Cancer Survivorship in Adults

Cecilie E. Kiserud, Alv A. Dahl, Jon Håvard Loge and Sophie D. Fosså

Abstract

With the favorable trend regarding survival of cancer in the Western world, there is an increasing focus among patients, clinicians, researchers, and politicians regarding cancer survivors' health and well-being. Their number is rapidly growing and more than 3 % of the adult populations in Western countries have survived cancer for 5 years or more. Cancer survivors are at increased risk for a variety of late effects after treatment, some life-threatening such as secondary cancer and cardiac diseases, others might negatively impact on their daily functioning and quality of life. The latter might include fatigue, anxiety disorders and difficulties returning to work while depression does not seem to be more common among survivors than in the general population. Still, the majority of survivors regain their health and social functioning. The field of cancer survivorship research has been rapidly growing. Models for follow-up care of cancer survivors have been proposed, but how to best integrate the knowledge of the field into clinical practice with adequate follow-up of cancer survivors at risk for developing late effects is still an unsolved question.

C. E. Kiserud (✉) · A. A. Dahl · J. H. Loge · S. D. Fosså
National Resource Center for late effects after Cancer Treatment, Oslo University Hospital, Radiumhospitalet, 4953 Nydalen 0424, Oslo, Norway
e-mail: CKK@ous-hf.no

A. A. Dahl
e-mail: a.a.dahl@ibv.uio.no

J. H. Loge
e-mail: j.h.loge@medisin.uio.no

S. D. Fosså
e-mail: s.d.fossa@medisin.uio.no

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Contents

1 General Aspects

The number of cancer survivors has been steadily increasing in the Western world during the last decades due to increasing cancer incidence, better diagnostic procedures, and more effective treatment modalities. Today, the relative 5-year survival is 60–65 % for patients diagnosed with cancer (American Cancer Society 2012, Verdecchia et al. 2007). In Norway, cancer survivors alive ≥5 years from diagnosis represent 3.3 % of the total population (The Cancer Registry of Norway 2010). For some cancer types such as testicular cancer, breast cancer, and Hodgkin's lymphoma, the 5-year relative survival exceeds 90 %. According to cancer types the most common survivor groups are survivors of female breast, prostate, colorectal, and gynecologic cancer (American Cancer Society 2012).

Cancer survivorship can be defined differently according to time since diagnosis and state of the tumor, and for this chapter we define a cancer survivor as a person who has lived at least 5 year beyond diagnosis and is regarded as tumor-free.

The favorable development as to survival after a cancer diagnosis has been followed by a growing clinical and scientific interest concerning health and quality of life among cancer survivors.

Chemotherapy, radiotherapy, surgery, and hormone therapies are the mainstay of cancer treatment, and they are often combined in various multimodal treatments. Adverse effects may occur during these treatments, and eventually continue for a long time after treatment or become permanent. Other adverse effects have their onset some time after treatment has been terminated, but then continue for a

long time. Thus, cancer survivors are at increased risk of various medical and psychosocial complications (Fossa et al. 2008, Fosså and Vassilopoulou et al. 2008). Some late effects might be life-threatening, such as second cancer or cardiovascular disorders, while others such as hypogonadism, infertility, sexual dysfunctions, or chronic fatigue (CF) might have negative impact of the survivors' daily function and quality of life, but do not threaten their lives.

One of the challenges related to studies of late effects is that some late effects like second cancer and cardiovascular diseases typically emerge many years after the termination of treatment. Results of such studies might not completely reflect the risk experienced by patients diagnosed today, since they undergo therapies which have been modified compared to those used 10–20 years ago. Therefore, the studies of late effects by its nature most often lag behind treatment currently given. Concerning new and improved treatments we will have to wait 10–30 years in order to identify their adverse effects. And so the chase for late effects will go on.

Many of the conditions that are described as late effects, like sexual dysfunction, cardiovascular disorders, and fatigue, are also prevalent in the general population. The prevalence of these conditions increase with older age and cancer is primarily a disease of older age since two-third of cancers is diagnosed after 60 years of age.

The goals of survivorship care are twofold: (1) To reduce the risk or cancer recurrence, second cancer and other severe diseases, and adverse effects. (2) To alleviate existing and expected physical and psychological adverse effects. These goals have several challenging implications: (1) To what extent shall cured cancer patients be informed of risks far in the future? (2) How often and how intensively shall survivors be screened for possibly upcoming severe adverse effects? (3) Considering the rapidly growing number of cancer survivors, how shall their health care be organized? To our knowledge there are no countries yet that have found the definite answers to these challenges.

In this chapter we will give an overview of the field of cancer survivorship, including the most important somatic, psychological, and psychosocial late effects and aspects regarding follow-care of cancer survivors and challenges for research in survivorship issues.

2 Somatic Late Effects

Approximately 15 % of cancer survivors will be bothered with treatment-related somatic late effects. An overview of the most important is presented here.

2.1 Second Cancer

Selected groups of cancer survivors are shown to have increased risk for development of a second cancer, which might be related to an iatrogenic effect of the cancer therapy and/or a genetic predisposition. Treatment-related solid second

cancers are usually diagnosed at a latency of 10–30 years after radiotherapy, and their development is related to the radiation dose within the target field, but also to scattered irradiation beyond the field borders. A typical example is development of breast cancer after mediastinal irradiation/mantle field irradiation for Hodgkin's lymphoma (Swerdlow et al. 2000) and esophageal cancer after thoracic radiotherapy in women with breast cancer (Morton et al. 2012).

