11] found no significant impact of gender or cancer type (breast cancer versus other), cancer stage (non-metastatic versus mixed), or time since cancer diagnosis. However, this study did find a significant effect for patient age, with larger effects found for studies with younger samples.

Both meta-analyses also examined differences in effects based on characteristics of the intervention. Xunlin and colleagues [10] examined differences between intervention types and found that MBAT showed the largest effect in reducing anxiety, followed by MBSR and MBCR, with no significant effect for MCBT. For depression, MBAT also had the largest effect size following by MBCT and MBSR/MBCR. However, these findings should be interpreted with caution given the small number of studies included in the subgroups (e.g., only two studies used MBAT interventions). Cillessen and colleagues [11] examined differences in effects based on the degree to which the intervention was modified from the original MBI (major versus minor) and found that larger effects were found in studies that adhered more closely to the original protocols. Other study characteristics examined in subgroup analyses included the type of control group (passive vs active), use of intent-to-treat analyses, time to post-intervention, intervention dose, home practice, attrition rate at post-intervention, publication year, and MBI quality [11]. Of these, only control condition and time to post-intervention were significant, with studies using passive control conditions and those with a shorter time to follow-up having stronger effects.

Finally, Cillessen and colleagues [11] explored associations between potential MBI mechanisms and the effects of MBIs on psychological distress. While they had planned to examine mindfulness skills, self-compassion, and rumination as mediators, there were not enough studies that included measures of self-compassion and rumination to conduct these analyses. Results from analyses focused on mindfulness skills confirmed that improvements in mindfulness skills were associated with greater reductions in psychological distress at post intervention.

Effects of Mindfulness on Biologic Outcomes. A number of studies have examined the impact of MBIs on potentially important biologic markers of stress and health, including measures of immune function, hypothalamic-pituitary-adrenal axis functioning, prostate-specific antigen levels, and autonomic nervous system activity. Matchim and colleagues [12] reviewed four studies of MBIs in cancer patients and found small significant effects for most measured biologic outcomes, with the exception of cytokine production which showed large effect sizes at 6- and 12-month follow-up in an uncontrolled study of breast and prostate cancer patients. A subsequent review of eight studies found small significant effects of MBIs on biomarkers including cortisol, interleukin 6, and natural killer cell activity [13]. Two recent RCTs in patients with breast cancer found evidence that MBIs may positively impact telomere length and telomerase activity, biomarkers that have been associated with cancer mortality [14, 15].

Taken together, these findings suggest that participation in MBIs may lead to changes in a variety of biologic markers of stress and health, and these may represent mechanisms through which psychological processes could impact physical health. However, much remains unknown about the potential relevance of these biomarker changes for health outcomes. Rouleau and colleagues [9] point to several important gaps in knowledge. They note that little is known about differences in biomarker response to MBIs as a function of patient sex, cancer type and stage, and baseline biologic values, and that these and other factors, such as phase of treatment, may determine whether a particular biologic change is desirable. They also highlight that the direction of causality between stress reduction and biological activity is unclear, as biological changes may be a cause and/or effect of behavioral comorbidities, such as psychological distress, fatigue, and sleep disturbance. Thus, wile results pertaining to the impact of MBIs on biomarkers are promising, much work remains before we are able to understand the potential relevance of these findings or optimize MBIs to produce clinically meaningful biologic effects.

Effects of Mindfulness on Fatigue. Given the prevalence of fatigue among cancer patients and survivors, several meta-analyses have focused specifically on the effects of MBSR on cancer-related fatigue. Xie and colleagues [16] reviewed 14 RTCs, and He and colleagues [17] reviewed 5 RCTs that compared MBSR (or a shorter modified version of MBSR) with usual care/no intervention, resulting in 16 unique studies. All studies involved at least 6 weeks of MBI, with the exception of one intervention that was conducted 3 hours per day for 8 days. Overall, results indicated that MBIs had a large effect on fatigue. Subgroup analyses indicated that MBIs had a significant moderate effect for patients with breast cancer and a large effect for patients with lung cancer [16]. When 8 weeks of expertly supervised MBSR was delivered, large effect sizes on cancer-related fatigue were observed [16].

Effects of Mindfulness on Positive Psychological Outcomes. Post-traumatic growth (PTG) refers to the positive psychological change that occurs as a result of the struggle to cope with very challenging life events [18]. Most psychosocial interventions have focused on ameliorating the negative impact of cancer, while research on the coping strategies that may enhance PTG in patients with cancer is limited. Li and colleagues [19] conducted a meta-analysis of RCTs of psychosocial interventions that targeted PTG in patients with cancer to summarize and evaluate the efficacy of these psychosocial interventions and to provide clinical practitioners with evidence-based strategies to promote PTG among cancer patients. Of the 15 RCTs included in this meta-analysis, six contained a mindfulness-based program as the primary intervention. Analyses of these six studies demonstrated a significant effect of MBIs on PTG. Compared to cognitive-behavioral, self-management, and social support interventions, MBIs were more effective for improving PTG. Subgroup analysis also indicated that breast cancer patients benefited more from the psychosocial interventions than did patients with other types of cancer.

Other studies have also reported that MBIs are associated with improvements in positive changes, such as spirituality, positive affect, meaningfulness, acceptance, happiness, and relaxation. However, these positive psychological outcomes have not consistently been superior to usual care or active comparison groups [9]. Qualitative data collected from participants who completed MBIs provide additional insight into the potential benefits that individuals derive from mindfulness training. When queried, participants report benefits in domains, such as spirituality, personal growth, optimism, peacefulness, confidence, acceptance, openness, connectedness, and happiness. Participants from one study reported that mindfulness practice initiated a positive process of change, characterized by an increased ability to be still, relax, and take time for themselves, as well as greater awareness and insight into their thoughts and feelings which led to both acceptance and behavior change [20]. Taken together, these findings suggest that mindfulness might have a unique impact on promoting positive adaption rather than simply decreasing distress.

Studies Focused on Breast Cancer

Congruent with general trends in psychosocial cancer research, and as reflected in the reviews described above, a large proportion of studies examining the effectiveness of MBIs have been conducted with breast cancer patients and survivors. Two recent reviews and meta-analyses examined MBIs on psychosocial outcomes specifically for women with breast cancer. Q. Zhang and colleagues [21] reviewed 14 studies and J. Zhang and colleagues [22] reviewed 7 studies; 2 studies were overlapping resulting in 19 unique studies. These authors reported pooled emotional and physical outcomes and health-related quality of life immediately post receipt of MBI, thus all findings are short-term effects. Subgroup analyses and analyses of moderating factors were not calculated in either meta-analysis secondary to the small number of eligible studies.

Overview of Studies. The majority of the reviewed studies were conducted with early-stage female breast cancer patients; only one study included patients with metastatic cancer. Of the 19 unique studies included, 13 were RCTs and all studies compared MBI with usual care or no MBI control condition. Of the types of MBI, 9 studies followed the standardized MBSR protocol with a 2-hour meeting per week for 8 weeks, in addition to a day of mindfulness, whereas 10 studies modified the standard MSBR protocol, with a shortened 6 week intervention as the most common modification.

Main Effects of MBIs. Findings from both meta-analyses showed that MBIs had statistically significant effects on emotional and physical outcomes. Both meta-analyses showed that participants who received MBSR or a slightly modified version reported significantly lower anxiety, depression, and fatigue, as well as greater emotional and physical wellbeing. The effect sizes were generally moderate to large. Q. Zhang and colleagues [21] also found significant moderate to large effects on cognitive functioning, stress, distress, and mindfulness, while J. Zhang and colleagues [22] found a significant moderate effect for fear of recurrence and a small effect on physical health. In both meta-analyses, MBI effects on pain and sleep trended in the expected direction, although they were not statistically significant. Significant effects were not found for MBI on participants' quality of life.

These findings suggest that the original and slightly modified versions of MBSR are most consistently beneficial across studies in reducing anxiety, depression, and fatigue and improving emotional and physical wellbeing among breast cancer patients immediately following receipt of the intervention. MBIs were also shown to improve breast cancer patients' cognitive functioning, mindfulness, physical health and decrease stress, distress, and fear of recurrence. More research is needed to clarify the impact of MBIs on pain, sleep, and quality of life among women with breast cancer, as both meta-analyses failed to show statistically significant outcomes in these areas. Many studies were excluded from both meta-analyses due to problems in methodology and inadequate data reported; thus, more high-quality studies are needed and will allow for subgroup and moderating effects analyses. Furthermore, all of the findings were found to be short-term effects. More studies measuring long-term effects are needed.

Studies Focused on Male Cancer Patients

While the aforementioned meta-analyses were heavily weighted by the inclusion of MBIs for women with cancer, Ford and colleagues [23] examined mindfulness-based interventions, Thai Chi, Chi/Qigong, and yoga which they defined as meditative cancer interventions or MCIs, and psychosocial outcomes (quality-of-life, depression, and posttraumatic growth) for men with cancer. Their meta-analysis included 17 RCTs and 666 patients, the majority of whom were college-educated, White, and non-Hispanic. Most studies were in person and conducted in group format. There was considerable variability in the length and number of sessions (3–24 sessions and 20–150 minutes per session). Overall, small significant effects were found for MCIs across all psychosocial outcomes assessed immediately post intervention. However, significant effects were limited to studies that used a standard care control arm; studies using an active control group did not find a superior effect of MCIs. These effect sizes for men are smaller than the outcomes reported in much of the mindfulness-based literature for the general population and for cancer, which is comprised of predominantly female participants. The fact that statistically significant outcomes were limited to studies with standard care control arms also raises concerns about the possibility of non-specific therapeutic effects. In addition, high drop-out rates were observed in the majority of studies reviewed which may reflect lack of acceptability of the intervention content and/or delivery format. Men may prefer to participate in an individual rather than group format for MBIs, especially in the context of discussing personal or sensitive issues [24]. Clearly, additional research is needed to better understand the acceptability and efficacy of MBIs among male participants.

Studies Focused on Patients with Advanced Cancer

MBIs may be of particular benefit to patients with advanced cancer who often struggle with high levels of psychological distress and symptom burden. However, there have been few studies evaluating MBIs designed specifically for patients with advanced disease. A 2017 review focused on MBIs in the context of palliative care [29] identified three RCTs conducted with patients with advanced cancer. One intervention [30] found significant reductions in perceived stress immediately following a single 5-minute mindfulness practice delivered by a physician in the hospital. A second study [31] found that a single nurse-led 90-minute session, combined with instructions for daily guided practice, led to lower levels of pain and better mental health. Finally, a six-session home-based MBI with instructions for daily practice led to beneficial effects on symptom severity and interference, mental health, vitality, and pain, and large effects on physical and social function [32].

A second systematic review focused on MBIs for adults with Stage III and IV cancer [33]. Eight studies were identified, five of which were RCTs, while three used an open trial design. Interventions included MBSR, only the body scan meditation from MBSR, MBCT, and MBAT. In many cases, the traditional intervention protocols were adapted to reduce the number of sessions and/or shorten the duration of the sessions. Overall, findings suggested that MBIs are acceptable and beneficial to patients with advanced cancer, leading to improvements in quality-of-life, use of mindfulness skills, and acceptance, and reductions in depression and anxiety. However, there was considerably variability in findings. Some of the strongest effects were seen in an RCT testing a 12-session ACT intervention among 47 women with ovarian cancer. In this study, conducted by Rost and colleagues, there were large effects of ACT on psychological distress, quality of life, and cancer acceptance compared to an attention control condition [34]. In contrast, a large, methodologically rigorous study conducted by Chambers and colleagues [35] examined an 8-week MBCT intervention among 189 men with advanced prostate cancer and had null findings. Compared to an enhanced treatment-as-usual condition, there were no significant effects of MBCT on psychological distress, cancer-specific distress, prostate-specific antigen anxiety, quality of life, benefit finding, or mindfulness [35]. The authors note that compared to younger, female samples, mindfulness skills may be more stable and difficult to shift among older men. It is also possible that men may have different preferences for support and coping. It is notable that both studies had high rates of dropout; in the Rost and colleagues [34] study, 32% of participants dropped out prior to the first follow-up assessment due to death or declining health, while in the Chambers and colleagues [35] study, only 52% of the men assigned to MBCT participated in four or more sessions.

Also notable is the fact that most of the eight studies included in this review excluded patients who were in the terminal phase of illness. A published case study illustrated the potential benefits of mindfulness for patients nearing end-of-life who are struggling with death anxiety, defined as feelings of dread or apprehension when thinking about dying, as well as what happens after death. Tacon [36] described an MBI conducted with a hospitalized patient with aggressive metastatic breast cancer and overwhelming death anxiety. The psychologist met with the patient weekly for 7 weeks and provided training in mindfulness meditation strategies appropriate for the patient's physical condition, including body scan and sitting meditation, as well as instruction for daily practice guided by CDs. Over the course of the intervention, the patient and observing nurses reported that the patient was increasingly calm, peaceful, and grounded. Scores on objective measures of death anxiety and losses and grief trended downward throughout the intervention.

Overall, there have been few high-quality studies evaluating the potential benefits of MBIs for patients with advanced cancer. Some, but not all, of the studies conducted have reported benefits similar to those seen in patients with earlier stages of disease, including reductions in psychological distress and improvements in quality of life. Consistent with literature cited earlier, studies with female participants found stronger intervention effects. Many of the interventions tested varied significantly from the original protocols, with several studies involving only one or two sessions. Studies reported difficulties with recruitment, with many eligible patients declining participation due to time, the level of commitment involved, and competing demands. Attrition also tended to be high, primarily due to poor health. Thus, for patients with advanced disease, researchers need to balance issues of feasibility and dose. It is not clear that a one or two session intervention is adequate to produce lasting benefits; however, previous research shows that many eligible patients may not agree to or complete a typical eight-session group-based intervention.

Individual rather than group sessions may be more beneficial in this context as they allow greater flexibility in scheduling, as well as the ability to address patients' personal needs [33]. More research is needed to determine the adequate dose of intervention, which could include a combination of facilitated sessions and home practice. In addition, it is important to expand measurement of outcomes to include those that may be relevant for patients with advanced cancer, such as symptom severity and interference, acceptance of cancer, meaning, and peace.

Summary

Taken together, the literature suggests that there is good evidence that MBIs lead to significant benefits for cancer patients and survivors, including decreases in psychological distress, fatigue, and sleep disturbance, and increases in positive psychological adaptation. There are also studies suggesting that MBIs may have positive biologic effects. While overall the size of the literature is robust, there are a number of limitations.

First, the majority of studies have been conducted with female breast cancer patients with early-stage disease, and the majority of participants are white, well-educated, and middle-aged. The acceptability and effects of MBIs on male patients, minority and underserved populations, older patients, and those with advanced disease are less clear. Results of some meta-analyses suggested that MBIs may be more effective for female versus male and younger versus older patients.

Second, findings are generally limited to those assessed immediately post-intervention, thus the extent to which effects maintain over time is unknown. A meta-analysis focused on the effects of MBIs on anxiety in patients with cancer examined effects up to 1 year post-intervention [25]. They reported that MBIs significantly reduced anxiety in the short-term (<1 month post-intervention) and medium-term (1–6 months post-intervention) but not long-term (6–12 months post-intervention). Similarly, results of secondary analyses indicated short-term and medium-term but not long-term improvements in depression and health-related quality of life. However, only nine of 28 trials reported on medium-term effects, and only two reported on long-term effects. Thus, additional research is needed to determine the long-term efficacy of MBIs, as well as strategies, such as booster sessions, that may enhance the maintenance of effects.

Third, while a number of different types of MBIs have been tested, the majority of studies have used MBSR. Findings with regard to intervention type are inconsistent. Results of some meta-analyses suggest that MBSR may not be the most effective type of MBI. However, other meta-analyses suggest that MBSR, when delivered as per original protocol, produced the strongest intervention effects. Given the intensive nature of MBSR (as well as some other MBIs, such as MBCT, MBCR, and MBAT), there is likely a significant self-selection bias of participants who enroll in these studies. Many patients may be unwilling to make the time commitment or unable to participate due to their health issues, work and family demands, or distance (for interventions delivered in person). High-intensity interventions may also be associated with high levels of attrition.

Fourth, there has been little attention to the role of practice of mindfulness skills. While some studies include a description of instructions given for home practice, few measure or report on the amount of practice that participants engage in, and whether this is associated with treatment effects. In studies of mindful yoga interventions with women with metastatic breast cancer, we have found that greater daily practice of yoga and meditation exercises is associated with lower levels of pain and fatigue and higher levels of invigoration, acceptance, and relaxation on the same and the following day [26, 27]. In addition, in research of MBIs in non-cancer populations, more frequent daily mindfulness practice has been associated with more positive outcomes [28]. Clearly, home practice of mindfulness skills has important implications for the design and delivery of MBIs and should be a focus of further investigation.

Finally, few studies have empirically examined the theorized mechanisms of MBIs. While there is some evidence that increases in mindfulness skills leads to greater reductions in psychological distress among MBI participants, more research is needed to examine other hypothesized mediators (e.g., acceptance, self-compassion, rumination). More research is also needed to understand the temporal dynamics of changes in biomarkers and psychological and behavioral factors.

eHealth Delivered Mindfulness Interventions

Electronic health, or eHealth studies, have proliferated over the past few years due to increasing access to the internet, computers, tablets, and smartphones. Delivering mindfulness interventions via eHealth has increased reach and dissemination. In a review of technology-delivered MBIs (mainly web-based approaches) conducted from 1990 to 2015 for chronic medical conditions, MBIs were shown to have positive effects on patients' general health and psychological wellbeing [37]. As app technology becomes increasingly accessible, mindfulness interventions via mobile health (mHealth) apps are being delivered to patients with cancer.

Initial findings from feasibility and effectiveness studies utilizing existing commercially available mHealth mindfulness apps are promising. Two recent studies have evaluated the efficacy of the commercially available mindfulness apps Headspace, Calm, and 10% Happier among patients with cancer. The first study [38] found that women with breast cancer randomized to the Headspace app condition reported higher quality of life and more dispositional mindfulness relative to participants in a wait list condition. Sixty percent of woman in the Headspace condition downloaded the app and used it an average of 18 days over the course of the 12-week trial with an average duration of 13.4 minutes per day. Another study examined patients with myeloproliferative neoplasm (MPN) who used the apps 10% Happier and Calm [39, 40]. Small effects on anxiety, depression, sleep disturbance, physical health, symptom burden, and fatigue were seen with both apps, however, results of quantitative data reflected greater satisfaction with the Calm app, as well as increased use of Calm (71 minutes per week) versus 10% Happier (31 minutes per week). Based on these findings, the researchers are using Calm in an RCT testing the effects of meditation on symptom burden in patients with MPN.

Research is also underway to create and examine novel cancer-specific app-based interventions that are tailored to the needs of cancer patients and their family members [41–44]. While eHealth interventions have many benefits with regard to increasing the accessibility of therapeutic interventions, some patients may prefer face-to-face delivery over internet delivery of an intervention [45]. More research is needed to determine for whom eHealth and mHealth delivered MBIs are most beneficial.

Discussion

Overall, there is strong evidence that mindfulness-based interventions have beneficial effects for patients with cancer, leading to a range of positive outcomes including reductions in psychological distress and symptoms, such as pain and fatigue, and improvements in physical and cognitive function and sleep. There are also very few, if any, adverse effects of mindfulness among patients with cancer or other populations. Thus, it is reasonable for healthcare providers working with individuals with cancer to recommend mindfulness-based interventions to help them adapt to the challenges associated with cancer treatment and survivorship.

There are a number of limitations to the existing research that should be noted. First, the predominance of studies has been conducted with samples of patients who are primarily female, white, and have early-stage cancers or are in the survivorship phase. There have been fewer studies that include large samples of men or have focused on patients with advanced disease. Research suggests that gender and age may moderate treatment effects [10, 11]. More research is needed to understand the efficacy of mindfulness interventions among patients who are older, male, minority, and/or underserved, as well as the acceptability of mindfulness interventions among these individuals. In addition, few studies have specifically targeted patients with high distress and/or symptom burden who are most likely to benefit. It is possible that intervention content and/or delivery may need to be modified to best meet the needs of various subgroups. For example, in an intervention targeting pain, it might be important to include educational material about the biopsychosocial model of pain and the potential benefits of mindfulness for managing pain.

There are a number of other important questions that remain to be addressed. First, what is optimal and/or sufficient dose, in terms of both intervention and home practice? There is wide variability in terms of intervention dose (one to 12 sessions) as well as recommended home practice (none to 45+ minutes per day). Research findings suggest that studies that adhere to the standard MBSR or MBCT protocols (approximately 8, 2-hour sessions) appear to have larger effect sizes compared to modified interventions which often involved a lower dose [11]. However, there is also some evidence that brief interventions can have positive effects [31]. The benefits of more intensive interventions need to be weighed against the feasibility and acceptability of this approach. Requiring attendance at multiple lengthy intervention sessions may reduce the reach, limiting participation to the select subgroup of patients who are willing and able to comply, and may be one reason that many studies of MBSR have had primarily white, well-educated samples.

With regard to home practice of mindfulness exercises, there has been little attention to measuring or evaluating home practice in studies of MBIs for cancer. However, a recent review and meta-analysis of home practice among 43 studies testing MBSR and MBCT in non-cancer populations found that, on average, participants' home practice was 64% of the assigned amount, equating to about 30 minutes per day, 6 days per week [28]. There was a small but significant association between participants' self-reported home practice and intervention outcomes. These findings support the concept of mindfulness practice as a form of mental training [46], such that greater practice leads to greater benefits. However, it remains unclear whether the amount of practice recommended in MBSR (45 minutes per day) is necessary. Recent studies in non-cancer populations suggest that as little as 10 minutes per day can produce significant benefits [47].

Another important question pertains to the best mode of intervention delivery. Traditionally, MBSR has been delivered in person in groups. There is evidence that some patients value the social context of the group setting. The experience of others in the group can help in forming a meta-understanding of mindfulness practice [48]. For patients with advanced cancer, groups may help normalize end-of-life issues. However, conducting group-based sessions can be challenging logistically, requiring participants to commit to attending classes at a specific time and place. This may be a particular obstacle for patients with advanced disease due to high symptom burden, reduced physical function, and competing priorities [49]. Group interventions may also be less acceptable among men, particularly those who adhere to traditional masculine gender roles and may be reluctant to display their sensitivity and emotionality in a group setting [24]. Younger patients who have work and family responsibilities may also have difficulty attending group sessions. Evidence suggests that MBIs are also effective when delivered to individuals. For example, Rost and colleagues [34] found large to very large effect sizes for a mindfulness-based intervention conducted individually with patients with advanced cancer. To our knowledge, there have been no head-to-head comparisons of individual versus group-based delivery, thus there is no empirical evidence regarding their relative efficacy. Recently, there is growing interest in delivery of both individual and group-based psychosocial interventions via videoconference.

This may remove barriers to attendance of in-person sessions and increase the reach and accessibility of these interventions.

As discussed earlier, there is also increased interest in delivering mindfulness interventions via app. Research into this modality is in its early phases. While preliminary findings suggest that app-based interventions are feasible, acceptable, and show promise in improving outcomes, the efficacy of this approach is not clear. There are also questions regarding content (e.g., do apps contain key mindfulness elements) and adherence (how many people will use the app regularly without prompting). Interventions delivered entirely via technology must also address issues of safety. For some people, the practice of mindfulness can temporarily increase psychological distress; this can be readily addressed and mitigated with the guidance of an interventionist, but may go undetected in an app-based intervention and could possibly worsen.

Finally, there are important questions regarding the mechanisms of mindfulness interventions. There is some evidence that increases in mindfulness are associated with more positive outcomes [11], however little is known about the importance of other hypothesized mediators, such as acceptance or coping. Also, because the majority of studies have utilized usual care (no intervention) control groups, it is possible that non-specific therapeutic effects, such as relaxation and social support, contribute to post-intervention improvements. Future studies should use methodologies that enable rigorous examination of intervention mechanisms and control for non-specific therapeutic effects. In addition to psychological and behavioral mediators, changes in biologic processes, such as stress hormones and immune function, could represent mechanisms through which MBIs could impact physical health. Interestingly, findings from laboratory studies in non-cancer populations suggest that mindfulness can alter physiological reactions to stress. For example, one RCT showed that 5 days of meditation training, including mindfulness, significantly reduced cortisol response to acute mental stress [50]. A second study found that increased meditation practice was associated with significantly lower stress-induced levels of inflammation (interleukin-6) [51]. As noted earlier, while there are some promising findings with regard to impact of MBIs on biomarkers in patients with cancer, additional research is needed to determine the impact on health outcomes.

In conclusion, mindfulness shows promise as an effective nonpharmacological approach for helping patients with cancer manage symptoms and psychological distress and enhance positive adaptation. More methodologically rigorous research is needed to fully address important questions regarding the generalizability of MBIs' effects, optimum dose, mode of delivery, and mechanisms of action. However, the considerable evidence to date indicate that MBIs should be offered to patients with cancer who are seeking effective methods for self-management of cancer-related symptoms and stressors.

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Social Genomics and Cancer: Neural Regulation of the Cancer Genome

Jennifer M. Knight and Steven W. Cole

Introduction

Clinicians have long observed that patient psychosocial conditions appear to affect the progression of at least some cases of cancer (e.g., as noted by Galen in the second century [1]). Epidemiological studies support this observation in documenting accelerated progression of many types of cancer among individuals with high levels of stress or low social support [2, 3] (although there is less evidence that stress biology affects the initiation or incidence of cancer). Over the past decade, a growing body of basic laboratory research has identified physiologic pathways that may mediate these effects by modulating the biology of tumor progression and metastasis. This chapter provides a brief overview of those findings and highlights some potential treatment implications that might help promote health in the context of the inevitably stressful context of cancer.

Two scientific developments have played a key role in advancing our understanding of psychobiological influences on cancer progression: (1) recognition that the "tumor microenvironment" surrounding the cancer cell interacts with tumor cells to shape disease progression [4, 5] and (2) research in "social genomics," which has begun to map the biological pathways through which social and psychological processes can regulate gene expression in both healthy and diseased tissues [6, 7]. Both dynamics involve stress response systems in the body that have long been known to regulate normal physiology. However, their implications for cancer biology have not been widely recognized until recently. Translational studies have begun to document the clinical significance of these pathways, both as an explanation for accelerated disease progression in adverse life circumstances and as a mechanism for potential health impacts of supportive psychosocial interventions. In addition to providing a biological underpinning for somatic health effects of psychological processes, these studies suggest new opportunities for intervention to protect the health of cancer patients as they confront the highly stressful experiences of cancer diagnosis, treatment, and survivorship.

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The Tumor Microenvironment

Cancer is fundamentally a disease of dysregulated gene expression that originates from structural damage to the genome of a single cell, such as chromosomal amplifications, deletions, mutations, and rearrangements. As an "initiated" cancer cell gains a growth advantage, it begins to interact with and alter the function of the surrounding healthy tissue or the tumor microenvironment [4, 5]. Reciprocal physiological responses by the tumor microenvironment also occur and play an essential role in determining whether a tumor will grow, thrive, and metastasize or whether it will collapse and regress. For example, a growing mass of tumor cells would rapidly die if blood vessel cells in the vicinity of the tumor did not respond to signals of cellular hypoxia by enhancing blood supply to the tumor (a process known as angiogenesis). As the growing tumor damages surrounding healthy tissues, immune cells known as macrophages are recruited into the tumor microenvironment and activate a cellular wound healing program known as epithelial-mesenchymal transition (EMT). While activation of the EMT is adaptive for healing acute wounds, in the context of a tumor ("wounds that never heal") it inadvertently frees cancer cells from the normal extracellular matrix and allows them to move freely about the body (i.e., promoting metastasis). If genomic aberrations are sufficiently severe to generate novel proteins that can be recognized as foreign to the body, another class of immune cell, T lymphocytes, are recruited to kill cancer cells by triggering their normal cellular suicide programs (which are also the targets of many types of chemotherapy). In each case, whether and how quickly a cancer progresses from a small localized mass to a widely distributed population of metastases depends on both the cancer cell itself (i.e., the particular profile of genomic damage present and its implications for cell growth and survival) and the nature of response by the tumor microenvironment (e.g., blood vessels, macrophages, and T cells).

Neural Regulation of Gene Expression

Like any cell of the body, tumor cells and the cells in the tumor microenvironment are subject to regulation by stress physiology. People experiencing threatening or stressful life circumstances show physiological reactions, such as activation of the sympathetic nervous system (SNS), which mediates fight-or-flight stress responses, and the hypothalamus–pituitary–adrenal (HPA) axis, which mediates the more profound defeat/withdrawal responses to severe overwhelming threats [3, 8]. At the molecular level, these biological stress responses are mediated by "neuroeffector" molecules, such as norepinephrine, the neurotransmitter released by SNS nerve fibers, or cortisol, the hormone released into the blood by the adrenal gland during HPA axis activation. These neuroeffector molecules can reach the tumor microenvironment through circulating blood (cortisol) or by release from nerve fibers in the local vicinity of the tumor (norepinephrine). Many tumor-supplying blood vessels bear SNS nerve fibers, and some tumors actively recruit additional nerve fibers by secreting nerve growth factors [9–11]. Neuroeffector molecules trigger cellular responses by binding to receptors on the surface of cells (e.g., the beta-adrenergic receptor mediates many cellular responses to norepinephrine) or within cells (e.g., the intracellular glucocorticoid receptor mediates biological responses to cortisol when it penetrates the cell membrane).

Each type of cell is evolutionarily programmed to generate a characteristic set of molecular responses to the receipt of a signal from stress effector molecules, and many of these effects involve changes in the expression of genes. The transcriptome refers to the particular subset of our ~20,000 DNA genes that is actively transcribed into RNA in a given cell at a given point in time. Transcriptomes vary spatially and temporally depending on the identity of the cell, its developmental history (e.g., history of environmental exposure) and the nature of the physiologic signaling molecules present in the cell's microenvironment (including levels of norepinephrine or cortisol). In the context of cancer, the tumor cell transcriptome is also shaped by the particular set of genetic lesions that serve to initiate the cancer.

Social Signal Transduction

Regulation of neuroeffector molecules released by the nervous system provides a biological pathway by which psychological and social processes can affect patterns of gene expression throughout the body. For example, a growing body of research in human social genomics has found a characteristic pattern of change in immune cell gene expression profiles in individuals who are exposed to extended periods of threat or uncertainty [6, 7]. This pattern is known as the conserved transcriptional response to adversity (CTRA) and involves up-regulated expression of genes involved in inflammation (e.g., *IL1B*, *IL8*, *PTGS2*/COX2) and a complementary down-regulation of genes involved in antiviral responses (e.g., *IFIT*-, *OAS*-, and *MX*-family genes). This gene expression profile has been observed across a wide variety of adverse life circumstances including poverty, social isolation, PTSD, chronic stress, low social status, and unstable social hierarchies [6, 7]. Studies in cellular and animal models have shown that CTRA gene expression is evoked primarily by SNS signaling through beta-adrenergic receptors on immune cells and involves both changes in gene expression by existing cells and increased production of a subset of immune cells by the bone marrow (the circulating monocytes that subsequently develop into macrophages in tissue) [12, 13]. This specific genomic response profile provides one molecular explanation for the increased risk of cardiovascular, neurodegenerative, and neoplastic disease seen in people exposed to long-term chronic stress, as well as their reduced resistance to viral infections [6, 7]. Because leukocytes are easy to sample from circulating blood, the CTRA has served as a paradigmatic model system for studying the process of "social signal transduction" or the flow of information from external life circumstances through brain-mediated perceptual and interpretive processes into changes in neuroeffector activity and consequent activation of specific gene modules within a particular type of target cell.

Social Genomics in the Tumor Microenvironment

As epidemiologic and natural history studies have linked specific psychosocial risk and resilience factors associated with differential disease progression in cancer, a number of studies have begun to employ a social genomics research strategy to understand how those relationships might come about on a cellular and molecular level in the tumor microenvironment. Initial studies examined gene expression profiles in tumor tissues resected during surgery and found several specific profiles of transcriptome alteration that might contribute to differential disease progression. Studies of ovarian carcinoma tissues found increased expression of genes involved in inflammation, angiogenesis, and EMT in tumors from patients with low social support and high depressive symptoms [14]. Similar findings have emerged in analyses of breast cancers [15], with results additionally suggesting that a transcriptomic polarization of macrophages toward an "M2" phenotype might contribute to the increased angiogenesis and EMT. Analyses of the molecular signaling pathways underlying the observed transcriptome changes implicated increased beta-adrenergic signaling from the SNS in both cases [14, 15]. Similar findings have also emerged from studies of blood exosomes, which are small bundles of cellular contents that are shed from cancer cells (as well as healthy tissues) and can serve as a kind of "liquid biopsy" of tumor tissues. RNA profiling of exosomes from ovarian cancer patients found greater expression of EMT- and M2-related transcripts among those with low social support [16].

These clinical observations are consistent with a rapidly growing body of research from laboratory cellular and animal models showing that chronic stress and SNS/beta-adrenergic signaling can impact a wide array of gene expression programs involved in tumor development and progression, including macrophage recruitment and M2 polarization [17, 18], angiogenesis [19–21], EMT and related cell motility and invasive capacities [22, 23], inhibition of normal cell death programs [24, 25], and inhibition of anti-tumor immune responses by T lymphocytes (including reduced efficacy of "checkpoint inhibitor" immunotherapy drugs) [26, 27]. Studies using pharamacologic antagonist drugs have found that SNS/beta-adrenergic signaling mediates many chronic stress influences on the tumor microenvironment [22]. However, antagonist studies have also documented a role for HPA axis activation in some cases, particularly through the inhibition of cell death programs involved in cancer cell responses to chemotherapy and anti-tumor T cells [28].

In the context of cancer, the temporal scope of psychosocial risk factors and their neurobiological effects play a major role in determining the magnitude of their impact on cancer progression and treatment response. Classical SNS "fight-or-flight" responses can increase blood epinephrine and norepinephrine levels by >10-fold within seconds [29]. However, these responses are typically transient and may not have much impact on the course of the comparatively slower pathophysiological processes involved in cancer, which evolve over the course of many months or years. However, chronic anxiety is also associated with increased SNS activity and the chronic nature of that effect may ultimately yield a greater impact on tumor biology due to its longer time scope. Moreover, neuroeffector levels are modulated both centrally and peripherally and can vary based on tissue type (solid tissue versus blood) and environment [29]. Within the central nervous system (CNS), multiple neural signaling pathways are involved in generating anxiety; however, tumor-promoting responses in the periphery so far appear to be specific to the SNS/beta-adrenergic signaling pathway, and there is little current evidence of influence by other anxiety-related neurotransmitter effector systems in the periphery (i.e., GABA, serotonin, etc.). Future research is needed to quantify the effects of these and other specific variables on risk for cancer progression.

Translational Implications: Pharmacologic Approaches

The development of a social signal transduction map that conveys psychosocial conditions into tumor gene expression dynamics provides a roadmap for rationally targeted interventions to block such effects. One obvious approach is to deploy the same beta-adrenergic antagonist drugs used in preclinical studies to block stress effects on tumor progression and metastasis in clinical settings. This approach is further supported by a significant body of retrospective pharmacoepidemiologic studies demonstrating reduced progression of incident cancers among individuals exposed to beta-adrenergic antagonists, in general, and nonselective (i.e., beta$_2$-inhibiting) agents, in particular [30–39] (although some exceptions are seen, particularly when beta$_1$-selective agents are predominant, as they appear to have little or no protective effects). However, interpretation of these observational retrospective results is complicated by the fact that cancer progression would likely be aggravated by many of the conditions that serve as current indications for beta-antagonist treatment (e.g., cardiovascular disease, anxiety disorders, hypertension). This "confounding by indication" greatly complicates the interpretation of both positive results and null associations (as beta-blocker indicating conditions would generally associate with poorer cancer outcomes in the absence of beta antagonists). As such, there is a great need for more rigorous and interpretable experimental data in which patient characteristics and cancer-related risk factors are independent of beta-antagonist treatment. Several small randomized controlled trials (RCTs) have examined this approach in breast, ovarian, colorectal, and hematopoietic cancers and found promising initial results showing favorable changes in tumor gene expression profiles (e.g., reduced EMT, M2 macrophage, and metastatic signatures) following relatively brief periods of beta-blocker (vs placebo or control) treatment [40–47].

