Chapter 1
What Is Comorbidity?

Diana Sarfati and Jason Gurney

Abstract Comorbidity is "*any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient that has the index disease under study*". It is related to, but distinct from other constructs such as multimorbidity, functional status, disability, allostatic load, frailty, burden of disease and patient complexity. As populations age, the prevalence of chronic disease increases. As a consequence, many people live with, rather than die from chronic health conditions. Cancer is often a chronic disease itself, and is also more prevalent among the elderly. This confluence in timing means that many cancer patients (if not most) live with at least one other chronic disease, although the prevalence of comorbidity varies markedly across populations with different types of cancer. There are several reasons why cancer and comorbidity co-exist; cancer and other long-term conditions share common risk factors, some chronic conditions or their treatments are causally related to cancer and there may be some instances where there are common physiological pathways between cancer and other conditions.

Keywords Comorbidity · Cancer · Complexity · Chronic disease

Key Points

- The presence of chronic disease—comorbidity—in addition to cancer is now the norm rather than the exception.
- While comorbidity is common among cancer populations, the precise prevalence of comorbidity is difficult to determine; however, it is clear that the prevalence of comorbidity varies considerably by cancer site.
- There is substantial evidence of differing comorbidity burden between population sub-groups, with those in ethnic minority groups and those living in poverty or deprivation carrying a greater burden.

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- The reasons why cancer and comorbidity coexist are multiple and varied. Cancer and other long-term conditions share many risk factors; there are also many examples where specific comorbid conditions or their treatments may be involved in the aetiology of cancer, or vice versa. There may also be common genetic or physiological links between some chronic conditions and cancer.

1.1 What Is Comorbidity?

> Management of patients with several chronic diseases is now the most important task facing health services in developed counties, which presents a fundamental challenge to the single-disease focus that pervades medicine.
>
> – Chris Salisbury, The Lancet [1]

As populations age, the prevalence of chronic disease increases. Almost all chronic diseases are more common among the elderly than younger adults, and are not life threatening in the short term. Consequently, many people live with, rather than die from chronic health conditions.

Cancer is often a chronic disease itself, and is also more prevalent among the elderly. Via a natural convergence in the timing of peak occurrence, concomitant chronic disease—which we term *comorbidity*—in addition to cancer is now the norm rather than the exception. This confluence has the potential to profoundly impact affected individuals [2–5].

Comorbidity results in increased risk of hospitalisation, adverse effects of treatment, multiple competing demands on both patient and health care professionals, high health care costs, reduced quality of life and higher mortality [4–15]. Despite this, much of the research and planning relating to cancer and cancer care assume a single disease paradigm. For example, patients with comorbidity are often excluded from randomised controlled trials, which means that it is difficult to generalise the findings of such trials to those with chronic health problems, or to predict the difficulties or complications from treatment that such patients may face [16–19]. Partly as a consequence of this, clinical practice guidelines tend to be very poor at addressing the needs of older patients with comorbidity [18, 20, 21]. Health care service providers, policy makers and researchers need to be able to respond adequately to the requirements of individuals with complex health needs [15, 22].

Despite the importance of comorbidity in the care of cancer patients, there is no consensus about how to define it, and even less on how to measure it. To add to the confusion, there are multiple other constructs that are related to—but distinct from—comorbidity.

1.2 The Evolution of the Concept of Comorbidity

In 1970 Feinstein noted that "*although patients with more than one diagnosed disease are frequently encountered in modern medical practice, the inter-relationships and effects of multiple diseases have not received suitable taxonomic attention in clinical science*" [6]. Feinstein argued that this "*neglect of comorbidity*" had many detrimental effects, although his focus was largely on defining comorbidity in order to ensure comparability between study groups in studies of treatment effectiveness, and to ensure that *statistics* relating to disease were accurate. Feinstein defined comorbidity as "*any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient that has the index disease under study*". He noted the importance of comorbid disease in terms of its potential effects on diagnosis, treatment and outcomes of patients. Subsequent work by Kaplan and Feinstein in 1974 [23] resulted in possibly the first attempt to measure comorbidity as a separate construct in its own right. They found that comorbidity was related to increased risk of mortality, and higher severity of comorbidity with increased risk among patients with diabetes mellitus.

During the 1980s and early 1990s, the measurement of comorbidity developed into two distinct branches: diagnostic-based risk (or case-mix) adjustment systems, and clinically-based comorbidity indices. These approaches differed both in the underlying assumptions and constructs relating to comorbidity, and in the approaches that were used to measure comorbidity. While this dichotomy is clearly distinguishable, it is important to note that both approaches have been used in a variety of study types with varying aims and objectives [3, 24–29].

1.3 Diagnostic-Based Risk (or Case-Mix) Adjustment Systems

These were developed largely in the United States in response to the need to allocate health care resources in managed care environments where populations were enrolled in health care organisations where there was pressure to develop systems which could predict future cost and utilisation of healthcare.

These systems were based on routinely collected data that could be applied to large populations, and often included factors other than comorbidity. The concept of comorbidity for these tended to be focused on conditions or categories of conditions that were associated with increased health service utilisation or health care costs [25, 28, 29].

The ACG system developed at John Hopkins University is an example of a diagnosis-based risk adjustment system. It was developed in response to the recognition of the increasing costs of health care, the rapid expansion of managed and capitated care in the US, and an increasing emphasis on ambulatory care [28, 29]. This system uses administrative data to categorise individuals into groups

(ACGs or Adjusted Clinical Groups) with similar health resource use expectations, based on specified individual or categories of conditions as well as patient factors such as age and sex [28, 29]. This system has been used in a number of settings, primarily for health care management purposes, including setting capitation rates and profiling the efficiency of health care organisations and clinicians [25–34].

1.4 Clinically-Based Comorbidity Indices

Clinically-based comorbidity indices were developed primarily for clinicians and researchers to assess the role of comorbidity in outcomes for their patients, often in the context of clinical or epidemiological studies.

They employ a range of approaches and data sources in an attempt to optimise the measurement of comorbidity [24, 35, 36]. Comorbidity in this context tends to be focused on conditions that have an impact on patient outcomes, most commonly mortality.

The best known example of a clinically-based comorbidity index is the Charlson Comorbidity Index (CCI) developed by Mary Charlson and colleagues in 1987 [37]. The Charlson index includes seventeen conditions (in 19 categories) which are allocated a weight of 1–6, depending on their association with 1-year mortality. For each individual, these weights are summed to give an overall score. A higher score indicates a higher the level of comorbidity.

The Charlson index has been validated and used in a huge variety of clinical and research settings, and has been adapted for use with administrative data [38–41] and for use with patient self-reporting [42–44]. Subsequently, a number of approaches to measure comorbidity have been developed [2, 24, 35, 36, 45]. These are described in detail in the next chapter, but in general can be divided into three categories:

- Simple counts of conditions [46–48].
- Weighted indices that adjust for seriousness of conditions [23, 37, 49–51].
- Systems that depend on models involving varying numbers of individual conditions [52–54].

Data sources used to estimate comorbidity have also varied, including administrative data, medical charts, physical examination, personal interviews and self-reporting [3, 8, 45, 55].

1.5 Recent Evolution Relating to the Concept of Comorbidity

In October 2003, the National Institute on Aging (NIA) Geriatrics and Clinical Gerontology Program convened a taskforce on comorbidity. The objective of this taskforce was to '*explore conceptual and methodological complexities of comorbidity*' [14].

There was general consensus that comorbidity was a complex and heterogeneous concept, and that no single measure would be likely to adequately serve all research and clinical purposes. The taskforce determined that the definition and measurement of comorbidity depended on the objective that was being addressed, the setting and population(s) of interest, the extent to which comorbid conditions inter-relate, and the severity and timing of conditions. The conclusion, then, was that more research was needed on the measurement and impact of comorbidity, but that a balance needed to be maintained on advancing the conceptual and theoretical aspects of comorbidity on one hand, and not losing sight of the practical issues of measuring comorbidity on the other.