During the last two, decades increasing documentation has emerged that cytotoxic drugs in a dose-dependent manner are carcinogenic leading to an increased risk of leukemia (Travis et al. 1999; Kollmannsberger et al. 1998), but also of solid tumors (Swerdlow et al. 2001, Fung et al. 2013)

The association between second cancer and cytotoxic treatment (radiotherapy, cytostatics) has been one of the strongest arguments for the development of risk-adapted strategies in order to reduce the treatment burden as much as possible, while maintaining the highest possible cure rate.

2.2 Cardiotoxicity

Dependent of their previous treatment long-term cancer survivors may develop asymptomatic or symptomatic left ventricle dysfunction, heart failure, premature coronary atherosclerosis, arrhythmia, or sudden cardiac death, most often due to myocardial infarction (Lenihan et al. 2013). Mediastinal radiotherapy and treatment with certain cytotoxic drugs (antracyclines, trastuzumab) represent well-known cardiotoxic risk factors, with clear dose–effect associations to cardiac dysfunction. Age below 15 years at primary treatment increases the risk. Increased risk of late cardiotoxicity (after 5–30 years) is also reported in breast cancer survivors who have undergone adjuvant cytotoxic treatment (thoracic radiotherapy, systemic cytostatics) (Darby et al. 2013). The European Society of Medical Oncology has recently published recommendations regarding the early detection of cardiotoxicity in patients at risk (Curigliano et al. 2012), but currently there is no international consensus about the optimal procedure for early detection or follow-up of cancer survivors at increased risk of cardiotoxicity.

In addition to a direct cardiac injury due to cytotoxic treatment, the development of metabolic syndrome (overweight, hyperlipidemia, hypertension, hyperglycosuria) represents a risk to the heart. This syndrome is described in long-term testicular (Haugnes et al. 2010, Willemse et al. 2013) and ovarian cancer survivors after cisplatin-based chemotherapy (Liavaag et al. 2009), but is also responsible for the increased risk of cardiac mortality in prostate cancer patients in particular after long-term androgen deprivation therapy (Kenney et al. 2012). Patients at risk should therefore be educated about the importance of a healthy life style (physical activity, healthy diet, no smoking, and moderate use of alcohol).

2.3 Gonadal Dysfunction and Infertility

All surgery, radiotherapy, chemotherapy, and long-term hormone treatment can lead to primary or secondary hypogonadism dependent on whether the damage primarily affects the testicles/ovaries or the pituitary gland/hypothalamus. In addition, the transport of the ovum or the sperm cells may be impeded by fibrosis or stenosis of the ducts because of surgery or radiotherapy.

There are important gender-related differences as to development, prevention, and possible therapy of treatment-related hypogonadism in cancer survivors. After low or intermediate doses of most cytotoxic drugs or after testicular irradiation of less than 2 Gy the sperm cell production can recover as long as spermatogonial stem cells are preserved. The testosterone producing Leydig cells are relatively resistant to chemotherapy and radiotherapy. Severe endocrine hypogonadism is therefore rare after cancer treatment in males. However, clinicians should keep in mind that long-term cancer survivors' testosterone production appears to decrease faster than observed during physiological aging in the male general population.

The situation as to recovery of gonadal function is different in female survivors. At birth the ovaries contain approximately 10 million follicles. This number decreases along with aging up to menopause without replacement of follicles lost each month. After radiotherapy and chemotherapy the loss of follicles is accelerated. As no recovery is possible, female survivors are at risk of premature endocrine and exocrine ovarian failure (menopause before the age of 40).

Treatment of endocrine gonadal failure is based on the application of testosterone or estrogens, however, with important contra-indications in survivors after prostate and breastcancer. Prevention is the best way to limit infertility problems in cancer survivors. Updated guidelines are repeatedly published (Kenney et al. 2012; Metzger et al. 2013). Pretreatment sperm cell cryopreservation has been used for many years in adult male cancer patients, but is problematic in pre-pubertal boys. Pretreatment ovarian or testicular tissue cryoconservation is still experimental, but reimplantation of thawed ovarian tissue has been followed by pregnancies in a few cancer survivors after reimplantation of cryopreserved ovarian tissue. Overall pregnancy rates after adult-onset cancer are decreased by 26 % in male and by 39 % in female cancer patients compared to the general population. After implementation of risk-adapted cancer therapy, this discrepancy has been reduced for selected cancer types during the last three decades (e.g., in testicular cancer survivors or male survivors after Hodgkin's lymphoma) (Stensheim et al. 2011).

2.4 Peripheral Neuropathy

One of the most common late effects (20–30 %) is peripheral neuropathy caused by chemotherapy containing vinca alkaloids, cisplatin, or taxanes (Windebank and Grisold 2008). For some patients the complaints are limited to numbness of soles of the feet, whereas others suffer from pain in the legs that might cause severe

sleeping problems. Cisplatin is in addition ototoxic and can lead to tinnitus and hearing loss (Brydøy et al. 2009, Oldenburg et al. 2007). Though the latter toxicity most often is restricted to decibel frequencies of >4000 Hz, severe ototoxicity has a negative impact on a person's social and professional life.

2.5 Muscle and Skeletal Effects

As proliferating cells are particularly sensitive to any cytotoxic treatment, radiotherapy to the skeleton and muscles in young adults can be followed by severe muscle atrophy and retarded growth of bones. The negative impact of the target dose is increased by chemotherapy with radiosensitizing drugs (Actinomycin D, Anthracyclines, Cisplatin) often applied as a part of multimodal therapy.