Randomized-Controlled Trials

Breast cancer patients have been evaluated during treatment with propranolol alone [44], as well as in combination with COX-2 inhibitors [48, 49], demonstrating similar antimetastatic effects on tumor biomarkers as observed in their companion preclinical models. Propranolol administered alone for 1 week before surgery in early-stage breast cancer patients resulted in down-regulated expression of mesenchymal genes within the primary tumor without affecting epithelial gene expression—an indication of decreased tumor aggressiveness [44]. Propranolol also promoted immune cell infiltration into primary tumor tissues as evidenced by increased levels of $CD68^+$ macrophages and $CD8^+$ T cells. Results from this RCT of 60 women with early-stage breast cancer support the potential for beta-blockade to reduce metastatic potential, but this study involved only assessment of biomarker outcomes and was not powered to detect differences in clinical endpoints (e.g., survival or disease recurrence). Data from another RCT of 38 women with early-stage breast cancer receiving perioperative treatment with propranolol and the COX-2 inhibitor etodolac [48] have also demonstrated favorable impacts on tumor transcriptome profiles, including: (a) reduced EMT; reduced activity of pro-metastatic transcription factors; and reduced tumor-associated monocyte and increased tumor-associated B cell gene expression profiles [48]; (b) decreased circulating inflammatory parameters (serum and ex-vivo-induced cytokine levels, reduced classical monocyte influx, and increased NK-cell activation markers) [48]; and (c) decreased PBMC measures of transcription factor activity that in primary tumors would indicate poor prognosis, angiogenesis, EMT, proliferation, and glucocorticoid response [41]. Finally, in another RCT of breast cancer patients undergoing surgery and receiving propranolol and/or the COX-2 inhibitor parecoxib, propranolol administration—rather than parecoxib alone—abrogated the increased T regulatory cell activity and accompanying suppression of $CD4^+$T cell responses after surgery [49]. In this study, propranolol plus parecoxib did not demonstrate any additive or synergistic effects beyond those evident for propranolol alone.

Similar improvements in molecular biomarker patterns have been observed following propranolol exposure in other malignancies besides breast cancer. In a study of patients with multiple myeloma undergoing hematopoietic stem cell transplantation (HCT), peri-transplant propranolol was administered, with gene expression assessed before transplant twice following HCT [43]. Relative to the control group, propranolol-treated patients showed significantly greater decreases in the stress-related CTRA gene expression signature from baseline to post-transplant. Propranolol-treated patients also showed improvement in other pertinent hematological indices including upregulation of $CD34^+$ cell-associated gene transcripts and relative downregulation of myeloid progenitor-containing $CD33^+$ cell-associated gene transcripts. Results also indicated nonsignificant trends toward accelerated engraftment and reduced post-transplant infections in propranolol-treated patients, providing preliminary indications of potential clinical benefit of beta-blocker administration. In another RCT of ovarian cancer patients undergoing tumor debulking surgery, propranolol administered in the peri-surgical period significantly lowered plasma CA-125 levels, a marker of tumor burden, though it was not effective at reducing C-reactive protein, cortisol, or anxiety [46].

Non-randomized Trials

While RCT investigation of beta-blockers in cancer treatment is in its infancy, additional non-randomized treatment trials also suggest a potential positive influence of beta-blockade in cancer. In a prospective study of 53 patients with stage IB to IIIA cutaneous melanoma, patients who took daily propranolol were significantly less likely to experience melanoma recurrence than their non-propranolol counterparts [50]. This amounted to an 80% risk reduction for recurrence among propranolol users even after adjusting for known prognostic factors. In another study of 23 patients with stage II–IV epithelial ovarian cancer, overall QOL, anxiety, and depression improved and leukocyte expression of pro-inflammatory genes declined significantly after completion of chemotherapy accompanied by propranolol [45].

Despite accumulating experimental data supporting the use of beta-blockers to reduce cancer progression, non-experimental observational studies have shown more mixed effects. Several observational studies have indicated potentially protective effects, including retrospective epidemiologic studies linking the use of beta-blockers to reduced rates of progression for several solid and hematologic malignancies [30–32, 39, 51–53]. Among breast cancer patients, concomitant use of a beta-blocker at the time of diagnosis was associated with reduced distant metastases [30], cancer recurrence [30], and cancer-specific mortality [30, 31] and was associated with decreased odds of presenting with T4 tumor [31]. In 121 patients with thick melanoma, follow-up at 2.5 years indicated that only 3.3% of the 30 patients on a beta-blocker vs. 34.1% of patients in the untreated subgroup displayed tumor progression [32]. In a cohort of 514 patients with metastatic colorectal cancer, incidental use of a beta-blocker was a significant factor predicting both progression-free survival and overall survival [39]. This relationship has also been examined in the setting of non-small-cell lung cancer; in a cohort of 722 patients, beta-blocker use was associated with decreased distant metastasis-free survival, disease-free survival, and overall survival [52]. Finally, one published study has examined this relationship in the hematologic malignancy setting, demonstrating that beta-blocker intake is associated with a reduced risk of disease-specific death and overall mortality as compared to non-beta-blocker use [53].

In contrast to these findings suggesting potential protective effects, other observational studies have reached different conclusions. A research group out of the United Kingdom has performed several nested case control studies of beta-blockers in cancer patients utilizing the UK Clinical Practice Research Datalink. This group has evaluated thousands of breast [54], melanoma [55], and colorectal cancer [56] patients from this large population-based cohort with regard to post-diagnosis beta-blocker status and has failed to identify an impact on cancer progression (breast) or cancer-specific mortality (melanoma and colorectal). A large retrospective epidemiologic study of colorectal cancer patients from another group demonstrated a similar lack of association [57], while a smaller single-center study found that perioperative beta-blocker administration did not improve recurrence-free or overall survival in patients with non-small cell lung cancer [58]. Finally, two large retrospective epidemiologic studies of mixed cancer populations (mostly lung, breast, and colorectal) did not find an association between perioperative beta-blocker use and improved cancer-specific [59] and overall [60] survival. There are many candidate reasons for this lack of observed association, including potential variation by tumor subtype, incomplete data, sampling bias, or variation in surgical or other cancer interventions. However, the two most significant issues involve the nature of the beta-blockers studied and the potential for confounding in non-randomized/observational research. Preclinical and experimental studies primarily support the use of propranolol due to its inhibition of the beta$_2$-adrenergic pathway that mediates many observed effects. Selective beta$_1$-antagonists are the predominant agents studied in retrospective observational studies, but preclinical studies in experimental model systems typically do not find effects of psychological or physiological stress on cancer progression to be mediated by beta$_1$-adrenergic receptors. As such, the observational pharmacoepidemiologic evidence base is not well aligned with the most promising preclinical evidence suggesting a central role for beta$_2$-adrenergic signaling. This suboptimal exposure profile is further complicated by the potential for confounding by indication (as noted above), because beta-blockers are prescribed for (and thus statistically correlated with) many diseases that are likely to adversely impact cancer progression either directly or due to co-variation with age, adiposity, and other biodemographic risk factors. As such, there is a great need for additional experimental studies involving randomization of cancer patients to treatment with beta$_2$-covering antagonists (e.g., propranolol) in order to overcome the interpretive difficulties in the current observational pharmacoepidemiologic evidence base.

As noted above, several Phase II RCTs have yielded promising biomarker results in tumor tissues and circulating immune cells, but it is critical to note that none of these studies involved sufficient sample size or follow-up duration to detect any impact on clinical outcomes. However, there are an increasing number of larger ongoing beta-blocker RCTs aimed at assessing clinical outcomes in malignancies, such as pancreatic cancer (*N* = 210, NCT03838029), colorectal cancer (*N* = 200, NCT03919461), sarcoma (*N* = 50, NCT03108300), melanoma (*N* = 47, NCT03384836), and lung cancer (*N* = 400) [61]. However, recruitment for beta-blocker trials in the oncology setting remains a challenge as these studies compete with other traditional pharma-supported oncology trials that would typically prohibit additional treatment with another agent, such as propranolol [40]. As a result, many attempts to test the impact of beta-blockade in the context of cancer treatment have been terminated prematurely due to poor accrual (NCT02596867, NCT01857817, NCT03323710) or funding obstacles (NCT01988831).

At this point, the preponderance of rigorous (experimental) data supports the concept that neural activity can regulate tumor biology in ways that may accelerate disease progression and undermine health outcomes in the context of cancer. These observations underscore the translational need for larger Phase III clinical trials powered to detect the impact of beta-blockade on cancer recurrence and survival. However, the current molecular biomarker outcomes provide exactly the proof-of-concept evidence required to advance this adjunctive treatment concept to more robust Phase III clinical trials. Moreover, those molecular outcomes may serve as additional surrogate endpoints for prediction of longer-term clinical impacts in Phase III studies. It remains to be determined whether this pharmacologic intervention approach—additionally targeting the downstream neurobiological effects of psychosocial stress, rather than the psychosocial distress alone—will become a standard of care. However, this approach holds promise in augmenting traditional antineoplastic therapies; whether this will involve targeting particular patient subset populations (high distress scores, low socioeconomic status, worse depression, etc.) versus broad preventive administration is one of the ongoing topics for future research.

Translational Implications: Behavioral Approaches

Social signal transduction highlights the key role of central nervous system perceptual and interpretive processes in regulating neural outflow to the peripheral tumor microenvironment. Several studies have documented effects of psychological or behavioral interventions in reducing CTRA-related gene expression profiles in general [62–68] and more specifically in cancer patients [62, 65, 66, 68, 69]. One pioneering randomized controlled study of Stage 0–III breast cancer survivors found that cognitive-behavioral stress management reduced leukocyte CTRA profiles [62, 69], as well as reduced disease recurrence and mortality at 11-year median follow-up [70], and that the magnitude of CTRA reduction from pre- to post-intervention was predictive of reduced disease recurrence [69]. However, this was a post hoc analysis of archival blood samples and disease recurrence, and no study to date has examined behavioral intervention effects on tumor tissue gene expression.

In a younger cohort of premenopausal breast cancer survivors participating in a mindfulness meditation intervention, a decrease in CTRA-associated pro-inflammatory signaling as well as a reduction in stress, depressive symptoms, fatigue, and insomnia were present in the intervention group [68]. Similar salutary genomics outcomes were observed in a cohort of breast cancer survivors who participated in a physically engaged behavioral health yoga intervention targeted at patients with cancer-related fatigue [65]. Finally, among breast cancer patients with insomnia, another movement-based intervention—tai-chi—was also effective at reducing cellular inflammatory responses and expression of proinflammatory genes [66]. Though not targeted toward cancer patients, random assignment to pro-social behavior toward specific others resulted in reduction of leukocyte expression of CTRA indicator genes [67], providing yet another candidate intervention for oncology studies. Behavioral psycho-oncology interventions are also ripe for empirical investigation, given that several types of psychosocial intervention have now been linked to improved survival in cancer [70, 71].

Future Directions

A growing body of basic science evidence shows that CNS regulation of peripheral neural activity can allow host psychosocial conditions to impact the biology of cancer but much remains to be discovered about the scope, mechanisms, and clinical significance of such effects. Most of the existing evidence in this area comes from studies of solid epithelial tumors (e.g., breast, ovarian, prostate, lung, pancreatic), although some preclinical studies and one pilot RCT have suggested potential impacts on hematopoietic tumors as well [72]. Little is known about neural regulation of neural cancers or sarcomas. Most of the research base so far suggests that neural pathways exert their greatest effects on biological processes involved in progression from an initiated localized tumor to a more invasive and metastatic disease. There is less consistent evidence that stress biology promotes either the earlier processes involved in tumor initiation or the later processes involved in disseminated metastatic disease [3, 22]. Many cancers are discovered only after pathological progression has occurred, so it remains unclear how much therapeutic leverage will be gained by inhibiting neural support for tumor biology. However, the notable change in tumor molecular profiles observed in the aftermath of brief pharmacologic interventions suggests that some salutary potential exists even in cases of established disease.

Much also remains to be discovered about the CNS processes involved in translating patients' experiences of general life circumstances and their encounter with cancer into peripheral neuroeffector activity. The CNS systems that directly regulate SNS and HPA output are well defined, but the brain structures involved are difficult to measure in functional neuroimaging studies (due to small size and complex anatomic locales), and they are subject to a complex array of inputs from higher cortical and sub-cortical systems. However, it is clear that CNS processes have the potential to exert significant effects on peripheral gene expression, as indicated by marked shifts in leukocyte gene regulation in response to psychoactive medications [73]. There is a great need for a more systematic survey of the peripheral molecular impacts of current pharmacotherapies and psychotherapies deployed in psycho-oncology.

The identification of peripheral molecular signatures of chronic neuroeffector activation such as the CTRA also provides new opportunities for identifying individuals who may fall at increased risk for poor biological outcomes without necessarily manifesting that in experiences of overt stress or negative affect. It has long been noted that subjective stress and negative affect do not necessarily correlate with somatic stress physiology; some individuals experience low levels of distress despite high levels of stress physiology, and others show high levels of distress but low levels of stress physiology. For example, the objective characteristic of low socioeconomic status—without any indices of subjectively experienced stress—was independently associated with increased CTRA expression and inflammation among a cohort of HCT recipients [74, 75]. Furthermore, increased expression of this somatic stress biomarker was independently associated with worse outcomes following HCT.

Neuroeffector molecules are notoriously volatile and blood levels of such mediators have not provided a reliable basis for identifying those at increased biological risk [8]. However, gene expression profiles are often less volatile due to the temporal smoothing that results from their relatively slow signal transduction and due to the large number of cells present in most tissue samples (which tends to smooth biological signals due to the law of large numbers) [76]. This raises the possibility that molecular biomarkers, such as the leukocyte CTRA or tumor gene expression profiles, might be examined to help identify patients who fall at increased biological risk and may thus benefit the most from psycho-oncological or neuropharmacological interventions. The same molecular biomarkers may also serve as surrogate endpoints to help gauge the impact of those interventions far in advance of their impact on clinical disease (e.g., cancer recurrence) or to help personalize interventions by empirically selecting the most impactful modality from an array of alternatives. In this approach, repeated assessments of gene expression over the course of treatment may provide a kind of genomic biofeedback that allows iterative optimization of clinical interventions [6].

Implications for Psycho-oncology

Neural regulation of tumor biology provides a plausible biological pathway through which the supportive care provided by psycho-oncologists might affect the course of disease in cancer patients. Such effects have long been hypothesized, and some post hoc analyses have provided evidence consistent with favorable effects on disease progression and survival [70, 71]. However, prospective tests of these hypotheses are challenging due to the large sample sizes and extended follow-up required to definitively assess clinical impact. As noted above, disease-predictive molecular biomarkers provide new opportunities for gauging the biological impacts of psycho-oncologic interventions, as well as selecting optimal intervention protocols on a patient-specific basis [6]. Advancing research in social genomics may also help expand the scope of interventions considered and the impact metrics examined. For example, social genomic research on resilience factors suggests that fostering a personally meaningful life with a self-transcendent purpose may have more salutary molecular effects than optimizing one's experience of hedonic well-being (e.g., positive affect or life satisfaction) [77–79]. Much remains to be discovered about the scope and mechanism of such effects, but they do suggest that helping cancer patients clarify their values and redouble their commitment to personally meaningful impact may help enhance personal adaptation in cancer survivorship [80]. Positive psychology interventions are also being explored for their utility to diminish adverse stress physiology. The Promoting Resilience in Stress Management (PRISM) intervention was effective at promoting benefit-finding and hopeful thinking [81], as well as improved resilience and cancer-specific quality of life, while reducing psychological distress and depressive symptoms [82]. Investigations are in process to evaluate the efficacy of this intervention to improve stress-related gene expression patterns among adolescent and young adult HCT recipients (NCT03640325). Given the loose relationship between subjective experiences of distress and somatic stress physiology, social genomics studies can also help identify other non-conscious behavioral indicators of CNS threat processing that may serve as useful metrics for psycho-oncological interventions (e.g., patterns of natural language use, which may correlate better with molecular profiles than do conscious self-reports of stress or negative affect [83]).

It is not hard to imagine a future in which psycho-oncologists add to their contemporary kit of psychological assessments additional behavioral and molecular indicators of well-being that can help guide the selection and deployment of specific psychotherapeutic and pharmacologic interventions tailored to the patient's distinctive needs and life circumstances. In this regard, molecular measures of the somatic impact of psychological well-being may help usher in a new era of precision psycho-oncology that parallels the precision medicine approach currently transforming clinical oncology. Much remains to be discovered, and even more remains to be done empirically to advance these ideas into clinical practice. But the road ahead provides some exiting new possibilities, and the need for new ideas remains great given the substantial challenge that cancer continues to pose for both somatic and psychological well-being.

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22

Psychological Aspects of Hereditary Cancer Risk Counseling and Genetic Testing: Toward an Expanded and More Equitable View

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Cancer is a common disease with many underlying etiologies. Most cancers are sporadic occurrences related to aging, environmental exposures, or the interactions of low-penetrance genes. However, approximately 5% of cancers occur due to an inherited cancer predisposition syndrome [1]. Families with hereditary cancer syndromes are generally characterized by multiple occurrences of cancer on the same side of the family, individuals with multiple primary cancers, and an earlier than average age of cancer onset.

Hereditary cancer risk counseling (HCRC) is the process of informing families about their cancer risks and options for genetic testing and management, with the ultimate goal of minimizing cancer-related morbidity and mortality. This is typically achieved when members of families known to have a hereditary cancer syndrome are recommended to engage in earlier and more frequent screening and other risk-reducing strategies. In addition to improved medical management, HCRC and genetic testing are intended to have important psychological benefits, such as reducing uncertainty about cancer risk, increasing perceived control over cancer risk, motivating adherence to recommended prevention and screening behaviors, and providing information about children's cancer risk [2–5].

The purpose of this chapter is to describe the major elements of hereditary cancer risk counseling and to review both behavioral and psychological outcomes of genetic counseling and test reporting for such cancer syndromes as hereditary breast and ovarian cancer (HBOC), hereditary colon cancer (Lynch syndrome and FAP), and familial melanoma. We will examine the implications of these outcomes for both research design and clinical application. This chapter does not present an exhaustive review, but instead a selective consideration of research on the major cancer syndromes for which genetic counseling and testing have been extensively studied. As such, we could not cover several important issues, including differences between patients who self-select into clinical genetic counseling versus those recruited for research studies (see [6] for review), differences between relatives at risk for a familial mutation (pathogenic variant) who elect genetic counseling and those who decline

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[7–9] or the impact of genetic counseling and test reporting on the accuracy of cancer risk perceptions [10]. Finally, our review does not cover rare hereditary cancer syndromes (e.g., Li-Fraumeni syndrome [LFS] and Von Hippel-Lindau [VHL]) that are associated with the development of cancer in early childhood and a very high risk for cancer development in multiple parts of the body rather than one or two predominant cancer risks [7].

Throughout this chapter, we will examine ways in which hereditary cancer risk counseling and genetic testing may be seen as powerful tools in an ongoing effort to manage hereditary cancer risk rather than as isolated or new stressors. Consistent with this view, we present a model that integrates new research on the antecedents and outcomes of hereditary cancer risk counseling and genetic testing with an analysis of the key elements of different cancer syndromes and their management. We conclude with an examination of the continuing underrepresentation of members of racial and ethnic minority groups in cancer genetic testing. These issues may guide the design of future studies and interventions.

Components of Hereditary Cancer Risk Counseling

Table 22.1 outlines the essential components of hereditary cancer risk counseling. The recommendations outlined by the National Society of Genetic Counselors and the American Society of Clinical Oncology for providing HCRC have served as the basis for clinical practice and many research studies [11, 12]. As shown in Table 22.1, these recommendations include educating patients about their cancer risk, reviewing basic genetics, inheritance patterns and management options, and exploring the psychological implications of this information for patients and their families.

As shown in Table 22.1, hereditary cancer risk counseling includes the assessment and provision of detailed risk information, including personal risk for developing cancer, likelihood of harboring a genetic mutation, and risks for other family members. In addition, patients are informed of the options available for managing their cancer risk and the effectiveness of these approaches for reducing cancer risk or detecting cancer at an ear-

Table 22.1 Components of hereditary cancer risk counseling

Component	Description
Review of patient history	A detailed review of the patient's personal and family history is needed to distinguish between familial clusters of cancer due to sporadic occurrence, shared environmental/lifestyle factors, or low-penetrance genes compared to those families that may have a hereditary cancer syndrome. Ideally, medical records, particularly pathology reports, are obtained to confirm reported cancers in the family. However, genetic testing is increasingly indicated for several cancer diagnoses (e.g., epithelial ovarian cancer, pancreatic adenocarcinoma) regardless of age or family history.
Psychological assessment	Evaluation of psychosocial factors will allow the clinician to understand the patient's motivation for seeking cancer risk assessment and level of understanding of medical information, and to anticipate whether cancer risk assessment may lead to negative psychological consequences. Psychological assessment includes evaluation of the following: Motivations for seeking counseling, such as planning medical management, determining risk for family members, and/or relief from uncertainty. Beliefs about the cause(s) of cancer and their estimated cancer risk. Cultural and familial beliefs and fears about cancer and its inheritance. Health literacy. Socioeconomic factors such as health insurance status and concerns about potential discrimination. Potential psychological responses to cancer risk information. Attitudes about efficacy of screening and risk-reducing options. Coping resources that the patient may utilize.

Component	Description
Cancer risk assessment	Cancer risk estimates can be made based on personal and family history information, computer-based models (e.g., Gail model, CancerGene), and the results of genetic testing. During hereditary cancer risk counseling, several different types of risk information may be presented: Risk of developing particular types of cancer. Risk of harboring a genetic mutation that may cause an increased cancer risk. Risk of passing a genetic mutation on to family members. How risk may be modified by certain behavioral, screening, or surgical approaches.
Pre-genetic testing	When appropriate based on personal and family history, genetic testing may be offered to the patient. Prior to genetic testing, the following should be discussed: Purpose of the genetic test. Implications of a result indicating a mutation, no variant, or variation of uncertain significance (VUS). How results may affect the management of patient's cancer risk. Implications for family members' cancer risk and its management. Possibility of health or life insurance discrimination. Potential psychological responses, such as increased distress, cancer worry, or survivor guilt. Potential benefits, such as relief from uncertainty, more informed decision-making, proactive planning for prevention and screening behaviors as appropriate for the patient and family members. Likelihood that a mutation will be identified based on the strength of the pattern of cancer in the family and sensitivity of the testing technology. Accuracy and limitations of the test. Cost of the test.
Post-genetic Testing	When genetic testing is pursued, disclosure of genetic test results also includes a discussion of the following: Impact of the result on cancer risk. Implications for screening and management. The need to inform other relatives about the outcome of genetic testing, implications of their risk, and the options available to them for counseling, testing, and clinical care. Prevention and testing options for minors (as applicable).
Surveillance/ treatment/ follow-up	Individuals should receive screening, prevention, and treatment options that are tailored based on their test result, family history, and personal medical history. They will need to be scheduled for appropriate interventions and offered referrals to appropriate resources and screening interventions (e.g., other medical specialists, support groups, online resources). Hereditary cancer syndromes typically affect cancer risk throughout the lifespan and ongoing screening and follow-up are usually necessary.

lier, more treatable stage. Table 22.2 summarizes the general population prevalence, causative gene or genes, lifetime cancer risks (often for multiple cancers), and management recommendations for each of the major hereditary cancer syndromes. Of the more than 50 hereditary cancer syndromes that have been identified [13], hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (formerly referred to as hereditary nonpolyposis colorectal cancer, HNPCC) are the two most common and well-studied conditions.

The model of pre-test genetic counseling outlined in Table 22.1 has been both the clinical standard of care and the basis for research studies of genetic counseling and testing outcomes [12]. However, due to increasing demand for genetic services and limited availability of genetic counselors, clinical practice and genetic services research are increasingly looking to models in which pre-test assessment and counseling are minimized. This change is driven largely by advances in genetic testing technology that allow testing of multiple genes for minimal cost and the

Table 22.2 Features of common hereditary cancer syndromes and corresponding management recommendations

Condition	Genes	Population prevalence of gene mutations	Inheritance	Lifetime cancer risks		Management recommendations
Hereditary breast/ ovarian cancer (HBOC)	*BRCA1* *BRCA2*	1/400	Autosomal Dominant	*BRCA1*		*Breast* Annual breast MRI beginning at age 25, and annual mammogram added beginning at age 30. Consideration of prophylactic mastectomy. *Ovarian* Prophylactic removal of the ovaries and fallopian tubes between 35–40 years of age.
				Breast	50-–80%	
				Ovarian	40%	
				BRCA2		
				Breast	50–80%	
				Ovarian	10–20%	
Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer [HNPCC])	*MLH1* *MSH2* *EPCAM* *MSH6* [a] *PMS2* [a]	1/400	Autosomal Dominant	Colon	50–80%	*Colon* Colonoscopy every 1-2 years beginning at age 25. *Endometrium* Consider prophylactic hysterectomy after completion of childbearing. *Other* Upper endoscopy examinations every 1-3 years beginning at age 30. Annual urine cytology.
				Endometrium	25–60%	
				Stomach	6–13%	
				Ovary	4–12%	
				Urinary tract	1–4%	
				Small bowel	3–6%	
				Brain	1–3%	
Familial adenomatous polyposis (FAP)	*APC*	1/3000	Autosomal Dominant	Colon	Approaches 100% without prophylactic removal of the colon	*Colon* Colonoscopy beginning at age 10. Colectomy when polyps become too numerous to monitor. *Duodenum* Upper endoscopy exams every 1-3 years beginning at age 25. *Thyroid* Annual physical exam of the thyroid.
				Duodenum	4–12%	
				Pancreas	2%	
				Thyroid	1–2%	

Table 22.2 (continued)

Condition	Genes	Population prevalence of gene mutations	Inheritance	Lifetime cancer risks		Management recommendations
Hereditary melanoma	*CDKN2A* (also called *p16*)	1/2500	Autosomal Dominant	Melanoma	67%	*Skin* Dermatology exams every 6–12 months beginning at age 10–12. Monthly self-skin exams. Minimize UVR exposure. *Pancreas* Beginning at age 40 annual screening with endoscopic ultrasound or MRI of pancreas. Annual fasting blood glucose and/or hemoglobin A1C.
				Pancreatic	17%	

Note. ^{a} Associated with significantly lower cancer risks and modified screening recommendations

development of targeted treatments for cancer patients with certain germline mutations [14–17]. These advances have expanded the patient populations that can benefit from genetic testing and simplified test selection by allowing providers to test multiple cancer predisposition genes without needing detailed phenotype and family history assessment. Testing is now recommended for several cancer patient populations based on pathology regardless of age or additional family history due to likelihood of mutation detection or treatment planning (e.g., epithelial ovarian cancer, pancreatic adenocarcinoma, triple-negative breast cancer, advanced prostate cancer [18]). Pre-test counseling with a genetic counselor may be replaced with educational aids or genetic education from a physician or other member of the healthcare team [19–21]. Research on alternative genetic service delivery models has generally focused on the efficiency of the process, uptake of testing, and short-term psychological outcomes. Of note, findings concerning the psychological and behavioral outcomes derived from research based on traditional standard-of-care genetic counseling approaches reviewed here cannot necessarily be extrapolated to settings in which pre-test counseling has been minimized.

Ideally, genetic testing is most informative when performed first in a family member with a personal history of the type of cancer for which the family is being evaluated. This increases the likelihood of detecting a mutation if one is present in the family. Testing the first person in the family involves a comprehensive analysis of the gene or genes associated with the syndrome in order to try to identify a mutation. Cost is less of a barrier to accessing genetic testing than in the past, as genetic testing is covered by most insurers, commercial laboratories offer financial assistance, and technology has dramatically reduced costs such that testing for multigene panels is now available for less than $300. Once a mutation is identified, testing for the mutation can be offered to other family members. There are three possible outcomes from genetic testing: positive, negative, and variant of uncertain significance [VUS]. A positive result means that a mutation (pathogenic variant) was identified. This result confirms the diagnosis of a hereditary cancer syndrome in the individual and provides a likely explanation for the increased number of cancers seen in the individual's family. Once a mutation is identified, testing for the mutation can be offered to other family members to determine their risk and allow those who have inherited the mutation to take preventive action. Throughout this review, we refer to family members with a history of the particular hereditary cancer as *affected* family members and to those without a personal history as *unaffected* family members. Furthermore, we refer to family members who test positive for a mutation as *carriers* and to individuals who test negative for a family mutation as *noncarriers*.

A negative result in the initial individual being evaluated means that no mutation was identified; however, this result cannot rule out the possibility of a hereditary predisposition to cancer in the family. Because current technologies may miss some types of mutations and there may be other hereditary causes of cancer risk yet to be identified, families with strong cancer histories should be counseled that a negative result indicates that the cause of the cancer in their family remains unknown and that screening to promote early detection is still recommended. Because no definitive explanation of the cause of the cancer risk in the family is provided, this type of result is often referred to as "uninformative" in this review. This type of negative result should be distinguished from the *noncarriers* mentioned above who are considered to be at population risk after being confirmed to not have the causative mutation in their family.

A third possible outcome from genetic testing is finding a variant of uncertain significance. This is a result in which a genetic alteration is identified, but there are not sufficient data to determine whether this alteration is associated with cancer or if it is simply a benign alteration due to normal human genetic variation. Variants of uncertain significance are often eventually reclassified, most commonly as benign results and rarely as pathogenic [22, 23]. However, as we will review, the initial disclosure of a VUS can be frustrating and confusing for patients, and these results may be misunderstood by surgeons as well. Prior to reclassification, this result should not be used to guide medical management.

Behavioral Outcomes of Cancer Genetic Counseling and Testing

Table 22.2 summarizes the management recommendations for each of the major cancer syndromes we review in this chapter. In the following sections, we review major behavioral outcomes of cancer genetic testing for each of these syndromes, including more frequent screening and uptake of prophylactic surgery (as applicable). We also highlight how genetic counseling for hereditary melanoma may promote potentially life-saving improvements in both screening and primary prevention behaviors.

Hereditary Breast and Ovarian Cancer

As shown in Table 22.2, female *BRCA1/2* mutation carriers are advised to have careful breast surveillance with breast imaging beginning at age 25 or to consider prophylactic mastectomy. Since there is no effective screening for ovarian cancer, prophylactic removal of the ovaries and fallopian tubes (prophylactic oophorectomy) is recommended between 35 and 40 years of age. Prophylactic mastectomy is associated with a 90% reduction in breast cancer risk, and oophorectomy is associated with an 85–90% reduction in ovarian cancer risk [24, 25].

Breast Imaging Early reviews found that mammography rates increased among *BRCA1/2* mutation carriers following counseling and testing, with 59–92% of carriers receiving a mammogram in the year following testing, compared to 30–53% of noncarriers [26]. Screening recommendations now include breast MRI, and women with *BRCA* mutations age ≥ 30 years are recommended to have both an annual breast MRI and mammogram, staggered, so there is imaging of the breasts every 6 months. A study of 400 women at high risk for breast cancer due to genetic mutation or family history found that only 59% were adherent to a comprehensive screening program [27]. Having children, particularly young daughters, and high perceived risk were predictors of adherence. Self-reported adherence data from 97 *BRCA1/2* carriers found that over half were adherent to breast cancer risk management with the level of adherence increasing from 54% for women ages 25–29 to 75% for women over 40. Of those reporting adherence, 51% were considered to meet management guidelines after having had prophylactic mastectomy, while 49% were adherent to the breast imaging recommendations. Cost was more likely to be a barrier to getting breast MRI than mammograms in this population [28].

Prophylactic Mastectomy Uptake of risk-reducing mastectomy has increased over time, with early studies showing an uptake of 0–15% among unaffected mutation carriers and more recent studies reporting rates of 20–37% [29]. A review of 8 studies found that rates of prophylactic mastectomy among carriers ranged from 0 to 51% in the year post-testing [26]. A study that followed 374 women who had *BRCA1/2* mutation testing for an average of 5 years found that 37% of carriers underwent mastectomy following testing, as did a small proportion of participants with uninformative results (6.8%) [29]. As expected, no noncarriers in this study underwent mastectomy. In this study, an additional 24 carriers had risk-reducing mastectomy (potentially in conjunction with treatment of a breast cancer) prior to undergoing genetic counseling and testing. Therefore, 47% of carriers overall had undergone risk-reducing mastectomy either before or after testing.

Several factors have characterized individuals who choose to undergo mastectomy. First, carriers with cancer are typically more likely to undergo mastectomy than unaffected carriers [30] because of the role of mastectomy in breast cancer treatment. Second, rates of mastectomy following *BRCA1/2* genetic testing may be higher in countries other than the United States, where concerns about financial and insurance discrimination are lower [30]. Older women (but see [29]) and women with children are more likely to undergo mastectomy due to lower concern about consequences that may influence reproductive decisions [30, 31]. Additionally, women who had their ovaries removed, and for whom it had been greater than 10 years since their cancer diagnosis, were less likely to elect mastectomy [29]. The authors suggested that women who undergo oophorectomy prior to menopause reduce their breast cancer risk significantly, which reduces the overall benefit of a mastectomy.

Prophylactic Oophorectomy Uptake of oophorectomy is often higher than mastectomy uptake, 13–65% [26], because there are strong recommendations for removal of the ovaries and fallopian tubes as no effective screening approach for ovarian cancer is available [32]. One study of 91 *BRCA1/2* mutation carriers found that women who underwent oophorectomy were more likely to have children than those who did not and were somewhat older; no women without children underwent oophorectomy [33]. Of note, some high-risk women undergo prophylactic surgery due to their familial history prior to the identification of a genetic mutation. Once a genetic mutation is identified, some of these women will subsequently test negative for the mutation (53% of 80 women who underwent prophylactic surgery in one study [34]). Therefore, hereditary cancer risk counseling is not only beneficial for identifying those at high risk but also for identifying noncarriers who have not inherited the causative mutation and can be spared unnecessary procedures.

Risk-Management Decisions Among Patients Receiving Test Results That Are Uninformative or Indicate a Variant of Uncertain Significance It is important to note that the reviews we have described thus far did not generally assess behavioral outcomes among individuals who received uninformative results. Such women have personal and/or family histories of breast and/or ovarian cancer, but either no identifiable mutation or a VUS. For these individuals, counselors derive empiric risk estimates from an individual's personal and family history which are used to determine management recommendations. Receiving a breast cancer diagnosis is a time at which many medical decisions need to be made and genetic testing is increasingly being incorporated into that process.

Several studies have examined factors that predict uptake of contralateral prophylactic mastectomy (CPM) at the time of therapeutic surgery in breast cancer patients who receive uninformative negative or VUS results. A study of women with breast cancer randomized to receive rapid genetic counseling and testing prior to surgery or standard of care found that CPM was chosen by 75% of those found to have a mutation, 43% of those who carried a VUS, 29% of those who tested negative, and 15% of those who declined genetic testing. Having pre-surgical genetic counseling and testing and a priori mutation risk predicted choosing CPM [35]. However, the most significant predictor was whether CPM was discussed by the patient's surgeon. Similar outcomes were found among 92 breast cancer patients who received uninformative negative genetic test results prior to surgery. CPM was elected by 25%, and physician recommendation, perceived risk, and perceived benefit of CPM were predictors [36].