Subsequent work has tended to shift into more complex conceptualisations of comorbidity. For example, Karlamangla et al. [56] suggested a categorisation of comorbidity that was based on body systems (i.e. mental function, sensory, pain, voice and speech functions, and movement, skin, cardiovascular, haematological, immunological, respiratory, digestive, metabolic, endocrine, GU/reproductive/sexual, and neuromusculoskeletal systems). They suggested each could be classified on a spectrum ranging from high-functioning, through subclinical abnormalities and through to clinically-manifest disease of various severities. For example, in the endocrine system, abnormal fasting blood glucose levels may be categorised as a subclinical abnormality, where overt diabetes mellitus controlled by diet may be considered disease on the less severe end of the spectrum, while insulin dependent diabetes mellitus with complications may be on the more severe end of the spectrum. The authors also suggested that interactions between domains could be included; for example, the known synergies between hypertension and diabetes could be included in the estimate of overall patient comorbidity, although it was unclear how this would be achieved. In this way, sub-clinical disease could be explicitly recognised, disease clusters would be accounted for, the system would not depend solely on diagnosed disease and high functioning would be measured as well as low functioning. Whilst these aims are laudable, the collection of data required for such a measurement tool would be intensive, expensive and often not feasible.

In their narrative review, Valderas et al. [12] attempted to 'define and measure the concept of comorbidity'. They identified four distinctions that could be made in relation to comorbidity. The first three are related to the definition of comorbidity itself:

1. The requirement to be clear about what a comorbid entity is, and how these can be identified and defined.
2. The relative importance of the primary condition, and given the co-existence of multiple conditions, which can be considered primary.
3. The chronology of the conditions—i.e. are they co-occurring, and does the order in which they occur affect genesis, prognosis or treatment.

The fourth distinction highlighted was that related to 'expanded conceptualisations' relating to comorbidity. Such conceptualisations, expanded on below,

included those of *multimorbidity*, where no single condition is considered primary; *burden of disease,* which includes elements of multimorbidity and functional status; and *patient complexity,* which expands this idea further into other factors which may influence patient outcomes and healthcare resource requirements, such as socioeconomic status, lack of social support or language difficulties. Other related constructs not explicitly included in the paper by Valderas et al. include allostatic load, disability and frailty [57–60].

1.6 Constructs Related to Comorbidity

The multiple constructs related to comorbidity are further described below.

1.7 Multimorbidity

Multimorbidity is the "*the co-occurrence of multiple chronic or acute diseases and medical conditions within one person*" [61]. It is distinct from comorbidity in that the latter implies an index disease under study. The concept of multimorbidity shifts the focus from a single disease paradigm to one where the causes and effects of multiple combined conditions are explored.

Multimorbidity is a particularly useful concept in the context of primary care, where practitioners are responsible for the overall health of their patients rather than the management of a single disease entity [62]. However more recently, there have been strong calls to reorient the health system in general away from a single-disease orientation [1, 18, 19, 63]. Much of the research on multimorbidity has focused on the epidemiology and effects of multimorbidity. For example, van der Akker et al. [64] used data from a network of family health practitioners in the Netherlands to identify permanent, chronic or recurrent conditions. They found that 29.7 % of the population had two or more conditions, and that multimorbidity was more common among older people, women and those with lower education, or those who did not have private health insurance. There was also evidence that certain conditions tended to cluster. They concluded that this clustering of diseases was likely to be due to a combination of *causal* mechanisms, such as common genetic, immunological, environmental or behavioural risk factors, or *artefactual* mechanisms, particularly chance clustering, or detection bias where a patient is more likely to have a second condition diagnosed because of health service contact related to a first condition.

More recently, Barnett et al. analysed data from primary care databases in the United Kingdom for 1.75 million patients [65]. They found that nearly a quarter of all patients had more than one chronic condition, that the likelihood of multimorbidity increased with increasing deprivation, and that whilst multimorbidity was

more common among those aged over 65 years, in absolute terms there were more people under 65 years with multimorbidity.

Multimorbidity, like comorbidity, has been found to be associated with an increased risk of disability, poor functional status, higher health care expenditure, polypharmacy, and complications of care [18, 19, 42, 63, 65–71].

1.8 Functional (or Performance) Status

Functional limitations are defined as limitations in performance at the level of the whole organism or person [58]. Functional status is broader than this, and is the ability or otherwise to carry out everyday tasks. Scrag (2008) articulately describes it as "*captur [ing] much of what seasoned clinicians ascertain in an instant as they watch a patient enter a room, rise from a chair, or clamber onto an exam table*" [72].

The presence of chronic disease is directly related to functional status. Pain and stiffness in arthritis, shortness of breath in chronic respiratory disease, and dysphasia or dyspraxia as a result of a stroke, all lead to a loss of ability to carry out everyday tasks. Functional status is measured by the ability or otherwise to carry out such tasks, and is often related to both the presence and the consequences of chronic disease [73]. Assessment of functional status may be based on self-reporting or proxy reporting of ability to carry out specified tasks; for example the World Health Organisation performance status instrument (WHO-PS) or the physical functioning scale of the SF-36, or physical performance tests such as ability to open and close fasteners, gait speed, ability to climb stairs or rise from a chair [74]. Functional status is a predictor of morbidity, mortality, length of hospital stay and hospital charges independent of other characteristics, including age and comorbidity [9, 75–77]. The measurement of functional status as an outcome is also useful in determining the impact of the consequences of chronic disease.

1.9 Disability

Disability is closely related to the concept of functional status. It is defined as a *"limitation in performance of socially defined roles and tasks within a sociocultural and physical environment*" [58]. Functional impairments can lead to disability, but the extent to which this occurs depends on the physical, social and psychological environments in which people live [60]. Environments can be more or less disabling. For example, an individual with severe arthritis may be considerably less disabled if they have access to mobility aids, and aids to assist with tasks requiring dexterity.

Disability, like functional status, is most commonly assessed using self-reported difficulty in specific tasks, and these are assessed in the clinical setting by screening tools such as Activities of Daily Living (ADLs) and Instrumental Activities of daily Living (IADLs) [57].

1.10 Allostatic Load

While disability takes explicit account of a person's environment, allostatic load is a purely physiological measure of ill-health. It is a measure of cumulative, chronic physiological dysfunction across multiple body systems [59]. Seeman's hypothesis was that organisms must adapt body systems to alter their internal milieu in response to environmental challenges. When these adaptive responses are no longer able to cope with such challenges, progressive dysregulation occurs and can be measured. Allostatic load is related to, but is not the same as comorbidity. Chronic disease may result in a cumulative physiological burden which results in an increase of the allostatic load. Seeman et al. see the measure of allostatic load as an indicator that an individual may be decompensating as a result of various internal and external challenges including comorbid disease:

> No single form of comorbidity occurs with high frequency, but rather a multiplicity of diverse combinations are observed (e.g. osteoarthritis and diabetes, colon cancer, coronary heart disease, depression and hypertension). This diversity underscores the need for an early warning system of biomarkers that can signal early signs of dysregulation across multiple physiological systems [59].

Allostatic load was initially measured using 10 biological parameters, which are physiologically related to a number of homeostatic metabolic processes, such as the hypothalamic-pituatary-adrenal axis, the sympathetic nervous system, and the cardiovascular system. The parameters were systolic and diastolic blood pressure, waist/hip ratio, serum high density lipoprotein and total cholesterol, plasma glycosylated haemoglobin, serum dihydroepiandrosterone, 12 h cortisol excretion and urinary norepinephrine and epinephrine excretion [59]. In later work, serum fibrinogen, C-reactive protein and interleukin 6, all measures of chronic inflammation, were added to the measure of allostatic load [59, 78].