In breast cancer survivors reduced function of the ipsilateral arm/shoulder, pain and/or lymphoedema have represented frequent complaints, but the incidence of these late effects has been reduced after the introduction of breast conserving surgery and improved radiotherapy techniques (Nesvold et al. 2011)

Osteoporosis related to male and female endocrine hypogonadism may become a problem in all cancer survivors (Lustberg et al. 2012). Prostate cancer and breast cancer survivors are at particular high risk of developing this late effect as complete intermittent or permanent hypogonadism is an important part of their treatment. Today several drugs are available which together with Vitamin D, calcium application and physical activity reduce the risk of osteoporosis by nonhormonal mechanisms (Zoledronic acid, Denosumab).

3 Fatigue

Fatigue is defined as a subjective experience of tiredness, exhaustion, and lack of energy (Radbruch et al. 2008). Formal diagnostic criteria for "cancer-related fatigue" (CRF) as a syndrome were proposed in 1998, but has attracted relatively little attention in the scientific community (Donovan et al. 2013). In this context fatigue is regarded as a symptom.

For most cancer patients, fatigue is experienced as a side-effect during treatment and resolves by recovery from therapy. This can be conceptualized as acute fatigue. However, for some patients, fatigue may persist for years after completed cancer therapy and without any signs of active cancer disease. The term CF, defined as fatigue lasting for 6 months or more or after the stimuli has ended, applies well to such fatigue because the term differentiates between fatigue as part of everyday strains such as acute infections or psychosocial strains and the feeling of being chronically exhausted. Such a distinction is also supported by the fact that fatigue is a very common symptom in the general population (Loge et al. 1998).

The prevalence of fatigue among cancer survivors vary by assessment method, cancer type and definitions, but most prevalence figures vary between 19 and 38 % (Stone and Minton 2008). Survivors of Hodgkin lymphoma and breast cancer are the types most studied. Recent data also indicate that fatigue is common among long-term survivors of cancer in childhood and adolescence (Hamre et al. 2013). Fatigue is therefore probably the commonest late effect across all cancer survivors.

The present knowledge about etiology and mechanisms of fatigue among disease-free cancer survivors is limited (Stone and Minton 2008). It is also unlikely that any single mechanism will be identified because fatigue is multifactorial in origin and is also observed across a variety of noncancer diseases and illnesses. The etiology is therefore best considered as multifactorial, involving both physical and psychological factors. Psychological distress, pain, sleep disturbance, depression, anxiety, inactivity, late medical effects, inflammation, and anemia have all been associated with CRF (Stone and Minton 2008). Except for anemia, all are relevant in relation to CRF among cancer survivors.

Interventions to improve CRF among cancer survivors broadly fall into three categories; drug interventions, exercise interventions, and psychosocial interventions (Stone and Minton 2008). A recent update of a 2008 Cochrane review on drug therapy concluded that psychostimulants are promising but large-scaled randomized controlled trials are warranted (Minton et al. 2010). However, many of the reviewed studies included cancer patients with active disease, and the administration of psychostimulants to disease-free cancer survivors has ethical and legal aspects that need to be clarified. Exercise interventions, mostly consisting of graded aerobic exercise, have slightly to moderate positive effects upon CRF among cancer patients in general (Cramp and Daniel 2008). The strongest effects were observed among cancer survivors, but optimal type, amount and timing of interventions need to be sorted out. Psychosocial interventions include education, coping strategy training, behavioral therapy, cognitive therapy, and supportive therapy. These interventions have slight to moderate effects (Pachman et al. 2012). Education about fatigue, teaching self-care, energy conservation and activity management are easily applied in ordinary clinical contexts. In combination with sleep regulation focusing on night-time sleep, rest without sleeping during daytime, and graded physical exercise, are the best documented interventions that are applicable in ordinary clinical practice.

4 Anxiety and Depression

Longitudinal studies of depression and anxiety after cancer diagnosis suggest that the high early prevalence rates fall slowly over time. The prevalence of depression in long-term cancer survivors was similar to that of healthy controls (Mitchell et al. 2013). The proportion of depressed individuals among spouses of cancer survivors was similar to that of survivors.

Some studies have observed low levels of depression and distress as well as good quality of life (QOL) in long-term cancer survivors. In several studies QOL in long-term cancer survivors is similar to that of the general population (Mykletun et al. 2005).

In contrast, the risk of anxiety disorders is significantly higher among cancer survivors than among healthy controls. Anxiety has also been reported to be as common in spouses as in survivors (Mitchell et al. 2013). In the time frame of 10 years since diagnosis, anxiety shows a more persistent pattern than depression. The distribution of anxiety disorders among cancer survivors did not differ from that of the general population (Greer et al. 2011). In general, presence of anxiety has a negative effect on QOL. The common factor may be distressed (type D) personality, which is the conjoint effect of negative affectivity and social inhibition. The prevalence of type D personality among cancer survivors (19 %) is similar to the general population (13–24 %), but such survivors are at increased risk for impaired QOL and mental health problems (Mols et al. 2012).