Physician recommendation is often an important predictor of uptake of health behaviors, and communication with the treating physicians may be even more impactful when the results of genetic testing do not provide a clear answer. However, medical professionals do not always have the training and knowledge to accurately discuss genetic test results with patients. A survey of 3672 breast cancer patients and their attending physicians found that 51% of patients opted to have CPM based on the finding of a VUS [37]. The accompanying survey of the physicians found variability in their understanding of a VUS, with 24% of surgeons who frequently ordered genetic testing and 50% of surgeons who rarely ordered genetic testing incorrectly responding that patients with a VUS should be treated the same as those with a mutation. In this cohort, only 50% of patients had an opportunity to discuss their result with a genetic counselor. More research is needed on behavioral outcomes of uninformative negative and VUS test results, and future studies should consider both individuals with cancer and those who are unaffected and being tested due to family history.

Hereditary Colon Cancer

Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer, or HNPCC) and familial adenomatous polyposis (FAP) are the two most common causes of hereditary colorectal cancer. As shown in Table 22.2, Lynch syndrome is associated with an increased risk for multiple cancers, especially colorectal and endometrial cancer [38]. Individuals with mutations in the highest penetrance Lynch syndrome genes, *MSH2*, *MLH1*, and *EPCAM*, are recommended to begin annual screening at age 25. Individuals with Lynch syndrome who have a colonoscopy every 1 to 2 years have substantially reduced mortality [39], though the effectiveness of approaches for screening for other Lynch-related cancers is less well-established [40]. Research has demonstrated that the cancer risk varies by which gene harbors the mutation, and risks are lower for *MSH6* and *PMS2* carriers [41, 42]. More recent analyses are beginning to consider carriers of mutations in the various genes separately, but most historical studies discussed here combine all gene carriers.

FAP is characterized by the development of numerous precancerous colonic polyps, and without surgery to remove the colon, the risk for progression of these polyps to colorectal cancer approaches 100%. As shown in Table 22.2, individuals with FAP are also at increased risk for developing cancers in the beginning of the small intestine (duodenum), stomach, and thyroid. Other rare manifestations of FAP include the development of fibrous tumors called desmoids. While benign, these tumors can grow aggressively and be associated with significant morbidity and mortality. Infants and young children are also at increased risk for developing hepatoblastoma, a rare form of liver cancer. Unlike most hereditary cancer syndromes, which present in adulthood, FAP is associated with a risk for cancer early in life, and genetic testing is recommended for at-risk children by age 10 [38]. Individuals with FAP are recommended to begin having colonoscopies at age 10 and to have prophylactic colectomy when the polyps become too numerous to manage endoscopically. Removal of the colon rarely requires a colostomy because usually the rectum can be left intact or an internal pouch can be formed from the distal end of the small intestine (ileoanal pouch). Annual surveillance of the rectum or ileoanal pouch is still necessary. Upper endoscopy exams beginning between 20–25 years of age are also recommended to monitor polyp development in the stomach and duodenum.

Colonoscopy Multiple studies have found that between 58 and 100% of Lynch syndrome mutation carriers underwent colonoscopy in the two years following testing, compared to only 0–40.5% of noncarriers [26; see also 30, 43–46]. These rates are consistent with recommendations made to carriers and noncarriers, respectively, and represent increases from baseline for carriers. In one study, respondents (regardless of mutation status) who at 1 month following testing reported at least a moderate amount of control over developing colon cancer were more likely to undergo colonoscopy than those who reported little or no control [47]. Stoffel [43] found that both having a close relative with early-onset colorectal cancer and having had hereditary cancer risk counseling predicted adherence to colon cancer.

Gynecological Screening and Prevention Screening for endometrial cancer has not been found to be particularly efficacious for women with Lynch syndrome. Guidelines suggest that this could be considered in consultation with a physician. Assessment of patient preferences has found that women's most preferred option was annual screening, but biannual screening and chemoprevention with oral contraceptives were also strongly endorsed [48]. Prophylactic hysterectomy was the least preferred option, and this was strongly influenced by age and parity. In contrast to what might be expected, women with a first-degree relative with a gynecologic cancer were *less* likely to endorse screening or prophylactic surgery. The attitude was hypothesized to be due to the fact that these women had observed that their relatives had good outcomes and that awareness of symptoms, such as uterine bleeding, is often sufficient for early detection.

Uptake of FAP Testing and Screening Adherence Douma et al. [49] reviewed all papers published between 1986 and 2007 (17 total) regarding behavioral and psychological outcomes in FAP. Uptake of testing was high, ranging from 62 to 97%, and adults undergoing testing indicated concerns about their own and their children's future health as primary motivators. FAP differs from hereditary breast/ovarian cancer and Lynch syndrome in that it is appropriate to test children. Prior genetic testing to identify the mutation in the family and provider recommendation were the most significant factors associated with parents electing to have their children undergo genetic testing for FAP. Lack of provider recommendation and cost were found to be significant barriers to the uptake of FAP genetic testing for minors [50].

There are limited data on screening outcomes after receiving a diagnosis of FAP [49]. Medical management of individuals with FAP is difficult for researchers to track, in that it typically involves an initial evaluation to determine the extent of polyposis, a decision to proceed with prophylactic surgery, and then continued screening of remaining at-risk organs and tissues. Recommendations for patients vary considerably based on the extent of polyposis and whether and what type of surgery has been performed. One study of 150 members of FAP families [51] found that only 54% of individuals who had a diagnosis of FAP were compliant with management recommendations. Factors that predicted increased adherence to screening were having the diagnosis confirmed by the identification of a mutation, having insurance coverage, provider recommendation for screening, and perceiving a higher than average risk for colon cancer. Furthermore, a 2002 study [52] found that 42% of noncarriers were not reassured by testing negative for the mutation that had caused FAP in the family and intended to continue screening. Similar lack of confidence in genetic results has rarely been reported with other syndromes [44]. When genetic testing first became available for FAP, it was performed via linkage analysis and other modalities that were less reliable than the sequencing technology being used currently. Because FAP is associated with a distinctive colonic phenotype, follow-up assessment of the colon was recommended [53]. There have not been recent studies assessing confidence in genetic testing results among people being tested for FAP, but it is likely that perceptions would be similar to other syndromes now that testing is available via equally reliable platforms and follow-up endoscopy is no longer routinely recommended.

Hereditary Melanoma

Genetic testing for hereditary melanoma has entered clinical practice relatively recently, with the first formal recommendation for its use published in 2009 [54]. Of all melanomas, 5–10% have a familial clustering, and 20–40% of these are associated with a pathogenic mutation in *CDKN2A/p16* (or simply *p16*), a tumor suppressor that regulates cell cycle and senescence. As shown in Table 22.2, recommendations to *p16* mutation carriers include not only monthly skin self-examinations (SSEs) and annual or semiannual professional total body skin examinations (TBSEs) but also recommendations to minimize ultraviolet radiation (UVR) exposure. This recommendation stems from the finding that the penetrance of *p16* mutations shows striking geographic variation which correlates with regional levels of UVR intensity, ranging from 58% in the United Kingdom to 76% in the United States and 91% in Australia [55]. Thus, members of high-risk families are counseled to avoid UVR exposure, to wear sunscreen of at least SPF 30, and to wear protective clothing. For this reason, the study of behavioral adherence among melanoma-prone families has the potential to elucidate how genetic counseling and testing may influence daily prevention behaviors.

Sun-Protection Behaviors In general, in melanoma-prone families, family members with a history of melanoma report much greater adherence to prevention and screening recommendations than do family members who have yet to develop the disease [56]. In our initial prospective study of 60 adults (including 33 mutation carriers) from two large Utah *p16* kindreds undergoing genetic counseling and test reporting, participants reported increased intentions to practice sun-protection behaviors in the next 6 months, and follow-up data at the 2-year mark indicated significant improvements in photoprotective clothing use among both unaffected carriers and noncarriers and a significant decrease in sunburn frequency among affected carriers [57].

We extended these findings in a separate prospective longitudinal study that compared the outcomes of *CDKN2A/p16* counseling and testing among unaffected family members to those of a nonexperimental control group of unaffected members of high-risk families who received equivalent melanoma genetic counseling but no test result [58]. Both unaffected carriers and those who received equivalent counseling based on family history evidenced significant reductions in UVR exposure in the next year as measured by UVR dosimetry; however, only participants who received positive melanoma genetic test results were significantly less tan at the one-year follow-up as measured by reflectance spectroscopy. Both carriers and no-test controls reported fewer sunburns than noncarriers, and noncarriers did not change on any of these measures of UVR exposure.

Skin Self-Examinations As was the case for sun-protection behaviors, pre-testing adherence among unaffected family members in our initial study was highly variable and frequently poor—nearly two-thirds reported conducting skin self-examinations less frequently than the recommendation of one per month [59]. At the 1-month follow-up, all unaffected carriers reported conducting one or more skin exams since the counseling session, and 54.6% of them reported either having adopted a new screening behavior or modifying their existing practice to be more frequent and/or more thorough. Of particular importance, the reported thoroughness of these exams also showed improvement. Results from the 2-year follow-up indicated that these gains in thoroughness were sustained, resulting in SSEs that were nearly as thorough as those reported by affected family members [60].

Clinical Total Body Skin Examinations We also examined the impact of genetic counseling and test reporting on intentions to receive a professional total body skin exam and on receipt of these exams at follow-up. Intentions to obtain TBSEs increased significantly in all groups immediately following counseling and test reporting. At the 2-year follow-up, dramatic improvement in the proportion of unaffected carriers receiving a TBSE in the past year was reported—from 21.4% to 66.7% [60]. Similarly, high rates of TBSE adherence in the year following test reporting among *p16* mutation carriers have been reported by Kasparian et al. [61].

In sum, melanoma genetic testing seems to be successful in promoting improvements in daily sun-protection behaviors, the frequency and thoroughness of monthly skin self-examinations, and compliance to recommendations for annual professional total body skin examinations. Moreover, unaffected family members who received positive genetic test results reported levels of prevention and screening behavior that were comparable to the high level of adherence reported by family members with a melanoma history. These results suggest that melanoma genetic testing may successfully alert high-risk patients prior to disease onset, facilitating early detection and perhaps even prevention.

Pancreatic Cancer Screening As shown in Table 22.2, *p16* mutations also confer an up to 17% lifetime risk of pancreatic cancer [62]. To date, the impact of screening on survival outcomes is still unknown, but clinical trials have demonstrated that early pancreatic neoplasms can be detected through screening. Recent consensus guidelines now recommend screening for pancreatic cancer for all *p16* carriers beginning at age 40 [18, 63]. However, this is a very recent recommendation for carriers and the psychological and behavioral impact of this information remains an important future direction for research on *p16* counseling and testing [64, 65].

Psychological Outcomes of Cancer Genetic Counseling and Testing

Since the advent of cancer genetic testing in the early 1990s, researchers have been concerned that advances in personalized medicine may come with a psychological cost, namely inducing or exacerbating anxiety, depression, or cancer worry [e.g., 6, 66, 67]. In the following sections, we will review what is known from both quantitative and qualitative research about negative and positive psychological outcomes of cancer genetic testing and describe multiple measures that have been designed to capture these outcomes. We review new evidence concerning the informational and motivational benefits of genetic testing and present an emerging view that hereditary cancer genetic counseling and testing may be best conceptualized not as new stressors with which people must cope, but rather as powerful tools to be used in an ongoing and often long-standing effort to understand and manage familial cancer risk [3, 4].

Psychological Distress

A large body of literature has examined distress and other negative responses reported by patients waiting for a genetic test result and at various time intervals after learning results (typically up to one year later [2, 68–72]). In general, there is little evidence for sustained increases in distress after receiving a positive genetic test result for cancer susceptibility (i.e., HBOC or Lynch syndrome) up to 3–7 years after genetic testing [2, 44, 68, 69, 71, 73]. Instead, depression and anxiety decrease among both carriers and noncarriers of genetic mutations, with these decreases tending to be greater and to occur more quickly among noncarriers [6, 68]. Melanoma genetic testing similarly does not increase anxiety, depression, or cancer worry but rather seems to result in either short- or longer-term decreases in psychological distress [61, 65].

Though psychosocial issues in FAP families appear to be relatively understudied, elevated reports of anxiety and depression following FAP testing and among FAP patients, in general, [74] are a potential exception to this pattern of low distress. In Douma et al.'s review [49], 2 of the 3 studies examining psychological outcomes found evidence of clinical levels of anxiety and/or depression following genetic testing, with particularly elevated rates of anxiety among adult mutation carriers with low self-esteem or low optimism [75]. However, FAP is unique among hereditary cancer syndromes, in that it is nearly completely penetrant, and that a positive test result is often followed by colectomy for management of cancer risk. The greater certainty of disease presentation and the need for surgical intervention may contribute to the sustained emotional response to testing.

Understanding Short-Term Increases in Psychological Distress Following Positive Test Results Despite this general consensus, some researchers have found slight to moderate short-term increases in distress among individuals testing positive for genetic mutations [70, 76–78], particularly among unaffected individuals [2, 79] and those with high levels of baseline (pre-testing) anxiety [71, 80]. However, distress returned to baseline 1 year following testing [77, 81] or was comparable to distress among noncarriers [82].

A study of *BRCA1/2* testing by Beran and colleagues [76] illustrates some of the psychological and methodological complexities of understanding adaptation to genetic test results. The researchers examined prospective changes in depression, anxiety, positive and negative mood, and cancer-specific distress from baseline to 1, 6, and 12 months following receipt of test results among 155 women (38 mutation carriers), of whom more than half had a personal history of breast or ovarian cancer. Across nearly all psychological outcomes (except anxiety), mutation carriers' reports of depression, mood, and cancer-specific distress showed a curvilinear pattern, such that distress increased significantly at 1 and 6 months before either returning to or approaching baseline. The authors explained, "For mutation carriers, the immediate months after test receipt often involve decisions about prophylactic options and communication of results to family and friends; these activities, accompanied by one's own emotional and cognitive processing of the result, may explain the heightened distress observed during this period" (p. 114). These findings suggest that, if resources allow, researchers should assess psychological outcomes at multiple time points in the year following test reporting to identify the points at which intervention and other kinds of support may be needed for counselees undergoing testing for different cancer syndromes.

Understanding Variability in Responses to Positive Genetic Test Results Although group means for depression and anxiety among mutation carriers may be within normal limits in most studies, it is important to consider variability in responding, both to understand psychological adjustment to genetic counseling and testing and to tailor programs to address the psychological needs of different groups of patients. Some reviews suggest that women who are younger, single, and who have sisters with breast cancer may be at higher risk of sustained distress following HBOC counseling and test reporting ([72], although not all studies have shown support for these patterns). Other studies have identified high baseline anxiety—but not the receipt of a positive test result—as a significant predictor of anxiety one year after *BRCA1/2* testing [81, 83]. For these reasons, it is essential to elucidate the individual differences (e.g., neuroticism, monitoring), socioeconomic factors (e.g., income, education), coping factors, and relationship and familial support factors that may contribute to these different outcomes at different times.

One particularly interesting approach to understanding which patients may be more likely to experience distress surrounding genetic testing comes from Roussi et al.'s use of measures of perceived risk, perceived coping ability to regulate emotions when thinking about cancer or undergoing cancer screening, belief in the predictive utility of positive or negative genetic test results, and belief in the effectiveness of risk-reducing measures, among other variables, to identify four distinct clusters [84]. Of these, one cluster—defined by high perceived risk and low self-ratings of ability to regulate emotions around cancer—was comprised by 27.5% of respondents and associated with significantly higher cancer worry, intrusive thinking, and depression scores. The other three clusters differed in their rated value of screening and their confidence in the effectiveness of prevention measures but did not differ in distress. The clusters also differed in age, education, and number of first-degree relatives affected with HBOC. This work highlights the benefit of considering multiple health cognitions in conjunction with patients' beliefs about their ability to regulate cancer-related distress in identifying patients who might benefit from specific kinds of intervention and support.

Another valuable approach to understanding differences in psychological adaptation to genetic test results comes from a study by Ho and colleagues [85]. Drawing on the different trajectories of psychological adaptation identified in the bereavement literature [86], Ho and colleagues examined trajectories of depression and anxiety 2 weeks, 4 months, and 1 year following testing in 76 Hong Kong Chinese adults who underwent genetic testing for Lynch syndrome. Of particular interest, only a few participants (4.3%) reported a "recovery pattern" defined by short-term increases in anxiety that subsided in the year following testing. Consistent with research showing low levels of distress, the most frequently reported pattern was a resilient pattern (67%) in which participants who were not particularly anxious or depressed before testing remained this way in the year following testing. However, a small subset of participants who were depressed or anxious prior to testing (7–9%) reported high distress at all follow-up assessments, suggesting that testing itself did not cause or exacerbate anxiety or depression (see also [81, 83]). A fourth subset of patients (13–16%) showed delayed reaction trajectories in which depression and anxiety were low immediately following testing, but increased by 1 year.

Finally, researchers have identified particular concerns and experiences with familial and personal cancer that patients may bring to the counseling setting that may create different outcome trajectories. Hamilton and colleagues [87] retrospectively assessed the events leading up to and following *BRCA1/2* testing among 44 female mutation carriers aged 18 to 39, approximately half of whom had a history of breast cancer. The researchers found that women typically described one of four major "life trajectories" of genetic testing. One subset of women was "acutely aware" of the risk in their family and essentially grew up aware that they had the potential for increased breast cancer risk. Women in this trajectory who did not elect to undergo prophylactic surgery often felt a high amount of distress and anxiety between clinical screenings, often prompting them to undergo risk-reducing surgery. A second subset of women was motivated to undergo genetic testing because of the death of their mother due to breast cancer, and many perceived mastectomy to be less anxiety-provoking than not electing surgery. A third subset of women was notified of their risk by a health care provider and saw the decision to undergo genetic testing as less emotionally laden than women in the first two trajectories and perceived that actions could be taken in order to take control of their health. Finally, a fourth subset of women was prompted to undergo testing due to a personal diagnosis of breast cancer. For this fourth group, treating breast cancer was the primary concern and genetic testing was of secondary importance—as such, some women often chose aggressive treatment strategies, such as bilateral mastectomy, prior to genetic testing. This study highlights the diverse personal experiences that young women with familial breast cancer risk bring to the counseling setting that may predict behavioral and emotional outcomes of genetic testing.

To further understand these patterns, it will be important to examine the effect of whether individuals engage in recommended cancer screenings on anxiety and depression. Engaging in preventive screening behaviors may serve to decrease negative psychological responses to undesired genetic test results [88]. While genetic testing serves to reduce uncertainty about cancer *risk*, it has been suggested that undergoing colonoscopy may serve as a coping strategy that serves to reduce uncertainty about cancer *status* [88]. It will be important to examine whether mammography and TBSE (as well as SSE) serve similar functions among those at risk for breast cancer and melanoma, respectively.

Testing-Specific Concerns Following Genetic Counseling

Researchers have also examined types of worry or concern that are specific to the testing context. Paramount among these are concerns about passing elevated cancer risk to one's children and being subject to health and life insurance discrimination [34, 89–91]. For example, our own studies of *p16* genetic testing for melanoma revealed similar concerns about children's cancer risk, which were especially elevated 1 month following counseling and test reporting [65]. Similar to psychological distress, such negative responses tend to be short-lived and may be the result of heightened cognitive processing regarding one's test result and future plans [76, 90]. Despite these potential short-term negative outcomes, there is no evidence that mutation carriers regret having undergone either *BRCA1/2* or *p16* genetic testing [34, 65].

Identifying and Supporting Patients Experiencing Cancer-Specific Distress Given that small subgroups of patients may experience distress, psychosocial questionnaires have been developed (a) to prospectively identify patients at risk for distress and (b) to elicit specific concerns to be addressed in either initial or follow-up genetic counseling sessions [92, 93]. Esplen and colleagues' Genetic Psychosocial Risk Instrument (GPRI [92]) assesses anticipated or experienced impact of having a disease risk or genetic mutation (including concerns about passing disease risk to children), personal history of mental health issues, and personal and familial experiences (including caregiving and bereavement) with the disease for which they are receiving counseling and testing. The GPRI successfully identified 84% of participants who displayed distress one month following genetic testing results.

A second measure, the Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaire [93], assesses patient concerns in six problem domains: genetics (worry about chance of being a carrier, worry about choice of screening or surgery), practical issues (in daily life, obtaining insurance or mortgage), family communication and coping surrounding genetic testing, emotions surrounding genetic counseling and testing, living with cancer, and concerns about children's risk and how to communicate with them about it. In an RCT, all participants completed the PAHC and then roughly half were assigned to the intervention in which their genetic counselors received their questionnaire results prior to their initial counseling session. This study found that psychosocial problems were more frequently discussed in the intervention group and that counselors initiated discussion of psychosocial problems significantly more often and were more aware of patients' psychosocial concerns in multiple areas [94]. Importantly, these benefits were achieved without increasing the length of the counseling session compared to the control sessions. Furthermore, the intervention group reported significantly lower levels of cancer worry and distress one month after counseling. A follow-up study found that reported prevalence of some of the specific issues at one month had declined significantly, but had increased at a five-month follow-up session, suggesting that greater follow-up and support may be more useful to participants some months after their initial counseling session [95].

A third measure, the Genetic Risk Assessment Coping Evaluation (GRACE [96]), assesses similar testing-specific stressors, with a focus on how patients may cope with the experience of being referred for genetic counseling and awaiting test results. Measures like the three described here could be used to identify people who might benefit from interventions to help people reduce anxiety and avoidant behaviors while awaiting the outcomes of cancer genetic risk assessments [97]. Furthermore, researchers and genetic counselors might also look to research on uncertainty navigation to better understand how to help patients manage the uncertainty of waiting for test results [98, 99]. Post-counseling interventions have successfully deployed trained peer volunteers to provide peer support to *BRCA1/2* carriers to manage distress and provide information in the four months after test reporting [100], with some focusing on the support needs of young women from HBOC families [101].

Responses to Uncertain Test Results Many patients who undergo genetic testing do not receive a conclusive test result. Instead, these patients may receive test results that are uncertain such that they are uninformative (i.e., no cause for the cancer risk was identified) or they indicate a variant of uncertain significance (VUS [102]). VUS results may be found approximately 25% of the time [102]. Given that uncertainty is associated with these types of test result, concerns exist that individuals receiving uncertain test results may experience increased distress or have difficulty coping with the uncertainty (although uncertainty may be threatening to some, it can also allow room for increased optimism and hope [103]).

Researchers have increasingly sought to understand the experiences of patients who receive uncertain test results. A narrative review of communication of uncertain cancer genetic test results found that nearly all identified studies focused on genetic testing for HBOC and included female participants only [104]. Across studies, distress and worry tended to decrease following testing and counseling, although patients who specifically received a VUS—compared to uninformative results—were more likely to show increased distress and worry. This conclusion is similar to that of an earlier review that found that women receiving uninformative *BRCA1/2* results reported small decreases in cancer-specific distress at both short-and long-term follow-up assessments comparable to those reported by noncarriers [70]. With respect to behavior, the authors of the 2020 review [104] concluded that findings concerning family communication and treatment decisions were inconsistent across studies, and thus inconclusive. Ultimately, Medendorp and colleagues [104] determined that there was not strong evidence to suggest that communicating uncertain genetic test results was harmful (see also [105] for additional description of various studies concerning patient perspectives on VUS; [106] for a review of how patients experience uncertainty in the context of cancer genomics, including in response to receipt of a VUS; and [107] for a meta-analysis of outcomes of multigene panel testing and exome sequencing for hereditary disorders).

Perhaps of more concern than increased distress is that patients who receive uncertain test results will misinterpret these results. For example, a retrospective interview study of 24 women found that 73% misinterpreted their VUS as a genetic predisposition for cancer, and 29% recalled having been given a pathogenic result as opposed to an uncertain result. Nearly half of the participants who interpreted the VUS as pathogenic underwent prophylactic surgery [108]. In another study, individuals who received inconclusive results and who did not have a personal cancer history reported greater decreases in distress than those with a cancer history, suggesting that they may have interpreted inconclusive test results as negative test results [70]. According to the narrative review, seven of nine studies that examined test recall and understanding found that participants had difficulty interpreting or understanding their result [104]. Difficulty understanding the implications of uncertain test results may be exacerbated by low numeracy [109]. Ensuring that genetic counselors are able to adequately explain uncertain test results may be one solution (see [110] for an examination of genetic counselors' beliefs about VUS), but even when a summary statement was provided to patients, accurate information about uncertain test results was infrequently communicated to at-risk family members [111]. It is also recommended that the possibility of an uncertain result is discussed in pre-test counseling [104]. Finally, although some limited evidence suggests that patients may not react negatively to reclassification of VUS [112], more research is needed, and steps should be taken to ensure that patients understand the implications of such reclassification.

Toward an Expanded View: Understanding Both Positive and Negative Psychological Outcomes of Cancer Genetic Testing

In comparison with the large number of studies and measures assessing potential increases in distress, the assessment of positive emotional responses and other informational and motivational benefits of genetic counseling and test reporting has received less attention. We first highlight key qualitative studies of the perceived advantages and disadvantages of having undergone counseling and testing for HBOC, Lynch syndrome, and hereditary melanoma. In many cases, these qualitative studies provided insights into patient perceptions and experiences that were subsequently developed into survey items that could be administered to larger samples. The resulting instruments permit the reliable assessment of a broader range of emotional and motivational outcomes, including emotional costs and benefits, both positive and negative effects on the self-concept, changes in feelings of mastery and self-efficacy with respect to managing cancer risk, and increased or decreased motivation to manage that risk through prevention and early detection.

Qualitative Accounts of the Costs and Benefits of Hereditary Cancer Risk Counseling and Testing

Hereditary Breast and Ovarian Cancer Several studies provide retrospective assessments of patients' perceived advantages and disadvantages of having undergone HBOC genetic testing. For example, Lim et al. [113] interviewed 47 women (23 carriers, 24 noncarriers) without a history of breast or ovarian cancer. Participants had undergone counseling and testing 1–70 months earlier (median = 13 months). In terms of perceived advantages, particularly for carriers, two predominant themes were identified—(1) that knowledge is powerful (concerns about being at high risk had been validated by the test; removal of uncertainty concerning cancer risk had produced a sense of control; and knowledge afforded an "opportunity to prepare emotionally and mentally"), reported by 73.9% of carriers; and (2) that counseling and testing had provided increased access to and more favorable attitudes toward screening programs and surgical options, reported by 56.5% of carriers. One carrier said "I can do something about it and have more control" (p. 123), while another noted, "Knowing allows me to do something positive." Another stated, "Now I know it is a priority and have a more positive attitude toward screening." Most carriers reported no disadvantages. Participants who reported disadvantages described intrusive thoughts about cancer risk and loss of innocence. The authors note that of the minority of women reporting these concerns, all were less than 48 years old and had received their results less than 13 months earlier.

Almost all noncarriers reported perceived advantages of genetic testing, primarily peace of mind ("Now I don't think I am next in line") and feeling normal ("I now feel like part of the normal population"). Noncarriers also expressed relief that they had not passed the mutation onto their children. Only one noncarrier, who subsequently underwent prophylactic surgery, reported no perceived advantages. Most noncarriers indicated no disadvantages of having undergone testing, with the exception of one participant who reported concerns about becoming complacent about breast cancer risk.

Similar results were obtained by Claes et al. [114] in an interview study of 41 women (20 carriers, 21 noncarriers) who had undergone genetic testing for HBOC one year earlier. All respondents reported at least one advantage, and the two most frequent responses were "instrumental advantages" consisting of increases in perceived control or knowledge about health behavior options (75% of carriers) and "certainty/reduction of uncertainty" (40% of carriers; 23.8% of noncarriers). The most common advantage noted by noncarriers was reassurance and relief (71.4%). Of particular interest, 70% of carriers and 25% of noncarriers reported at least one disadvantage, with wide variation in the particular disadvantages reported (e.g., uncertainty, survivor guilt, feelings of hopelessness, increased anxiety, increased risk perceptions). Participants also reported a variety of changes in specific domains, particularly in body image ("different experience of breasts," consequences of preventive surgery), emotions (experience of personal growth, increased anxiety), and relationships with relatives (more or less closeness and support).

Lynch Syndrome Claes et al. [115] interviewed 72 participants following testing for Lynch syndrome. Consistent with the above findings, participants reported both advantages and disadvantages of testing. All but one carrier and two noncarriers reported at least one advantage, and again, the two most frequently cited advantages by carriers were instrumental advantages (89%) and reduction of uncertainty (33%). For noncarriers, the most frequently cited advantages were reassurance (50%), learning that children were not at risk (39%), and decreased need for screening (33%). In contrast to the above studies of HBOC, more than half of the carriers, as well as 17% of noncarriers, reported at least one disadvantage of knowing their results. For carriers, the major disadvantages reported were the burden of regular medical examinations (22%) and psychological burdens (19%); for noncarriers, disadvantages involved difficulties arising from having different results compared to their relatives (i.e., survivor guilt, feelings of exclusion, relatives' negative reaction to the disclosure of a favorable test result). As in the HBOC studies reported above, participants reported some degree of change in different life domains, such as body image (especially the perception of physical symptoms and whether they were interpreted as signs of potential cancer), and both heightened worry and personal growth.

Hereditary Melanoma The availability of preventive options to reduce melanoma risk through daily reduction of UVR exposure makes possible a different set of perceived costs and benefits of genetic test reporting and counseling. We asked respondents at three times in the year following counseling and test reporting to describe any benefits or limitations of having received their test results [65]. The results were striking—nearly all participants (approximately 95%) at each assessment listed one or more positive aspects of learning their genetic test results, while only 15.9% overall (11.9% at 1 month, 8.1% at 6 months, and 3.3% at 1 year) listed a negative aspect at any assessment. Similar to findings from interviews with patients who have undergone testing for HBOC or Lynch syndrome, all participants who listed a disadvantage also listed one or more benefits.

Participants described benefits in three major thematic areas: emotional, informational, and behavioral. Perceived emotional benefits were reported by 71.4% of noncarriers and 26.1% of carriers. Noncarriers were especially likely to report feelings of relief for themselves and their children that they did not carry the mutation, while carriers reported decreased fatalism and guilt concerning melanoma risk. For example, one noncarrier wrote, “I grew up thinking I was doomed to get melanoma. Knowing that I am negative for the *p16* gene has brought me much relief.” One carrier noted, “I feel that there are choices and options for the better about taking steps to prevent melanoma. It is not hopeless.” For another carrier, a positive test result provided an explanation for prior cancer. (“I don’t feel quite so guilty about having had melanoma, as I did when I thought it was all due to my sun exposure.”)

For mutation carriers, the primary perceived benefits were informational and behavioral: 78.3% reported increased knowledge about melanoma risk and its management, and 65.2% reported improvement in health behaviors or plans to increase their practice of photoprotection and screening for themselves and their families. The informational benefits reported by carriers conveyed a strong sense of perceived control and empowerment. One carrier wrote, “The more information the better. The more I know, the more I’ll be able to take precautionary measures and get skin checkups,” while another wrote, “I like being informed and have the chance to prepare for the challenges that come in life. Prevention is half the battle!” Reported improvements in prevention and screening behaviors conveyed the same sentiment: “I think more about what I’m doing in the sun and take more measures to protect myself and my family. I also feel more in control of what happens to me by the knowledge I have,” and “Having the test results be positive has increased my vigilance. And it has made me more aware of increased risk to my children.” A majority of noncarriers (95.2%) also reported increased knowledge about melanoma risk and its management, with a smaller proportion (38.1%) reporting improved prevention and screening behaviors.

Finally, disadvantages of receiving test results were rarely reported (15.9% of respondents overall) and included discouragement (“A little discouraging, but I would rather know”), frustration (“Just that there is no genetic way of fixing it yet—it ticks me off”), and insurance concerns. Only one participant, a noncarrier, reported decreased vigilance as a disadvantage of receiving test results.

Summary These qualitative studies indicate that hereditary cancer risk counseling and testing have both positive and negative outcomes, but rarely exclusively negative ones. Among the consistent benefits reported by mutation carriers are increased knowledge about risk and appropriate management and increases in perceived control over cancer risk. Depending on the particular cancer syndromes, these advantages may come with costs, such as altered body image and feelings of being burdened by the demands of accelerated screening. Noncarriers consistently reported feeling relieved about their own and their children’s risk. We turn now to quantitative assessments of these and other costs and benefits.

Quantitative Assessment of Positive and Negative Psychological Outcomes of Hereditary Cancer Risk Counseling and Testing

In this next section, we review several instruments that have been designed to capture the specific kinds of costs and benefits reported by participants in qualitative studies. As we will describe, some of the measures are likely applicable to testing for all or most genetic risks, while others are necessarily specific to particular cancer syndromes. The increased use of standardized measures in future research will facilitate comparisons of the psychological impact of hereditary cancer risk counseling and testing for different cancer syndromes, for different groups of patients, and with different counseling protocols. It will also permit formal meta-analyses, which to date have been hampered by the large variety of measures used. Importantly, as we will illustrate below, these quantitative measures also permit researchers to examine how different kinds of psychological outcomes may be related to each other and to the adoption of recommended prevention and screening behaviors.

Reduction in Uncertainty Regarding Cancer Risk The potential for cancer genetic testing to reduce uncertainty (or alternately, to increase certainty) for both carriers and noncarriers is frequently mentioned as a benefit in qualitative studies. The Psychological Adaptation to Genetic Information Scale [PAGIS, 116] includes a certainty subscale consisting of items assessing counselees' understanding of how they came to have a particular gene alteration, the health risks their relatives face, the chances of passing the gene alteration to one's children, and the ability to explain to other people the meaning of having a particular gene alteration. In our prospective nonexperimental control group study of melanoma genetic test reporting, counseling paired with test reporting produced greater increases in reported understanding of melanoma risk than family history-based counseling, despite comparable magnitude of melanoma risk in the two groups [5]. Interestingly, there were two other consequential sets of cognitions about melanoma risk and its management that differed between the testing and no-test control groups. Specifically, participants who received a genetic test result were (a) less likely to derogate or question the quality of the risk information provided and (b) more likely to view the prevention and screening recommendations presented in the counseling session as personally applicable to them. These cognitions were related over time, such that participants who engaged in less derogation of the quality of the risk information immediately after testing reported greater understanding of their risk and greater perceived personal applicability of prevention recommendations one month later. One possible explanation is that a specific genetic test result is interpreted as concrete and objective, thus facilitating acceptance of the risk information.

Perceived Personal Control, Self-Efficacy, and Mastery with Respect to Cancer Risk Three inventories assess perceptions of improved control following counseling and test reporting. The Perceived Personal Control measure [PPC; 117] captures multiple aspects of understanding and managing familial cancer risk. Sample items are, "I feel I know the meaning of the problem for my family's future," "I feel I have the tools to make decisions that will influence my future," and "I feel I can make decisions that will change my family's future." Originally conceptualized as three subscales (cognitive control, decision control, and behavior control), the scale was recently found to form a single reliable factor [118]. The PAGIS self-efficacy subscale assesses perceptions of self-efficacy for managing the effects of having a disease-causing genetic mutation or genetic disorder. Sample items are "I am confident that I can work out any problems having this gene might cause," and "I believe that there are things I can do to avoid the problems that may arise from having this gene." The third inventory that assesses mastery perceptions following genetic counseling and testing was specifically developed with both focus groups and large-scale surveys of people who had undergone *BRCA1/2* testing and testing for hereditary colorectal cancer [91, 119, 120]. In this framework, mastery perceptions are described as an element of the self-concept, and thus this work will be described more fully in the next section.