In the development of the measure of allostatic load, each of these parameters was measured in a group of 70–79 year olds. Each parameter was categorised into quartiles, and the number of parameters for each individual that fell into the highest risk quartile was summed to give a total score. Higher scores were cross-sectionally and longitudinally related to all-cause mortality, cardiovascular disease, and a poorer cognitive and physical functioning, and frailty [59, 78, 79].

1.11 Frailty

Frailty has been defined as a "*physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and … dysregulation, of multiple physiologic systems*" [57]. Frailty is considered a physiological syndrome related to, but separate from comorbidity and disability [57, 80]. Frailty is characterised by weakness, decreased endurance and slowed performance. It is related to poor nutrition, concurrent chronic disease, loss of muscle mass, reduced

metabolic rate, decreased activity and energy expenditure [81]. It has been measured in a variety of ways, for example, Fried (2001) categorised those with frailty as having a combination of any three of unintentional weight loss, weakness, poor endurance, slowness or low physical activity [81], whereas Baldaucci used age greater than 85 years, high ADL score, three or more comorbidities and the diagnosis of a geriatric syndrome (any one of delirium, dementia, depression, osteoporosis, incontinence, falls, etc.) [80, 82]. Frailty is strongly related to increasing age and is most common in the very elderly. It has also been found to be more common among cancer patients than similarly aged patients without cancer [83]. Frailty may cause disability independently of coexisting disease and may be caused by comorbidity [57]. Frailty is strongly associated with adverse outcomes including disability, mortality and dependency [57, 80, 81, 84–86].

1.12 Burden of Disease/Illness

Burden of disease (in this context) expands the concept of multimorbidity to include the functional status of individuals. Burden of disease is a combined measure of the number of chronic diseases, their severity and their impact on functional status [9]. It is therefore a measure of chronic disease, and its impact on the individual concerned. There is no gold standard measure for burden of disease. The first attempt to measure this construct was in 1995 by Greenfield et al. [87]. Their aim was to measure a "*composite illness-based measure of risk for substantial declines in health*" (Total Illness Burden Index or TIBI). They did this by identifying the presence of chronic disease divided into categories (such as pulmonary disease, heart disease, stroke and neurological disease, gastrointestinal disease, other cancers, arthritis, eye problems, hearing problems, hypertension, diabetes mellitus and arthritis) among a cohort of patients. For each category or condition, they assessed the likely impact on functional status, both through clinician assessment and through statistical assessment of the association of each, with outcomes such as the physical functioning scale of the SF-36 instrument. TIBI scores have been associated with poorer outcomes in general, and among cancer patients specifically [87, 88].

Mandelblatt (2001) assessed burden of disease by examining the separate roles of comorbidity and functional status, as well as life-expectancy and self-rated health on treatment patterns and outcomes, for a cohort of older women with early stage breast cancer [9]. They posited that biological aging and the effects of chronic disease would result in physiological dysregulation, which is in turn a determinant of functional status and disability (Fig. 1.1). These three components of total illness burden (number of chronic conditions, physiological dysregulation and functional status) would then impact on life expectancy and other health outcomes. They found that whilst these separate constructs were correlated with each other, the strength of the correlation varied considerably, suggesting that each was capturing a different dimension of illness burden. However, they also found that, even in

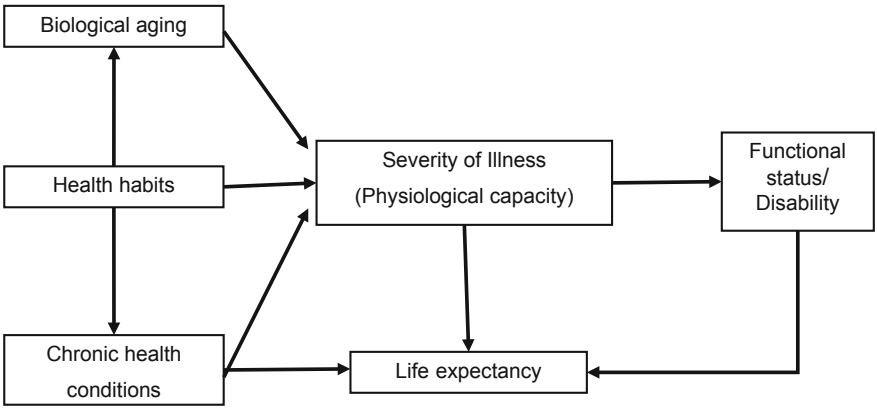

Fig. 1.1 Conceptual model of total illness burden. *Source* Buchner and Wagner (1992); cited in Mandleblatt et al. [9]

combination, these variables did not explain much of the variance in number of treatments received among this cohort of patients. Interestingly, this group of patients were healthier than average breast cancer patients, so the authors concluded that their estimates of the effects of burden of illness on cancer treatment were likely to be somewhat conservative.

Clinically, total illness burden may be measured using instruments such as the Comprehensive Geriatric Assessment (CGA) tool. This tool provides data on patient functional status, comorbidity, polypharmacy, existence of geriatric syndromes, nutritional status, social support and psychological status [89–93]. Studies that have used the CGA tool among older patients with cancer have found that people who score poorly on CGA tend to have poorer survival, higher levels of treatment toxicity, and higher mortality [85, 94–96].

1.13 Complexity

Complexity is the broadest related construct [97, 98], as it includes all determinants of health at an individual level. These include a broad range of factors including, but not limited to socioeconomic, cultural, and environmental factors that are likely to impact on patient care and outcomes.

Safford (2007) developed a graphical model of patient complexity that involved a series of vectors, each relating to individual determinants of health, and each with a force and magnitude resulting either in increasing or decreasing complexity (Fig. 1.2) [97]. The concept of complexity reflects the intricate interactions between a multitude of factors that impact on care and outcomes at an individual level. The presence of chronic disease is one of these, but it is only one part of a highly complex and dynamic system [98, 99].

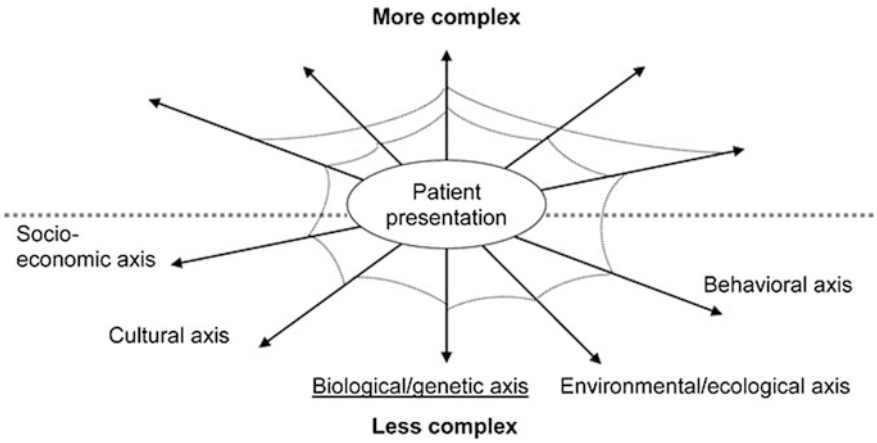

Fig. 1.2 Vector model of complexity. *Source* Safford et al. [97]

1.14 How Are the Comorbidity-Related Constructs Linked?

There is considerable overlap between these inter-related concepts, and the boundaries between them are blurred.