4.1 Fear of Recurrence

Recently, more empirical studies have addressed fear of recurrence (Simard et al. 2013). Although defined in various ways, increasing consensus focuses on a fear that cancer could return or progress in the same place or in another part of the body. Various definitions have lead to multiple self-report measures for assessment of fear of recurrence without international recommendations so far (Thewes et al. 2012). This situation may also explain the wide range of prevalence rates reported. According to the review of Simard et al. (Simard et al. 2013) based on 130 papers, across cancer sites, 39–97 % of cancer survivors reported fear of recurrence, 22–87 % reported moderate to high degree, and 0–15 % high degree of such fear. Fear of recurrence seems to remain stable over time, even if the risk of recurrence decreases as time goes on. This finding points to an element of irrationality in fear of recurrence which is common to all kinds of pathological anxiety. The risk of recurrence among long-term testicular cancer survivors is minimal, but still 7 % reported ‘very high’ and 24 % ‘quite a bit’ fear of recurrence in our national Norwegian follow-up study (Skaali et al. 2009). This finding has to be considered in the light of the ‘focusing illusion’ phenomenon which implies considerable exaggeration if people are asked to focus on just one factor concerning their well-being (Kahneman et al. 2006).

4.2 Posttraumatic Stress Disorder

Posttraumatic Stress Disorder (PTSD) is a mental disorder due to exposure to a life-threatening event either personally or as a bystander. Since 1994 “being diagnosed with a life-threatening illness” has been defined as such a potentially

traumatic event, and the studies of PTSD among cancer patients have flourished since then. The PTSD symptoms are quite specific with intrusion in the mind of experiences of cancer diagnosis and treatment, and avoidance and hypervigilance in relation to all associations with cancer. The level of PTSD symptoms is regularly high during diagnosis and treatment and then the level gradually tapers off.

Most studies of cancer survivors do not report elevated prevalences of PTSD in cancer survivors compared to the general population. These findings indicate that getting cancer on a group level is not among the most potent traumas in life. However, Smith et al. reported a prevalence of 37 % among survivors of non-Hodgkin lymphomas at a median of 12.9 years after diagnosis, indicating that cancer may be a tougher trauma than expected (Smith et al. 2011). However, in Germany Mehnert and Koch found that 12 % of breast cancer survivors had persistent PTSD (>60 months after diagnosis) (Mehnert and Koch 2008). This prevalence is similar to that observed in the general German female population. Presence of PTSD was associated with younger age, lower level of education, less social support, and progressive disease. These risk factors as well as previous traumas, mental disorders, chemotherapy, and somatic-comorbidity are reported in many studies.

5 Cognitive Problems

Subjective cognitive problems cover cancer patients' complaints concerning memory, concentration, word finding, planning, and doing multiple tasks. A considerable proportion of patients describe such problems when treated with chemotherapy. However, usually these complaints follow the course of anxiety and depression with gradual reduction over time. A minority gets permanent subjective problems. In an American population study, 14 % of cancer patients (brain tumors excluded) reported subjective cognitive complaints versus 8 % among cancer-free controls (Pierre et al. 2011).

Objective evidence for cognitive problems can be documented through neuropsychological tests. Koppelmanns et al. reported considerable neuropsychological deficits in long-term breast cancer survivors compared to cancer-free controls (Koppelmanns et al. 2012). This result has been replicated in several studies with repeated measurements showing long-term neuropsychological deficits particularly after chemotherapy. Functional brain imaging can visualize reduced metabolism in relevant brain areas during neuropsychological testing. For example, de Ruiter et al. showed that long-term breast cancer survivors treated with high-dose chemotherapy 10 years previously, showed significantly less metabolic activation under testing compared to controls (Ruiter et al. 2011).

One problem within this field is the lack of correspondence between subjective complaints and objective findings, which should not be hold against the patient. Another is that cognitive reduction is multifactorial, which makes it difficult to tease out the specific effect of chemotherapy among other factors. For the clinician

it is important to keep in mind that cognitive reduction can be a long-term adverse effect after cancer therapy, and that this effect may reduce work ability in particular.

6 Sexual Problems

In this field clinicians should be aware of two facts: (1) Various sexual problems are common in the general population, and information about precancer function is important, not least in order to understand to what extent preexisting problems later on are attributed to cancer. (2) After cancer treatment the optimal aim is to regain the precancer level of sexual function. Cancer hardly improves sexual function, although more openness and emotionality between partners eventually can improve intimacy.

A useful distinction is to separate sexual function in younger and older cancer survivors. Younger survivors are more sexually active, and fertility (see separate section) is still an important issue. Younger survivors concerns mainly survivors of breast and gynecological cancer, lymphomas and other hematological cancers, and sarcomas and testicular cancer. Finally, a general complaint is the lack of communication about sexuality between survivors and both clinicians and general practitioners.

There are few studies of sexuality in long-term survivors. A recent review did not specify time of survival and was thereby less helpful (Bober and Varela 2012). The same critique can be raised toward a review of studies in gynecological cancer survivors (Abbott-Anderson and Kwekkeboom 2012).

Among younger survivors the issue of sexual function in long-term testicular cancer survivors has been debated, however the controlled study with the largest sample, hardly observed significant differences from population-based controls (Dahl et al. 2007). In contrast, long-term male survivors of lymphomas had significantly poorer sexual function than such controls (Kiserud et al. 2009). Young female breast cancer patients often experience long-term lack of sexual interest. The attitude of their partners toward their body and femininity is very important for their sexual well-being. Premature menopause and hormone therapy also is of considerable importance, but less so for long-term survivors.