The importance of using measures that are sensitive to potential increases and decreases in perceived control is highlighted by findings from our first melanoma genetic test reporting study [121]. First, qualitative assessments immediately following counseling and test reporting indicated that participants overwhelmingly thought it was possible to either prevent (64.9%) or decrease the likelihood (28.1%) of future melanomas. We next examined trajectories of perceived control ratings over a two-year period. Noncarriers showed sustained gains in perceived control, whereas unaffected carriers showed short-term increases from baseline both immediately following counseling and one month later. In contrast, affected carriers reported no changes from baseline. Finally, an examination of individual changes in perceived control indicated considerable variability. Although 45% of participants reported increases in perceived control, 38.3% reported no change, and 16.7% reported decreases. Furthermore, increases in perceived control following counseling and test reporting tended to be correlated with increases in reported use of photoprotective clothing over the two-year period. These findings suggest both (a) that information about genetic causes of serious diseases may not necessarily undermine perceived control and (b) that individuals may differ in their response to this information in ways that may be consequential for subsequent adherence.

Impact of Cancer Genetic Counseling on the Self-Concept A particularly rich set of studies by Esplen and colleagues [91, 119, 120] has identified multiple ways in which cancer genetic counseling and the receipt of a positive test result may influence the self-views of high-risk patients. Individual interviews and focus groups were conducted with both affected and unaffected patients who had undergone counseling and testing to assess how that experience changed what they thought about themselves. Based on these interviews and focus groups, Esplen and colleagues developed specific scales to assess the impact of cancer genetic testing for *BRCA1/2*, FAP, and Lynch syndrome. The scales were then subjected both to factor analysis and convergent and divergent validation with other related concepts.

The resulting *BRCA* Self-Concept Scale consists of three factors: *stigma* (e.g., “I feel isolated because of my test result,” “I feel labeled,” “I feel burdened with this information”), *vulnerability* (e.g., “I distrust my body,” “I feel like a walking time bomb,” “I am worried that cancer will be found when I go for screening”), and *mastery* (e.g., “I know my body well,” “I am in control of my health,” “I am hopeful about myself in the future”). Higher scores indicate a more negative impact of genetic test results on self-concept. In two large validation samples of women attending high-risk breast cancer clinics, mean reported impact was greatest for vulnerability (3.85 on a scale ranging from 1 = strongly disagree to 7 = strongly agree), lower for stigma (2.72), and lowest for the negative impact on perceptions of mastery (1.46). Importantly, if one were to reverse score the mastery subscale so that higher scores indicated greater mastery, the resulting mean would indicate perceptions near the maximum value of the scale.

The self-concept scales developed for FAP [119] and Lynch syndrome [120] illustrate the importance of understanding how the specific demands of different cancer syndromes influence the self-concept. For example, the FAP self-concept scale [119] includes diminished feelings of physical and sexual attractiveness, as well as concerns about bowel control in addition to the stigma, self-esteem, and mastery items described above; concerns about bowel control and gastrointestinal symptoms, such as pain and bleeding, are also a major component of the Lynch syndrome self-concept scale [120]. Importantly, given the focus on women in most studies of *BRCA1/2* outcomes, the validation study of the FAP self-concept scale included a large number of men with a diagnosis of FAP and scores on the subscales, as well as the total impact on the self-concept, were similar for men and women.

As suggested by Esplen and colleagues [91, 119], these scales have many potentially important uses in both research and practice. First, the scales may be used to identify patients who may benefit not only from longer-term follow-up but also from different forms of counseling. For example, the psychosocial support needs of a patient who feels stigmatized and isolated are likely to be different from one whose concerns center around cancer fear and body image or low perceived mastery and diminished hope for the future. The particular impacts assessed by the three subscales may also suggest specific interventions—for example, support groups to assist those who feel isolated and stigmatized. Second, an important goal for future research is to examine how these specific impacts of genetic testing are related to subsequent decision making about screening and prevention options. For example, Esplen and colleagues [91] note that feelings of stigma and vulnerability may increase anxiety, and thereby interfere with screening attendance. Conversely, a resulting sense of empowerment or mastery through genetic knowledge may promote health behaviors to manage risk. Third, the scales may be used to examine the cancer-related self-concept of members of high-risk families prior to testing. Esplen and colleagues [91] hypothesized that the pre-testing self-concept may differ based on whether patients have experienced multiple losses due to cancer in the family or have observed survival among affected family members (see [92] for a related assessment of personal and family history factors that may predispose patients to psychosocial risks of genetic testing). Finally, these authors suggest that the scales may be used to examine family members who receive negative test results and have difficulty incorporating this new and unexpected information into the self-concept. Examining how feelings of cancer vulnerability may persist in such patients may be useful in understanding and assisting those who have difficulty disengaging from the intensive surveillance programs they may have lived with for many years [see 44, 45, 121–123].

The scale development efforts undertaken by Esplen and colleagues highlight several important issues for understanding psychological outcomes of hereditary cancer risk counseling and testing. First, all three disease-specific self-concept scales include both positive (mastery, self-esteem) and negative impacts (vulnerability, stigma, diminished physical and sexual attractiveness) among mutation carriers following counseling and testing, and patients appear to endorse (on average) low perceptions of stigma, intermediate perceptions of vulnerability, and high levels of mastery. Second, the specific impacts on self-views are different for different hereditary cancers, likely due to the different recommendations concerning prophylactic surgery and the implications of such surgery for sexual behavior and body image. As genetic testing becomes available for more hereditary cancers, it will be important to understand which aspects of different cancer syndromes (e.g., age of onset, involvement of reproductive system, availability of preventive options, etc.) have different effects on the self-concept. Third, this more nuanced view of the impact of hereditary cancer risk counseling and testing on the self-concept suggests areas in which to focus intervention efforts to reduce negative changes and promote feelings of mastery and self-esteem.

Motivation to Perform Recommended Prevention and Screening Behaviors Based on the qualitative work described here, including our own initial findings concerning specific emotional, informational, and behavioral benefits of melanoma genetic testing [65], we created a series of items assessing perceived benefits of melanoma genetic counseling for the management of one's personal melanoma risk and, as applicable, for the management of children's and grandchildren's melanoma risk. Participants in the BRIGHT Project completed these items one month and one year after undergoing melanoma genetic counseling with or without test reporting [4]. These items were subjected to factor analysis, which yielded reliable multi-item assessments of the degree to which participants felt better informed and prepared to manage their risk, motivated to reduce sun exposure, and motivated to perform screening, along with separate assessments of negative emotions about melanoma risk (discouraged, frustrated, hopeless), positive emotions about melanoma risk (hopeful, peace of mind, relieved), and worry about being in the sun. Following adjustment for covariates, unaffected participants who received positive melanoma genetic test results reported feeling more informed and prepared to manage their melanoma risk and more motivated to reduce their sun exposure than no-test controls from melanoma-prone families who had received equivalent counseling about their risk and its management but no test results. All groups reported low negative emotions about their melanoma risk, but carrier parents reported greater (but moderate) negative emotions about their children's risk. These findings suggest that genetic counseling and test reporting promotes sustained increases in the degree to which members of high-risk families feel informed and prepared to manage their risk and particularly their degree of motivation to reduce sun exposure.

Additionally, regardless of testing group, we found that women, older, and more educated respondents reported greater informational and motivational benefits, suggesting that interventions might profitably examine changes to the counseling protocol that might better serve to inform and motivate men, younger respondents, and those with less education.

Studies of attitudes toward screening among participants undergoing testing for Lynch syndrome suggest similar sustained increases in the year following counseling and test reporting in carriers' commitment to obtaining regular colonoscopies, and self-efficacy for doing so, in perceived benefits of screening, and in reduced barriers to screening [124].

An Integrative Model for Understanding Multiple Determinants of the Psychological and Behavioral Impact of Hereditary Cancer Risk Counseling and Genetic Testing

Having illustrated that there are multiple positive and negative psychological outcomes of cancer genetic counseling and testing, as well as different potential trajectories of outcomes, the next steps for research are to understand the multiplicity of factors that may influence these outcomes and to further develop and implement interventions to address negative outcomes for the subset of individuals who experience them. Fig. 22.1 presents a schematic of potentially impactful

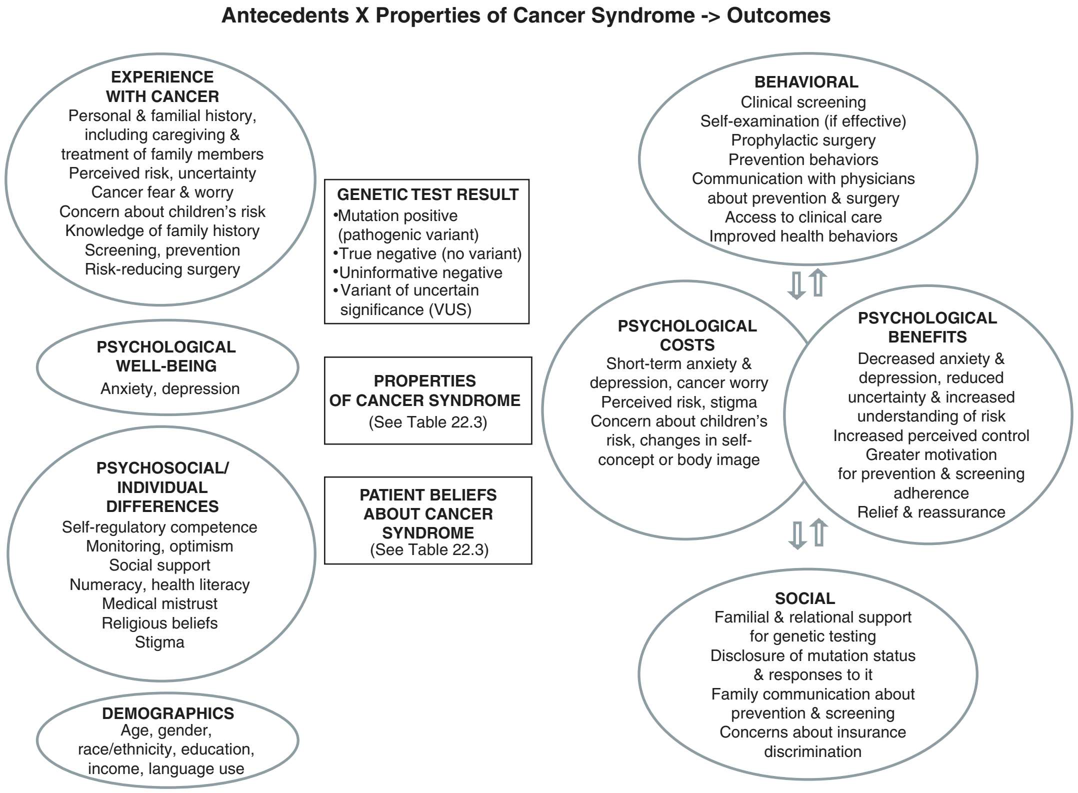

Fig. 22.1 A model for understanding multiple antecedents and outcomes of responses to hereditary cancer risk counseling and genetic testing for different cancer syndromes. Note. Interrelations among the sets of antecedents, as well as those among properties of the cancer syndrome and patient beliefs about them, are not shown for ease of presentation

antecedent factors, properties of the cancer syndromes themselves that may moderate responses to counseling and testing, and an expanded set of behavioral and psychological outcomes identified by our review. We will describe each part of the model in turn and discuss what might be gained from a more detailed understanding of some of these antecedent factors.

Potential Predictors of Responses to Genetic Testing

Antecedents of Testing Figure 22.1 illustrates multiple potential antecedent factors, including demographics, baseline and lifetime history of anxiety and depression, prior risk perceptions and associated worry and uncertainty about cancer, experience with cancer in the family, psychosocial factors, individual differences, and adherence to screening and prevention recommendations. The inclusion of these factors highlights the recognition that, rather than conceptualizing perceived risk, uncertainty, and distress as outcomes of genetic testing, baseline levels of these factors may be important elements of patients' motivations for seeking counseling and testing that may influence their responses to such testing. That is, as we have suggested throughout this chapter, the information provided by hereditary cancer risk counseling and genetic test reporting provides input to ongoing efforts to understand and manage familial cancer risk. Understanding these antecedent factors should improve efforts to better understand and support patients who may experience different outcomes. Thus, researchers should ask for which patients and for what cancer syndromes will counseling and test reporting reduce distress and uncertainty, and for which patients does hereditary cancer risk assessment have the potential to maintain or exacerbate distress.

As suggested by our discussion of different trajectories, baseline anxiety and depression have received attention as potential moderators of responses to hereditary cancer risk counseling and testing, and there has been some limited examination of other individual differences that may influence responses to testing, such as optimism [75] and monitoring [125]. It remains a challenge for future research to recruit and retain sufficient sample sizes to allow a prospective examination of how individual differences are related to specific outcomes of genetic testing for different cancer syndromes, especially as participants should optimally be stratified by mutation status and personal cancer history. However, such efforts will be important to understanding whether and how hereditary cancer risk counseling protocols might be tailored to people with different beliefs about the future and preferences for health information. Similarly, understanding how religious and spiritual beliefs predict uptake of and responses to genetic testing represents an important avenue for future research [see, e.g., 126–128].

Important Properties of the Cancer Syndrome As Fig. 22.1 highlights, the particular psychological outcomes one might expect from hereditary cancer risk counseling and testing may depend on properties of the cancer syndrome itself, particularly the management options available for different cancer syndromes, as well as developmental concerns, such as age of onset and age at which either prophylactic surgery or other prevention and screening options are recommended. Table 22.3 provides more detail about these syndrome-specific properties. For example, age of onset and age at which prophylactic surgery is recommended distinguish FAP from other syndromes, whereas hereditary melanoma is distinguished by the availability of preventive measures that should be implemented as early as possible to reduce cumulative UVR exposure. As *p16* counseling and testing for minors become more widely implemented, it will be important to understand both the prospective medical and psychosocial outcomes of proactively managing UVR exposure in young members of high-risk families [129, 130]. Furthermore, the particular management recommendations required by different cancers pose different adaptational challenges. As described in Table 22.3, the presence of embarrassing and/or uncomfortable symptoms and treatments that have implications for

Table 22.3 Properties of specific cancer syndromes and beliefs about them that may moderate behavioral, psychological, and social outcomes of genetic counseling and testing

Properties of the cancer syndrome			
Penetrance and tumor spectrum of the specific gene/mutation			
Age of onset			
Actionability and management approaches			
	Magnitude of risk-reduction or improved outcomes provided by screening and preventive measures.		
	Strength of data supporting management recommendations.		
	Types of management.		
		Prophylactic surgery.	
			Age at which prophylactic surgery is recommended.
			Implications for sexual behavior and reproductive capacity.
			Symptoms, loss of function, and other sequelae of surgery.
		Screening for early detection of cancer.	
			Age at which screening is recommended.
			Frequency of recommended screening procedures.
			Cost and accessibility of recommended screening procedures.
			Likelihood of false positive and negative screening exams.
			Degree to which symptom awareness or self-examinations are informative and reassuring.
		Risk-reduction measures.	
			Age at which to begin risk-reduction measures.
			Side effects and secondary risks associated with risk-reduction measures.
			Implications for lifestyle and other daily health behaviors.
Treatability/prognosis when cancer occurs			
Potential for recurrence and/or multiple primary cancers			
Beliefs about the cancer syndrome and modifiability of genetic contributions to it			
Causal theories regarding cancer risk, prevention, screening, and treatment			
	Genetic determinism.		
	Gene–behavior interaction beliefs.		
	Illness coherence, other illness representations, and health beliefs.		
	Cancer fatalism.		

sexual behavior and body image may pose unique, ongoing challenges [91, 119, 120].

Another property of hereditary cancer syndromes that has yet to be fully examined for its psychological impact is vulnerability to multiple primary cancers and to more than one kind of cancer. For example, melanoma may develop anywhere on the body where there is skin (not necessarily in existing nevi, not necessarily in sun-exposed areas). Furthermore, the successful excision and treatment of one melanoma do not reduce vulnerability to future melanomas. Thus, there is no single prophylactic surgery that could prevent all melanoma—lifelong vigilance is required. These distinctions may have important consequences for understanding the impact of genetic testing on survivorship issues for different forms of hereditary cancer, as a positive genetic test result makes one's risks for new cancers or different cancers an ever-present, lifelong possibility.

Last, cancer syndromes differ in the residual risks that apply to noncarriers of the particular mutation. In general, testing negative for a familial mutation returns a person's risk to general population status. However, there may be cases in which a patient's personal history may still indicate an elevated risk even when a mutation is not identified, such as a patient who previously had colon polyps but is a noncarrier of a Lynch syndrome mutation, or a patient with phenotypic risk factors for melanoma, such as dysplastic nevi, who is a noncarrier of a *p16* mutation. The ways in which such patients synthesize clinical and genetic information may influence risk perceptions, cancer worry, and adherence to screening following counseling about a negative test result.

Beliefs About the Cancer Syndrome and the Modifiability of Genetic Contributions to It Although our review has to this point focused on the objective properties of different cancer syndromes and the effectiveness of prevention and screening behaviors, there are large literatures in experimental social and clinical psychology and scientific communication that examine lay beliefs about genetic determinism and beliefs about whether personal behavior or environmental exposure can increase or decrease genetic risks [131–133]. These beliefs, listed in Table 22.3, are likely to influence responses to genetic counseling and testing. In our own work, such beliefs, particularly the belief that unhealthful behavior can amplify genetic disease risk, are robust predictors of improvements in sun-protection behavior following melanoma genetic counseling [134]. Researchers have also shown that the coherence between a risk-increasing genetic cause and the specific risk-reduction behaviors recommended in counseling is an important factor in motivating adherence to behavioral recommendations to reduce colon cancer risk [135]. Similarly, beliefs about the effectiveness of screening behaviors in improving cancer outcomes and other aspects of cancer fatalism are related to multiple aspects of learning about and managing cancer risk [136].

Multiple Potentially Interrelated Psychological and Behavioral Outcomes

Figure 22.1 details multiple potential behavioral, psychological, and social outcomes of genetic counseling and testing. Throughout this chapter, we have emphasized that members of high-risk families report both positive and negative psychological outcomes of genetic testing, for example, increased vulnerability to cancer, but also increased perceptions of self-efficacy to manage cancer risk. Thus, continued attention to measurement of both kinds of outcomes should be a priority for future research. Furthermore, research that examines how these positive and negative outcomes are functionally related—for example, the idea that some distress is necessary to promote benefit finding and personal growth [137, 138]—would enrich understanding of how participants incorporate the information provided by counseling and testing into their ongoing efforts to manage familial cancer risk.

We have also emphasized that the psychological and behavioral outcomes of cancer genetic counseling and testing should not be seen as independent of one another, in that many of the recommendations, particularly those involving prophylactic surgery, may affect important psychosocial outcomes [see, e.g., 139, 140]. Furthermore, as shown in Fig. 22.1, there are also important reciprocal relations to consider, as several authors have theorized that psychological outcomes, such as anxiety and depression, may influence adherence to screening recommendations. Specifically, anxiety among carriers may lead to avoidance of screening [e.g., 91], and carriers may elect accelerated screening or prophylactic surgery to reduce anxiety and cancer worry [see, e.g., 28, 87, 88]. Persistent anxiety and cancer worry may also account for overutilization of screening among noncarriers. These outcomes may depend, in important ways, on the management options available for different cancer syndromes, as well as on access to specialty clinics which have expertise in management and coordination of services.

Importantly, the list of behavioral outcomes to consider in conjunction with psychological outcomes includes other changes made to promote health, in general, such as changes in diet, exercise, smoking, and stress management [33]. Behavior change may also occur among family members, as patients encourage relatives to improve prevention and screening efforts [65, 141, 142]. Finally, another set of behavioral outcomes to assess involves patient communication with physicians about their prevention or surgical options following genetic testing [143]. Such discussions may predict medical management decisions, given the ability of physician recommendations to influence patient choices.

Familial and Relational Processes Involved in Discussing and Managing Hereditary Cancer Risk Finally, psychological outcomes may be influenced by social responses to disclosure of mutation status and family support and communication processes [144]. As many authors have noted, genetic testing poses unique challenges to the understanding of familial communication and support, especially as multiple family members receive different test results [145, 146]. Furthermore, spouses and partners are also affected. This recognition has led to many interesting studies of the dynamics of family communication [147–151], including the impact on the index patient of factors such as spousal anxiety that may influence how the patient manages the implications of a positive *BRCA1/2* test [152]. Interventions may accordingly focus on family communication processes [153, 154].

Toward Equity: Understanding Racial and Ethnic Disparities in Genetic Testing Knowledge, Referrals, and Uptake

There has been unparalleled progress in cancer prevention, detection, and treatment. However, such progress has not benefitted all individuals equally [155]. A critical issue for both research and clinical application involves increasing representation of members of racial and ethnic minority groups in cancer genetics research [156–158]. As we will review, there are important racial and ethnic disparities in cancer genetic testing knowledge and uptake, striking disparities in rates of referral for cancer genetic risk assessment, and a relative paucity of research on the psychological and behavioral outcomes of genetic testing among racial and ethnic minority individuals. For example, non-White and Hispanic patients are less likely to be offered or to pursue genetic testing [37, 159]. As another example, White adults are more likely to self-refer for *BRCA1/2* genetic testing than African American adults [160], and in one study, less than 50% of African American women who underwent counseling for *BRCA1/2* mutations underwent genetic testing [161]. Similar differences in uptake have recently been found for melanoma genetic testing between non-Hispanic Whites and Latinos in New Mexico, even in the context of an RCT that offered online information in English and Spanish and mailed kits for *MC1R* testing [162].

These disparities in genetic testing uptake may contribute to disparities in cancer morbidity and mortality rates among racial and ethnic minority groups in the United States, given that one goal of genetic testing is to promote cancer screening and early detection. Cancer diagnosis at advanced stages contributes to increased death rates, and African Americans are more likely to be diagnosed at advanced stages for cancers for which screenings are available [155]. For over four decades, African Americans have had the highest cancer mortality rate compared to any other racial and ethnic group in the United States [155], and cancer is the leading cause of death for Latinos in the United States [163]. Therefore, it is imperative to find ways to promote early detection to improve treatment outcomes among racial and ethnic minorities and, in particular, to determine how to increase uptake of HCRC and genetic testing.

Contributors to Health Disparities in Hereditary Cancer Genetic Counseling and Testing

Knowledge and Awareness of Genetic Testing Numerous studies have identified disparities in awareness of cancer genetic testing among racial and ethnic minorities [164, 165]. For example, one study that used the U.S. National Cancer Institute's 2017 Health Information National Trends Survey (HINTS) data reported that over half of participants were aware of genetic testing; however, Non-Hispanic Asians and non-Hispanic Blacks were less likely to have heard of genetic testing than non-Hispanic Whites [166]. Cancer-related testing uptake remained extremely low among those who were aware of genetic testing [166]. Similarly, awareness of cancer genetic testing remains low among Hispanics [167–170]. Members of minority groups are less aware of *BRCA*1/2 genetic testing than are Whites [170–173]. These racial differences are only partly explained by demographic factors such as SES or insurance status [174]. However, length and region of residency in the United States and education account for a large portion of the difference in genetic testing knowledge and awareness between Whites and Hispanics [174].

Cultural factors may contribute to disparities in knowledge about genetic testing. For example, a content analysis comparing genetics-related stories published in a national sample of 24 Black weekly newspapers to stories published in general audience newspapers in the same communities found several differences [175]. First, genetics-related stories, including stories with cancer as the main topic, were more frequent in Black newspapers. Black newspapers were more likely to focus on family history, risk factors, and screening, but less likely to mention specific genetic causes of diseases or other topics like genetic testing and genetic therapy. The authors suggested that the focus on family history in Black newspapers may reflect collectivist cultural values. Understanding the sources from which members of different ethnic and racial groups receive cancer genetics information would enable researchers to target these sources to better disseminate and encourage use of genetic counseling resources.

Other evidence suggests that refusal of genetic testing may be associated with a lack of family medical history knowledge due to a patient's attempt to avoid stigma [176]. For example, Latinos from older generations may hesitate to disclose to family or their own Latin community about a cancer diagnosis. Similarly, Asian American women may be concerned with having a "bad gene" and with not wanting their family name to be associated with it [176]. Latinas have reported greater perceived disadvantages (such as anticipating feeling ashamed if they tested positive) of cancer genetic testing than African American women, although ethnicity did not predict these attitudes above and beyond the sociodemographic characteristics of income, education, language preference, and years in the United States [173]. Additionally, Latinas may prioritize household and family needs before personal health or genetic counseling needs, reflecting the belief that family responsibilities should be prioritized over one's own personal health [173, 177].

Medical and Healthcare System Mistrust Research increasingly suggests that ethnic minorities' mistrust of the healthcare system, or of individual physicians, contributes to differential engagement in the healthcare system [178]. For example, Latinas high in medical mistrust report fewer perceived benefits to genetic testing, greater barriers, and greater concerns about abuses of genetic testing [179]. Similarly, African Americans are "more likely to report that the government would use genetic tests to label groups as inferior, and less likely to endorse the potential health benefits of testing" [180, p. 363; see also 160, 173]. Provider communication, patient satisfaction, and trust in one's provider are factors associated with medical mistrust [181–183]. Among both affected and unaffected African American women at risk for *BRCA1/2* variants, participants who reported a greater lack of confidence in genetic counseling and testing also reported greater medical mistrust [184]. This highlights the importance of addressing patients' needs, concerns, and uncertainties [144, 185–187] in order to build their confidence in medical providers and in genetic counseling and testing.

The most commonly reported concerns about breast cancer genetic testing among Latinos and African Americans have been emotional distress, fear, lack of insurance, insurance discrimination, and financial costs [169]. Specifically, mistrust of the medical system described by Latinos included beliefs that physicians spend too little time with them, make money from extraneous procedures, and exhibit a lack of empathy [169]. Medical mistrust and a preference for speaking Spanish predicted greater perceived disadvantages of genetic testing above and beyond ethnicity, sociodemographic factors, and genetic testing awareness [173]. In Gómez-Trillos et al.'s (2020) study of 20 Latinas at increased risk for HBOC, participants reported not feeling comfortable asking the interpreter questions, due to lack of trust that their interpreter would give them accurate information, and reported that the genetic information communication lacked cultural sensitivity [177].

In contrast, some researchers reported an unexpected finding that African American women had more positive attitudes toward genetic testing for HBOC than Caucasian women, as well as less knowledge [188]. It should be highlighted that although African Americans continue to show medical system mistrust, they show the opposite in their patient–provider relationship. African American women report having high trust in their personal providers [189, 190]. Preliminary studies have found that Latinas with breast cancer undergo *BRCA1/2* genetic counseling when offered by their healthcare providers, indicating patients may be more likely to accept genetic counseling if offered to them at their clinic visit [191, 192]. These study outcomes are consistent with the finding that physician recommendations continue to be a motivator for genetic testing uptake in African Americans [193] and Latinos [194]. Despite racial and ethnic minorities' limited awareness of genetic testing, African Americans and Latinos have high interest in participating in cancer genetic testing [193, 195]. These findings highlight the importance of understanding specific kinds of mistrust as previous studies have focused on mistrust concerns in regards to genetic testing data, medical systems, and insurance, and suggest that researchers should additionally examine trust in patient–provider relationships that may promote genetic testing uptake.

Provider Discussion and Referrals for Genetic Counseling Another potential explanation for the disparities in Hispanic genetic testing uptake is lower rates of provider discussion and genetic counseling referral [164, 196–198]. One recent study of breast cancer survivors found that Black women were 16 times less likely to have reported discussing genetic testing with a provider than non-Hispanic White women, while Spanish-speaking Hispanic women were half as likely to have had these discussions as their non-Hispanic White counterparts [199]. Similarly, Spanish-speaking Latinas diagnosed with stage 0–III breast cancer were five times more likely to report unmet needs for discussion about cancer genetic testing compared to non-Latina patients [200]. These issues may be compounded by language barriers and the lack of bilingual genetic health professionals [201]. These findings are especially important as discussion with one's provider is often the single strongest predictor of genetic testing uptake [199].

One explanation for these differences is that African Americans and Latinos may see physicians with lower rates of both ordering genetic tests and of referring patients for genetic testing [160], as physicians with primarily ethnic minority patients are less likely to have ordered genetic tests or referred patients to genetic testing services than physicians with a lower proportion of ethnic minority patients [202]. However, these disparities have also been found in data from a single urban hereditary breast and ovarian cancer center, at which non-Hispanic Whites were more likely than people of all other ethnicities to be referred due to family cancer history, whereas non-Hispanic Blacks, Hispanics, and Asians were more likely to be referred due to a personal cancer history [203]. Strikingly, many of these patients would have met one or more criteria for genetic testing based on family history prior to their cancer diagnosis. Non-Hispanic Whites were more likely than individuals of other ethnicities to undergo increased cancer screenings and/or risk-reducing surgery once *BRCA1/2* mutations were confirmed. Hispanics and Blacks were more likely to have advanced-stage disease at time of testing [203]. These disparities reflect missed opportunities for cancer prevention and early detection for both ethnic minority patients and their family members and suggest that systemic changes, such as automated referrals, may be useful.

Healthcare System Barriers Additional contributors to the disparity in uptake are health insurance status and concerns about potential insurance discrimination. Lack of health insurance is disproportionately more common among members of racial and ethnic groups. African American, Hispanic, and American Indian/American Native women were over 30% more likely to be diagnosed at a later stage of breast cancer compared to White women, and almost half of this disparity was a consequence of being uninsured or a Medicaid recipient [204].

With respect to insurance discrimination, the Genetic Information Nondiscrimination Act 2008 (GINA) was enacted by the United States Congress to prevent insurance companies from denying coverage based on one's genetic information. This law only protects the individual from discrimination up until the onset of the disease [205]. Other U.S. laws, most significantly the Affordable Care Act, limit how diagnoses and symptoms can be used in determining insurability. Green and colleagues found that the majority of participants from a U.S. online survey were unaware of GINA; however, once informed, 30% of respondents reported greater concerns about genetic discrimination in health insurance [206]. Other studies confirmed lack of awareness of GINA but did not find that this was a barrier to testing, or that those who were unaware of the protections provided by GINA harbored concerns that genetic information could be misused [167]. GINA affords protection for most patients against the use of pre-symptomatic genetic information by insurers. GINA does not address the use of genetic information by life or disability insurers. Broadening the prohibition of using pre-symptomatic genetic information to determine eligibility for other types of insurance is being considered nationally. In 2020, Florida expanded its genetic non-discrimination law to include life and disability insurance.

Comprehension and Discussion of Genetic Test Results Even following genetic counseling and testing uptake, there remain disparities in understanding of genetic test results, their implications, and the recommended actions to take. In one recent study, Latinas who had undergone genetic testing could not describe either the purpose of the genetic test or the implications of the results [177]. Kamara et al.'s (2018) findings indicated that genetic counseling sessions with Latinas were often one-sided conversations [207]. Genetic counselors would ask "yes" and "no" questions to test patients' understanding, and the patient would respond without further comments or discussion. More research should be done to improve communication between patients and providers in order to improve genetic testing understanding for all patients. The use of medical interpreters may also inhibit a two-way discussion between patient and genetic counselor, creating a barrier to patient comprehension [207]. Rajpal et al. [169] indicated that Latina breast cancer survivors report fear of being misunderstood by healthcare providers, feeling ashamed for not speaking English, and not understanding medical jargon.

Disparities in Understanding of Genetic Contributors to Cancer Among Ethnic Minorities

In addition to disparities in uptake, there is an even more pressing, fundamental set of disparities in knowledge about hereditary cancer in racial and ethnic minority groups, as most data on cancer genetics and inherited cancer risk are based on White individuals of Western European ancestry ([208]; see [155] for discussion). This limits knowledge of the genetics of cancer risk for ethnic and racial groups. Specifically, genetic counseling becomes less precise and informative for racial and ethnic minorities because the current knowledge on inherited cancer risks cannot be applied to all populations. As a result, members of racially and ethnically diverse groups are much more likely to receive VUS results [209, 210]. It is unknown how the receipt of an uncertain result may impact confidence in genetic testing and the medical system. Genetic research must include diverse populations in order for the benefits of these advances to be shared equally by all individuals.

Promoting Health Equity In the context of genetic testing, investigating health disparities that exist in racial/ethnic groups allows researchers and healthcare providers to develop programs and interventions focused on reducing disparities and enhancing health equity. For example, the U.S. National Institutes of Health (NIH) is prioritizing genetic studies in diverse populations. The "All of Us" program is collecting genome information from one million healthy individuals and providing genetic counseling [211]. Importantly, the program is projected to enroll more than 80% of their cohort from members of groups underrepresented in biomedical research, with more than half belonging to a racial or ethnic minority group [211]. Additionally, the NIH Breast Cancer

Genetic Study and NIH-Prostate Cancer Foundation RESPOND study are investigating genetics and biomarkers in African Americans. Such studies provide valuable genetic data that can be used to improve guidelines and treatments for genetic testing (see [155] for discussion). Furthermore, programs such as the U.S. National Cancer Institute (NCI) Community Oncology Research Program (NCORP) seek to increase access to cancer care prevention, screening, and clinical trials for minorities in their local communities [212]. These efforts may work in tandem with programs designed to train community health workers to increase lay people's genomics literacy, teach the importance of collecting cancer family history, educate on cancer prevention and risk, and access genetic services [213].

Programs and initiatives that promote health equity in the context of genetics research and clinical trials have a vital role to play in closing the cancer health disparity gaps among minorities. Furthermore, increasing the representation of members of racial and ethnic minority groups in cancer genetics research will not only improve the quantity and quality of information about the causes of hereditary cancer but also enable improved tailoring of genetic counseling materials to promote knowledge, uptake, and improved prevention and early detection behaviors among racial and ethnic minorities.

Conclusion and Future Directions

To ask how people cope with the knowledge of increased cancer risk following genetic testing misses the point that many members of high-risk families have grown up with this risk and are keenly aware of it based on their experience with multiple family members. Instead, an emerging view is that predictive genetic testing for hereditary cancer risk may best be seen as an important step in an ongoing process of managing both psychological and behavioral aspects of familial cancer risk [3]. Consistent with this view, we presented an organizing framework for future research on antecedents and outcomes of hereditary cancer risk counseling and testing for different cancer syndromes. This framework situates hereditary cancer risk counseling and testing as tools to be used by patients and their families in an ongoing process of managing familial cancer risk and psychological concerns arising from awareness of this risk.

Our review demonstrated that hereditary cancer risk counseling and testing have a powerful impact on screening adherence, other risk-reducing behaviors such as prophylactic surgery, and in the case of hereditary melanoma, primary prevention behaviors such as reduction of UVR exposure. These findings suggest that hereditary cancer risk counseling and testing may play a role not only in potentially life-saving early detection efforts but also in proactive efforts to reduce one's risk of developing cancer. As shown in our program of research on familial melanoma, these efforts extend beyond individual patients to family members, particularly minor children [65, 129, 130, 214].

With regard to psychological outcomes, our review suggests that early concerns that cancer genetic testing would induce enduring psychological distress are not supported by research. However, there is increasing recognition that there may be multiple trajectories of outcomes and particular subgroups of patients who may be vulnerable to increased depression and/or anxiety. Being able to predict who these patients will be in order to offer them additional support will allow for more targeted and successful intervention efforts.

Moving beyond depression, anxiety, and cancer worry, studies of other psychological outcomes indicate that patients often report both costs and benefits of hereditary risk counseling and testing. Qualitative data suggest considerable emotional, informational, and motivational benefits, and standardized measures have been developed to assess these outcomes. As suggested by this review, it is important to understand how different positive and negative psychological outcomes of receiving positive test results may be related to the subsequent practice of screening behavior and the adoption of other recommended health behaviors to manage risk. More broadly, work on benefit finding, post-traumatic growth, and adaptation to cancer may prove useful in understanding other psychological outcomes of living with elevated cancer risk [138, 215, 216].