Figure 1.3 is amended and expanded from Valderas et al. [12]. It shows the close relationship between *comorbidity* and *multimorbidity*, the difference being that

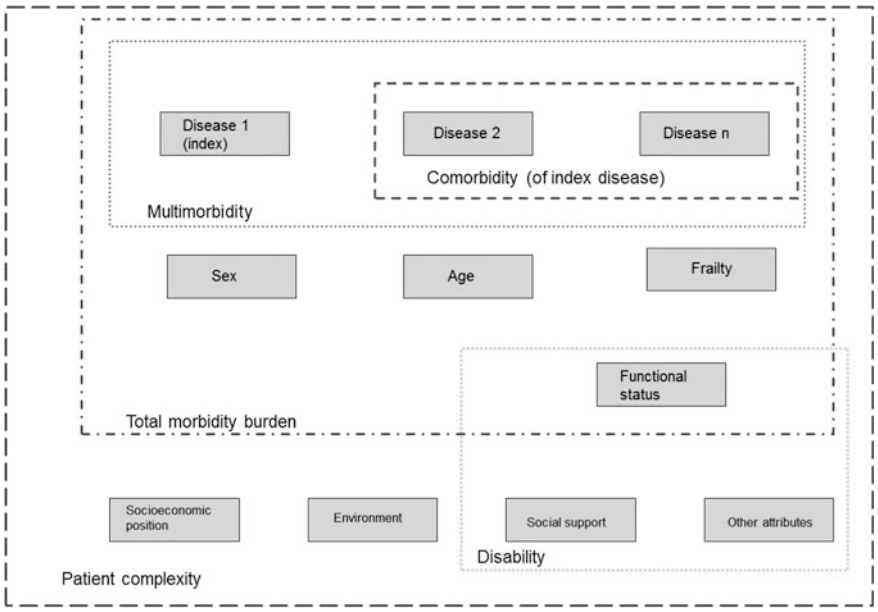

Fig. 1.3 Comorbidity and related constructs. Expanded from Valderas et al. [12]

comorbidity is measured in relation to a primary index disease, whilst multimorbidity is a total measure of all diseases occurring concurrently in an individual. In this figure, *functional status* and *frailty* are represented as separate constructs, but clearly they are both strongly related to each other and to other factors, particularly increasing age and presence of chronic disease. *Total morbidity burden* is a broader concept encompassing elements of comorbidity, frailty and functional status. *Disability* is closely related to the concept of functional status, but includes broader elements such as the degree of social support, and other disabling or enabling features of the environment. Finally at the broadest level, patient complexity encompasses all previous elements, as well as other factors that determine health outcomes in an individual.

1.15 Why Should We Focus on Comorbidity in Cancer?

There are many reasons why it is important for cancer researchers and clinicians alike to pay attention to comorbidity. We have outlined some of these reasons below.

Comorbidity is common. The exact prevalence of comorbidity among cancer patients varies both by cancer site and by the method used to measure comorbidity; but regardless, comorbidity is common among cancer patients [3, 100, 101]. For example, in New Zealand 70 % of those with colon cancer and 72 % of those with lung cancer have at least one comorbid condition [47, 102, 103]. As the population ages, comorbidity will become even more common.

Comorbidity affects outcomes. Comorbidity has a major negative effect on the likelihood of survival from cancer [2, 47, 51, 103–112]. Comorbidity acts on survival both through direct mechanisms, related to the increased physiological burden of disease, and through indirect mechanisms, related to the effects comorbidity has on treatment choice and/or effectiveness.

Cancer patients with comorbidity are substantially less likely to be offered active therapy [47, 108, 109, 113–116]. For example, among New Zealanders with stage III colon cancer, patients with comorbidity were considerably less likely to be offered adjuvant chemotherapy (84 % of patients with a Charlson score of 0, compared with 19 % of those with a Charlson score of 3). When chemotherapy was offered to those with the highest level of comorbidity (Charlson Score 3), there was a 60 % reduction in excess mortality [47, 102]. There is growing evidence that many such treatments are often both tolerated and effective among those with comorbidity [47, 108, 109, 114, 115, 117–121]. Comorbidity also has an important impact on other outcomes, such as functional status, quality of life, length of stay in hospitals, quality and costs of care [5, 8, 10, 12, 26, 46, 99].

Mental illness is also associated with substantially poorer outcomes from cancer. Cancer patients may have impaired functional status, poor nutritional status, be suffering from depression or anxiety, and are sometimes dealing with complex social issues. Despite this complexity, cancer treatment tends to be highly silo'ed

and delivered in specialised units that are focused, unsurprisingly, on the treatment of cancer.

The impact of comorbidity is modifiable. There is evidence that focusing at a clinical level on more complex patients with comorbidity can result in benefits in terms of both improved outcomes and satisfaction with care for patients [13, 57, 97, 122]. Systems can be redesigned to optimise healthcare processes for complex patients, and from a policy perspective, incorporating complexity of patient mix into quality measurements and performance profiling, results in a more comprehensive understanding of health service quality and processes [1, 5, 15, 18, 19, 63].

As we will see in the next section, comorbidity is common among cancer populations. Despite this fact, there is a scarcity of evidence about how to manage these patients. Patients with comorbidity are routinely excluded from randomised controlled trials that are designed to identify the benefits and harms of cancer treatment, and there is lack of consensus on how best to manage these patients. Clinicians are left to weigh up the benefits and potential harms of treatment strategies for themselves, without evidence to inform them.

1.16 How Common Is Comorbidity in Cancer?

Whilst there is general agreement that comorbidity is common among cancer patients, it is remarkably difficult to state with any certainly how common it is. This is because the prevalence of comorbidity varies, sometimes dramatically, depending on the measure of comorbidity used, the data available, the study population, and the cancer site.

In their review of the impact of comorbidity on chemotherapy use and outcomes among patients with solid tumours, Lee et al. reported a wide prevalence range for comorbidity of 0.4–90 % among cancer patients [100]. Data from the New Zealand context suggests that approximately half of all cancer patients have at least one other chronic condition recorded, and a third have two or more [123, 124]. In their Annual Report to the Nation on the Status of Cancer, Edwards et al. reported that approximately 40 % of U.S. cancer patients have at least one comorbid condition [101].

Not surprisingly, studies that use a more inclusive measure of comorbidity demonstrate a higher prevalence of comorbidity than those that use a more restrictive approach. For example, Tammemagi et al. used an extensive and inclusive approach to identify comorbid conditions from computerised medical records in their cohort of patients with breast cancer, and found that 72 % had at least one condition [118]. This compares with Gonzalez et al., who used data extracted only from routine discharge abstracts and found that 13 % of women with breast cancer had at least one Charlson index-related comorbid condition [125]. Even if the approach to measuring comorbidity is limited to a single comorbidity index, the Charlson index, there is still a large range of prevalence estimates. Most studies that use the Charlson index report that 10–75 % of cancer patients have at

least one Charlson index-related condition [47, 125–132]. The variation is largely due to characteristics of the study population and the data collected. For example, studies that are restricted to older patients generally demonstrate higher levels of comorbidity. Comorbidity also tends to be higher among patients with certain cancers, particularly smoking-related cancers such as lung, head and neck and bladder cancers [105]. Studies based on administrative data, often, but not always, report lower levels of comorbidity than those based on medical notes review or self-reporting [40, 110, 133–136].

Is comorbidity more or less common among cancer patients compared to the general population? There is universal agreement that comorbidity is common among cancer patients in general. However, it is less clear whether cancer patients have higher rates of comorbidity than similarly aged non-cancer populations. Some authors have noted generally similar prevalence rates of comorbid conditions among cancer patients compared with non-cancer populations [137, 138]. In contrast, other studies have reported that cancer patients have somewhat higher levels of comorbidity than the general population [101, 139, 140]. Two studies compared the self-reported prevalence of conditions from the US National Health Interview Study among those with a history of cancer to those without [139, 140]. Hewitt et al. found that among those aged over 65 years, 3.9 % of cancer patients reported having three or more chronic medical conditions, compared with 2.3 % of those without a history of cancer [140]. Similarly, Smith et al. found that, with the exception of patients with melanoma, non-Hodgkin's lymphoma and prostate cancer, cancer patients were more likely to report two or more conditions than those without cancer [139]. More recently, Edwards et al. reported that 40 % of lung, breast, colorectal and prostate cancer patients had at least one comorbid condition compared to 31 % of time period-, age- and sex-matched individuals from the general population [101].