Most of the same issues are relevant for older breast cancer survivors. In gynecological cancer survivors lack of interest, vaginal dryness, and pains during intercourse are common complaints. Colorectal cancer is followed by high rates of sexual dysfunctions in both males and females at a mean of 4 years since diagnosis (Ousten et al. 2012). Both radical prostatectomy and radiotherapy for prostate cancer as well as adjuvant hormone treatment are mostly followed by severe long-term erectile dysfunction, and sexual recovery is seldom achieved (Wittmann et al. 2009).

7 Work and Economy

Work ability is a concept which covers a person's ability to take part in ordinary work life and has three components: physical, mental, and social ability (van den Berg et al. 2009). Cancer most often infers a weakening of the physical work ability that can be temporary or permanent. However, cancer can also affect the mental and social work ability. In the Nordic countries over 80 % of men and women are active in work life, the big difference being that most of the men, but only half of the women hold full-time work. For those at work, when they get their cancer diagnosis, *return to work* is the first important issue. Within 2 years after diagnosis approximately 60 % (range 30–93 %) reenter work life (Taskila et al. 2007). Based on 26 studies, de Boer et al. reported a general unemployment rate of 33.8 % in cancer patients compared to 15.2 % in controls (RR 1.37, 95 %CI 1.21–1.55) (Boer et al. 2009).

These findings point not only to return to work, but also to the problem of *staying at work* for cancer survivors. Several studies have examined the *problems of cancer survivors at the workplace.* Most studies concern women with breast cancer who report that cognitive problems, hot flashes, and arm-shoulder morbidity reduced their work productivity. Pain in general and fatigue were common problems for survivors of both genders. In patients treated with surgery for prostate cancer physical tasks like lifting and stooping, can be associated with socially incapacitating urinary leakage, but cognitive problems at work were also common in men treated for prostate cancer. Difficulties of coping with previous job demands and expectation of employers and colleagues were common. Interestingly, over-protectiveness from colleagues was also commonly reported as a problem. Follow-up studies concerning *stability in work life over time* are uncommon so far. In our unpublished studies of testicular cancer survivors and survivors of breast cancer stage I, we observed that long-term stability in work life in these groups of cancer survivors which have very good prognosis, was similar to that of the general population.

When work ability is permanently reduced, persons have to leave the work force and go on to disability pension. Compared to matched controls without cancer, survivors have a significantly higher rate of disability pension (Carlsen et al. 2008, Hauglann et al. 2012) Compared to being at work, disability pension implies an income reduction, and several studies have shown that cancer survivors have permanently lower income compared to matched controls without cancer. However, due to generous welfare compensations in Norway the income reduction for cancer survivors is small compared to the general population (Syse and Tønnessen 2012).

Cancer survivors as a group display a reduction in working hours and >10 % decline in overall earnings. There are differences across diagnoses with survivors of lymphomas, lung, brain, bone, colorectal, and head-and neck cancer being mostly affected by decline in earnings. Other factors negatively effecting upon

earnings are low level of education, lower social support, chemotherapy, self-employment, shorter tenure in the job, and part-time work (Mehnert 2011).

8 Marriage Rates

Marriage rate is a relevant outcome among survivors of cancers hitting in childhood, adolescence, and early adulthood. Generally, negative effects upon marriage rates are depending upon several disease-treatment and host-related factors including late medical effects and their interplay. Further, cultural and societal differences might modify or exaggerate the effects implying that findings from one country not necessarily are transferrable to other countries with for example different school or health care systems (Syse and Geller 2011).

A registry-based study from Norway including all Norwegian cancer survivors 17–44 years old diagnosed in the period 1974–2001, found the marriage rates of survivors of most types of cancer to be similar to the age-matched Norwegian population as a whole. Some subgroups such as women with brain and breast cancer had lower marriage rates than their cancer-free counterparts (Syse 2008).

9 Lifestyle Factors

Lifestyle factors are important for cancer survivors since they represent risk factors for relapse of the primary cancer, development of secondary cancer, and development of comorbid diseases, like diabetes, which reduce the health status and quality of life of the survivors.

The lifestyle factors are well-known: smoking, diet, low physical activity, and high alcohol consumption. Although the severe consequences of unhealthy lifestyle are well-known, permanent lifestyle changes have proved difficult to implement by health campaigns or other types of mass influence. Getting cancer has been considered a "teachable moment" for life style change, but even rather intensive long-term interventions report only moderate success.

Compared to men in the general population, a higher proportion of testicular cancer survivors are daily smokers (Thorsen et al. 2005).

Although regular alcohol intake is associated with increased risk for many types of cancer, the relation of such a habit with cancer recurrence and morbidity is unclear. However, the risk for development of additional comorbid somatic diseases is considerable.

Obesity increases the risk of cancer recurrence and mortality, particularly in survivors of breast and prostate cancers (Ligibel 2012). However, weight gain in the survivorship period does not represent a significantly increased risk for these outcomes, and weight loss does not seem to reduce the risk. However, weight loss is important for physical function and reduces the risk for lifestyle diseases like diabetes or hypertension. Among six prospective cohort studies, five have reported

a decreased risk of cancer recurrence and related death if the survivors engage in modest levels of physical activity. The documentation is most convincing for survivors of breast, colon and prostate cancer, and concerns walking for 3 h a week at an average pace.