Finally, the ultimate goal in achieving an expanded and equitable view of the costs and benefits of cancer risk counseling and testing is to understand how best to support all high-risk individuals and families in understanding and managing their cancer risk. This understanding in turn will help maximize the potential benefits of personalized medicine for cancer prevention through early detection and treatment. Efforts to remedy racial and ethnic health disparities may lead to new research questions and a different understanding of the outcomes of cancer genetic testing than what we have described here. For example, we have suggested that genetic counseling and testing are important inputs to an ongoing, lifelong process of managing familial cancer risk, but as researchers and clinicians use different methods of population-based testing (for example, universal multigene panel testing of cancer patients [17] or offering free testing to all members of a regional healthcare system [217]), more people who may have been unaware of their family cancer history or who do not have a strong family history will learn they carry mutations associated with cancer risk. For example, in a recent panel-testing study of African American women with breast cancer, the majority of the mutations detected (385 of the 530) were from individuals without a first-degree family history [218, 219]. Similar findings have been reported from the Healthy Nevada Project in which population screening successfully identified new carriers of risks for HBOC, Lynch syndrome, and familial hypercholesterolemia, 90% of whom had not been previously identified and only a quarter of whom reported a relevant family disease history [217]. These healthcare system-wide efforts will also reach people with lower levels of income and education, which will put an even greater premium on understanding how to tailor counseling materials for people with lower levels of health literacy, different levels of experience with, and trust in, healthcare providers and systems, and different resources to manage financial, logistic, and psychological barriers to accelerated screening and other preventive measures.

Finally, while research is beginning to address multiple explanations for racial and ethnic disparities in genetic testing knowledge and uptake, it is important to note that African Americans and Caucasians have received the most attention from researchers. Very few studies focus on the knowledge of, interest in, and actual uptake of genetic testing among Latinos, Asian Americans, or American Indians. Accelerating efforts to make sure that this technology is equally available to and beneficial for all— and understanding the specific structural, social, and cultural challenges involved in these efforts— should be a priority in the United States and throughout the world.

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Meaning-Centered Psychotherapy

23

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Introduction

A diagnosis of an advanced, life-limiting cancer commonly brings with it a sense of fear and despair for patients and their family members. The impact of cancer, and often its treatment, leads to significant physical limitations and changes in patients' capacity to carry out important roles and activities. This in turn can lead to a sense of hopelessness and even a desire for hastened death. Such patients may not be suffering from a clinical depression [1] but rather may be confronting an existential crisis of loss of meaning, value, and purpose due to their advanced disease. Meaning-Centered Psychotherapy (MCP) arose from a need to address this specific challenging clinical problem—a problem for which no effective intervention was yet available. Inspired primarily by the works of Viktor Frankl [2] and further informed by the contributions of Irvin Yalom [3], our research group utilized Frankl's "logotherapy" as the foundation of our approach. We created a brief, manualized intervention centered on the importance of meaning in human existence to help patients with advanced cancer cultivate a sense of meaning and purpose in their lives, even in the face of death.

While based heavily on Frankl's concepts of meaning, MCP also incorporates other fundamental existential concepts related to the search for, connection with, and creation of meaning. Through a series of didactics and experiential exercises, therapists and patient(s) work together to help patients understand the importance and relevance of sustaining, reconnecting with, and creating meaning in their lives through accessible and consistent sources of meaning [4–7]. Importantly, they explore how these various sources of meaning can serve as *resources* to help patients cope with and diminish feelings of despair that emerge at particularly challenging times.

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The Impact of Meaning and Spiritual Well-Being on Psychosocial Outcomes in Advanced Cancer

Research from the past 20 years has highlighted the importance of moving beyond pain and physical symptom control in palliative care [8]. It is now well-recognized that the provision of psychiatric, psychosocial, existential, and spiritual care is critical to the provision of high-quality, comprehensive end-of-life care [8]. Our conceptualization of spirituality in this context is aligned with the definition offered by the Consensus Conference on Improving Spiritual Care as a Dimension of Palliative Care, which described it as "the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred" [8]. Others include both meaning and religious faith in their definition of spirituality [7].

In the context of MCP, we discuss with patients how having a sense that one's life has meaning involves the conviction that one is fulfilling a unique role and purpose in a life that is a gift [2]. It comes with a responsibility to live to one's full potential as a human being; in so doing, one is able to achieve a sense of peace, contentment, or even transcendence, through connectedness with something greater than one's self [2]. Faith is differentiated from meaning as it reflects a belief in a higher transcendent power, not necessarily identified as God, and not necessarily through participation in the rituals or beliefs of a specific organized religion.

There is growing evidence that spirituality plays an important role for patients coping with cancer, particularly at the end of life [9–11]. For example, patients who are able to maintain a sense of meaning report higher satisfaction with their quality of life and tolerate severe physical symptoms better than those reporting lower levels of meaning [9]. Our research group has demonstrated a central role for spiritual well-being, which includes a sustained sense of meaning, as a buffering agent that protects against depression, hopelessness, and desire for hastened death among terminally ill cancer patients [1, 10]. Furthermore, a study by Meier and colleagues [12] found that physicians believed "loss of meaning in life" accounted for 47% of patient requests for assisted suicide.

Given the significant impact of spiritual well-being on psychosocial outcomes in advanced cancer, it is unsurprising that cancer patients report needs related to meaning, spirituality, and hope as among the most important aspects of end-of-life care. In a study of the psychosocial needs of 248 patients with cancer, 51% reported that they needed help overcoming fears, 41% needed help finding hope, 40% needed help finding meaning in life, 43% needed help finding peace of mind, and 39% needed help finding spiritual resources [13]. Singer et al. [11] found that patients in their sample reported that "achieving a sense of spiritual peace" was among the most important aspects of end-of-life care. As such, addressing such spiritual and existential concerns is critical to quality end-of-life care.

Meaning-Centered Psychotherapy: Theoretical Framework

Concepts of Meaning

Our findings described above led to an exploration and analysis of the work of Viktor Frankl [2] and his concepts of logotherapy or meaning-based psychotherapy. Frankl highlighted the spiritual component of the human experience and underscored the central importance of meaning. He conceptualized the will to find meaning as a driving force or instinct in human psychology. The understanding that humans are driven to find and cultivate meaning in life is at the core of the theoretical framework of MCP [4–7]. Some of the specific meaning-related concepts that are highlighted in MCP include:

1. *Meaning of life*: Life has meaning and never ceases to have meaning, from the very first moment of life up to our very last breath. While meaning may change in its context, it

never ceases to exist. When we feel our lives lack meaning, it is because we have become disconnected from meaning in our lives, not because it no longer exists. This concept is interpreted and expressed in MCP in the following way: *The possibility of creating or experiencing meaning exists throughout life, even up to the last moments of life*.

2. *Will to find meaning*: The desire to find meaning in human existence is a primary motivating force in human behavior. Human beings are creatures who innately search for and create meaning in their lives and are thereby conceptualized as meaning-making creatures.
3. *Freedom of will*: We have the freedom to find meaning in existence and to choose our attitude toward suffering. We have the capacity to choose how we respond to limitations, obstacles, losses, and uncertainty. Moreover, we have the responsibility to create an existence of meaning, direction, and identity. We must respond to the fact of our existence and create the "essence" of what makes us human.
4. *Sources of meaning*: Meaning in life has specific and available sources (Box 23.1). The four main sources of meaning in life that are explored in MCP are derived from legacy (meaning exists in a historical context, thus legacy—past, present, and future—is a critical element in sustaining or enhancing meaning), attitude (the attitude one takes toward suffering and existential problems), creativity (work, deeds, dedication to causes), and experiences (connection through love, beauty, humor).

Box 23.1 Sources of Meaning in Meaning-Centered Psychotherapy

Historical: *Legacy given (past), lived (present), and to give (future)*. Examples include our story, our family history, traditions, the history of our name, our accomplishments, and whatever we hope to pass on to others.

Attitudinal: *Encountering life's limitations* by turning personal tragedy into triumph, things we have achieved despite adversity, rising above or transcending difficult circumstances. Examples include achieving an education despite personal/financial challenges, overcoming grief/loss, persevering through cancer treatment, etc.

Creative: *Engaging in life* through work, deeds, causes, artistic endeavors, hobbies, etc. Examples include our careers/job, volunteer work, involvement with faith or religious communities, engagement in political and social activism, etc.

Experiential: *Connecting with life* through love, beauty, and humor. Examples include our family, children, loved ones, watching the sunset, gardening, beaches, museums, playing with pets, etc.

Drawing from these principles, MCP seeks to enhance patients' sense of personal meaning by helping them to reflect on, understand, and use various sources of meaning in their lives as resources for coping with challenging times [4–7]. The resulting enhancement in meaning plays a role in improving other psychosocial outcomes, such as quality of life, psychological distress, and despair [14]. As such, meaning is conceptualized as an intermediary outcome, and a mediator of change, in these important psychosocial outcomes.

Although the emphasis of MCP is on meaning and sources of meaning, the psychotherapeutic work is enriched when therapists are well versed in basic conceptual framework and theories of existential philosophy and psychotherapy [2, 3, 15]. Existential concepts such as freedom, responsibility, choice, creativity, identity, authenticity, engagement, existential guilt, care, transcendence, transformation, direction, being unto death, being and temporality, and existential isolation are incorporated in the theoretical framework of MCP and are utilized throughout treatment [2, 3].

Meaning-Focused Coping

Relevant to the theoretical framework of MCP, Park and Folkman [16] described conceptual models for finding meaning in relation to traumatic events and coping. Their "meaning-focused coping" can involve re-evaluating an event as positive; enumerating ways in which life changed, sometimes for the positive, because of an event; answering the question of why an event occurred (or "Why me?"); and stating the extent to which one has "made sense of" or "found meaning" in an event [17]. Frankl [2] viewed meaning as a state and believed that individuals can move from feeling demoralized and as if their lives hold no value, to recognizing their personal sense of meaning and purpose. This conceptualization of meaning as a state subject to change helps patients to recognize their agency in constructing meaning and suggests that personal meaning may be a target that is particularly responsive to intervention.

Frankl [2] also viewed suffering as a catalyst for both the need for meaning and an opportunity for finding it. Therefore, the diagnosis of an incurable illness may be seen as a crisis in the fullest sense—an experience of distress or even despair that may offer an opportunity for growth and meaning. In the face of a crisis, one may experience a loss of meaning and purpose in life or one may sustain or even heighten a sense of meaning, purpose, and peace, which can allow one to more positively appraise events and to more profoundly value life.

Meaning-Centered Psychotherapy: Formats and Themes

MCP is a brief (7 weeks for IMCP, 8 weeks for MCGP)* intervention that integrates didactics, discussions, and experiential exercises focused on finding and sustaining a sense of meaning in the context of advanced cancer (Table 23.1; for the comprehensive text on MCP, see Breitbart [4]). Patients are taught to identify sources of meaning in their lives and to use those most meaningful aspects of their lives as coping resources. Discussions reinforce the importance of reconnecting to sources of meaning when

Table 23.1 Meaning-Centered Psychotherapy session content

Session	Session title	Content
1	Concepts and Sources of Meaning	Introductions; review of concepts and sources of meaning; *Meaningful Moments* experiential exercise; homework is to read *Man's Search for Meaning* and to reflect on Session 2 experiential exercise
2	Cancer and Meaning	Discussion of sense of identity before and after cancer diagnosis; *Who am I?* experiential exercise; homework is to reflect on Session 3 experiential exercise
3	Historical Sources of Meaning (Past Legacy)	Discussion of life as a legacy that has been given (past); *Historical Sources of Meaning-Past* experiential exercise; homework is to reflect on Session 4 experiential exercise
4	Historical Sources of Meaning (Present and Future Legacy)	Discussion of life as a legacy that one lives (present) and gives (future); *Historical Sources of Meaning-Present and Future* experiential exercise; homework is to share one's story with someone and to reflect on Session 5 experiential exercise
5	Attitudinal Sources of Meaning: Encountering Life's Limitations	Discussion of confronting limitations imposed by cancer, prognosis, and death; *Encountering Life's Limitations* experiential exercise; introduction to Legacy Project; homework is to reflect on Session 6 experiential exercise
6	Creative Sources of Meaning: Engaging in Life Fully	Discussion of creativity, courage, and responsibility; *Creative Sources of Meaning* experiential exercise; homework is to reflect on Session 7 experiential exercise
7	Experiential Sources of Meaning: Connecting with Life	Discussion of experiences as sources of meaning, such as love, nature, art, and humor; *Love, Beauty, & Humor* experiential exercise; homework is to complete Legacy Project for presentation in Session 8

Table 23.1 (continued)

Session	Session title	Content
8	Transitions: Reflections, and Hopes for the Future	Review of sources of meaning, as resources, reflections on lessons learned; *Hopes for the Future* experiential exercise; goodbyes

*In individual Meaning-Centered Psychotherapy, which consists of 7 sessions, Sessions 3 and 4 are combined into a single session on Historical Sources of Meaning

patients' feel disconnected because of their disease-related concerns. Existential concepts, such as freedom, responsibility, authenticity, existential guilt, transcendence, and choice, are also highlighted and attended to as they emerge in sessions. Therapists support the expression of emotion and validate patients' suffering as it arises, though the focus is primarily on how one makes meaning of that suffering and utilizes sources of meaning to cope. Table 23.1 provides a brief overview of each MCP session.

Psychoeducation Through Didactics and Experiential Exercises

MCP is a psychoeducational intervention in many ways, as therapists teach patients about concepts of meaning and their applications as one faces a life limiting illness. Each session includes didactics about a specific meaning-centered topic followed by an experiential exercise that is designed to facilitate learning of these abstract concepts through patients' own emotional experiences. The sources of meaning explored therein can ultimately become resources for the patient coping with advanced cancer. Flexibility in drawing on sources of meaning is emphasized, as selected sources of meaning may become unavailable due to disease progression. Therapists support *moving from ways of doing* to *ways of being* to assist patients with recognizing that meaning can be derived in more passive ways. Therapists also call attention to *meaning shifts* when patients begin to incorporate the vocabulary and conceptual framework of meaning into the material they share.

Therapists are encouraged to deliver MCP flexibly, though there is a logical progression to the presentation of content as sessions unfold. It is therefore ideal for patients to attend all sessions in order to theoretically obtain the optimal response. However, if all of the material designated for a specific session is not completed, discussion and exercises can be carried over to the subsequent session.

Integration of Existential Concepts and Themes

Humans are creators who construct values, roles, responsibilities, and ultimately, their lives. Therefore, therapists should incorporate additional existential concepts such as responsibility, transformation, authenticity, and existential guilt, as these often emerge as patients engage in the experiential exercises. Therapists may strive to *detoxify death* by speaking openly about death as the ultimate limitation that causes suffering and for which meaning can be derived through the attitude that one takes toward suffering (e.g., transcendence, choice). Therapists may also employ an *existential nudge* to gently challenge the resistance of patients to explore difficult existential realities, such as the ultimate limitation of death or existential guilt.

Administration of Meaning-Centered Group Psychotherapy

In Meaning-Centered Group Psychotherapy (MCGP), each patient shares the content of their experiential exercises, and the process of experiential learning is reinforced through the comments of co-facilitators and patients, as well as through the identification of commonalities among patients' responses. Therapists should be aware of the "co-creation of meaning" between therapists and patients, as well as between group members. Therapists and patient participants are "witnesses" or repositories of meaning for each other and are therefore part of a meaningful legacy created by each of the patient participants in MCGP.

Attention to the basic tenets of group processes, dynamics, and etiquette remains important in facilitating MCGP groups, and therapists should promote group cohesion and a safe and open atmosphere. While MCGP is not intended to be primarily a supportive group intervention, therapists inevitably provide support as patients share and express emotion.

Administration of Individual Meaning-Centered Psychotherapy

One of the primary challenges in delivering MCGP to patients with advanced cancer is that participants cannot always commit to and regularly attend weekly sessions at a specified day and time. As a one-on-one intervention, Individual Meaning-Centered Psychotherapy (IMCP) addresses this issue by affording more flexibility in the delivery of the meaning-centered work. Therapists can delve deeper into the patient's past and personal goals. However, since there is more time and space in the session, it is easier to get "off track" and so therapists should be mindful of accomplishing each session's goals.

Meaning-Centered Psychotherapy: An Efficacious Intervention

Prior to the development of MCP, research on interventions focusing on existential or spiritual issues, particularly in patients with advanced cancer, was limited. Thus, we conducted several large-scale trials of MCP, focusing advanced cancer patients with stage III or IV solid tumor cancers. We also focused on patients with elevated distress as indicated by a score of 4 or higher on the Distress Thermometer from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [18]—particularly if issues involved emotional problems and spiritual/religious concerns. We further deemed patients with physical, psychiatric, or cognitive limitations sufficient to preclude participation in outpatient psychotherapy not well-suited for this intervention.

To evaluate the efficacy of MCP in improving spiritual well-being and a sense of meaning, as well as in decreasing anxiety, hopelessness, and desire for death, we conducted a large pilot randomized controlled trial of MCGP in 90 patients with advanced cancer [6]. Patients received either eight sessions of MCGP or a standardized supportive group psychotherapy (SGP), with 55 patients in total completing the eight-week intervention. Thirty-eight patients completed a follow-up assessment 2 months later, with attrition due largely to patient death or physical deterioration. Results demonstrated significantly greater benefits of MCGP as compared to SGP, particularly in enhancing a sense of meaning and spiritual well-being [6]. Notably, improvements in patients who received MCGP appeared even stronger at the two-month follow-up assessment, while patients who received SGP failed to demonstrate any such improvements, either post-treatment or at follow-up. In a larger randomized controlled trial of MCGP versus SGP in 253 patients with advanced cancer, results similarly demonstrated significantly greater benefits from MCGP as compared to SGP in improvement in depression, hopelessness, desire for hastened death, spiritual well-being, and quality of life [7].

A separate pilot randomized controlled trial evaluated individually delivered MCP, comparing seven sessions of IMCP to therapeutic massage (TM). Patients with advanced cancer who received IMCP demonstrated significantly greater improvement in spiritual well-being, symptom burden, and symptom-related distress among participants than those who received TM [5]. Importantly, attrition from this study was lower than that reported in the pilot randomized controlled trial of MCGP (43%); of the 120 patients with advanced cancer randomly assigned to receive either IMCP or TM, 65% completed the two-month follow-up assessment. In a second, large-scale randomized controlled trial of IMCP, 321 patients with advanced cancer were randomly assigned to IMCP, supportive psychotherapy, or enhanced usual care. Assessments were conducted before the intervention, mid-treatment (4 weeks), 8 weeks after treatment, and 16 weeks after treatment [19]. When compared to enhanced usual care, patients who received IMCP demonstrated significant improvements in quality of life, sense of meaning, spiritual well-being, and significant reductions in anxiety and desire for hastened death. Furthermore, the effect of IMCP was significantly greater than the effect of supportive psychotherapy for quality of life and sense of meaning. As in our previous studies, the strongest treatment effects for IMCP were observed for measures of sense of meaning, spiritual well-being, and overall quality of life [19].

Research has consistently demonstrated stronger effects for MCP compared to supportive psychotherapy, though we have not addressed the extent to which the effectiveness of MCP is due to its theoretical mechanism of change: improvement in a sense of meaning. A recent analysis of a combined sample from the two randomized controlled trials of MCGP [6, 7] examined the extent to which improvement in sense of meaning and peace accounted for improvement in psychosocial outcomes [14]. This study provided strong support for the theoretical foundation underlying MCP, as an improved sense of meaning and peace-mediated improvement in distress, and specifically, improved quality of life and decreased depression.

Overall, there is strong support for the efficacy of MCP as a treatment for psychological and existential/spiritual distress among patients with advanced cancer. Both the group and individual formats of MCP are novel and effective interventions for the enhancement of quality of life for patients with advanced cancer at the end of life. Given the importance of spiritual well-being and sense of meaning among patients confronting a terminal illness, the availability of a manualized, empirically supported intervention, such as MCP, has tremendous potential for improving patient quality of life at the end of life.

Adaptations of Meaning-Centered Psychotherapy

MCP was designed originally for patients with advanced cancer. However, this approach—centered on enhancing meaning and quality of life—has broad applicability across a range of patient populations with chronic and terminal illnesses, and even for those patients in survivorship. Multiple adaptations of MCP are in development, and several have already demonstrated efficacy in improving the quality of life in various patient populations.

Meaning-Centered Psychotherapy for Cancer Survivors

MCP has been adapted for the treatment of cancer survivors [20–22], who often face significant challenges to their sense of meaning in life as they attempt to move forward in life after active treatment concludes. They often experience a heightened desire to live meaningfully and intentionally, but struggle with fear of cancer recurrence; coping with negative treatment side-effects and physical changes; and losses in physical, social, and occupational domains, leaving them feeling "stuck" [21]. van der Spek and colleagues [20, 22] adapted MCP and developed Meaning-Centered Group Psychotherapy-Cancer Survivors (MCGP-CS). MCGP-CS has demonstrated efficacy in improving personal meaning, psychological well-being, and mental adjustment to cancer, while reducing psychological distress and depressive symptoms among cancer survivors [20]. In collaboration with the American Cancer Society, Lichtenthal et al. [21, 22] developed a version of MCGP-CS specifically for breast cancer survivors and found that distressed breast cancer survivors randomized to receive eight sessions of the Meaning-Centered Group Psychotherapy reported a greater sense of meaning than those who received eight sessions of a standardized support group.

Meaning-Centered Psychotherapy for Cancer Caregivers

Given the universal will to find and sustain meaning in life, the utility of a meaning-centered approach to clinical care extends beyond the treatment of medically ill populations. One such population for which MCP has been adapted is cancer caregivers, family members, and friends who provide care to patients with cancer, often with minimal training and support [23]. Caregivers face numerous physical, psychological, and existential challenges as a result of their responsibilities. Existential distress may lead to increased feelings of guilt and powerlessness and is likely a driving force behind the burden that is so well documented in the caregiving literature [24, 25]. For example, the competing demands of cancer caregiving, other caregiving responsibilities (i.e., childcare), paid employment, and personal life goals have the potential to lead to psychological, spiritual, and existential distress. Such distress may lead caregivers to become disconnected from important aspects of their identity, prioritized activities and relationships, and an overall sense of meaning and purpose [23]. Such loss of meaning ultimately increases suffering and burden and negatively impacts the quality of care provided to patients. This suffering, however, may exist concurrently with positive emotions, connectedness, and growth, and therefore cancer caregiving may be looked upon as an opportunity for meaning-making and growth [26]. Through an exploration of the unique experience of providing care for a patient with cancer, including caregivers' previous experiences of illness, loss, and care, the manner in which caregivers respond to limitations of the caregiving role, how providing care for another may serve as a catalyst for improved self-care, and relationship with oneself and the care recipient, caregivers may find great meaning in the caregiving role, which will ultimately improve their quality of life.

Meaning-Centered Psychotherapy for Cancer Caregivers (MCP-C) was therefore developed to help caregivers connect to a sense of meaning and purpose in the caregiving role, mitigate caregiver burden, and improve their overall quality of life [23]. Modeled after MCP for delivery among patients with advanced cancer, in its original format, MCP-C includes seven individually delivered sessions. While the topics and themes are overall similar to MCP, MCP-C specifically addresses the unique existential challenges of caregiving. For example, in discussions of *legacy* in Session 3, a key focus is on caregivers' previous experiences with or familial examples of caregiving and loss. While most caregivers feel that they did not have a choice in becoming a caregiver, the discussion of *attitude* in Session 4 assists caregivers in recognizing how they are choosing to face current limitations and ways in which such choice can engender a sense of pride in one's caregiving role. In lieu of exploring what a good death would be for caregivers specifically, this session allows for a discussion of advanced care planning through exploration of what a good or meaningful death would mean for their loved one and steps caregivers may take to ensure such outcomes. In Session 5, responsibility to the self and self-care is emphasized, and in addition to the *Legacy Project* introduced in Session 4, caregivers are specifically asked in Session 5 to complete a *Self-Care Project* to facilitate a commitment to self-care. Exploration of the *experiential* source of meaning in Session 6 specifically addresses how connecting through life through the five senses and through experiences of love, beauty, and humor may be used in service of self-care. Together, these sources of meaning are presented as resources to which caregivers may connect throughout—and after—their caregiving journey.

Similar to patients with cancer, cancer caregivers report barriers to psychosocial service use, including limited time to travel to and from treatment centers, financial constraints, and guilt. As such, supportive services are generally underutilized by caregivers [27] and telehealth is increasingly relied upon for the delivery of support [28, 29]. Therefore, in addition to delivery of MCP-C in person, we adapted MCP-C for web-based delivery. In lieu of seven individually delivered sessions, this adaptation consists of a series of five self-administered webcasts, each of which includes didactic components, video clips of therapeutic interaction of MCP-C therapists and (trained actors portraying) caregivers demonstrating the MCP-C principles, and a message board where participants post responses to the experiential exercise questions that form the backbone of MCP-C. Results from a randomized controlled trial evaluating the efficacy of web-based MCP-C indicated that at 3 months follow-up, participants randomized to MCP-C demonstrated significant improvement in meaning and benefit finding, as compared to caregivers randomized to Enhanced Usual Care [30].

The benefits of MCP-C have also been explored in unique groups of caregivers, such as those of patients with malignant brain tumors like glioblastoma multiforme (GBM). Such caregivers are at risk for existential distress and burden due to the devastating neurologic and oncologic sequelae of these diseases [31]. Personality changes, mood disturbances, and cognitive limitations are ubiquitous in the course of illness and make caregiving particularly challenging [32]. The care needs of patients are complex due to cognitive and language deficits [33], diminished decision-making abilities, and progressive personality changes. This places tremendous responsibility on caregivers to attend increasingly to activities of daily living [34] and to engage in treatment decision-making and advanced care-planning [35]. Our group is currently evaluating the efficacy of MCP-C delivered to caregivers of patients with GBM, and our preliminary results are promising: caregivers who engage in MCP-C experience clinically meaningful improvements in a sense of meaning and purpose, spiritual well-being, anxiety, depression, and benefit finding [36].

Meaning-Centered Grief Therapy

Given the challenges to caregivers' sense of meaning and purpose that can occur following the patient's death, an adaptation of MCP for grieving individuals has also been developed. Efforts to develop Meaning-Centered Grief Therapy (MCGT) were initially focused on parents who lost a child to cancer because of the unique struggles they often experience finding meaning in their child's illness and untimely death and in their lives following their loss [37, 38]. MCGT is a one-on-one intervention that incorporates the principles of MCP, as well as meaning reconstruction and cognitive-behavioral approaches to help grievers adaptively find meaning in their loss and enhance their sense of meaning while co-existing with their grief [37, 38]. Over 16 sessions, MCGT systematically explores aspects of meaning commonly challenged by loss, highlighting the choices parents have in how they face their pain, how they tell their and their child's story, and how they connect to sources of meaning in their lives, including their child's legacy [37]. MCGT has demonstrated promise in improving bereaved parents' sense of meaning; connection with their child; and symptoms of prolonged grief, depression, and hopelessness [37].

Future Directions

In light of the efficacy of MCP demonstrated in randomized controlled trials, replication studies of MCP are being conducted internationally, and several other adaptations of MCP have been developed [4]. MCP has been adapted for inpatient palliative care and hospice patients, oncology care providers, and various cultural groups, with intervention manual transcreation in several languages [4]. Efforts are now focused on disseminating MCP through workshops and a federally funded training program.

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24

Quality of Life

Elizabeth J. Siembida and John M. Salsman

Introduction

Over the past 40 years, quality of life has emerged as an important outcome for evaluating the impact of cancer across the continuum of care. With improvements in early detection and advances in diagnosis and treatment, more and more people are surviving cancer and living longer. The National Cancer Institute (NCI) estimates that at least 16.9 million Americans were living with a history of cancer in January 2019, and the current 5-year survival rate is 69%, up from 49% in the 1970s [1]. Whereas survival time or *quantity* of life was an early and important objective indicator of treatment success, *quality* of life has proven to be a recent and meaningful subjective complement to the survival benefits derived from treatments. Weighing survival vs. quality of life benefits is a critical part of medical decision-making for cancer patients [2], and measuring quality of life has thus taken on added significance. Accordingly, in 2009, the Food and Drug Administration (FDA) coined the term "patient-reported outcomes" (PROs) as "measurement of any aspect of a patient's health status that comes directly from the patient" (e.g., quality of life) and proposed criteria for selecting and integrating HRQOL PRO measures into therapeutic clinic trials [3].

Given the subjective nature of quality of life, efforts to operationalize the construct have led to multiple, overlapping definitions. The World Health Organization defined quality of life as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment" [4]. Others have noted the importance of the subjective comparison between an individual's current level of functioning or well-being and their expected level of functioning or well-being to their perceived quality of life [5]. For the purposes of this chapter, we are primarily concerned with health-related quality of life (HRQOL), defined as the extent to which one's usual or expected physical, mental, and social well-being are affected by a medical condition or its treatment [6, 7]. Collectively, these definitions highlight two critical aspects of HRQOL: (1) patients' subjective judgment of their well-being and (2) the multiple dimensions of HRQOL.

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Assessing Health-Related Quality of Life with Patient-Reported Outcomes

HRQOL is Multidimensional HRQOL can be examined using a global evaluation (a single question rating the patient's overall perception of HRQOL) or a total score (summary of sub-domain scores), and many HRQOL PROs include these overall assessments. Multiple sub-domains of HRQOL have been proposed within the literature. An earlier review found over 30 different names for HRQOL dimensions [8]. This same review suggested that seven HRQOL dimensions were independent contributors to overall HRQOL: physical concerns (symptoms, pain, etc.), functional ability (activity), family well-being, mental well-being, treatment satisfaction, sexuality (including body image), and social functioning.

More recently, three or four dimensions of HRQOL have been proposed as adequate to fully describe HRQOL: physical, mental, social, and, in some cases, spiritual [9]. The physical domain refers to perceived physical function (e.g., ease of walking without assistance) and physical symptoms (e.g., pain, nausea, and fatigue). The mental domain refers to positive and negative mood and other emotional symptoms. The social domain measures relationships with friends and family, enjoyment of social activities, and sexuality. The spiritual domain refers to the degree to which an individual finds comfort in their spiritual beliefs when coping with illness.

Levels of Measurement Because HRQOL is a multidimensional construct, the level of measurement selected for assessing HRQOL in cancer patients and survivors must be carefully considered. HRQOL in cancer patients and survivors can be organized conceptually under broad domains of generic and cancer-specific concepts. Generic concepts include global evaluations of HRQOL, as well as the commonly used dimensions of physical (symptoms and function), mental (affect, behavior, cognition), and social (relationships and function) HRQOL. Cancer-specific concepts include both disease- and treatment-specific measures of HRQOL. While this framework provides a useful model for conceptualizing the hierarchical relationships among various dimensions of HRQOL, it does not readily capture the number and type of HRQOL questionnaires available for use with cancer patients and survivors. These questionnaires can be appropriately grouped within generic and cancer-specific domains, but within each of these domains, there is much overlap of the physical, mental, and social dimensions, and thus they resist simple categorizations. Table 24.1 provides

Table 24.1 Measures of HRQOL used in patients with cancer and survivors

Generic
Medical Outcomes Study 36-Item (SF-36) & 12-Item (SF-12) Short-Form Health Surveys [147–149]
Patient-Reported Outcome Measurement Information System (PROMIS) [22, 49]
Nottingham Health Profile (NHP) [150]
Psychological Adjustment to Illness Scale – Self Report (PAIS-SR) [151]
Sickness Impact Profile (SIP) [152]
Spitzer Quality of Life Index (QL-I) [153]
Cancer-Specific
Cancer Rehabilitation Evaluation System (CARES) [154, 155]
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CORE 30 (EORTC QLQ-C30) [156]
Functional Assessment of Cancer Therapy-General, Version 4 (FACT-G) [17]
Functional Living Index-Cancer (FLIC) [157]
McGill Quality of Life Questionnaire-Revised (MQOL) [158, 159]
Quality of Life Index-Cancer Version III (QLI-CV III) [160]
Cancer Problems in Living Scale (CPILS) [161]
Impact of Cancer version 2 (IOCv2) [162, 163]
Long Term Quality of Life Scale (LTQL) [164–166]
Quality of Life in Adult Cancer Survivors (QLACS) [167]
Quality of Life - Cancer Survivors (QOL-CS) [168, 169]
Disease-Specific
EORTC modules: brain cancer (QLQ-BN20) [170], breast cancer (QLQ-BR23) [171], cervical cancer (QLQ-CX24) [172], colorectal cancer (QLQ-CR38) [173], endometrial cancer (QLQ-EN24) [174], head and neck cancer (QLQ-H&N35) [175], lung cancer (QLQ-LC13) [176], multiple myeloma (QLQ-MY24) [177], oesophago-gastric cancers (QLQ-OG25) [178], ovarian cancer (QLQ-OV28) [179], pancreatic cancer (QLQ-PAN26) [180] and prostate cancer (QLQ-PR25) [181]

Table 24.1 (continued)

FACT modules: breast cancer (FACT-B) [182], bladder cancer (FACT-Bl), brain cancer (FACT-Br) [183], colorectal cancer (FACT-C) [184], cancer of the central nervous system (FACT-CNS), cervical cancer (FACT-Cx), esophageal cancer (FACT-E) [185], endometrial cancer (FACT-En), gastric cancer (FACT-Ga), head and neck cancer (FACT-H&N) [186], hepatobiliary cancer (FACT-Hep) [187], lung cancer (FACT-L) [18], leukemia (FACT-Leu) [188], lymphoma (FACT-Lym) [189], melanoma (FACT-M) [190], multiple myeloma (FACT-MM), nasopharyngeal cancer (FACT-NP) [191], ovarian cancer (FACT-O) [192], prostate cancer (FACT-P) [193], and vulvar cancer (FACT-V) [194]
UCLA Prostate Cancer Index (UCLA PCI) [195]
HNQoL (Head and Neck Quality of Life Instrument [196]
Lung Cancer Symptom Scale (LCSS) [197]
Quality of Life -Breast Cancer (QOL-BC) [169, 198]
Colorectal Cancer-Specific Scale [199]
Symptom and Treatment Specific
McCorkle and Young Symptom Distress Scale (SDS) [200, 201]
M.D. Anderson Symptom Inventory (MDASI) [202]
Edmonton Symptom Assessment Scale (ESAS) [203]
Memorial Symptom Assessment Scale (MSAS) [204]
Rotterdam Symptom Checklist [205]
Symptom Checklist 90 (SCL-90) [206]
Brief Symptom Inventory (BSI) [207, 208]
Brief Fatigue Inventory (BFI) [209]
Brief Pain Inventory (BPI) [210]
Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [55, 56]
National Comprehensive Cancer Network (NCCN)/ FACT symptom indices: bladder cancer (NFBISI-18), brain cancer (NFBrSI-24) [211], breast cancer (NFBSI-16) [212], colorectal cancer (NFCSI-19), head and neck cancer (NFHNSI-22), hepatobiliary cancer (NFHSI-18), kidney cancer (NFKSI-19) [213], lung cancer (NFLSI-17) [214], ovarian cancer (NFOSI-18) [215], prostate cancer (NFPSI-17) [216] and lymphoma (NFLymSI-18) [217]
Pediatric Measures
Miami Pediatric Quality of Life Questionnaire (MPQOLQ) [218]
Minneapolis–Manchester Quality of Life Form (MMQL) [219, 220]
PedsQL Cancer Module [221–224]
Pediatric Oncology Quality of Life Scale (POQOLS) [225, 226]
Pediatric PRO-CTCAE [63, 64]
Pediatric PROMIS [32, 35, 36]

a list of several frequently used PROs for HRQOL, as well as several promising new PROs for assessing HRQOL.

Selecting Measures Since there is no gold standard when it comes to measuring HRQOL, selecting an appropriate PRO measure can be a challenge, because there are numerous options available. When selecting a measure of HRQOL, researchers and clinicians should consider the reliability, validity, and responsiveness of the PRO instrument. Reliability is primarily concerned with the stability and reproducibility of a measure over time. Reliability is a necessary but not sufficient condition for the validity of a measure. Validity refers to an instrument's ability to accurately measure what it claims to measure. Several types of validity can be considered when evaluating the relative strengths of a measure with content, criterion, and construct validity among the most common. Finally, the responsiveness or sensitivity of a measure is the ability of the measure to differentiate between groups of patients expected to provide different HRQOL scores as a result of disease or treatment characteristics.