By contrast, there are two studies that have reported that cancer patients actually have lower levels of comorbidity than age matched controls. The first study, by Repetto et al., compared cancer patients to patients admitted to hospital medical or geriatric services who would be expected to have higher levels of multimorbidity than people of a similar age in the general population [141], while the second study, by Piccirillo et al., compared comorbidity data extracted from hospital notes for cancer patients with self-reported national data on similar conditions. Both these sets of authors concluded that the differences between the cancer and non-cancer populations were likely to reflect inadequacies in the data comparison [142].

One obvious reason for inconsistencies in the comparison of the comorbidity burden between cancer and non-cancer populations is likely to be that the prevalence of comorbidity varies considerably by cancer site. In their matched case-control study of men with newly diagnosed cancer, Driver et al. found that the overall (modified Charlson) comorbidity scores were similar for men with and without cancer [143]. However, they found that there was variation by cancer type: in particular, men who had been diagnosed with potentially screen-detected cancers (such as prostate cancer and melanoma) had lower comorbidity scores than

age-matched population controls, whilst those with smoking-related cancers had higher scores [143]. Other studies have also found a similar pattern [101, 144, 145].

As well as variation in terms of the general burden of comorbidity, there is also natural variation in the types of comorbidities that patients are affected by, according the cancer type. In some instances, there is a clear association between the kind of comorbidity and the cancer type: for example, in the New Zealand context, more than half of liver cancer patients have cirrhosis of the liver [146]. Unsurprisingly, recent data from the U.S. suggests that more than a third (34 %) of lung cancer patients also have Chronic Obstructive Pulmonary Disorder (COPD) compared to just 10 % of breast cancer patients [101].

Tables 1.1, 1.2, 1.3, and 1.4 show a range of prevalence estimates for the most common conditions for patients with lung, breast, colorectal and prostate cancers, respectively. They show that there is variation in prevalence estimates of specific conditions even within cancer sites. For example, estimates of the prevalence of diabetes among colorectal cancer patients range between 6 and 18 %, of hypertension between 16 and 47 % and of chronic respiratory disease between 5 and 22 %. As with global comorbidity measures, these variations are a function of the study populations, the data collected and the definitions used for specific comorbid conditions. These tables do usefully show that the most common concomitant conditions include hypertension, respiratory disease, heart disease, cerebrovascular disease, previous cancer, arthritis and diabetes. They also show that the prevalence of some comorbid conditions varies between sites, for example respiratory conditions are (unsurprisingly) particularly high among patients with lung cancer, with estimates ranging from 15 to 47 % compared with prostate (1–30 %), colorectal cancer (5–22 %) and breast (all 3–14 % except for one outlier at 52 %).

1.17 Cancer, Comorbidity and Disparity

The prevalence of long term health conditions is not evenly distributed across the population. Disparities in health occur across many axes, including gender, socioeconomic position, geography and sexual orientation. However, health inequities between people of different ethnicity and/or different socioeconomic status are perhaps the largest and most persistent [147, 148].

Comorbidity is generally more common among ethnic minority and Indigenous populations, and among those with higher levels of poverty or deprivation, both within the general population and within cancer populations. The causes of these disparities are related to the uneven distribution of determinants of health, and deficits in health care systems and infrastructures (expanded in Chap. 1.3) [149–151]. For example, the indigenous populations of Australia, New Zealand, the U.S. and Canada, all have a higher prevalence of comorbidity, and are more likely to have multiple, complex comorbidity than non-Indigenous people [147, 152–154].

These patterns are echoed in cancer populations. For example, in the New Zealand colon cancer context only 23 % of Māori had no recorded comorbidity

Table 1.1 Prevalence of specific conditions among patients with prostate cancer from selected studies (%)

Paper	Driver (2010)	Janssen-Heijnen (2005)	Janssen-Heijnen (2005)	Klabunde (2007)	Piccirillo (2008)	Fleming (2006)	Fleming (2006)	Fan (2002)	Putt (2009)	Putt (2009)	Edwards (2014)
Age range (years)	40–84	65–79	80+	66+	All	67+, White men	67+, Black men	All	65+, White men	65+, Black men	65+
Data source	From Dr	Medical notes	Medical notes	Admin data	Medical notes	Admin data	Admin data	Self-report	Admin data	Admin data	Admin data
Hypertension	19	17	12		37	55	88	59	40	58	
Other cancer		9	14		6	9	11	13			
CHF/heart disease		24	27	10	2	13	20	9	4	6	6
COPD/respiratory	21	12	15	16	8	26	30	24	1	13	10
Diabetes		8	9	19	10	16	27	24	14	23	13
Cerebrovascular disease				7	3	11	12		2	4	4
Angina					13			31			
Previous MI				3	7			22			2
PVD				5		13	17		6	7	3
Arthritis	20							59			

Table 1.2 Prevalence of specific conditions among patients with colorectal cancer from selected studies (%)

Paper	Driver (2010)	Janssen-Heijnen (2005)	Janssen-Heijnen (2005)	Gross (2006)	Klabunde (2007)	Klabunde (2007)	Ogle (2000)	Piccirillo (2008)	Sarfati (2009)	Edwards (2014)
Age range (years)	40–84	65–79 males	65–79 females	67+	66+ males	66 + Females	All (colon)	All	>25 (colon)	65+
Data source	From Dr	Medical notes	Medical notes	Admin data	Admin data	Admin data	Self-report	Medical notes	Medical notes	Admin data
Hypertension	16	21	25				47	41	38	
Other cancer		15	14					14	5	
CHF/heart disease	15	28	14	19	4	5		5	11	12
COPD/respiratory	19	15	8	21	5	5	15	12	22	13
Diabetes		10	14	18	6	7	6	16	16	17
Cerebrovascular disease				10	2	2	7	5	7	7
Angina								12	12	
Previous MI					1	<1		8	8	2
PVD				7	2	2			4	4
Arthritis	15						5			

Table 1.3 Prevalence of specific conditions among patients with lung cancer from selected studies (%)

Paper	Driver (2010)	Janssen-Heijnen (2005)	Janssen-Heijnen (2005)	Klabunde (2007)	Klabunde (2007)	Ogle (2000)	Piccirillo (2008)	Tammemagi (2003)	Blanco (2008)	Colinet (2005)	Stevens (2008)	Edwards (2014)
Age range (years)	40–84	65–79 males	65–79 females	66 males	66 females	All	All	All	>70	All	All	65+
Data source	From Dr	Medical notes	Medical notes	Admin data	Admin data	Self-report	Medical notes	Computerised medical records	Medical notes	Medical notes	Medical notes	Admin data
Hypertension	16	15	21			37	38					
Other cancer		16	16				18	1.2	13	12		
CHF/heart disease	21	34	22	7	5		5	8				12
COPD/respiratory	28	24	24	19	15	37	29	29	42	44	47	34
Diabetes		10	12	8	5	5	11		16	9	13	15
Cerebrovascular disease				4	3	9	5		12			7
Angina							14					
Previous MI				2	2		10					3
PVD				4	2			10				7
Arthritis						5						

Table 1.4 Prevalence of specific conditions among patients with female breast cancer from selected studies (%)