10 Follow-up Care Organization

Follow-up practices for long-term cancer survivors are probably suboptimal in most countries both regarding content and organization. Specialized late-effects clinics have been established in some countries and most of them provide care for survivors of childhood cancers. However, the evidence base for the effects of different models is presently weak (Earle and Ganz 2012). For providers, the challenge is to develop and institute care models that address the needs of the fast growing population of survivors. To our knowledge, the only European national initiative has been launched in Great Britain, the National Cancer Survivorship Initiative (http://www.ncsi.org.uk/). In the United States, both the American Cancer Society and the National Cancer Institute are engaged in developing cancer survivorship care. Due to differences in cultures, resources, and structure of health care systems, models found to be effective in one setting are not necessarily optimal in other settings.

Follow-up of cancer survivors includes three distinct parties: the specialist with expertise of the disease, treatment and risk for late effects; the Primary Care Physician (PCP) with specific knowledge of their patients but often not updated on their risks for late effects; and finally the patient with his/her level of knowledge, attitudes and behavior. Follow-up care might theoretically be delivered by the specialist, the PCP or combinations of the two (shared care). A fourth option is to give the survivor the full responsibility without involving the health care system unless the survivor asks for it.

Follow-up by the treating oncologist for all cancer survivors is not feasible due to lack of manpower and resources in general. Further, not all survivors are in need of specialized follow-up care, and the National Cancer Survivorship Initiative has estimated that about 75 % of all survivors can manage their health themselves with support from the primary health care system (http://www.ncsi.org.uk/). On this background, the concept of risk-based care has been launched and includes development of a systematic plan for prevention and surveillance based on risks associated with the cancer therapy, genetic predispositions, the survivors' lifestyle and comorbidities (Oeffinger and McCab 2006).

For the cancer survivor to be able to make the optimal decisions regarding own present and future health, they need information regarding the long-term health risks they face and how to best handle them. The literature indicates that today's cancer survivors are not aware of their risks for later adverse health events (Kadan-Lottick et al. 2002; Hess et al. 2011). These findings might not only relate to

lacking information per se. We must also assume that the survivors have an ambivalent wish for information about future health risks.

Survivorship care plans have been proposed as a means to operationalize the recommendations regarding follow-up care. The idea is that a comprehensive care summary and follow-up plan is written by the principal provider of the oncology care. However, a recent randomized trial could not demonstrate positive effects of such plans among survivors of breast cancer (Grunfeld et al. 2011).

Thus, the present status is that organization and content of follow-up care is still under development. As stated by Earle and Ganz, in this setting it is timely not to let the perfect be the enemy of the good (Earle and Ganz 2012).

11 Cancer Survivorship Research

With the shift from cancer having a poor prognosis to being curable diseases, research questions assessing late effects, who are at particular risk of developing them, how can they best be prevented and managed and how does having had cancer impact upon the living conditions of the survivors, became increasingly relevant as the number of survivors rapidly increased (Rowland et al. 2013).

At the start of cancer survivorship research in the 1970s, survivors of cancers that had recently become curable, that hit early in life and the survivors had a long life expectancy after cure such as childhood cancers, testicular cancers, and Hodgkin's lymphoma, first attracted the researchers' attention. The research field has later rapidly expanded, and by year 2011 nearly 17,500 citations related to cancer survivorship science were identified (Rowland et al. 2013). The rapid expansion includes studies of new groups of survivors and broadening of the research field to include not only quantity of life but also the survivors' quality of life. Noteworthy is the finding that late medical effects continue to emerge decades after end of treatment making continuous surveillance and research on their mechanisms, prevention and treatment even more relevant now than 40 years ago. In conjunction with the expansion of molecular biology, research on the mechanisms of late effects has greatly advanced from year 2000 onward. In the same period, models for providing health care to the survivors and their cost-effectiveness have emerged as a new field of great relevance for the survivors themselves but also for health administrators and health authorities.

Representative national or regional cancer registries or not available in all countries, but when they are, they provide unique opportunities for studying unselected cohorts of survivors. Some research groups have studied survivors previously included in clinical trials. As opposed to registry data, clinical trials usually provide a broad range of variables for characterization of the exposure—i.e., the disease and treatment, and the host at start of treatment. A limitation of using participants form previous clinical trials is the very low rate of cancer patients being included in trials, which infers that the study subjects are highly selected and the findings will have limited external validity. Observational studies

by postal questionnaires have probably been the most frequently used design. Questionnaires specifically developed for cancer survivors have been developed and tested (Pearce et al. 2008). Generic questionnaires, disease-specific questionnaires, or questionnaires specifically developed for cancer survivors have been used. The generic questionnaires allow for comparisons with other populations including the general population but lack cancer-specific content. The cancer-specific questionnaires often include content of particular relevance for patients receiving treatment but such content might be less relevant after treatment and when the patient is cured. Cancer survivorship-specific questionnaires such as the Impact of Cancer (IOC) scale (Zebrack et al. 2006) addresses important aspects of survivorship such as personal growth, but has limitations regarding comparisons with populations not affected by cancer. The terms health-related quality of life (HRQOL) and quality of life have been used interchangeably although most studies have used HRQOL-measures (Rowland 2007).