Measurement properties like reliability, validity, and responsiveness are important to consider when choosing any measurement tool. For HRQOL, however, a clinician or researcher must also consider dimensional or aggregated assessment. There has been some debate as to whether dimensional assessment (i.e., separate scores for each dimension, evaluated independently) or aggregated assessment (i.e., evaluation of only the total HRQOL score incorporating all four dimensions) is most clinically relevant. While dimensional assessment gives a richer and more detailed picture of HRQOL, and is often preferred by clinicians, aggregated scores may be more meaningful in areas such as clinical trials research in order to enable decisions to be made adjusting survival time for its quality [10] or in population health surveillance research in order to inform global assessments of health status, facilitate subgroup comparisons, and track patterns and trends [11, 12].

Dimension scores provide more nuanced data than an aggregated score, but also have differential sensitivity to various cancer symptoms. For instance, compared with physical scales (e.g., physical functioning, functional ability, sexuality, etc.), psychosocial scales, such as mental well-being and social functioning, are less sensitive to changes in performance status or other primarily physical ratings. Psychosocial dimension scales are also less sensitive to disease-related characteristics, such as stage and type of disease [13, 14]. Several studies have found that the EORTC is unable to detect change in performance status rating or extent of disease [15, 16], and similar findings have emerged for the FACT measurement system [17, 18].

These findings make logical sense in the context of research suggesting that mental well-being may be no different in individuals diagnosed with cancer and those without cancer [19, 20]. It should be noted, however, that this finding has not always been replicated in all disease types and stages of illness (e.g., Lee et al) [21]. When the physical components of well-being are evaluated alongside measures of mental well-being, the relationship between the two is modest [9]. The fact that earlier and less refined measures of HRQOL may not adequately measure psychological distress is precisely due to the fact that these measures are comprised largely of physical symptoms such as nausea, appetite, and sleep.

In summary, if focusing on aggregate HRQOL scores only, the significant impact of cancer on any one dimension of HRQOL may be obscured. Including more targeted disease or treatment-specific measures along with general measures of HRQOL will permit comparisons across diseases while allowing for a level of sensitivity to issues or symptoms arising from a given disease or treatment. In addition, including multiple measures enhances the breadth of content coverage which may maximize one's ability to identify the efficacy of a treatment or intervention on HRQOL outcomes. A useful strategy is to select the measure most closely aligned with study objectives, confirm the relevant psychometric properties, and augment the selected measure(s) with a few additional questions targeted to the condition, disease, or treatment under study. Two recently developed measurement systems, the Patient-Reported Outcome Measurement Information System (PROMIS)® and the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), provide the necessary psychometric rigor, breadth, precision, and flexibility for optimal assessment of a variety of HRQOL domains.

Patient-Reported Outcomes Measurement Information System (PROMIS)® The PROMIS is a National Institutes of Health (NIH) Roadmap initiative designed to improve PROs using state-of-the-art psychometric methods (see https://www.healthmeasures.net/explore-measurement-systems/promis). The PROMIS domain framework is informed by the World Health Organization's tripartite model of physical, mental, and social health but is further divided into a variety of symptom, affective, and interpersonal item banks (Fig. 24.1). PROMIS includes over 300 measures of physical, mental, and social HRQOL from 102 adult and 25 pediatric domains [22]. PROMIS has developed and calibrated measures to capture multiple areas of health and functioning [23–31] and has extensive evidence of its validity and reliability in both pediatric and adult cancer populations [32–39].

The PROMIS approach involves iterative steps of comprehensive literature searches, the development of conceptual frameworks, item pooling, qualitative assessment of items using focus groups and cognitive interviewing, and quantitative evaluation of items using techniques from both classical test theory and item response theory (IRT) [33, 40–44]. PROMIS is the most ambitious attempt to date to apply IRT models to HRQOL assessment. IRT is an alternative to classical test theory and models the likelihood that a person at a specific latent trait or symptom level will respond to an item in a particular way [45–48]. Based upon one's overall pattern of responses to measure items, IRT modeling can produce a more precise estimate of a particular symptom or domain of HRQOL. This information can then be used to evaluate the quality of individual items, calibrate test scoring, and develop item banks for HRQOL domains. An item bank is comprised of carefully calibrated questions that can be used for item comparison and selection.

Calibrated item banks help set PROMIS apart from other established HRQOL measures and permit the application of computerized adaptive testing (CAT) tools, thus enabling tailored individual assessment while maintaining measurement precision and content validity. Other established HRQOL measures have a limited number of questions to assess each HRQOL construct (e.g., 5 questions on physical functioning, 8 questions on fatigue). PROMIS item banks (one bank for each PRO) include a much larger number of questions that have undergone extensive testing using qualitative and quantitative methods. Every PROMIS short form measure or CAT draws a select number of questions from the calibrated item bank to provide reliable and valid assessments of the HRQOL domain of interest. In short, PROMIS item banks offer the potential for efficient, flexible, and precise measurement of commonly studied dimensions of HRQOL. They are efficient because they minimize the number of items administered without compromising reliability, flexible because they allow the use of interchangeable items, and precise because they minimize the standard error of estimate [49]. Consequently, application of IRT

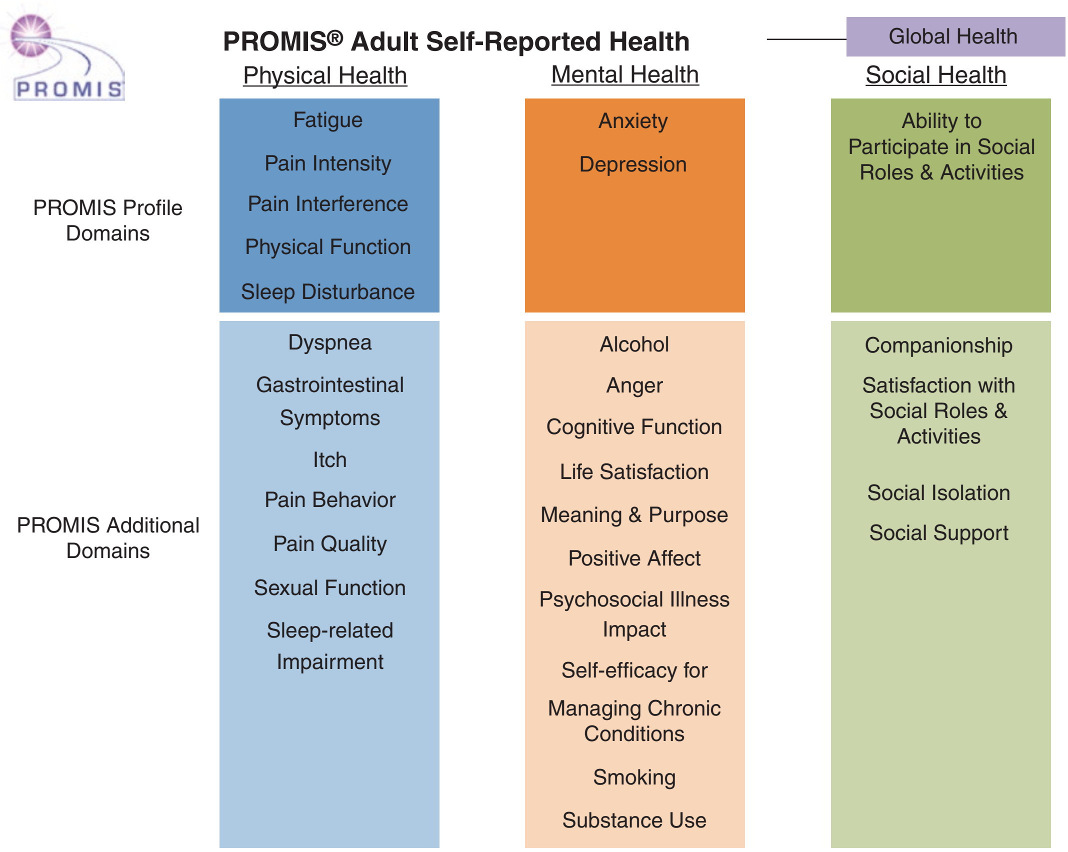

Fig. 24.1 The PROMIS Profile Domains Organized into the World Health Organization's Tripartite Model of Physical, Mental, and Social Health

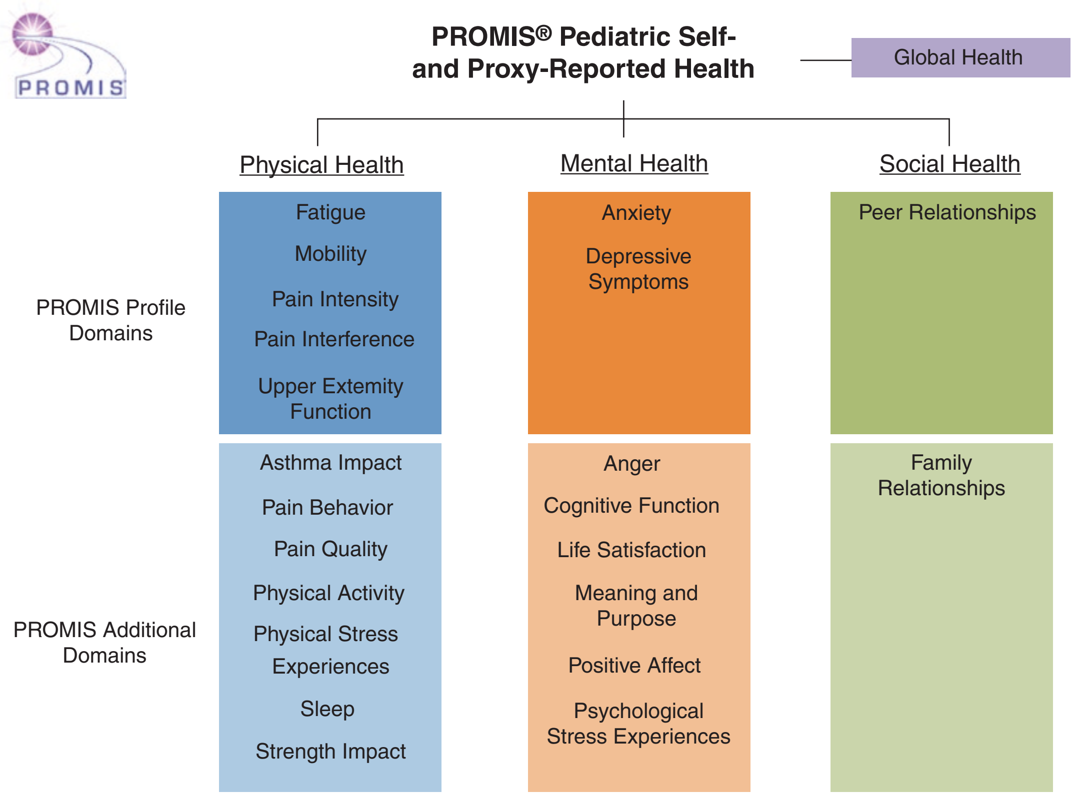

Fig. 24.1 (continued)

and CAT tools may allow for briefer assessments, more efficient assessments, and assessment of more symptoms and HRQOL domains of interest than has been typical in traditional assessments.

An added advantage of PROMIS is that scores are easily interpretable. Scoring is standardized so that the mean of all PROMIS measures is 50 and the standard deviation is 10. Higher scores represent more of the underlying construct. For example, higher depression scores may indicate more negative mood and negative cognitions, thus suggesting poorer mental well-being; whereas higher physical function scores may indicate a greater ability to successfully complete daily activities and household chores, thus reflecting better physical well-being. Available reference values include norms based on the U. S. general population, as well as clinical samples, such as patients with cancer. In addition, the initial PROMIS norming sample was large enough to estimate subgroup norms by gender and age range [50].

To inform the clinical utility of PROMIS measures, severity thresholds were identified for multiple measures. These “cut points” enable individual practitioners to assess patient response to interventions and modify treatment plans accordingly. PROMIS scientists created score graphs for PRO domains to enhance the meaningfulness of PROMIS scores (see Fig. 24.2). Drawing from the large-scale calibration testing data [49, 51], the percentage of participants that would fit into each category (0.5, 1.0, and 2.0 standard deviations) were reviewed. Then, through a process known as “Bookmarking,” thresholds for severity levels (e.g., no problems, mild problems, moderate problems, severe problems) were established in several clinical samples [52]. Notably, severity

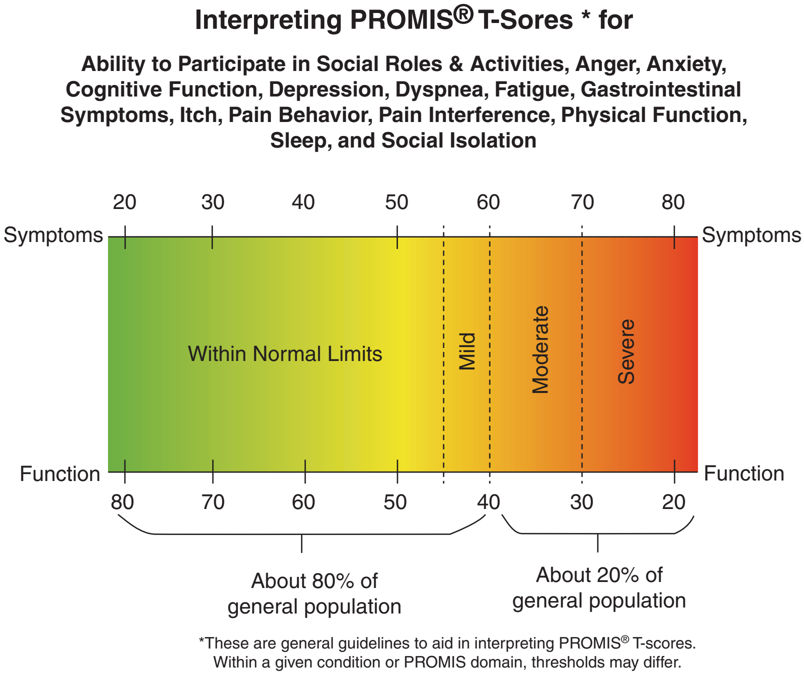

Fig. 24.2 An Example of a PROMIS Score Graph Created to Enhance the Meaningfulness of PROMIS Scores

thresholds in patients with cancer exist for PROMIS Pain Interference, Fatigue, Anxiety, Depression, Physical Function, Cognitive Function, and Sleep Disturbance [53, 54].

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) From 2008 to 2014, the NCI and its contracted researchers developed PRO-CTCAE for use in cancer therapeutic trials and other cancer-related research in order to integrate the patient's voice and experience in describing toxicity, symptoms, and adverse events (AEs) from cancer treatment [55, 56]. PRO assessment in cancer therapeutic trials is important because it provides the patient's perspective on how a treatment is affecting their HRQOL, facilitates higher quality patient–provider communication on the trade-offs between survival benefit and treatment-related morbidities [57, 58], and PRO toxicity reporting may be more accurate than clinician ratings for certain symptoms [59, 60]. To develop PRO-CTCAE, researchers identified the AEs most amenable to patient self-report (e.g., subjective AEs like pain), created items to represent each AE domain and ensure it aligns with the CTCAE criteria, conducted qualitative and quantitative studies to evaluate and refine the PRO-CTCAE items, created software for the collection of PRO-CTCAE data, conducted usability testing of the PRO-CTCAE software, and established guidelines for implementation of PRO-CTCAE in cancer therapeutic trials (see Basch et al., 2014 [55] for a complete review of this process).

The multidisciplinary team had to ensure that a PRO version of the CTCAE reporting system was flexible enough to allow investigators to choose only the AEs most relevant to their specific trial (as opposed to a fixed list of symptoms/constructs as in most existing HRQOL measures), include AEs that occur infrequently (e.g., blurred vision) to very frequently (e.g., nausea), capture the worst magnitude of each AE, and assess the AEs at appropriate intervals. The final PRO-CTCAE standardized measurement system assesses 78 AEs using 124 items and allows clinicians and researchers to select the AEs most relevant to their trial.

All PRO-CTCAE items follow the same structure. They use a plain language term for the AE of interest, include the attribute of interest (frequency, severity, interference with activities of daily living), and a recall period (typically the previous 7 days). The attributes assessed in each item were determined based on the attributes used in grading the corresponding CTCAE domain. For example, some CTCAE domains grade the AE based on both the frequency of the symptom and the severity of the symptom. In this example, the PRO-CTCAE domain would include one item assessing frequency (e.g., In this past 7 days, how often did you have [symptom]?) and a second item assessing severity (e.g., In the past 7 days, what was the severity of your [symptom] at its worst?). With the seven-day recall period, it is recommended that PRO-CTCAE items are answered on a weekly basis to ensure no AEs are missed. On average, it takes patients between 4 and 6 min to complete approximately 28 PRO-CTCAE items [61], thus minimizing participant burden in completing PRO items throughout the trial [55].

The validation studies of PRO-CTCAE found that all PRO-CTCAE items were correlated in the expected direction with validated HRQOL measures, and the majority of PRO-CTCAE items were higher in patients whose physicians scored their performance status as more impaired compared to patients with less impairment [62]. Additionally, most items had high test–retest reliability when assessed approximately 1–6 weeks apart, and the correlation between PRO–CTCAE item changes and the change in the corresponding HRQOL domain were statistically significant in most of the prespecified items [62]. PRO-CTCAE was originally developed for use in adult cancer patients and was translated to a few common languages (e.g., Spanish). Since 2014, the PRO-CTCAE has been translated into 31 languages and pediatric PRO-CTCAE items (both patient self-report and caregiver-report) have also been validated and are now available for use [63, 64]. To find the most up-to-date information on PRO-CTCAE, please see the NCI's website for PRO-CTCAE (https://healthcaredelivery.cancer.gov/pro-ctcae/).

Integration of PROs into Cancer Clinical Trials

The use of PROs to assess HRQOL among cancer patients and survivors has grown exponentially, as described above. With the growth in this area of research and the development of rigorous measures, the current scientific focus has shifted to the usefulness of PROs in a variety of settings, specifically cancer clinical trials and cancer care delivery. The shift toward including PROs in cancer clinical trials started after research documented that the inclusion of baseline HRQOL (assessed by PROs) in multivariable models improved survival and mortality predictions over and above clinical variables [65–70]. Population-based data suggests that baseline HRQOL is significantly associated with all-cause mortality [68], and data pooled across multiple clinical trials found that inclusion of baseline HRQOL improved prognostic accuracy by 5.9–8.3% [69]. Overall HRQOL, physical function, dyspnea, pain, and appetite loss appear to be the most predictive indicators of mortality/survival [65, 66]. Baseline HRQOL was also found to be a better predictor of survival than performance status [65]. In 21 of the 39 studies (54%), clinician-rated performance status was no longer a significant predictor of survival if at least one HRQOL PRO was included in multivariable models [67]. In addition to improved survival predictions, HRQOL data can also provide the patient's perspective on a treatment's impact on function and well-being, supplement efficacy and safety data, and facilitate higher-quality patient–provider communication on the balance between survival benefit and treatment-related morbidities when choosing a treatment option [57, 58]. Therefore, the inclusion of HRQOL PRO endpoints should become standard practice in trial design, especially in oncology where treatments often carry a high side-effect burden with marginal improvements in survival benefits.

However, the inclusion of HRQOL PROs in clinical trials, their use in drug labeling claims, and their dissemination in the scientific literature are subpar [71]. Even among trials that have incorporated PROs as primary or secondary outcomes, complete reporting of the PROs rarely occurs. Among 794 randomized controlled trials, only half provided a rationale or hypothesis for the chosen PRO, a quarter included information on how missing data was handled, and slightly more than half actually described the results of the HRQOL PROs [72]. To ensure accurate reporting of PRO findings, to utilize PRO findings in drug labeling claims, and to disseminate PRO findings to clinicians for use in treatment discussions, specific guidelines on how to integrate HRQOL PROs have been developed by both researchers and regulatory agencies.

Professional Organization Guidelines and Recommendations Researchers and professional organizations focused on the study of PROs and HRQOL have developed PRO-specific extensions to the widely used Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) guidelines to assist researchers in integrating HRQOL endpoints into trial designs. Both the SPIRIT-PRO [73] and CONSORT PRO [74] extensions added PRO-specific expansions to existing items and added new items for trials that include HRQOL primary or important secondary outcomes. A complete, detailed overview of the guideline development process and the updated SPIRIT-PRO [73] and CONSORT PRO [74] checklists can be found elsewhere but are described briefly here.

Clinical trials including HRQOL as a primary outcome or an important secondary outcome should (1) provide a rationale for including PROs and why specific HRQOL domains were chosen; (2) state any HRQOL-specific objective and/or hypothesis; (3) describe which PRO measure will be used to assess each HRQOL dimension, and include measurement properties (e.g. reliability, validity), who is completing the PRO (e.g., patient or proxy), and data collection method (e.g., paper survey, telephone interview); and (4) identify the statistical methods used for analyzing each HRQOL outcome and approaches used to handle any missing data. Additionally, for trials that include HRQOL as a primary endpoint, sample size calculations should be described.

The SPIRIT-PRO guidelines recommend additional points specific to clinical trial protocols: (1) indicate the individual(s) responsible for any HRQOL PRO-related trial content; (2) describe any PRO-specific eligibility criteria that is different from eligibility criteria for the overall trial (e.g., language requirements), and, if applicable, provide the rationale for choosing to collect PROs from only a subsample; (3) outline the schedule of HRQOL PRO assessments, provide rationale for the chosen time points, describe the order of assessments (e.g., multiple questionnaires, PROs assessed at same visit as clinical indicators), and, if applicable, provide a justification for measuring baseline HRQOL prior to randomization; (4) indicate what metric will be used in analysis (e.g., change in HRQOL PRO from baseline); (5) list any strategies that will be employed to minimize missing data; and (6) outline how you will use PRO data for patient monitoring in a standardized manner, if applicable. In reporting the final results of a clinical trial, the CONSORT PRO guidelines also recommend that trials (1) identify the HRQOL domain as a primary or secondary outcome in the abstract; (2) outline any PRO-specific limitations or concerns of generalizability to larger population and/or clinical practice; and (3) interpret HRQOL findings in the context of the trial's clinical findings, if applicable. Finally, the CONSORT PRO guidelines emphasize the importance of publishing HRQOL findings with the primary publication even if this data is included as a supplement.

Regulatory Agencies Guidelines and Recommendations Regulatory bodies such as the FDA, the oncology-specific divisions of the FDA (e.g., Office of Hematology and Oncology Products, Oncology Center of Excellence), and the

European Medicines Agency (EMA) have developed their own recommendations and guidelines for integrating HRQOL PRO endpoints into clinical therapeutic trials in order to use the data to support drug labeling claims. These recommendations and guidelines include many of the points highlighted above. For example, the FDA's Office of Hematology and Oncology Products recommends that researchers select HRQOL PRO endpoints closely related to the disease and/or treatment under study, and they have identified symptomatic AEs, physical function, and disease-related symptoms as the key PROs for oncology drug labeling assessments [75]. The complete guidance documents from the FDA for the use of PRO endpoints in drug labeling claims and in medical device approvals, and the EMA's guidance for anticancer drug labeling claims can be found elsewhere [3, 58, 76], and we have summarized this guidance in Table 24.2.

Table 24.2 Guidelines for Integrating HRQOL PROs into Clinical Trials

Recommendation	FDA	EMA
Rationale for inclusion of PRO measure	X	X
List PRO-specific study objectives and hypotheses	X	X
Provide PRO instrument details		
The instrument's conceptual framework	X	
Copy of instrument (including previous versions)	X	
Instructions/user manuals	X	
Data collection method (e.g., electronic, patient-administered, etc.)	X	X
Documentation of instrument's psychometric properties (e.g., reliability, validity), including complete results of all studies done to ensure validity (e.g. cognitive interview transcripts)	X	X
Demonstrate validity/reliability in the same population being studied in trial	X	X
Any modifications made to the instrument, rationale for modification, the process for making the modification, and data supporting that all psychometric properties were maintained	X	X
Scoring algorithm	X	X
Describe targeted labeling claim(s), disease/condition, and population of focus	X	
Describe how scores are interpreted to be clinically meaningful	X	
Provide methodological details		
Timing of PRO assessments	X	X
Trial duration and demonstrate that it provides enough time to assess PRO endpoints	X	X
Plans for missing data	X	X
Statistical analysis plan, including power/sample size calculations	X	X
Plans for clinical management of adverse events assessed via PRO measures		X
Follow the CONSORT PRO checklist		X

Note: FDA Food and Drug Administration, *EMA* European Medicines Agency

PRO Endpoints in Oncology Drug Labeling Claims Despite the development of the SPIRIT-PRO and CONSORT PRO recommendations and the FDA's guidelines, few oncology drugs have FDA-approved PRO claims. From 2010 to 2014, the FDA's Office of Hematology and Oncology Products approved 40 oncology-focused products (25% of all submitted applications). Of the approved oncology drugs, only three (7.5%) received an HRQOL PRO claim [77], a figure substantially lower than seen across all drugs approved by the FDA in a similar time period (16.5%) [78]. Among oncology drugs approved by both the FDA and the EMA between 2012 and 2016, 70.3% of the applications included HRQOL PRO data, but no FDA-approved products included PRO labeling [79]. In contrast, the EMA included HRQOL PRO-focused claims in 46.7% of their oncology product labeling [79]. The reasons for this discrepancy include the EMA's higher likelihood of accepting legacy PRO instruments, like the EORTC and the FACT measures for PRO-specific product labeling, and the nature of oncology trials [77, 79]. Oncology trials are often fast-tracked, and this shorter time frame precludes the ability of the investigative team to develop a PRO measure that conforms to FDA's standards. Additionally, the FDA has typically not approved a PRO-based claim unless the trial is double-blinded, and oncology trials are most often conducted as open-label trials. Despite a recognition by the FDA that these characteristics of oncology trials are present, there has not be substantial progress or collaboration between the FDA, industry, clinicians, and PRO researchers to identify alternative solutions [80].

Importance of the Patient Voice HRQOL data provide important information about treatment side effects and this data play a central role in patient–provider discussions about treatment options. Given the lack of inclusion of HRQOL PRO data in oncology drug labeling claims, the FDA's Oncology Center of Excellence has tried to make progress in improving patient and clinician access to HRQOL data from therapeutic trials by creating Project Patient Voice. Project Patient Voice is an online platform for cancer patients, their caregivers, and clinicians to look at patient-reported symptom data from the therapeutic trials of approved anticancer treatments [81]. Project Patient Voice is currently in its pilot phase and is displaying the HRQOL data collected during the first six months of one drug trial. Visitors to the website can click on individual symptoms to see graphical depictions of the data. If Project Patient Voice is found to be a usable and informative website for cancer patients, their caregivers, and clinicians, the FDA's Oncology Center of Excellence has plans to include results from other trials.

Within the context of therapeutic trials, the patient voice is particularly meaningful for better understanding the adverse events or unexpected medical problems that occur during treatment. Adverse events have traditionally been assessed through clinician ratings of the CTCAE. However, data from cancer therapeutic trials suggest substantial disagreement between patient- and clinician-ratings, and likely under-reporting of toxicities/symptoms by clinicians [59, 60]. A pooled analysis of more than 1000 patients who participated in cancer therapeutic trials found that agreement between clinicians and patients (measured by Cohen's k) was low, ranging from 0.15 to 0.45 [60]. Di Maio et al. (2015) also found that clinicians likely under-reported 40.7–74.4% of toxicities reported by patients.

Clearly, improving both clinician and patient assessments of HRQOL domains, adverse events, and symptoms is important. HRQOL's ability to predict survival is improved when both clinician- and patient-ratings are included in multivariable models [69]. Research among 1636 patients enrolled in therapeutic trials found that the disagreement between clinician- and patient-ratings of performance status and nutrition was a significant predictor of mortality [82]. This discrepancy between patient and clinician perceptions and the resulting implications for care were primary catalysts for the development of the PRO-CTCAE as described above.

Next Steps in Improving HRQOL Integration in Clinical Trials The use of HRQOL PRO endpoints in clinical trials, both therapeutic and supportive care trials, provides opportunities to include the patient's voice, understand treatment side effects, make informed decisions on the best available treatments for cancer, and identify potential interventions to improve HRQOL. Important governmental and regulatory bodies (e.g., FDA, EMA) have recognized the value of HRQOL PRO endpoints in developing, testing, and licensing cancer-specific drugs and medical devices. However, the inclusion of PRO endpoints in cancer clinical trials continues to be low, and work continues to fully integrate PROs into cancer therapeutic trials in a rigorous manner. Efforts by the NIH and the NCI to develop high-quality PRO measures for HRQOL, symptoms, functioning (PROMIS), and AEs (PRO-CTCAE) may begin to overcome barriers to PRO-based inclusion in cancer clinical trials.

Integration of HRQOL PROs in Cancer Care Delivery

With both the knowledge that assessment of HRQOL, symptoms, and treatment toxicity provide valuable information and the development of robust PRO measures (e.g., PROMIS, PRO-CTCAE), researchers and organizations have begun to consider the utility of integrating PRO measures into cancer care delivery. Eliciting the patient's voice during cancer treatment and survivorship has been shown to improve patient–provider communication, patient satisfaction, patient engagement, and HRQOL [83–86]. More recent studies of symptom tracking (using PROs) has demonstrated reduced emergency department visits, treatment-tailoring, increased tolerability to cancer treatment for longer intervals, and subsequent improvements in survival [87–91]. The integration of HRQOL PROs into cancer care has the potential to improve the quality of care delivery through the early identification of problems, improvements in symptom management, and triaging care based on needs (e.g., referrals and in-person intervention for severe symptoms, self-management for moderate symptoms) [83]. For healthcare organizations to achieve these goals, however, the integration of PROs must be evidence-based, aligned with their specified objectives, and follow implementation guidelines.

Evidence-Based Approaches to HRQOL Monitoring Researchers have identified feasible and acceptable approaches for monitoring changes in HRQOL among cancer patients. The most frequently studied methods for integrating HRQOL PROs into cancer care delivery are clinic-based assessments and home-based reporting using patients' own digital devices.

Options for clinic-based assessments of HRQOL PROs include paper-based surveys and tablet/touch-screen computers provided to patients in waiting rooms. Pilot studies of clinic-based assessments have demonstrated participation rates ranging from 59–90% [84, 92–98], reasonable retention rates (61–84% of study participants completing assessments throughout study period) [93–95, 97], and high patient and clinician satisfaction across samples diverse in age, gender, cancer type, disease stage, and treatment exposure [93, 99, 100]. Pilot studies have also found data equivalence across paper-based or electronic-based surveys completed in clinics with results suggesting lower levels of missing data for electronic collection [98, 99, 101–103].

The second method for HRQOL PRO assessment, home-based reporting, includes web-based portals patients' access from a home computer, telephone-assisted interviews, and smartphone apps. Across these different approaches, pilot studies found highly variable participation rates (35–86%) [70, 86, 104–113], but reasonable retention (58–91%) [70, 104, 106, 107, 114] and completion rates (most studies reporting 60% completion or above [104, 106, 107, 110, 112, 114–117], with some exceptions) [111, 118]. Systems that actively alerted/reminded patients to complete PRO assessments appear to have better participation rates. A pilot randomized controlled trial of a web-based app developed to improve medication adherence in breast cancer survivors found significantly higher completion rates in the group who received reminders (74%) compared to the group who did not receive reminders (38%) [119].

Patients were satisfied with these systems and found the electronic systems easy to navigate; this was true even for patients with lower technology literacy [92, 97, 104, 106, 107, 120–124]. In particular, patients liked home-based, self-monitoring because they felt more knowledgeable about their health, were able to self-manage, and were reassured that their healthcare team was monitoring their symptoms and functioning to ensure timely response to problematic trends [86, 88, 97, 115]. Both clinic-based and home-based approaches to HRQOL PRO assessments are feasible and acceptable approaches for cancer patients, and the numerous options available allow organizations to choose a mode of PRO collection that is tailored to their local resources and patient population.

Monitoring HRQOL PROs alone does not appear to be enough to make significant improvements in the outcomes important to cancer patients [94, 125]. PRO monitoring may increase the frequency of HRQOL discussions during clinic appointments, but data suggest that HRQOL and/or symptom distress improve only if PRO data summaries are provided to clinicians with clinically actionable information [94, 125].

For example, Ruland et al. (2010) provided clinicians a summary of the HRQOL and symptom domains patients had ranked as the most in need of management or attention, and they found significant reductions in symptom distress in the patients whose summaries were provided to their clinicians compared to patients whose summaries were not provided to clinicians. In contrast, Hilarius et al. (2008) provided nurses with a graphical summary of patients' responses to EORTC QLQ-C30 but provided no further information on how to utilize this information. When comparing the HRQOL of these patients to those who did not have a summary provided to their nurse, the authors found no significant difference in HRQOL. However, monitoring HRQOL does improve patient satisfaction and patient–provider communication [93, 121, 122].

PRO monitoring interventions that include one or more of clinician alerts, tailored self-management information, referrals, or clinical decision support (e.g., specific management recommendations) have been found to significantly improve HRQOL domains, including symptom burden and symptom distress [95, 109]. In a randomized controlled trial that assigned cancer patients to one of three distress screening groups (minimal screening [Distress Thermometer only], full screening + personalized summary, and triage (full distress screening and phone triage for referrals), receipt of a referral was the best predictor for changes in anxiety and depression [126]. A large-scale randomized controlled trial of cancer patients receiving chemotherapy (*N* = 766) randomized patients to clinic-based symptom monitoring (intervention group) or standard of care symptom monitoring (control group) [84]. In addition to completing the symptom assessments, intervention group participants also had their results summarized, provided to nursing staff, and nurses were immediately alerted when any symptom reached the severe threshold. Patients in the intervention group had significantly higher HRQOL, were less likely to be admitted to the emergency room, and remained on chemotherapy longer than patients in the control group. Similar patterns have also been found in studies examining home-based monitoring that delivers tailored symptom self-management information directly to the patient [127].

Systematic Approach to PRO Integration Regular HRQOL PRO assessments will only lead to improved outcomes if implementation is done in a systematic and rigorous manner.

Table 24.3 Integrating HRQOL PROs into Cancer Care Delivery

Recommendation	Examples
Identify goal of HRQOL PRO data collection	One-time screening tools (e.g. distress screening) Regular symptom monitoring (e.g. early identification of treatment toxicity)
Determine population of focus for HRQOL PRO collection	Disease or treatment Phase of the care continuum Minority group (age, race/ethnicity, rurality, sex/gender)
Identify the specific HRQOL domains to target	Physical domain Mental domain Social domain Spiritual domain
Determine timing of HRQOL PRO assessments	Post-discharge for cancer-related surgery [105, 112] Link assessments with clinic visits [117, 227] Specified intervals in posttreatment survivorship [118]
Choose the PRO instrument	Generic Cancer-specific Disease-specific Symptom or treatment-specific
Select mode of PRO administration	Paper (either in clinic or mailed to patients' homes) Electronic (using tablets/laptops in clinic or mobile/web-based on patients' devices) Telephone (by clinic staff or through automated services)
Identify who will receive HRQOL PRO results	Clinicians Patients Caregivers
Select format for PRO results presentation	One-page summaries Summary dashboards Graphical interpretations [228, 229]
Provide guidance on PRO score interpretation	Clinical thresholds for action Clinical decision support recommendations [96]

Researchers and professional organizations have outlined methodological and implementation considerations for the integration of HRQOL PRO assessment in clinical care [128], and we have summarized these recommendations in Table 24.3. The implementation of HRQOL PRO assessment and how PRO results are used will vary if organizations want to use PROs as one-time screening tools (e.g., distress screening) or for regular symptom and AE monitoring (e.g., early identification of treatment toxicity). Additionally, the PROs selected for assessment need to be relevant to the target patient population and amenable to intervention [129–131].