Paper	Janssen-Heijnen (2005)	Harlan (2009)	Klabunde (2007)	Patnaik (2011)	Piccirillo (2008)	Fleming (1999)	Mandelblatt (2001)	Satariano (1994)	Wang (2000)	Edwards (2014)
Age range (years)	65–79	All	66+	66+	All	67+	67+	40–84	20+	65+
Data source	Medical notes	Medical notes	Admin data		Medical notes	Admin data	Medical records	Medical records	Admin records	Admin data
Hypertension	29	28			35	69	48	44		
Other cancer	10			16	12	9	10	6		
CHF/heart disease	12	1.2	6	7		25			1	7
COPD/respiratory	6	10	7	9	8	52	14	5	3	10
Diabetes	13	8	11	13	10	32	11	8	4	15
Cerebrovascular disease			4	4	3	16		3	1	5
Angina		1			4	8				
Previous MI		1.4	1	2	3			1	1	1
PVD			2	3		15			<1	3
Arthritis		14					34	21		

compared with 37 % of non-Māori [102]. Māori colon cancer patients also had more than twice the risk of diabetes, heart failure, respiratory disease and renal disease than non-Māori, and were 80 % more likely to have three or more comorbid conditions [102]. In the U.S., Black lung cancer patients were more likely to have at least one comorbid condition that impacts on survival (65 % vs. 59 %) [111], while only 14 % of Black breast cancer patients had no recorded comorbidity compared to 34 % of White patients [118]. In Australia, only 50 % of Indigenous cancer patients had no recorded comorbidity compared to 69 % of non-Indigenous cancer patients, and were three times more likely to have diabetes (30 % vs. 10 %) [155].

Cancer patients of lower socioeconomic status (SES) are also at increased risk of comorbidity. For example, Schrijvers et al. observed that breast cancer patients from a low SES background were nearly three and a half times more likely to have at least one comorbidity compared to breast cancer patients from a high SES background, even after adjusting for age [156]. Louwman et al. observed that cancer patients from a low SES backgrounds were at 50 % higher risk of serious comorbidity compared to those with high SES across a considerable range of cancer types—with a particularly high prevalence of cardiovascular and cerebrovascular disease, COPD, diabetes and gastrointestinal disease [157].

Comorbidity has been shown to be in part responsible for ethnic and socioeconomic disparities in cancer survival. For example, a study by Hill et al. showed that a third of the disparity in colon cancer survival between Māori and non-Māori New Zealanders was due to comorbidity [102]. Similarly, Shepphard et al. found that comorbidity was the most important factor in explaining the three fold poorer survival among First Nations women with breast cancer in Canada, compared with non-Indigenous women [158]. Even for a given level of comorbidity, comorbidity may affect some groups of patients differently to others. For example, in Australia, Indigenous cancer patients with diabetes had an overall survival disadvantage compared to Indigenous cancer patients without diabetes, with an all-cause Hazard Ratio (HR) = 1.4 (95 % CI 1.1–1.8) adjusted for age, sex and cancer site [159]. Fewer non-Indigenous cancer patients had diabetes, and those that had diabetes showed no difference in survival compared to their counterparts without diabetes.

In the US, the evidence relating to the impact of comorbidities on ethnic/racial inequalities in outcomes is somewhat inconsistent. Several authors have found that comorbidity partially or completely explains such disparities [118, 160–165], while others have concluded that comorbidity may not be important in this regard [166–168].

1.18 Why Do Cancer and Comorbidity Coexist?

We have established that cancer and comorbidity commonly occur together—but why is this so? The principal reasons for this co-occurrence vary by (and within) cancer types, but the cause of this association might be attributed to one or more of the following.

1.18.1 Common Conditions Occur Commonly

The primary drivers of comorbidity patterns among cancer patients are the same as those that drive patterns of multimorbidity in the community at large. Thus the underlying pattern of comorbidity in the general population (for example, cardiovascular disease, metabolic disease and mental health disorders) are common to both cancer and non-cancer populations [65, 66, 101].

1.18.2 Cancer and Comorbid Conditions Share Many Common Risk Factors

The strongest single driver of the co-occurrence of cancer and other chronic conditions is increasing age. Smoking, poor diet, lack of physical activity, obesity and alcohol abuse are all risk factors for a range of common non-cancer conditions, including diabetes, hypertension, respiratory, cardiovascular and peripheral vascular disease and liver disease. They are also risk factors for many cancers, including cancers of lung, bladder, head and neck, colorectum, liver and breast [169].

In their Annual Report to the Nation on the Status of Cancer, Edwards et al. [101] compared the prevalence of comorbidity among cancer patients to that of the general (age-matched) population. Compared with the general population, they observed a similar prevalence of comorbidity for older breast and prostate cancer patients (30–32 % of those aged 66 years and over), considerably higher comorbidity prevalence among lung cancer patients (53 %), with colorectal cancer patients intermediate between the two (41 %). These results (and those of others [101, 123, 143–145]) suggest that the wide spectrum of comorbidity prevalence among cancer patients is informative with respect to the question of why cancer and comorbidity coexist: at one end of the spectrum—the lung cancer end—we have patients who are diagnosed with cancers that are strongly associated with risk factors (like particularly smoking), which are in turn also strongly associated with the development of other chronic conditions, such as COPD. At the other end of the spectrum—the breast and prostate cancer end—are patients diagnosed with cancers that are not strongly associated with such risk factors.

1.18.3 Comorbidity May Increase or Decrease Predisposition to Cancer

There are a number of chronic conditions, in particular chronic infections, diseases of the immune system and diabetes, which are causally associated with an increased risk of cancer. For example, Hepatitis B can cause chronic liver disease which is

strongly associated with hepatocellular carcinoma, and tuberculosis patients have an increased risk of lung cancer [170]. Conditions associated with immune suppression (such as HIV/AIDS) or dysregulation of the immune system (such as rheumatoid arthritis) are associated with a number of cancers [171–173]. HIV/AIDS is related to Kaposi's Sarcoma, Hodgkin's disease and anal cancers [171] and rheumatoid arthritis is associated with non-Hodgkin's lymphoma and other haematological malignancies [172, 173]. The exact mechanisms through which these associations occur have yet to be fully clarified, but are likely to be multifactorial [173].

We know that the presence of diabetes is associated with an increased risk of several cancers, including colorectal, pancreatic, liver, endometrial and bladder cancers [173–176]. Whilst in part, these associations may be related to common risk factors between diabetes and cancer (such as obesity), there is also evidence that there are specific biological pathways that directly link diabetes with cancer [173, 175, 176]. Type II diabetes is caused (in part) by insulin resistance, which in turn is associated with hyperinsulinaemia (high circulating levels of insulin) and high levels of other insulin-like growth factors, which promote cellular proliferation and affect programmed cell death (apoptosis), increasing the risk of cancer development. In addition to hyperinsulinaemia and hyperglycaemia, chronic inflammation is also thought to be an important neoplastic factor in the link between diabetes and cancer [177].

Whilst patients with diabetes are at increased risk of a number of cancers, they are also at lower risk of lung, and prostate cancers and Hodgkins disease [176, 177]. It is not known why this is the case, but it is postulated to be due to changes in hormone profiles, growth factors and steroids. Patients with hypothyroidism have also been found to have lower rates of breast cancer [173].

1.18.4 Treatment for Comorbidity May Increase or Decrease the Risk of Cancer

As well as the direct effect of long term conditions on cancer risk, medications used to treat such conditions may impact on risk. For example, long term use of immunosuppressive medications, such as those that might be taken by renal failure patients following transplant, are associated with an increased risk of cancer development [178–181]. In contrast, the use of Non-Steroidal Anti-Inflammatory (NSAID) drugs, such as those used chronically among arthritis sufferers, is associated with a reduced risk of colorectal cancer [182–184]. In addition, there is some evidence that metformin, an hypoglycaemic medication commonly used in the management of diabetes, is associated with a reduced incidence of cancer among diabetic patients [177, 185]. However, it is possible that the latter association is at least partly exaggerated by a methodological problem known as immortal time bias [178–181, 186].