Some important challenges of particular relevance for cancer survivorship research need to be pointed out. One is to define who is a cancer survivor. A second challenge is to identify the survivors 10–20–30 years after end of treatment. Legislations, the structure of the health care system and social mobility all effect upon the possibility to identify the survivors. For example, in Norway due to a unique personal identity number, a national uniform health care system and relatively low social mobility, we have been able to identify nearly all survivors of specific cancers more than 25–30 years after end of treatment. A third important challenge is how to control for age-related health effects when for example studying adult survivors in their 50s and 60s who were treated as children. Choosing an optimal control group is therefore critical and needs careful consideration. A fourth challenge is to have access to data that allows for detailed description of the exposure and the patient at time of exposure. Most studies till now have been cross-sectional and data on the exposure and the host at time of exposure are often not available or very limited. Cross-sectionals designs limit the possibility to draw inferences about causality. Fifthly, funding of research is a challenge in many countries exaggerated by the present financial crisis. Finally, the diversity of end-points, especially patient-reported, hinders comparisons of findings across studies.

References

Abbott-Anderson K, Kwekkeboom KL (2012) A systematic review of sexual concerns reported by gynecological cancer survivors. Gynecol Oncol 124:477–489

American Cancer Society (2012) Cancer Treatment and Survivorship Facts and Figures 2012–2013

Bober SL, Varela VS (2012) Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol 30:3712–3719

Brydøy M, Oldenburg J, Klepp O et al (2009) Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst 101:1682–1695

Carlsen K, Dalton SO, Frederiksen K et al (2008) Cancer and the risk for taking early retirement pension. Scand J Publ Health 36:117–125
Cramp F, Daniel J (2008) Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2:CD006145. doi: 10.1002/14651858.CD006145.pub2
Curigliano G, Cardinale D, Suter T et al (2012) Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol 23:155–1662
Dahl AA, Bremnes R, Dahl O, Klepp et al (2007) Is the sexual function compromised in long-term testicular cancer survivors? Eur Urol 52:1438–1447
Darby SC, Ewertz M, McGale P et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:987–998
de Boer AGEM, Taskila T, Ojajärvi A et al (2009) Cancer survivors and unemployment—a meta-analysis and meta-regression. JAMA 301:753–762
de Ruiter MB, Reneman L, Boogerd W et al (2011) Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum Brain Map 32:1209–1216
Den Ousten BL, Traa MJ, Thong MSY et al (2012) Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. Eur J Cancer 48:3161–3170
Donovan KA, McGinty HL, Jacobsen PB (2013) A systematic review of research using the diagnostic criteria for cancer-related fatigue. Psychooncology 22:737–744
Earle CC, Ganz PA (2012) Cancer survivorship care: don't let the perfect be the enemy of the good. J Clin Oncol 30:3764–3768
Fossa SD, Loge JH, Dahl AA (2008) Long-term survivorship after cancer: how far have we come? Ann Oncol S5:25–29
Fosså S, Vassilopoulou-Sellin R, Dahl A (2008) Long term physical sequelae after adult-onset cancer. J Canc Survivorship 2:3–11
Fung C, Fosså SD, Milano MT et al (2013) Solid tumors following chemotherapy or surgery for testicular nonseminoma: A population-based study of 12,691 patients. J Clin Oncol (in press)
Greer JA, Solis JM, Temel JS et al (2011) Anxiety disorders in long-term survivors of adult cancers. Psychosom 52:417–423
Grunfeld E, Julian JA, Pond G et al (2011) Evaluating survivorship care plans: results of a randomized, clinical trial of patients with breast cancer. J Clin Oncol 29:4755–4762
Hamre H, Zeller B, Kanellopoulos A et al (2013) High prevalence of chronic fatigue in adult long-term survivors of acute lymphoblastic leukemia and lymphoma during childhood and adolescence. J Adolesc Young Adult Oncol 2:2–9
Hauglann B, Benth JS, Fosså SD et al (2012) A cohort study of permanently reduced work ability in breast cancer patients. J Cancer Surviv 6:345–356
Haugnes HS, Wethal T, Aass N et al (2010) Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 28:4649–4657
Hess SL, Johannsdottir IM, Hamre H et al (2011) Adult survivors of childhood malignant lymphoma are not aware of their risk of late effects. Acta Oncol 50:653–659
Jean Pierre P, Winters PC, Ahles TA et al (2011) Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study. J Oncol Pract 8:30–34
Kadan-Lottick NS, Robison LL, Gurney JG et al (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment: childhood cancer survivor study. JAMA 287:1832–1839
Kahneman D, Krueger AB, Schkade D et al (2006) Would you be happier if you were richer? A focusing illusion. Science 312:1908–1910
Kenney LB, Cohen LE, Shnorhavorian M et al (2012) Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol 30:3408–3416
Kiserud CE, Schover LR, Dahl AA et. (2009) Do male lymphoma survivors have impaired sexual function? J Clin Oncol 27: 6019–6026

Kollmannsberger C, Beyer J, Droz JP et al (1998) Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. J Clin Oncol 16:3386–3391

Koppelmanns V, de Ruiter MB, van der Lijn F et al (2012) Global and focal brain volume in long-term breast cancer survivors exposed to adjuvant chemotherapy. Breast Cancer Res Treat 132:1099–1106

Lenihan D, Oliva S, Chow EJ et al (2013) Cardiac toxicity in cancer survivors. Cancer 119:2131–2142

Liavaag AH, Tonstad S, Pripp AH et al (2009) Prevalence and determinants of metabolic syndrome and elevated Framingham risk score in epithelial ovarian cancer survivors: a controlled observational study. Int J Gynecol Cancer 19:634–640

Ligibel J (2012) Lifestyle factors in cancer survivorship. J Clin Oncol 30:3697–3704

Loge JH, Ekeberg Ø, Kaasa S (1998) Fatigue in the general Norwegian population—normative data and associations. J Psychosom Res 45:53–65