When selecting HRQOL PRO measures, organizations should choose measures that are validated for use in the target population, ideally in the same mode the questionnaire will be administered in clinical practice, and are easy to implement [132]. Tailoring the mode of administration to patient preferences (e.g., paper- or telephone-based in older populations) will likely improve participation rates. The primary modes of PRO questionnaire administration (paper, web-based, phone) have had high response rates in prior literature [84, 104, 106, 107, 110, 115, 116]. Additionally, a number of publications have found similar completion times and data equivalence when the same measures are implemented in paper or electronic forms [98, 99, 101–103]. A meta-analysis of data equivalence in 278 scales found that the average mean difference between paper- and electronic-based surveys was 0.2% and the average weighted correlation between modes was 0.90, further supporting the recommendation to select a method tailored to patient preferences [133].

Clinicians prefer easy-to-interpret, digestible reports of PRO data (e.g., one-page summaries, summary dashboards with options for additional detail) that clearly highlight clinical thresholds for action [116, 134–136]. Patients like having summaries of their HRQOL results, but it is most important to them that their clinical team is tracking their HRQOL PRO results and using them in their care [110]. Identifying thresholds for meaningful PRO results can be done through both psychometric and consensus-building approaches. Psychometric options for score interpretation include using minimally important differences, comparisons to normative data, reference values, and benchmarks to identify meaningful change and/or severity thresholds across multiple HRQOL domains (e.g., symptoms, function, distress) [137–140]. Ideally, when selecting a PRO measure, it is preferable to find one with psychometrically derived severity thresholds in the population of interest. When this information is not available, organizations have used consensus-building approaches to identify thresholds (e.g., the bookmarking approach described above for PROMIS) [52, 141]. Regardless of the selected approach, organizations should regularly evaluate and modify these thresholds, as needed, to ensure that patients are receiving intervention at the appropriate time and level, when needed [83].

The results from HRQOL PRO assessments can be used in clinical care through two primary avenues: self-management resources delivered directly to patients and clinical alerts delivered to clinicians (with or without specific recommendations for management). Most often, organizations identify thresholds that categorize patients into four groups (no, mild, moderate, and severe symptoms/concerns), and clinical actions are tailored to increase clinical staff engagement with increasing severity [112]. For interventions that focus on home PRO monitoring, the most common approach is to deliver self-management information directly to patients in the mild/moderate categories and send alerts directly to clinical staff for patients in the severe category [97, 105, 112, 122, 142]. In some cases, patients in the moderate category will be told to contact their clinic team during business hours, and patients in the severe category will be told to go to the emergency room [143]. Regardless of which groups receive self-management information, patients prefer personalized and tailored self-management information [88, 105, 113, 142]. For interventions that focus on clinic-based PRO assessments, results are summarized and provided to clinicians, and in many cases, these summaries are coded to highlight scores that have reached different thresholds (e.g., moderate, severe), and clinical decision support recommendations are provided [96]. Clinical recommendations that are short, include both pharmacological and non-pharmacological management approaches, and are tailored to local resources are more likely to be implemented into clinic workflow and be rated more positively by clinicians [129, 130, 144].

HRQOL in Care Delivery The integration of HRQOL PROs into cancer care delivery has become more widespread and sophisticated across time, and the value of collecting HRQOL outcomes is well-accepted [145]. Regular assessment has been found to improve the timely identification of symptoms, referrals for psychosocial services, and patient–provider communication [83]. To ensure positive patient outcomes from HRQOL PRO assessments, organizations need to consider important implementation topics such as identifying the most appropriate HRQOL domains, measures, and clinical response options. Guidelines from professional organizations [128] and published papers [142, 146] describing the development of PRO systems can serve as useful starting points for institutions interested in integrating HRQOL assessment into cancer care.

Summary and Future Directions

HRQOL is a multidimensional concept that includes self-reported symptoms, functional abilities, and physical, mental, social, and spiritual health perceptions. HRQOL is measured with a variety of valid PROs. Global and specific approaches to assessing HRQOL may permit comparisons to healthy populations and within particular disease groups, respectively. Efforts to enhance and improve PROs that assess HRQOL are ongoing with initiatives such as PROMIS and PRO-CTCAE providing valid, brief, and flexible measurement approaches for patients with cancer and survivors. HRQOL is increasingly an important but underutilized PRO in cancer clinical trials and care delivery research. To further catalyze HRQOL research and maximize cancer clinical care, future research should incorporate a multi-level approach that accounts for patient (e.g., identifying HRQOL priorities across the care continuum, empowering decision-making and self-management), provider (e.g., minimizing workflow interruptions, making PROs actionable), and system (e.g., integrating PROs into the electronic medical record, harnessing technology as a rapid learning healthcare system) level perspectives. Optimizing patient-centered care, enhancing HRQOL, and attaining better outcomes are aspirational and achievable goals.

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"This Is What Kills Me": The Financial Toxicity of Cancer and Its Psychological Cost

Maria Chi

> *The financial stuff? This is what kills me, because there is nothing I can do.*
> (focus group participant discussing the financial strain of her cancer)
> *If it weren't for the money stress, I could deal with the cancer.*
> (patient discussing financial burden with his counselor)

The above remarks from people with cancer clearly speak to the concept of *financial toxicity*, a term used to reflect the high cost of cancer, both literally and psychologically [1]. Oncologists first coined the term to emphasize the harmful objective and subjective effects of cancer-related expenses [2], effects that may be as "toxic" as side effects of chemotherapy or other treatments. It is generally known that overall spending on cancer care is steadily rising in the United States, such that an estimated $137.4 billion was spent in 2010 [3], which grew to $150.8 billion in 2018 [4]. Less is known, however, about the nature and effect of those costs on the individual patient. While the estimated national expenditures take into account both system-level and patient-level spending, the actual day-to-day impact of those costs on the patient is not as widely known.

Identifying financial toxicity as "the patient-level impact of the cost of cancer care" ([1], p. 381) helps to diagnose the problem and point toward some solutions. Cancer-related medical expenses may include the portion that patients pay for hospitalizations, outpatient visits and procedures, physician services, administration of treatment, durable medical equipment and supplies, home healthcare, and hospice care [3], in addition to scans, tests and labs, health insurance costs, and pharmaceutical products. Cancer-driven, non-medical expenses may include the cost of transportation, loss of income, long-distance lodging, and accrual of personal debt [5, 6].

These many and varied expenses become more salient – both to individual patients and society as a whole – as the number of people diagnosed with cancer or having lived beyond a cancer diagnosis increases. For example, there were 16.9 million cancer survivors in the United States as of 2019, which is expected to rise to 22.2 million by 2030 [4]. Moreover, almost 40% of people will be diagnosed with cancer at some point in their lives [4]. Americans are also getting older: By 2040, it is estimated that 22% of the US population will consist of people aged 65 and older [7]. An aging population means that the incidence of cancer will rise further. Finally, as science and technology continue to advance, certain cancer treatments are likely to become even more expensive, putting added strain on patients and families already carrying the financial burden of cancer.

With objective financial hardship increasingly evident among people with cancer [8], it is per-

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haps unsurprising that many of those same individuals are experiencing toxic effects on their mental and emotional health. Indeed, in one survey of 174 people living with cancer in the United States, up to 47% reported "catastrophic" levels of financial stress related to their cancer ([9], p. 416). Another cross-sectional study examined 149 patients, half receiving care in public hospitals and half in private cancer centers: Regardless of their health insurance status or where they received treatment, both samples reported high levels of cancer-related financial distress [10]. In fact, 30% considered their financial stress to be higher than the physical, emotional, or relational distress of having cancer itself [10].

Furthermore, there is growing evidence that the subjective consequences of objective financial strain in people with cancer include greater anxiety and emotional distress [5, 11], increased depression [12], higher relationship stress [13], and diminished health-related quality of life [14, 15]. Given that people with cancer already experience high rates of depression, from sub-clinical distress and milder forms of dysthymia (22%) to major depression and disability (16%), [16, 17], the added element of financial hardship may only compound the psychological sequelae of cancer. According to Sharp et al. [12], patients with financial stress have approximately three times the risk of developing symptoms of depression and eight times the risk of severe depression than does the general population. In turn, depression in people with cancer is associated with longer hospital stays, more physical distress, less treatment adherence, and higher suicide rates [18]. Similarly, depression is correlated with greater cancer progression and mortality [19, 20]. The stakes are high.

Identifying Financial Toxicity

Objective Types of Financial Toxicity

Gordon, Merollini, Lowe, and Chan [21] conducted a systematic literature review of 25 studies on the phenomenon of financial toxicity; all studies had a sample size of at least 200 participants. Across those studies, financial toxicity in cancer survivors occurred 28–48% of the time.

Objective types of financial toxicity include the more concrete, measurable costs of cancer care, both medical and non-medical. Major medical expenses include the cost of health insurance (copayments, premiums, and deductibles), treatment and medication expenses, frequent physician visits, tests, scans and labs, medical supplies, hospital stays, and home care. Non-medical costs or consequences include transportation expenses, having to pay for lodging (depending on distance to treatment center), loss of job or income (due to depletion of or lack of paid sick time), exhaustion of savings, eviction or home foreclosure, the accrual of personal or familial debt to pay for basic living expenses such as food or housing, and increased medical bankruptcy [1, 5, 6]. Both medical and non-medical concrete cancer costs are amply identified in the psychosocial health literature.

Medical Expenses

Most of the medical expenditures on cancer care involve treatment and related costs (physician services, tests and lab work, hospitalizations, medical supplies, and homecare), which in turn comprise out-of-pocket expenses for patients. For example, in a large survey of 1170 prostate cancer survivors, respondents reported significantly higher medical expenses than a control group, spending an average of $3586 per year (patients under 65) or $3524 per year (patients 65 and older) [22]. Those average expenditures can be driven much higher by the cost of newer, more innovative treatments, such as immunotherapy and targeted therapies, which are often prohibitively expensive. Carrera, Kantarjian, and Blinder [23] observed that most targeted therapy medications cost more per month than the annual income of a person meeting the national criteria for poverty.

Non-medical Expenses

There is increasing evidence for the impact of cancer-driven medical costs on people's ability to afford their non-medical but basic needs. For example, in a national survey of 509 people with various types of cancer, one-third of respondents aged 25–54 reported having to sacrifice groceries to afford their cancer treatment. Twenty-one percent could not afford at least one utility bill, and 17% could not afford rent or mortgage while they received treatment [5]. In another study, Palmer et al. [24] analyzed patient surveys and found that 22% of people receiving radiation treatment experienced financial toxicity. Specifically, patients reported reduced income (24%), job loss (28%), and hardship in paying for housing (20%), food (13%), and transportation (15%). Shankaran et al. [6] found that 38% of patients with colon cancer ($N = 284$) identified at least one treatment-related financial hardship; moreover, 23% of those patients with financial toxicity reported having medical debt. Commonly, accrual of debt for medical reasons and depletion of one's savings or assets are major types of cancer-related financial hardship. In a recent longitudinal study of 9.5 million people (diagnosed with cancer between 2000 and 2012), 42% of them spent *all* of their personal assets within 2 years of being diagnosed [25].

Perhaps unsurprisingly, exhausting one's personal savings and resources while living with ongoing cancer-related financial challenges may lead to bankruptcy. In fact, people being treated for cancer are almost three times more likely to declare bankruptcy than people without cancer, controlling for age [26]. Five percent of the respondents in Cancer*Care*'s [5] national survey declared bankruptcy. A more recent study found that 66.5 % of bankruptcies in the United States are due to medical hardships, driven by high costs of treatment or loss of employment income [27].

Health Insurance and Socioeconomic Status

Significantly, all of the people surveyed in the preceding Cancer*Care* [5] study had health insurance or treatment coverage (through Medicare, Medicaid, the Affordable Care Act Marketplace, their employer, or hospital charity). There is evidence that having health insurance may help prevent the accumulation of medical debt [28]: One of the determinants of financial toxicity in Gordon et al.'s [21] systematic review was individuals' lack of health insurance. However, in its current forms, the protection that health insurance may provide is limited [29, 30]. The out-of-pocket expenses that people still incur with (or because of) health insurance, in the form of premiums, deductibles, and copayments, in addition to the non-medical costs of cancer, means that their financial burden may remain. After all, the other contributing factors to financial toxicity in Gordon et al.'s [21] analysis were loss of income, lower income pre-cancer, and distance from treatment centers (adding to transportation and/or lodging costs).

Pre-existing financial conditions such as unemployment, lower-paying jobs, and low-income status – signifiers of economic instability at the individual level – may contribute to the financial toxicity of cancer [31]. These conditions represent social determinants of health (SDH), or the social and physical circumstances of people's early and current educational, residential, and work environments [32]. An SDH such as socioeconomic status (SES) may contribute to people's vulnerability to the financial toxicity of cancer. In turn, their financial toxicity may amplify their poverty. People with lower-paying jobs are less likely to have paid sick leave, making it more likely that they will suffer income reduction or total job loss [23]. They also tend to have fewer assets which could be used to pay for medical and non-medical, cancer-related expenses [23]. Moreover, people with lower SES are more likely to be diagnosed with advanced cancers, which tends to increase cancer care costs [33].

Case example* Annie is a 70-year-old, widowed woman diagnosed with colon cancer. She requires weekly chemotherapy but cannot use public transportation in the city where she lives because her immune system is compromised due to treatment. Lacking a subsidized transportation benefit through Medicare, she must pay out of pocket for cab fare several times a week. Living on a fixed income (her Social Security retirement benefits), Annie rapidly depletes her limited funds to pay for transportation. She is soon prescribed an oral medication that she needs to take in conjunction with her chemo infusions. The medication costs $3000/month, even after Medicare pays its portion. Annie worked with the hospital's pharmacy specialists to locate a financial assistance program that may help pay for the drug; however, she did not qualify for the program because her Social Security income was considered too high. Annie was told that she could get an infection and die if she does not take the medication, so she withheld her rent for 3 months to pay for the prescription. In the meantime, she is getting eviction threats from her landlord. Annie seriously considers skipping treatment all together for a while in order to conserve her limited resources and not become homeless.

*Some details have been altered to protect patient confidentiality.

Treatment Non-adherence. Perhaps the most troubling consequence of concrete, objective types of financial toxicity is non-adherence to cancer treatment. What healthcare professionals often see as psychological resistance or willful non-compliance may in reality be a logical tool for managing financial hardship [23]. Despite using a variety of practical coping strategies, such as depleting savings, incurring debt, or sacrificing basic needs, patients are not always able to alleviate their cancer-related financial burden [31]. Sometimes, they must postpone or forgo treatment completely.

In the 2006 *National Survey of U.S Households Affected by Cancer*, 8% of respondents with health insurance and 25% without insurance either delayed or did not get treatment. Both groups identified the challenge of paying for treatment as the reason for sacrificing care [34]. Similarly, Cancer*Care's Patient Access and Engagement Report* [5] found that 39% of patients aged 25–54 had postponed or missed medical appointments; 38% delayed filling a prescription; and 34% skipped doses of their cancer-related medications, all due to financial strain. In a retrospective study of women with breast cancer, prescription copayments were directly related to the women's non-adherence to adjuvant hormonal therapy [35]. Unsurprisingly, non-adherence to cancer treatment is associated with higher mortality rates, which are higher in people experiencing the financial toxicity of cancer [25, 36].

Subjective Types of Financial Toxicity: Psychological Distress and Quality of Life

While treatment non-adherence is a troubling aspect of the objective types of financial burden, the more subjective types of financial stress – the perceptions of and emotional responses to the concrete burdens – also have serious consequences for patients' well-being. As noted earlier in this chapter, another key component of financial toxicity is the psychological distress that patients experience in relation to their cancer-related costs [2]. Financial hardships in cancer care are related to higher emotional distress, lower quality of life [14, 15, 37], and less patient satisfaction with overall care [9].

In one study, financial toxicity was found to be the strongest inverse predictor of quality of life in people with cancer [14]. One prospective study of medical and non-medical cancer costs in 512 patients identified a negative correlation between out-of-pocket expenses and health-related quality of life [33]. *Health-related quality of life*, or HRQoL, is defined as the perception of one's physical, mental, emotional, and social well-being over time [38]. Financial stress compounds the depression, anxiety, and feelings of helplessness that a cancer diagnosis may elicit on its own [16]. In a small qualitative study, for example, Klimmek et al. [11] found a positive association between health insurance-related hardship and patients' self-report of emotional distress. The researchers interviewed women in four different cancer centers about their experience with managed care companies, difficulty in getting authorization for treatment, being denied coverage for certain procedures, and trying to plan for out-of-pocket expenses. Participants disclosed high emotional distress and anxiety around these challenges [11].

Similarly, a cross-sectional study compared 149 adults with advanced cancer, half in private cancer centers and half in public hospitals [10]. Both samples reported high distress attributed to their financial problems, whether they had private or public health insurance coverage. Furthermore, those patients with high distress reported significantly more anxiety and depression [10]. Another study of 584 patients, 99% of whom had some type of health insurance, found that 30% of them were worried about how they would pay for their cancer treatment. Only 8% expressed confidence that they could afford their care [39].

In addition to decreased well-being and quality of life in individual patients, financial toxicity is connected to disrupted relationships. For example, participants in one qualitative study of 40 patients and 17 caregivers reported that financial strain had an adverse impact on their marriages, partnerships, or close relationships [13]. They also expressed high anxiety about their altered roles and responsibilities as a result of their financial hardship, for example changes in provider and dependent status, or when a spouse had to return to work for added income or take time off work to care for their loved one [13].

In a disconcerting parallel to the phenomenon of treatment non-adherence among patients with financial toxicity is the sacrifice of mental health treatment or psychosocial support. Just as it may be too expensive to afford doctor visit copays, treatment costs, transportation expenses, or unpaid time off work for medical appointments, the same objective challenges may preclude patients from getting the very psychotherapy or counseling they need to cope with their cancer and financial stress. While 58% of the people aged 25–54 surveyed in CancerCare's *Patient Access and Engagement Report* [5] reported cancer-driven financial distress, 24% of respondents in the same survey said they had to "often or always" skip a mental health appointment for financial reasons (p. 56). When they most need it, patients may be hindered from getting psychosocial support.

Along with the treatment non-adherence explored in the previous section, there is perhaps another tragic pathway to mortality that starts with the subjective stress of financial toxicity. Depression on its own is directly associated with cancer progression and mortality [19, 20]. There is some evidence to suggest that emotional stress stimulates tumor growth and metastasis, mediated by hormones and immune system factors [40, 41]. The stress of financial toxicity perhaps compounds that process, as well as intensifying cancer symptoms such as pain and diminishing HRQoL [42].

Case example[*] Carlos is a 30-year-old man in active treatment for Hodgkin's lymphoma. He has exhausted his paid sick time but cannot yet return to work due to his immunocompromised status and severe side effects from treatment. Carlos sought psychotherapy in his community for his heightened anxiety and the panic attacks he has had since starting treatment. He has health insurance through his employer but is now paying high monthly premiums through COBRA to keep his coverage while he is on medical leave. He relies on partial hospital financial assistance to pay for his chemotherapy and gets subsidized medications from a pharmaceutical company. However, he cannot afford to pay for mental healthcare without insurance. Meanwhile, his wife, who already works full-time, must take an extra job at night to pay for family expenses. Mourning his loss of independence and role as primary provider for his family, Carlos feels more and more helpless, discouraged, guilty, anxious, and depressed.

[*] Some details have been altered to protect patient confidentiality.

Financial Toxicity in People of Color

An exploration of financial toxicity would be remiss without identifying the significantly heavier burden that patients of color carry. In the pilot study to determine the validity and reliability of the COST measure, or the **CO**mprehensive **S**core for financial **T**oxicity, nonwhite race was positively associated with financial hardship, even when controlling for age, sex, marital status, and type of health insurance [31]. Similarly, in various studies, Black and Latino cancer survivors have reported greater financial burden than their white counterparts, after controlling for income, education, and employment status [43, 44].

In one large study of women with breast cancer, Black and Latina patients were significantly more likely to report treatment-related debt, loss of income, forgoing basic needs such as groceries, and anxiety about paying for cancer-related costs than were white women [44]. Moreover, Latina breast cancer survivors have less income and savings to cover medical expenses and are more likely to miss doses of treatment-related medications due to cost than are non-Latina, white cancer survivors [45, 46]. To this author's knowledge, the varying psychological corollary of these objective components of financial toxicity is not as well studied among different races and ethnicities. If the subjective impact of financial strain is as considerable and significant to patients of color as its more concrete manifestations, then further investigation is warranted.

Case example[*] Gail is a 55-year-old African American woman recently diagnosed with metastatic breast cancer. Although she works two jobs to make ends meet, neither job provides health insurance, so she purchases health insurance through the Affordable Care Act Marketplace in her state. Her plan has high copays, so she must cut spending on other basic necessities to afford treatment. Gail develops a serious infection while undergoing chemotherapy, and she ends up in the hospital for 10 days. Once she is discharged back home, she needs intensive rehab and homecare services to help her regain her independence and perform basic activities of daily living. However, her insurance plan does not cover more than a few hours of homecare a week for a few weeks at a time, and Gail ends up in the hospital again with another infection. She is not able to afford a private home health aide when she returns home. Because neither of her jobs offer prolonged paid sick time, she has suffered loss of income and is not sure when she can return to work.

[*] Some details have been altered to protect patient confidentiality.

Suggested Remedies: A Clinical Detox

Amid the bleakness of financial toxicity are options for intervention at the clinical level. While recent studies have generated multiple suggestions for relieving toxicity at the systemic, policy level – such as instituting universal health insurance, generating more non-profit funding for direct financial assistance to patients, expanding criteria to make more patients eligible for government benefits and private organizational grants, and establishing a more efficient and equitable healthcare delivery system [47] – the rest of this chapter will focus on clinical interventions at the patient level.

To alleviate the psychological impact of financial toxicity, psychosocial healthcare practitioners may use several different approaches. First, they may more proactively and routinely assess for financial stress, perhaps by using the COST (COmprehensive Score for financial Toxicity), an 11-item, patient-centered, validated tool [31]. For those patients scoring high on financial toxicity, clinicians may refer them to appropriate resource professionals, such as hospital patient navigators, financial counselors, social workers, or case managers. Providing guidance, support, and validation throughout a confusing, decentralized system becomes a clinical tool to empower patients. Ultimately, patients learn to engage in problem-solving through mobilization of their strengths and psychoeducation about how to access various resources (e.g., applying for copayment assistance to help defray the cost of cancer medications). Problem-focused coping is best utilized in circumstances that one can at least partially control [48].

Furthermore, patients sometimes feel that healthcare providers neglect to communicate both expected cancer-related expenses and options for addressing them [44]. Healthcare team members would do well to heed patients' preference for earlier and clearer dialogue about possible side effects of cancer treatment, which include financial effects. More timely connection to programs and concrete resources may provide a sense of hope and security [44].

Another way to disseminate information about financial toxicity and its antidotes is through the engagement of social support and other interpersonal approaches. Networking and informally connecting to one's peers (who are also experiencing the financial strain of cancer) may help reduce social isolation, provide normalization of stressful circumstances, and promote ongoing communication around psychosocial needs [47]. Representing a more structured intervention, support groups provide a medium through which to share valuable information and practical strategies for coping with psychosocial stress [49, 50].

Of course, some stressful circumstances cannot be completely changed. When facing financial challenges that are not easily resolved, cognitive behavioral therapy (CBT) can help patients change their perception of the problem [51–53]. For example, CBT may help them counter their unhelpful beliefs about asking for and accepting help (e.g., borrowing money, applying for a non-profit grant). Or clinicians may help patients identify the distortions they hold about the cause of their financial problems, reducing the shame they may feel over their situation (e.g., "I should have enough money all of the time to cover all of my medical expenses. Otherwise, I'm a failure."). Similar to CBT are the cognitive techniques that Stepanikova, Powroznik, Cook, Tierney, and Laport [54] labeled *interpretative strategies* in their study of how cancer survivors managed financial stress. Such strategies include shifting one's perception of what matters in life and reprioritizing goals and values. For example, someone who loses her job when she is too ill to work and must apply for disability benefits may choose to focus on her resourcefulness and adaptability instead of her loss of income and increased dependence.

Comparable to the CBT premise of recognizing what we can and cannot control, and adjusting our expectations and perspectives accordingly, is the principle underlying meaning-focused coping. This type of coping involves finding meaning in life despite major obstacles, such as life-threatening illness or significant financial burden. In fact, meaning-focused coping presents a way to express one's values, beliefs, and goals in order to make sense of those obstacles [55].

Breitbart and Poppito's [56] Meaning-Centered Psychotherapy (MCP), for example, has been shown to enhance a personal sense of meaning and purpose in people with advanced cancers, even at the end of life. Based on logotherapy, the existential therapy model of Viktor Frankl [57], MCP helps patients identify different sources of meaning, such as those we derive from everyday experiences and relationships, creative pursuits, or the impact we make on the world. Perhaps most importantly is the *attitudinal* source of meaning, or the way in which we face crisis or adversity when there is no immediate (or any) solution [56]. When one cannot "solve" the problem of cancer or financial toxicity, she may still choose her outlook toward it. Pain does not have to become suffering.

Meaning-making interventions (MMIs) have demonstrated utility in helping people cope with various types of cancer, suffer less anxiety [58], and increase their hopefulness [59]. MMIs have been positively associated with self-esteem and self-efficacy in people with breast or colon cancer [60] and more effective coping with overall life distress [61]. To this author's knowledge, there is no research examining a possible relationship between MMIs and financial stress, but their efficacy in alleviating cancer distress suggests their potential for addressing related financial problems.

Case example* Robert is a 60-year-old married man with early-stage prostate cancer. He just finished a course of radiation and is anxious about needing more treatment and having to take additional time off work, thus risking his job. Robert has exceeded his monthly budget on cancer-related expenses, including treatment copays and the cost of gas to travel to his treatment center, which is 45 miles from his house. He feels increasingly discouraged about his dwindling savings and has amassed $5000 of credit card debt so that he can keep paying for his mortgage. After seeking therapy to address his budding depression, Robert learns about meaning-focused coping. He learns how to take stock of the sources of joy and purpose in his life that existed before cancer and before his financial stress. He invites his grandchildren to visit him more and takes weekend walks with his wife while photographing his neighborhood, which used to be a favorite hobby. Eventually he will create a social media account to share those photos and stay connected to friends and family. Although he still has significant financial strain, Robert begins to feel less helpless and more confident in reaching out to his hospital social worker for possible resources.

[*]Some details have been altered to protect patient confidentiality.

Discussion

The phenomenon of cancer-related financial stress, also known as financial toxicity, is well documented and ongoing. However, there is greater familiarity with the concrete, objective types of financial burden. Less well documented but no less pertinent are the subjective components of financial toxicity, namely, its psychological impact and decline in patients' quality of life.

Both medical and non-medical cancer care costs comprise the concrete, objective types of financial toxicity. These costs are a growing problem in the United States due to an aging population, advanced treatment expenses, and the pervasive challenge of providing adequate and universal healthcare coverage [4, 7]. The more subjective and personal costs of cancer care place a heavy burden on patients in the form of depression, anxiety, hopelessness, and diminished quality of life [10]. Notably, race and socioeconomic status compound the burden of financial toxicity. African Americans and Latinos carry a disproportionate share in relation to whites, as do people living in poverty or economic instability [44].

One especially toxic effect of cancer-related financial stress is treatment non-adherence. Because of high and varied medical costs in addition to transportation, limited or loss of income, and personal debt accrual, many patients must make the Faustian choice between paying for their cancer care or affording basic necessities, forgoing food or skipping treatment. There is a direct pathway from non-adherence to greater mortality [25].

In a similar vein, the subjective costs of cancer care manifest in depression, anxiety, strain on relationships, and poorer health-related quality of life. Markedly, patients suffering with the stress of decreased mental health may be at higher risk of mortality, possibly through hormonal or immune system response [19]. Quoted at the beginning of this chapter, the patient who remarked "The financial stuff, this is what kills me" may have spoken more truth than he realized.

Potential remedies to reduce the toxicity of cancer-related expenses include an earlier and more thorough assessment of financial burden at the patient level. The COST measure [31], for example, may lead to more timely referrals to appropriate resources, more fruitful navigation through the psychosocial healthcare system, and assistance with problem-solving skills. Accessing social support networks, both informal (e.g., peer-matching, community, and civic groups) or formal (cancer support groups) is another effective way to share information and problem-solve financial toxicity. More informed and transparent communication from healthcare providers around expected treatment costs may inform patients' financial planning and facilitate their access to resources [47].

When financial toxicity is not so easily remedied with planning or external assistance, CBT and MMIs may help patients shift attention to the things they *can* control, such as *how* they cope with their financial hardship and how to enhance the meaning and purpose in their lives. Those patients most affected by financial toxicity can be taught to systematically engage in MMIs. Clinicians can routinely elicit what matters most to their patients by integrating meaning-making questions and interventions into their regular practice [62].

Conclusion

Ideally, future research would quantitatively examine how meaning-making interventions can be further enhanced, cultivated, or applied to the population of people with both cancer and financial stress. We would be remiss to wait for widespread structural changes in our healthcare system while ignoring possible remedies at the individual patient level. Although clinical interventions cannot cure financial toxicity, they may soothe its effects. Cancer-related financial stress should not be more lethal than the cancer itself.

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Bringing It All Together

Brian I. Carr

Introduction

The preceding sections address many of the ongoing areas of research and development of ideas and treatments relating to the cancer patient and his/her human environment and are presented in seven groups: (a) biological basis explains the possible mediators for a mind–body interaction, which in itself may be bidirectional; (b) prevention and decision-making discusses some genetic predispositions to cancer and preventive actions to be taken, as well as how the decisions for screening and preventive actions can be influenced; (c) theory in psychosocial oncology discusses several aspects of hope and coping and how ideas of world-view, religiosity, spirituality, and philosophy form a background to patient fears and attitudes, as well as a review of some controversial aspects of patient support; (d) the social context emphasizes that patients do not exist without a social context of partners and families and the consequences of this; (e) patient support examines some of the methodologies in evaluating quality of life, as well as some new ideas (exercise, hallucinogens, and complementary techniques) and concepts (placebo, long-term post-treatment emotional distress) in the management of patient stress during the cancer continuum; (f) advanced cancer discusses approaches to both the patient near the end-of-life and associate partner and family and the bereavement issues and coping of those who are left behind after the death of the patient; and (g) reviews all the sections and presents a useful list of patient and caregiver resources.

Psychological Symptoms and Tumor Biology

Dr. Fagundes and colleagues examine the feedback loops and underlying mechanisms involved in the effects of stress, depression, and bodily function, including effects on cancer. They describe the effects of stress on dysregulation of the immune system, which in turn can impact fatigue and depressive symptoms. They report a meta-analysis of 165 studies linking stress-related psychosocial factors with cancer incidence among those who were initially healthy. For example, women who experienced stressful life events such as divorce, death of a husband, death of a relative, or close friend during a 5-year baseline period were more likely to be diagnosed with breast cancer during the next 15 years than those who did not experience these events. There is even stronger evidence that psychological factors play an important role in cancer progression

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and mortality. They also report that women with breast cancer who were more depressed were more likely to die within 5 years compared to those who were less depressed. A recent meta-analysis of 25 studies revealed that mortality rates are 39% higher among breast cancer patients diagnosed with major or minor depression compared to those not depressed. Dr. Steel and I showed that hepatobiliary carcinoma patients who had higher levels of depressive symptoms at diagnosis had 6–9 months shorter survival than those who were less depressed [1–4]. Stress dysregulates immune function and enhances inflammation. It alters the function of the autonomic nervous system and the hypothalamo–pituitary–adrenal axis. Together, they affect levels of immune-mediator cells, norepinephrine, epinephrine, and catecholamines, which in turn can alter tumor cell growth and tumor angiogenesis, either directly on tumor cells, or via catecholamine modulation of vascular endothelial growth factor (VEGF) levels, which are important in tumor angiogenesis and thus in tumor growth. Psychological factors can also modulate VEGF, and colon cancer patients who were lonelier and/or depressed had higher levels of serum VEGF than those who were less lonely and/or depressed. VEGF also activates endothelial cells to produce matrix metalloproteinase (MMPs) enzymes, a family of matrix-degrading enzymes that contribute to metastasis. Higher levels of stress and depression were reported to be associated with elevated MMP-9 among women with ovarian cancer. A study showed that higher levels of depression and lower social support were associated with the up-regulation of over 200 gene transcripts involved in tumor growth and progression. Many interventions have been developed to reduce cancer-related distress. Given that depression and stress impact cancer biology, psychosocial interventions may impact cancer-related outcomes. However, at this time there are inconsistent results in the literature, as explained in the Controversies chapter.

Drs. Feridey Carr and Elizabeth Sosa point out that chronic inflammation has been linked with specific types of cancer, particularly those associated with viral infection or an inflammatory response, and that chronic inflammation is likely involved in cancer development. Chronic bronchitis in smokers is epidemiologically linked to subsequent lung cancer development, as is chronic hepatitis to hepatocellular carcinoma (HCC) development and inflammatory bowel disease (IBD) to risk of later colon cancer and chronic human papilloma virus infection predisposes to subsequent cancer of the cervix uteri. There is an increasing body of literature indicating that psychosocial factors directly contribute to the development and maintenance of chronic inflammation. Inflammation involves the presence of inflammatory cells and mediators, which include chemokines and cytokines in tumor tissues. Several pro-inflammatory cytokines have been related to tumor growth, including IL-1, IL-6, IL-8, and IL-18. Interleukins (ILs) are involved in different steps of tumor initiation and growth. A key molecular link between inflammation and tumor progression is transcription factor NF-κB, which regulates tumor necrosis factor (TNF), interleukins, and several chemokines. The relationship between the brain and the peripheral organs, often referred to as the “mind–body” connection, is based on alterations in the endocrine and immune systems that lead to the chemical changes that occur in clinical depression. Pro-inflammatory cytokines, particularly IL-6 (interleukin-6), have been found to occur in greater quantities in depressed patients. It has been shown that symptoms of fatigue and decreased appetite can be triggered by pro-inflammatory cytokines. These cytokines are responsible for developing the body’s inflammatory response. There is thus a two-way process in which the mind can influence inflammatory processes, and they in turn can influence the mind. It has been suspected that IL-6 could be related to colon cancer through its role in affecting the low-grade inflammation status of the intestine. Thus, mood and depression can modulate IL-6, an inflammatory mediator and IBD predisposes to bowel cancer.

There are psychotherapeutic implications of these lines of research. Higher serotonin levels are associated with lower levels of inflammatory mediators, and vice versa, suggesting that serotonin levels, and thus mood in general can influence inflammation. Several anti-depressive agents (selective serotonin re-uptake inhibitors) can cause significant decrease in IL-1, IL-6, and TNF-alpha. Thus, clinical treatment of depression could result in both amelioration of depressive symptoms and decreased inflammation in the general population.

This biological framework provides a basis for proposing that treatment of depression might result in lower inflammation, and thus decrease the incidence of cancers that result in such predisposed people. Even more intriguing is the possibility that such psychological interventions could affect the course of established cancers that are associated with inflammation.

Cancer Prevention and Decision-Making

The chapter by Dr. Aspinwall and colleagues reminds us that while most cancers are sporadic, about 5% occur due to an inherited cancer predisposition syndrome. Families with hereditary cancer syndromes are generally characterized by multiple occurrences of cancer on the same side of the family, individuals with multiple primary cancers, and an earlier than average age of cancer onset. Hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (formerly referred to as hereditary non-polyposis colorectal cancer, HNPCC) are the two most common and well-studied conditions. A major problem for families being counseled, with factors predisposing to breast cancer is that while risk-reducing mastectomy (RRM) significantly reduces the risk for developing breast cancer by 90%, the survival benefit in choosing RRM over annual breast screening is small. In addition, reports suggest that sustained psychological distress following hereditary cancer risk counseling and testing is rare. A framework is provided that situates hereditary cancer risk counseling and testing as tools to be used by patients and their families in an ongoing process of managing familial cancer risk and psychological concerns arising from awareness of this risk. It is shown that hereditary cancer risk counseling and testing have a powerful impact on screening adherence, other risk-reducing behaviors such as prophylactic surgery, and in the case of hereditary melanoma, primary prevention behaviors.