1.18.5 Treatment for Cancer May Cause or Exacerbate Comorbidity

As well as comorbidity affecting cancer outcomes, the inverse can also be true, wherein treating a cancer can impact on comorbidity outcomes. Therapies for cancer can increase the risk of developing a comorbid condition, including cardiovascular, musculoskeletal, metabolic or other complications. For example, hormonal treatment for breast and prostate cancer will affect the metabolism and may, in turn, lead to associated complications of diabetes control, and an increased risk of osteoporosis [187]. Some forms of chemotherapy (anthracyclines), as well as anti-HER2 therapies, have been associated with cardiac failure [188], while androgen deprivation therapy for prostate cancer is associated with a greater risk of cardiovascular problems and worsening of pre-existing cardiac disease [189, 190].

It is likely that the impact of cancer treatment on the development or exacerbation of comorbid disease is greatest amongst those who are at highest risk of developing these conditions in the first place, or those who already have some pre-existing (likely related) comorbid disease. However, we really do not know how much cancer and its treatment impacts on patient comorbidity, for the reasons given earlier. Patients with significant comorbidity are generally excluded from clinical trials, and also because data pertaining to cancer patients tends to focus on cancer-specific outcomes rather than broader health outcomes.

1.18.6 There May Be Common Genetic or Physiological Pathways Between Cancer and Comorbidities

A possible example of this is the inverse relationship between neurodegenerative disorders (such as Alzheimer's and Parkinson's disease) and cancer [191–198]. For example, Roe et al. [196] found that there was both a low risk of cancer among Alzheimer's disease patients (HR = 0.31; 012–0.86) and low risk of Alzheimer's disease among cancer patients (HR = 0.57; 0.36–0.90) after adjustment for demographic, smoking and other factors.

Neurodegenerative diseases are related to neuronal loss and cellular destruction, while cancer is a disease of unchecked cellular proliferation. At the cellular level, there is a fine balance between mechanisms that repair DNA and promote cell growth, and those that stop cellular replication and induce apoptosis. The hypothesis relating to the negative correlation between cancer and neurodegenerative disorders is that if the balance favours cell growth and repair, then an individual may be protected from neurodegenerative disorders but may be at increased risk of cancer; whilst if the balance favours effective inhibition of cell growth and replication the opposite will be true [198]. However it is also possible that these associations are at least in part related to methodological problems in the studies that have investigated them, including immortality bias.

1.19 Future Directions for Practice or Research

We have outlined some suggested areas of future practice and/or novel research below:

- There is a need to monitor, at a national and international level, the prevalence of comorbidity among cancer populations, and disparities within these populations. Ongoing collection of comorbidity data among cancer populations (perhaps as a legislated part of regional and national cancer registers) would have multiple benefits, for example, there is a paucity of information regarding how the prevalence and impact of comorbidity is changing over time. As will be discussed in the next chapter, there are methods of measuring comorbidity using routinely-available datasets that would make such monitoring possible.
- There is also a need for further research on how specific comorbid conditions or their treatments interact to either increase or decrease the risk of cancer. Such research would require large, high quality, population-level datasets in order to be informative, particularly for those comorbid conditions and/or cancers that are not highly prevalent.
- There is a need for a greater understanding of the role of genes in determining the predisposition to certain comorbid conditions, and how this predisposition relates (either directly or indirectly) with the development of cancer. The advent of population-level genome data in combination with population-level routine healthcare data will assist in potentially ground-breaking discoveries in this area.
- Finally, there is a general need for the inclusion of more comorbid patients in clinical trials. Our understanding of whether cancer treatment might cause or exacerbate comorbidity is limited by the fact that there is a tendency for patients with comorbidity to be excluded from clinical trials. The exclusion of such patients ignores clinical reality, where many (if not most, in some cancer contexts) cancer patients live with at least one comorbid condition. Stratification of comorbid patients into treatment arms is one mechanism of overcoming this problem.

References

1. Salisbury C (2012) Multimorbidity: redesigning health care for people who use it. Lancet 380 (9836):7–9
2. Extermann M (2000) Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 35(3):181–200
3. Extermann M (2000) Measuring comorbidity in older cancer patients. Eur J Cancer 36 (4):453–471
4. Satariano WA, Silliman RA (2003) Comorbidity: implications for research and practice in geriatric oncology. Crit Rev Oncol Hematol 48(2):239–248
5. Sarfati DBK, Jackson C (2016) The impact of comorbidity on cancer and its treatment. CA Cancer J Clin (in press)

6. Feinstein A (1970) The pre-therapeutic classification of co-morbidity in chronic disease. J Chron Dis 23:455–469
7. Fortin M, Bravo G, Hudon C et al (2006) Relationship between multimorbidity and health-related quality of life of patients in primary care. Qual Life Res 15(1):83–91
8. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA (2001) Causes and consequences of comorbidity: a review. J Clin Epidemiol 54(7):661–674
9. Mandelblatt JS, Bierman AS, Gold K et al (2001) Constructs of burden of illness in older patients with breast cancer: a comparison of measurement methods. [Erratum appears in Health Serv Res. 2007 Oct; 42(5):2088 Note: Maserejan, N [corrected to Maserejian, N]]. Health Serv Res 36(6 Pt 1):1085–1107
10. Parekh AK, Barton MB (2010) The challenge of multiple comorbidity for the US health care system. JAMA 303(13):1303–1304
11. Valderas JM, Starfield B, Roland M (2007) Multimorbidity's many challenges: a research priority in the UK. BMJ 334(7604):1128
12. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M (2009) Defining comorbidity: implications for understanding health and health services. Ann Fam Med 7(4):357–363
13. Wagner EH, Austin BT, Von Korff M (1996) Organizing care for patients with chronic illness. Milbank Q 74(4):511–544
14. Yancik R, Ershler W, Satariano W, Hazzard W, Cohen HJ, Ferrucci L (2007) Report of the national institute on aging task force on comorbidity. J Gerontol A Biol Sci Med Sci 62 (3):275–280
15. Institute of Medicine (2013) Delivering high-quality cancer care: charting a new course for a system in crisis. The National Academies Press, Washington, DC
16. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L (2006) Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med 4(2):104–108
17. Starfield B (2006) Threads and yarns: weaving the tapestry of comorbidity. Ann Fam Med 4 (2):101–103
18. Mangin D, Heath I, Jamoulle M (2012) Beyond diagnosis: rising to the multimorbidity challenge. BMJ 344:e3526
19. Tinetti ME, Fried TR, Boyd CM (2012) Designing health care for the most common chronic condition–multimorbidity. [Erratum appears in JAMA. 2012 Jul 18;308(3):238]. JAMA 307 (23):2493–2494
20. Vitry AI, Zhang Y (2008) Quality of Australian clinical guidelines and relevance to the care of older people with multiple comorbid conditions. Med J Aust 189(7):360–365
21. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW (2005) Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 294(6):716–724
22. van Weel C, Schellevis FG (2006) Comorbidity and guidelines: conflicting interests. Lancet 367(9510):550–551
23. Kaplan MH, Feinstein AR (1974) The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 27(7–8):387–404
24. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM (2003) How to measure comorbidity. a critical review of available methods. J Clin Epidemiol 56(3):221–229
25. Duckett SJ, Agius PA (2002) Performance of diagnosis-based risk adjustment measures in a population of sick Australians. Aust N Z J Public Health 26(6):500–507
26. Perkins AJ, Kroenke K, Unutzer J et al (2004) Common comorbidity scales were similar in their ability to predict health care costs and mortality. J Clin Epidemiol 57(10):1040–1048
27. Reid RJ, MacWilliam L, Verhulst L, Roos N, Atkinson M (2001) Performance of the ACG case-mix system in two Canadian provinces. Med Care 39(1):86–99
28. Starfield B, Weiner J, Mumford L, Steinwachs D (1991) Ambulatory care groups: a categorization of diagnoses for research and management. Health Serv Res 26(1):53–74