Lustberg MB, Reinbolt RE, Shapiro CL (2012) Bone health in adult cancer survivorship. J Clin Oncol 30:3665–3674

Metzger ML, Meacham LR, Patterson B et al (2013) Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239–1247

Mehnert A, Koch U (2008) Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors. J Psychosom Res 64:383–391

Mehnert A (2011) Employment and work-related issues in cancer survivors. Critical Rev Oncol/Hematol 77:109–130

Minton O, Richardson A, Sharpe M et al (2010) Drug therapy for the management of cancer-related fatigue. Cochrane Database Syst Rev. 7:CD006704

Mitchell AJ, Ferguson DW, Paul J et al (2013) Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls. Lancet Oncol. doi: 10.1016.S1470-2045(13)70244-4

Mols F, Thong MSY, van de Poll-Franse L et al (2012) Type D (distressed) personality is associated with poor quality of life and mental health among 3080 cancer survivors. J Affect Dis 136:26–34

Morton LM, Gilbert ES, Hall P et al (2012) Risk of treatment-related esophageal cancer among breast cancer survivors. Ann Oncol 23:3081–3091

Mykletun A, Dahl AA, Haaland CF et al (2005) Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer. J Clin Oncol 23:3061–3068

Nesvold IL, Reinertsen KV, Fosså SD et al (2011) The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Canc Surviv 5:62–72

Oeffinger KC, McCab MS (2006) Models for delivering survivorship care. J Clin Oncol 24:5117–5124

Oldenburg J, Kraggerud SM, Cvancarova M et al (2007) Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. J Clin Oncol 25:708–714

Pachman DR, Barton DL, Swetz KM et al (2012) Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain. J Clin Oncol 30:3687–3696

Pearce NJ, Sanson-Fisher R, Campbell HS (2008) Measuring quality of life in cancer survivors: a methodological review of existing scales. Psychooncology 17:629–640

Radbruch L, Strasser F, Elsner F et al (2008) Fatigue in palliative care patients-an EAPC approach. Palliat Med 22:13–32

Rowland JH (2007). Survivorship research: past, present and future. In: Ganz PA (ed) Cancer survivorship today and tomorrow. Springer, New York, pp 28–42

Rowland JH, Kent EE, Forsythe LP et al. (2013) Cancer survivorship research in Europe and the United States: where have we been, where are we going, and what can we learn from each other? Cancer 119(S11):2094–2108

Simard S, Thewes B, Humphris G et al (2013) Fear of cancer recurrence in adult cancer survivors. J Cancer Surviv. doi:10.1007/s11764-013.0272-z

Skaali T, Fosså SD, Bremnes R et al (2009) Fear of recurrence in long-term testicular cancer survivors. Psychooncology 18:580–588

Smith SK, Zimmerman S, Williams et al (2011) Post-traumatic stress symptoms in long-term non-Hodgkin's lymphoma survivors. Does time heal? J Clin Oncol 29:4526–4533

Stensheim H, Cvancarova M, Møller B et al (2011) Pregnancy after adolescent and adult cancer: a population-based matched cohort study. Int J Cancer 129:1225–1236

Stone PC, Minton O (2008) Cancer-related fatigue. Eur J Canc 44:1097–1104

Swerdlow AJ, Barber JA, Hudson GV et al (2000) Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol 18:498–509

Swerdlow AJ, Schoemaker MJ, Allerton R et al (2001) Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. J Clin Oncol 19:1610–1618

Syse A (2008) Does cancer affect marriage rates? J Cancer Surviv 2:205–214

Syse A, Geller B (2011) A cross-cultural perspective on challenges facing comparative cancer survivorship research. J Cancer Epidemiol 2011:689025. doi:10.1155/2011/689025

Syse A, Tønnessen M (2012) Cancer's unequal impact on incomes in Norway. Acta Oncol 51:480–489

Taskila T, Martikainen R, Hietanen P et al (2007) Comparative study of work ability between cancer survivors and their referents. Eur J Cancer 43:914–920

The Cancer Registry of Norway (2010) Cancer in Norway 2010

Thewes B, Butow P, Zachariae R et al (2012) Fear of cancer recurrence: a systematic literature review of self-report measures. Psycho-Oncol 21:571–587

Thorsen L, Nystad W, Stigum H et al (2005) The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample. Support Care Cancer 13:637–646

Travis LB, Holowaty EJ, Bergfeldt K et al (1999) Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med 340:351–357

van den Berg TIJ, Elders LAM, de Zwart BCH et al (2009) The effects of work-related factors on the work ability index: a systematic review. Occup Environ Med 66:211–220

Verdecchia A, Francisci S, Brenner H et al (2007) Recent cancer survival in Europe: a 2000–2002 period analysis of EUROCARE-4 data. Lancet Oncol 8:784–796

Willemse PM, Burggraaf J, Hamdy NA et al (2013) Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. Br J Cancer 109(1):295–296 (in press)

Windebank AJ, Grisold W (2008) Chemotherapy-induced neuropathy. J Peripher Nerv Syst 13:27–46

Wittmann D, Northhouse L, Foley S et al (2009) The psychosocial aspects of sexual recovery after prostate cancer treatment. Int J Impotence Res 21:99–106

Zebrack BJ, Ganz PA, Bernaards CA et al (2006) Assessing the impact of cancer: development of a new instrument for long-term survivors. Psychooncology 15:407–421