Dr. Howard and colleagues review the issues concerning women who are found to carry a *BRCA1/2* mutation, bestowing a markedly increased probability of developing breast cancer and the management of their 45–87% lifetime risk of breast cancer. *BRCA1/2* carriers have the option of ongoing breast cancer screening (RRM), prior to the development of cancer, generally offered with the option of reconstructive surgery. This reduces risk of developing breast cancer by 95%. Although some women choose to do nothing, the majority of *BRCA1/2* carriers face choosing between ongoing breast cancer screening and RRM. She points out that a woman's decision about RRM is much more complex than interpreting the statistical risk of developing breast cancer. Decisions appear to be grounded in broader social and cultural contexts and vary regarding when decisions are made. Emotional distress and self-identity also factor in the decision-making. Thus, to maximize health outcomes, not only must we personalize healthcare services based on patient genetic profiles, but we must also personalize healthcare services based on patient psychosocial profiles. Dr. Leigl describes some aids to help patients in decision-making. She reminds us that the delicate balance between palliative goals of therapy, understanding prognosis, and preserving hope in the face of incurable malignancy is difficult to achieve. Decision aids are important tools to facilitate more informed decision-making for patients, to ensure that palliative treatment decisions are consistent with patient values for length and quality of life. Treatment decisions when the goal is not cure are increasingly complex, with a growing number of potential palliative treatment options, with uncertain and often modest benefits, while at least some toxicity from treatment is almost guaranteed. The majority of patients do wish to discuss prognosis in advanced disease, and they wish to be active participants in decision-making about their treatments, although this varies in the literature from 40% to 73% desiring shared decision-making with their physician. However, many patients are not well-equipped to make informed decisions about their care. Informed consent to treatment requires certain elements that include a discussion of prognosis with and without treatment, a review of risks and benefits, and of alternative options. Decision aids (DAs) are designed to help people make specific and difficult choices among options by providing information on the options and outcomes relevant to the person's health status and they help patients in clarifying their values for those different health outcomes and treatment options, to facilitate decision-making. They have been developed mainly for cancer screening, adjuvant therapy, and primary treatments in the setting of curable cancer. The chapter points out that balancing the potential benefits and toxicities of palliative therapy is complex, particularly when patients and families are unwilling to accept the limited goals of palliative therapy and that many patients get upset by the prognostic information. Accelerating the transfer of knowledge about limited prognosis and treatment benefit remains a major challenge in decision-making in advanced cancer, in order to minimize false hope and unrealistic expectations, while preserving reasonable hopes of modest improvements or symptom control at the end-of-life.

Theory Related to the Practice of Psychosocial Oncology

Dr. Cohen discusses various aspects of cancer fatalism, including its prevalence in different population groups and the correlates of fatalism with socio-demographic variables. Fatalism is a belief that events are pre-determined and that humans are unable to change their outcomes. She reviews the role of fatalism in screening behaviors and the delay in seeking help. Studies have shown that fatalistic beliefs are related to lower adherence to medical examinations and lifestyle regimens needed in the management of chronic diseases and to smoking and screening for the early detection of several types of cancer. Fatalism is incompatible with free will. Fatalism may or may not be based on belief in God. Believers tend to accept that God has control over every detail of life, while non-religious fatalism may be expressed in the belief that things happen by chance or luck. It thus has negative connotations in our modern society. A study reported from the United States suggested that individuals with high fatalistic beliefs lead less healthy lifestyles: they perform less regular exercise, are less likely to eat fruits and vegetables, and smoke more. Some longitudinal studies in cancer patients reported that patients who responded with a fighting spirit or with denial were more likely to be alive and free of recurrence at 5, 10, and 15 years after diagnosis than patients with fatalistic or helpless responses. The most important impact of fatalism is when it results in delays in seeking medical help after the first appearance of symptoms, as well as in the non-participation in screening programs or change to healthier lifestyles, on the basis that our fates are anyway pre-ordained. This is especially true of patients with genetic cancer predisposition genes, such as BRCA1 or 2, which can confer a sense of inevitability in some patients. In others, however, such knowledge about themselves leads to pro-active treatment or lifestyle choices.

Dr. Park describes "meaning-making" processes, spirituality, and stress-related growth in her chapter regarding positive psychology. A diagnosis of cancer can shatter aspects of a patient's extant global meaning. Thus, most people hold views of the world as benign, predictable, and fair and their own lives as safe and controllable. A cancer diagnosis is typically experienced as being at extreme odds with such beliefs, resulting in processes of distress and changes in meaning-making that ultimately lead to changes in survivors' situational and global meaning. The meanings that survivors assign to their cancer experience predict not only their coping and subsequent adjustment but also their treatment-related decisions and their well-being. In a breast cancer study, patients seeing their cancer as a challenge at diagnosis had less anxiety at follow-up than those who perceived it as the enemy. However, patients with various cancers who appraised with uncontrolled cancer had higher levels of stress. A longitudinal study of survivors of various cancers found that the extent to which the cancer was appraised as violating their beliefs in a just world was inversely related to their psychological well-being across the year of the study. Beliefs in a loving God may also be violated. Furthermore, having cancer almost invariably violates individuals' goals for their current lives and their plans for the future and calls into question their existential philosophy, such as living a healthy lifestyle protects people from illness. At diagnosis, individuals' pre-cancer spirituality may influence the situational meaning they assign to their cancer. Those with higher religious beliefs had a higher sense of efficacy in coping with their cancer, which was related to higher levels of well-being. Another study found that women diagnosed with breast cancer who viewed God as benevolent and involved in their lives appraised their cancer as more of a challenge and an opportunity to grow. Stress-related growth describes the positive life changes that people report that they experience following stressful events, including a diagnosis of cancer, and has garnered increasing research interest in recent years. Myriad studies of survivors of many types of cancer have established that a majority of survivors report experiencing stress-related (post-traumatic) growth as a result of their experience with cancer. Researchers have posited that meaning-making efforts are essential to adjustment to cancer by helping survivors either assimilate the cancer experience into their pre-cancer global meaning or helping them to change their global meaning to accommodate it. It has been proposed, therefore, that meaning-making is critical to successfully navigate these changes. However, there are thus far few studies with controls to validate these ideas in clinical oncology practice.

Dr. Folkman points out that hope and psychological stress share a number of formal properties: both are contextual, meaning-based, and dynamic, and both affect well-being in difficult circumstances. The relationship between hope and coping is dynamic and reciprocal; each in turn supports and is supported by the other and is involved in managing uncertainty and a changing reality. Conversely, hopelessness is a dire state that gives rise to despair, depression, and ultimately loss of will to live. Stress and coping theory originally posited two kinds of coping: problem-focused coping and emotion-focused coping. She reminds us that maintaining and restoring hope is seen as an important function of the physician. Coping with uncertainty, and especially the process of personalizing odds, can involve distortion of reality. Statements about odds, and the range of possibilities they imply, invite hope. Hope increases when the odds of a good outcome are favorable. She suggests that when odds are unfavorable, people initiate a re-appraisal process of their own personal odds that improves them and thus gives them hope. This coping strategy not only creates a toehold for hope but also reduces threat. In this process, patients identify reasons why the odds don't apply to their situation or search for information that contradicts the odds that were given. Hope has a very special quality that is especially important in managing uncertainty over time: it allows us to hold conflicting expectations simultaneously. She points out that individuals who rate high on hope as a trait have the advantage of approaching situations with a hopeful bias that is protective; they show diminished stress reactivity and more effective emotional-recovery than those low in dispositional hope.

Dr. Thune-Boyle tells us that studies have reported that religious coping is one of the most commonly used coping strategies in cancer patients in the U.S. cancer patients, where up to 85% of women with breast cancer indicate that religion helped them cope with their illness. However, there is potential confusion between religious coping cognitions versus religious service attendance, where an effect could be caused by perceived social support from the religious community rather than religious coping. Although many cancer patients experience clinical levels of distress and dysfunction including anxiety, depression, and some may even suffer from post-traumatic stress disorder, many patients are able to find meaning in their illness, such as experiencing profound positive changes in themselves, in their relationships, and in other life domains after cancer. Finding meaning in the cancer experience in the form of positive benefits is a common occurrence. This is described as positive psychological growth or post-traumatic growth. She points out that there is evidence that a higher level of faith/religiousness is linked to greater levels of perceived cancer-related growth and benefit finding and that having respect for patients' spirituality as an important resource for their coping with illness. In the United States, between 58% and 77% of hospitalized patients want physicians to consider their spiritual needs. However, religious/spiritual beliefs and practices are very different across cultures, and these findings may therefore not generalize to cancer patients outside the United States.

Dr. Stefanek describes four controversies in the field of psycho-oncology: (1) the benefit of screening for distress among cancer patients; (2) the effectiveness of psychological interventions among cancer patients; (3) the role of "positive psychology" (optimism, benefit finding) in cancer care; and (4) the benefit of group therapy in extending survival among cancer patients. Depression, anxiety, and distress are common following the diagnosis of cancer, with an overall prevalence in unselected cancer patients greater than 30%. It appears that screening, while offering a seemingly simple solution for early successful treatment of emotional distress, has yet to demonstrate a clear benefit over standard approaches, such as simply offering patients the chance to discuss their concerns, regardless of formal screening programs. He tells us that though the distress, anxiety, and depression accompanying a cancer diagnosis impact quality of life, and even satisfaction with and adherence to treatment regimens, there is not yet an unqualified answer to the question of whether interventions work, what interventions, and with whom. In addition, he points out that studies to date in cancer have not warranted the seemingly strong belief that optimism does indeed make a difference in health outcomes related to cancer. Regarding psychosocial interventions and their impact on survival, no randomized trial designed with survival as a primary endpoint and in which psychotherapy was not confounded with medical care has yielded a positive effect. A meta-analysis supported no overall treatment effect by psychosocial interventions on survival, by randomized or non-randomized trials. Chronic depression, social support, and chronic stress may influence multiple aspects of tumor growth and metastasis through neuroendocrine regulation. Work in this area may highlight how behavioral or pharmacological interventions might impact neuroendocrine effects on tumors and slow progression or increase survival, as noted in the first two chapters of this book. In addition, psychological factors seem to have an influence in apoptosis, which is considered as important in the balance between cell life and death in cancer development. However, both quality of life and psychological stress are important and achievable endpoints in their own right in cancer patient care and clinical trials of psychological-based interventions.

The Social Context

Dr. Badr and colleagues remind us that for most individuals diagnosed with cancer, their psychological adjustment depends strongly on their interpersonal relationships. Cancer patients identify their spouses or intimate partners as their most important sources of practical and emotional support, and coping with cancer treatment can also challenge a couple's established communication patterns, roles, and responsibilities, either in a positive or negative sense. A supportive spouse can serve as a resource for the patient in terms of providing assistance in cognitive processing, but other spouses can serve as a barrier to effective processing if unavailable or unsupportive. Physical intimacy is vital to maintaining satisfying relationships and may reduce emotional distress. Virtually, all cancers and their treatments (i.e., surgery, radiation therapy, chemotherapy, and hormone therapy) affect patients' sexual function. Despite this, the vast majority of studies addressing sexual problems in cancer patients have been confined to problems that affect the reproductive and sexual organs. Common cancer symptoms or treatment side effects include fatigue, pain, nausea, decreased sexual desire, and vaginal dryness and dyspareunia in women and erectile dysfunction in men. Cancer thus takes a toll on both patients and their partners.

The impact of cancer on an individual's sexuality is enormous and overwhelmingly negative in most cases, and Dr. Susan Carr tells us that this occurs in more than 50% of cancer patients. Women with cancer can experience disruption to sexual arousal, lubrication, orgasm, and develop pain on intercourse, particularly if they have experienced menopause as a result of chemotherapy or surgery. This functional disruption leads to lack of pleasure in sex and can result in total loss of libido or sexual interest. Commonest symptoms include loss of libido in males and females; in females-anorgasmia, vaginismus, and dyspareunia; in males, erectile dysfunction and premature ejaculation. Cognitive behavioral therapy is useful in female sexual dysfunction. Body image and sexual self-confidence are intrinsically linked. Cancer and its therapies can cause major alterations in body image which in turn can have negative impact on sexuality and sexual satisfaction. Physical changes in cancer patients include baldness following chemotherapy, weight fluctuations, body shape changes such as loss of breast, stoma onto the skin, lymphedema, or some disfiguring features following head and neck cancer. Changes in body self-perception, however, need not necessarily stem from outward change, and for a lot of young women, loss of fertility can greatly lower their feelings of femininity. Symptoms such as shortness of breath due to lung involvement, or severe pain are also major physical inhibitors of sex. None of this fails to have an emotional impact on the patient and their partner. In addition, lowering of self-esteem and feelings of being subsumed by the cancer, take their emotional toll. In relation to sexuality, a partner will almost invariably be also affected. Clinicians often avoid emotional issues by focusing on physical and physiological signs and symptoms. The standard clinician consultation does not always allow the patient opportunity to express sensitive or deeper sexual or emotional issues. Allowing silence and space in questioning allows the patient better opportunity to disclose sexual issues to the treating oncologist or psychologist.

The chapter by Dr. Kim focuses on the stresses of the caregiver, who is usually the spouse or another family member. This role includes providing the patient with cognitive/informational, emotional, and spiritual support, as well as facilitating communication with medical professionals and other family members and assisting in the maintenance of social relationships. These aspects of caregiving can contribute to caregivers' stress when they perceive it difficult to mobilize their personal and social resources to carry out each of the caregiving-related tasks. Studies have also reported caregivers improved sense of self-worth, and increased personal satisfaction and the degree to which family caregivers have negative and positive experiences in caregiving may affect their ability to care for the survivor. Spousal caregivers, who are the majority, can have a poorer quality of life, particularly when involved in long-term cancer care. Overall, caregiving burden, during the advanced stages of the patient's cancer, is the strongest predictor of caregiver *psychological* distress during this phase of caregiver ship, even more than the patient's physical and emotional status. Although survivorship ends at the death of the person with the disease, the caregivership continues. The death of a close family member is one of the most stressful of life events.

Patient Support

Drs. Benedict and Pinedo report that a significant number of cancer survivors report psychological responses that range from normal feelings of vulnerability, sadness, and fear to problems that can become disabling, such as clinical levels of depression, anxiety and panic disorder/attacks, interpersonal dysfunction, sexual dysfunction, social isolation and existential, or spiritual crisis. Distress may be experienced as a reaction to the disease or to its treatment, as well as disruption in quality of life. Not all psychological reactions are negative and many cancer survivors report finding some benefit in their cancer experience, such as a new appreciation of life and improved self-esteem and sense of mastery. Psychosocial distress associated with cancer exists on a continuum ranging from normal adjustment issues to clinically significant symptoms of mental disorder. Up to 47% of cancer survivors indicated clinically significant psychiatric disorders. Among patients receiving palliative care, estimates are that around 20% meet diagnostic criteria for depression. However, the majority of cancer survivors adjust relatively well. Though the initial reaction to a cancer diagnosis may be that of alarm and distress, and coping with treatment-related side effects may be difficult, most never have the diagnostic criteria for a mental health disorder. A number of common psychosocial factors have been shown to predict adjustment and well-being, including availability of inter- and intrapersonal resources, optimism and active coping styles, and higher levels of social support from partners, family members, and loved ones. Conversely, avoidance of cancer-related discussions has been associated with worse emotional well-being and quality of life. Psychosocial interventions for cancer survivors generally aim to reduce emotional distress, enhance coping skills, and improve quality of life. Many different types of interventions have been conducted among individuals, couples, and families, including supportive–expressive group therapy, psychoeducational interventions, and multimodal intervention approaches. The initial diagnosis of cancer is often a traumatic and distressing experience. Emotional reactions often include feelings of disbelief, denial, and despair. The spectrum of emotional reactions ranges from depressive symptoms, such as normal sadness, to clinically significant symptoms of adjustment disorder or major depressive disorder. Individuals must adjust to the idea of being diagnosed with a devastating illness that may be life threatening and often struggle with feelings of uncertainty and fear for the future. Although distressing, the initial emotional response to a diagnosis of cancer is often brief, extending over days to weeks. Psychological interventions are tailored to the pre-treatment decision and preparation period, active cancer treatment period, the treatment period of advanced or progressive cancer associated with the greatest level of psychological stress, and to the post-treatment survival period. Psychological interventions typically aim to improve adjustment and well-being by promoting adaptive coping strategies, improving support-seeking behaviors, reducing social isolation, and addressing maladaptive cognitions related to disease- or treatment-related outcomes. Many different types of interventions are described, typically involving an emotionally supportive context to address fears and anxieties, information about the disease and its treatment, and cognitive and behavioral coping strategies, including stress management and relaxation training, in an individual, couples or group setting, usually in person, but sometimes via the telephone or the Web. Several studies have also examined the effects of psychological interventions on patient survival, with conflicting results. In a meta-analysis of the effect of psychosocial interventions on survival time in cancer, neither randomized nor non-randomized studies indicated a significant effect on survival in studies performed thus far. However, several psychosocial factors have been linked to the development and progression of cancer and have been shown to be important considerations in cancer care, including helplessness/hopelessness, coping styles, and social isolation.

Dr. Salsman and colleagues review health-related quality of life (HRQOL) issues. Weighing survival versus quality-of-life benefits is a critical part of medical decision-making for cancer patients and *quality* of life has proven to be a recent and meaningful subjective complement to survival benefits derived from treatments, as the overall 5-year survival rate has increased to over 65% of patients. Physical, emotional, social, functional, and in some cases, spiritual domains are studied. An essential consideration in symptom assessment is that patient ratings of symptom importance are subjective and may differ from those of oncology professionals. However, treating oncologists can often have a good sense of their patient symptoms and HRQOL [5]. Furthermore, since around 30% of US households have a member giving caregiver support, caregiver HRQOL is receiving the increased attention that its importance requires. Dr. Mustian reviews the literature on the use of exercise in improving some of the most prevalent side effects experienced by cancer patients and increasing HRQOL before, during, and after cancer treatments. Cancer patients report cancer-related fatigue throughout the entire cancer experience from the point of diagnosis, throughout treatments and in many cases for years after treatments are complete, and it is one of the most frequent and troublesome of cancer patient symptoms. Over two-third of survivors report this symptom long after therapies have stopped, and there are few remedies. Exercise can be performed using a variety of modes, such as aerobic exercise, resistance training, and mindfulness-based exercise, all of which have been found to reduce various side effects from cancer and its treatment, as well as aerobic, resistance, and mindfulness exercise (Tai Chi and Yoga). Preliminary evidence consistently suggests that physical activity is not only safe but advantageous for cancer survivors in managing multiple side effects associated with cancer and cancer treatments.

Dr. Grob et al. report on the psycho-spiritual distress and demoralization that often accompanies a life-threatening cancer diagnosis, and the potential of a treatment approach that uses the hallucinogen psilocybin from mushrooms, a novel psychoactive drug, to ameliorate these symptoms. It is metabolized to psilocin, which is a highly potent agonist at serotonin 5-HT-2A and 5-HT-2C receptors and produces an altered state of consciousness that is characterized by changes in perception, cognition, and mood in the presence of an otherwise clear sensorium. Advanced stage and terminal cancer patients have been reported to have significant improvements of their psycho-spiritual status on psilocybin treatment. A growing body of research has shown that higher levels of spiritual well-being are correlated with lower levels of emotional distress and serve as a buffer against depression, desire for hastened death, loss of will to live, and hopelessness.

Drs. Schuricht and Nestoriuc explain that understanding the placebo and nocebo effect will help us to gain new insights into the interaction of psychological and physiological processes in health and disease. Placebos are often used in a no-treatment arm of clinical trials. The placebo effect raises the question of how something that is thought to be inert can actually cause desired effects. *Placebo response* refers to the psychophysiological processes attributed to the context of treatment. Nocebo refers to the administration of an inert substance (i.e., placebo) along with the suggestion or expectation to get worse and about 25% of patients in a placebo group report adverse side effects (i.e., nocebo effects). Discontinuation rates due to adverse effects have been shown to be equally high in drug and placebo groups. Nocebo (non-specific) side effects often appear as generalized and diffuse symptoms, such as fatigue, difficulties in concentrating, headache, or insomnia, they occur mostly dose-independent. Two placebo-controlled treatment trials showed high rates of both improvements and side-effects in the placebo arms. The placebo benefit effect has been observed in clinical trials for cancer-related fatigue, pain, and for chemotherapy-induced nausea and emesis. A randomized controlled trial examined innovative nonpharmacological approaches to cancer pain management. The effectiveness of transcutaneous electrical nerve stimulation (TENS), transcutaneous spinal electro analgesia (TSE), and a sham TSE (placebo) was compared, in 41 women with chronic pain following breast cancer treatment. TENS and TSE devices both used electricity to ease pain. The placebo devices had disabled wires but apart from that were identical to the active machines. The researchers found improved worst and average pain scores in all the three intervention groups throughout a 3-week trial. Furthermore, patients exhibited significantly lower anxiety scores after TENS and placebo use. The finding that improvements in pain were significantly more likely for patients in the placebo groups than in the best supportive care groups suggests that receiving a specific treatment, regardless of whether it is active or placebo, rather than receiving regular care, promotes analgesic effects. Ten to sixty percent of patients in placebo conditions experienced distressing symptoms that were quite similar among trials, including nausea and vomiting, abdominal pain, lethargy, dry mouth, and diarrhea. An association could be found between the incidence and type of negative effects in the placebo groups and side effects in the treatment groups, thus pointing to the potential role of specific expectations about adverse symptom profiles in the development of nocebo effects. Recent neuro-imaging research indicates that placebo treatments have broad effects on opioid activity in cortical and subcortical regions, as well as on their functional connectivity. These results point to the profound effects of patient expectations on symptomatology.

The chapter on psychological experiences in post-cancer treatment survivors by Dr. Beckjord and colleagues reports that emotional and psychological concerns are exceedingly common in this group that now numbers around 12 million in the United States, with less than 50% getting help that they need. Although most of them have insufficient distress to disrupt their lives, a significant minority have distress that is a cause for concern. For many patients with breast cancer who are treated with chemotherapy, the associated psychological distress tends to subside within 2 years, with or without psychological intervention. For other patients, psychological concerns can be long-lasting. Associations with better psychological outcomes in the post-treatment period include having a spouse or partner or adequate social support, higher socioeconomic status evidenced by level of education attained and annual income, and an optimistic personality. Emotion concerns include fear of recurrence, sadness and depression, grief and identity concerns, and concerns about family member risk for cancer. Thus, while emotional concerns were common, they were usually not accompanied by high levels of functional impairment. Younger age, female gender, and reporting more physical concerns were associated with reporting more emotional concerns. Emotional and physical concerns were strongly associated.

Complementary and alternative medicine (CAM) refers to a range of modalities and practices that are not part of the conventional and encompasses whole medical systems such as homeopathy and ayurveda; mind–body medicine such as meditation and art therapy; biologically based practices such as herbs and dietary supplements; manipulative and body-based practices such as chiropractic and massage; and energy medicine such as biofield therapies and magnets. At least 30% people are thought to use these treatments in addition to conventional medical care. Many patients do not let their physicians know this. Motivations for CAM use in oncology include improvement of quality of life, enhancement of immune function, coping with pain, and control of anxiety and other psychological symptoms. Mind–body therapies are chosen because several have at least some positive supportive data and many target stress reduction, which is a tangible endpoint that is associated with improved quality of life. Moreover, such interventions generally are not practiced as an alternative to regular oncological care; hence, they can be integrated into the overall cancer survivorship treatment plan. The CAM chapter reviews the most commonly used and available procedures.

Advanced Cancer

In the chapter on end-of-life communication, it is reported that currently over 500,000 people annually die of cancer in the United States. Optimal end-of-life care and effective communication represent key priorities in cancer care in all levels and settings, including family communication, clinical care, and public health and require a multidisciplinary team approach. Communication problems are among the most frequently identified factors associated with poor end-of-life care. These include delayed discussions about the end-of-life interventions such as ventilator use, mismatched understanding of the diagnosis and prognosis, and inadequate attention to patient emotions and preferences. While physicians have traditionally been trained to impart information and advice to patients, recent work has emphasized shared/joint decision-making between patient and healthcare professionals. In this context, five communication tasks of physicians have been identified: eliciting patient's symptoms, communicating prognosis while maintaining hope, responding to emotions, making end-of-life decisions, and helping the patient navigate the transition to hospice care. Nearly all of end-of-life communication research has been conducted in hospital and clinic settings, whereas little is known about the communication needs of home-based patients and their caregivers. However, many families are increasingly preferring a home death, and strategies to effectively prepare and transition a family to end-of-life care at home are needed. There is evidence that cancer survivors are increasingly engaging in health-related internet use, including participation in online support groups, emailing their providers, and seeking cancer information online. In the end-of-life context, Dr. Chou relates that opportunities exist to examine how Web 2.0 technologies (social media, blogs, and mobile devices) may provide social support as well as timely and useful information for patients and caregivers. In the clinical setting, with the implementation of electronic medical records and patient portals, work remains in how to effectively integrate education and support for seriously ill patients and their caregivers into evolving web-based communication systems. Recent findings demonstrate many benefits of integrating palliative and end-of-life communication throughout the care continuum to ensure continuity of care and improve transitions from curative to palliative care. The support from the medical team which cares for the patient often abruptly ends when treatment is discontinued, and for the minority of patients diagnosed with cancer who are referred to hospice, bereavement support is offered but rarely utilized for the caregivers after the loss of their loved one. The final chapter is devoted to those caregivers.

Dr. Steel reports that caregivers of patients with cancer who are at the end-of-life are at risk for psychological distress, and it is not yet clear how to best support them. No current interventions offer clear advantages. When a loved one is diagnosed with cancer, this may be the first time the patient or family caregiver has considered death. Unlike traumatic events that take a person's life immediately, cancer often allows the patient and family time to prepare. The quality of that time depends on several factors, such as the cancer symptoms, side effects of treatment, patient and caregiver personality and relationship, prior experience with loss, support from family and friends, spirituality, prior psychological functioning, and interactions with healthcare professionals. One study found that only 37% of patients had discussed end-of-life preferences with their physician. Another study demonstrated that discussions with physicians regarding end-of-life care resulted in earlier referral to hospice, less aggressive care, and better quality of life. The most feared symptom reported by patients is unmanaged pain. Pain symptoms can also be associated with worse survival [6]. Palliative care aims to integrate support for the physical and psychological needs of the patient and offer support to help the family cope, including bereavement counseling. Patient HRQL during the end-of-life and the medical team's communication and behaviors can have lasting effects on the family and caregiver and has the potential for resulting in long-lasting remorse, guilt, or pain on the part of the family, without sensitive and careful discussions of terminal care decision-making. Caregiver stress has been reported to be associated with increased risk of depression, perceived stress, poorer HRQL, increased risk of health conditions, and even mortality. Stress, depression, and prolonged grief are all treatable conditions. After the death of the patient, two different caregiver trajectories have been described. They are abatement of caregiver stress, or the opposite, with caregiver stress causing a diminishment of the psychological resources needed to cope during the bereavement process. Immune system dysregulation has been reported among caregivers during bereavement, possibly mediated by increased levels of inflammatory cytokines, with the potential to result in new health problems, including cardiovascular disease and some types of cancer. Given the large number of annual cancer deaths and thus grieving caregivers, these issues merit continued study and evaluation of potential clinical interventions.

Dr. Brian Carr describes Altruism as a term used (in recent centuries) to describe donation with expectation of direct recompense, and its general meaning in biology, in antiquity and for the world's great religions, for which it is one of the greatest of virtues. The medical literature is then surveilled regarding organ donor attitudes in modern times, since the whole idea is so fraught with fear, expectations, and some real suffering on the part of major organ donors. Four general types of conversation are described, between liver transplantation team members and potential live liver donors and their families, to illustrate the complexities and delicacies that medical personnel both encounter and must navigate in such pre-liver transplant living organ donor discussions.

Dr. Maizie Tsang and colleagues discuss Cancer and the Ageing Population. The number of older adults with cancer is expected to increase considerably, with all the morbidities in this age group in addition to cancer, and about 70% of all cancers expected to be in the over 65 years age group. The authors overview their approach to cancer in an aging population and the use of a comprehensive geriatric assessment prior to treatment, to identify individual characteristics that can help predict morbidity and mortality, as being an essential step in the care of these patients, especially considering their general frailty. They describe Geriatric Assessment (GA), which serves as a useful tool to identify and quantify frailty in older adults with cancer. GA consists of reliable and validated tools that assess age-related conditions that are important in determining the physiologic age of older patients, including functional status, cognition, comorbidities, physical performance, medication review, psychosocial health, social support, and nutritional status. The psychological domain relies on validated instruments to assess depression, distress, and anxiety in older adults, such as the Geriatric Depression Scale, Distress Thermometer, and Generalized Anxiety Disorder Scale (GAD-7), since studies have demonstrated a high prevalence of psychological impairment in older adults with cancer. The special problems of elder patients undergoing various cancer therapy types are discussed, as well as the under-representation of the elderly in cancer clinical trials. They point out that best practices for survivorship care are continuously evolving.

Drs Laura Porter and Tina Gremore discuss Mindfulness-Based Interventions for patients with cancer. They point out the increasing research on the application of mindfulness-based interventions (MBIs), which focus on training patients in skills to be fully present in the moment, to reduce distress and improve positive adaptation among patients with cancer. Numerous studies have found that mindfulness can be helpful at reducing cancer-related symptoms and psychological distress and promoting positive adaptation, and the authors consider why that MBIs should be offered to patients with cancer who are seeking effective methods for self-management of cancer-related symptoms and stressors. The authors discuss reviews and meta-analyses of MBIs for cancer; studies focused on patients with advanced cancer; and studies using eHealth interventions, with the goal of identifying the outcome variables for which MBIs have good empirical evidence and their limitations. Although group and individual patient interactions have been foremost to date, many might also be helped through videoconferencing.

Drs Jennifer Knight and Steven Cole write about Social Genomics, the emerging field relating how social and psychological processes might influence the physiologic pathways that might mediate the ability of elevated stress to accelerate cancer processes by modulating the biology of tumor progression and metastasis. This is based on epidemiological studies that document accelerated progression (but not the origination) of many types of cancer among patients with high levels of stress or low social support. The underlying mechanisms for this involve both the recognition that social and psychological-associated stresses can regulate gene expression in healthy and diseased tissues and that tumor microenvironment is important as a source of cellular and humoral influences on tumor cell biology. This tumor microenvironment can itself be altered by the consequences of psychological stress. In theory, this makes a lot of sense, since psychosocial stress activates the well-studied neuro–hypothalamus–pituitary–adrenal (HPA) axis, or the endocrine–immune axis, that in turn can alter cancer cell biology. These effects are mediated by neuroeffector molecules that include norepinephrine and cortisol. This has been studied indirectly, such as by measurement of conserved transcriptional response to adversity (CTRA), and involves up-regulated expression of genes involved in inflammation in immune cell gene expression profiles in individuals who are exposed to extended periods of threat or uncertainty. Fascinatingly, these gene expression profile changes have been observed across a wide variety of adverse life circumstances including poverty, social isolation, PTSD, chronic stress, low social status, and unstable social hierarchies. Whether related changes are evidence of causality is as yet unexplored in any depth. The sampling of peripheral blood cells instead of tumors, which are hard to access repeatedly, is another intriguing way to measure the biochemical and molecular consequences of stress in cells. This seems quite exciting, especially if it is an indirect index of tumor responses.

However, these processes are very complex, and poorly powered clinical trials designed to test the consequences of these ideas, namely that anti-inflammatory and anti-stress psychological or pharmacological intervention might alter clinical cancer outcomes has led to conflicting results so far. Despite this, the ideas are very attractive and derive considerable support from correlative science studies. These studies in part have been based on tumor angiogenesis recruitment from the microenvironment, to support continued tumor cell growth, and activation by microenvironment macrophages of the epithelial-mesenchymal transition (EMT). This EMT activation plays a role in protecting tumor cells from destruction by the immune system.

Dr. William Breitbart and colleagues discuss Meaning-Centered Psychotherapy (MCP), which they developed to help patients with advanced cancer sustain or enhance a sense of meaning, peace, and purpose in their lives in the face of the challenges they commonly face. They discuss the increasing evidence in support of the efficacy of MCP in improving meaning, quality of life, and spiritual well-being and in reducing psychological distress and despair at the end of life. They also consider adaptations of MCP in support of cancer survivors, cancer caregivers, and bereaved family members. They explain the impact that a diagnosis of advanced cancer can have in leading to a sense of hopelessness and even a desire for hastened death and that such patients may be confronting an existential crisis of loss of meaning, value, and purpose of their lives, as they consider their advanced tumor diagnosis. Through a series of didactics and experiential exercises, the patient works with therapists to gain an understanding of the importance and relevance of sustaining, reconnecting with, and creating meaning in their lives through accessible and consistent sources of meaning. This program explores how these various sources of meaning can serve as resource*s* to help patients cope with and diminish feelings of despair that emerge at these challenging times in their lives. This is based on the recognition that the provision of psychiatric, psychosocial, existential, and spiritual care is critical to the provision of high-quality, comprehensive end-of-life care in patients with advanced cancer. Discussions take place with patients on how having a sense that one’s life has meaning involves the conviction that one is fulfilling a unique role and purpose in a life that is a gift, which in turn comes with a responsibility to live to one’s full potential as a human being. In so doing, a person is able to achieve a sense of peace, contentment, or even transcendence, through connectedness with something greater than one’s self. That something is a belief in a higher transcendent spiritual power, as there is growing evidence that spirituality plays an important role for patients coping with cancer, particularly at the end of life. MCP highlights that life has meaning and never ceases to have meaning, from the very first moment of life, up to our very last breath. Associated with this is the conviction that we have the freedom to find meaning in existence and to choose our attitude toward suffering. We have the capacity to choose how we respond to limitations, obstacles, losses, and uncertainty.

The authors explain that MCP seeks to enhance patients' sense of personal meaning by helping them to reflect on, understand, and use various sources of meaning in their lives as resources for coping with challenging times. The resulting enhancement in meaning plays a role in improving other psychosocial outcomes, such as quality of life, psychological distress, and despair.

Summary

This collection of chapters describes a range of patient and caregiver needs and concerns over the cancer patient disease continuum, as well as many of the supportive and treatment approaches that are being used and evaluated. Given the staggering number of cancer patients and the increasing and large numbers of cancer survivors and the effects on their families, the psychological issues and care have become an important part of the total medical care of cancer patients. Evolving techniques, approaches, therapies, and advances in neuroscience, endocrinology, and molecular biology, as well as new molecular and neural imaging modalities, are underpinning a revolution in our approach to the mind–body relationship, in general, and in the cancer patient, in particular. As we better understand the biochemical basis of mind and behavior and how these mediators also alter bodily function, new ideas about the mechanisms underlying these psychological processes should translate into new and more effective therapies.

The availability of several approaches to the treatment of anxiety and depression gives hope for these to be used not only to benefit patient psychological reactions to cancer, but possibly to also alter the biology of the cancer itself and thus survival, since there is a likely bi-directionality to the mind–body relationship. There is greatly increased understanding of how cognitive and emotional influences might impact many of the known biochemical and molecular processes of cancer biology. Although it has long been known that psychological factors can influence biological pathways and even mortality, there are inconsistent findings with regard to whether interventions that reduce psychological morbidity can also influence disease outcomes, especially survival. The ideas presented in this book give an indication of a flourishing and developing area of bio-behavioral study in process of the healthy foment that characterizes new knowledge and change.

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