29. Weiner JP, Starfield BH, Steinwachs DM, Mumford LM (1991) Development and application of a population-oriented measure of ambulatory care case-mix. Med Care 29 (5):452–472
30. Chang H-Y, Weiner JP (2010) An in-depth assessment of a diagnosis-based risk adjustment model based on national health insurance claims: the application of the Johns Hopkins adjusted clinical group case-mix system in Taiwan. BMC Med 8:7
31. Fowles JB, Weiner JP, Knutson D, Fowler E, Tucker AM, Ireland M (1996) Taking health status into account when setting capitation rates: a comparison of risk-adjustment methods. JAMA 276(16):1316–1321
32. Greene BR, Barlow J, Newman C (1996) Ambulatory care groups and the profiling of primary care physician resource use: examining the application of case mix adjustments. J Ambul Care Manag 19(1):86–89
33. Orueta JF, Lopez-De-Munain J et al (1999) Application of the ambulatory care groups in the primary care of a European national health care system: does it work? Med Care 37(3): 238–248
34. Tucker AM, Weiner JP, Honigfeld S, Parton RA (1996) Profiling primary care physician resource use: examining the application of case mix adjustment. J Ambul Care Manag 19 (1):60–80
35. Hall SF (2006) A user's guide to selecting a comorbidity index for clinical research. J Clin Epidemiol 59(8):849–855
36. Sarfati D (2012) Review of methods to measure comorbidity in cancer populations: no gold standard exists. J Clin Epidemiol 65:924–933
37. Charlson M, Pompei P, Ales K, Mackenzie C (1987) A new method for classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
38. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45(6):613–619
39. Romano PS, Roos LL, Jollis JG (1993) Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 46(10):1075–1079 Discussion 81-90
40. Romano PS, Roos LL, Jollis JG (1993) Further evidence concerning the use of a clinical comorbidity index with ICD-9-CM administrative data. J Clin Epidemiol 46(10):1085–1090
41. Quan H, Sundararajan V, Halfon P et al (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43(11):1130–1139
42. Byles JE, D'Este C, Parkinson L, O'Connell R, Treloar C (2005) Single index of multimorbidity did not predict multiple outcomes. J Clin Epidemiol 58(10):997–1005
43. Fan VS, Au D, Heagerty P, Deyo RA, McDonell MB, Fihn SD (2002) Validation of case-mix measures derived from self-reports of diagnoses and health. J Clin Epidemiol 55 (4):371–380
44. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW (1996) Can comorbidity be measured by questionnaire rather than medical record review? Med Care 34(1):73–84
45. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano W, Silliman RA (2007) Methodology, design, and analytic techniques to address measurement of comorbid disease. J Gerontol A Biol Sci Med Sci 62(3):281–285
46. Davis P, Lay-Yee R, Fitzjohn J et al (2002) Co-morbidity and health outcomes in three Auckland hospitals. N Z Med J 115(1153):211–215
47. Sarfati D, Hill S, Blakely T et al (2009) The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. BMC Cancer 9:116
48. Verbrugge LM, Lepkowski JM, Konkol LL (1991) Levels of disability among US adults with arthritis. J Gerontol 46(2):S71–S83
49. Fleming ST, Rastogi A, Dmitrienko A, Johnson KD (1999) A comprehensive prognostic index to predict survival based on multiple comorbidities: a focus on breast cancer. Med Care 37(6):601–614

50. Greenfield S, Kaplan SH, Ware JE Jr, Yano EM, Frank HJ (1988) Patients' participation in medical care: effects on blood sugar control and quality of life in diabetes. J Gen Intern Med 3(5):448–457
51. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr (2004) Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 291(20):2441–2447
52. Elixhauser A, Steiner C, Harris DR, Coffey RM (1998) Comorbidity measures for use with administrative data. Med Care 36(1):8–27
53. Holman CD, Preen DB, Baynham NJ, Finn JC, Semmens JB (2005) A multipurpose comorbidity scoring system performed better than the Charlson index. J Clin Epidemiol 58 (10):1006–1014
54. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P (2003) Impact of comorbidity on lung cancer survival. Int J Cancer 103(6):792–802
55. Humphries KH, Rankin JM, Carere RG, Buller CE, Kiely FM, Spinelli JJ (2000) Co-morbidity data in outcomes research: are clinical data derived from administrative databases a reliable alternative to chart review? J Clin Epidemiol 53(4):343–349
56. Karlamangla A, Tinetti M, Guralnik J, Studenski S, Wetle T, Reuben D (2007) Comorbidity in older adults: nosology of impairment, diseases, and conditions. J Gerontol A Biol Sci Med Sci 62(3):296–300
57. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G (2004) Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 59(3):255–263
58. Nagi SZ (1976) An epidemiology of disability among adults in the United States. Milbank Mem Fund Quart Health Soc 54(4):439–467
59. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS (1997) Price of adaptation–allostatic load and its health consequences. MacArthur studies of successful aging. [Erratum appears in Arch Intern Med 1999 Jun 14;159(11):1176]. Arch Intern Med 157(19):2259–2268
60. Verbrugge LM, Jette AM (1994) The disablement process. Soc Sci Med 38(1):1–14
61. van den Akker M, Buntinx F, Knottnerus JA (1996) Comorbidity or multimorbidity: what's in a name. A review of literature. Eur J Gen Pract 2:65–70
62. Fortin M, Soubhi H, Hudon C, Bayliss EA, van den Akker M (2007) Multimorbidity's many challenges. BMJ 334(7602):1016–1017
63. Haggerty JL (2012) Ordering the chaos for patients with multimorbidity. BMJ 345:e5915
64. van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA (1998) Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol 51(5):367–375
65. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380(9836):37–43
66. Britt HC, Harrison CM, Miller GC, Knox SA (2008) Prevalence and patterns of multimorbidity in Australia. Med J Aust 189(2):72–77
67. Noel PH, Parchman ML, Williams JW Jr et al (2007) The challenges of multimorbidity from the patient perspective. J Gen Intern Med 22(Suppl 3):419–424
68. Tooth L, Hockey R, Byles J, Dobson A (2008) Weighted multimorbidity indexes predicted mortality, health service use, and health-related quality of life in older women. J Clin Epidemiol 61(2):151–159
69. van den Akker M, Buntinx F, Roos S, Knottnerus JA (2001) Problems in determining occurrence rates of multimorbidity. J Clin Epidemiol 54(7):675–679
70. Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW (2012) Adapting clinical guidelines to take account of multimorbidity. BMJ 345:e6341
71. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T (2012) Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. BMJ 345:e5205

72. Schrag D (2008) Enhancing cancer registry data to promote rational health system design. J Natl Cancer Inst 100(6):378–379
73. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano WA, Silliman R (2004) Methodology, design an analytic techniques to address measurement of comorbid disease. The National Institute on Aging's Comorbidity Taskforce, White Paper
74. Guralnik JM, Ferrucci L (2003) Assessing the building blocks of function: utilizing measures of functional limitation. Am J Prev Med 25(3 Suppl 2):112–121
75. Pompei P, Charlson ME, Ales K, MacKenzie CR, Norton M (1991) Relating patient characteristics at the time of admission to outcomes of hospitalization. J Clin Epidemiol 44 (10):1063–1069
76. Wedding U, Rohrig B, Klippstein A, Pientka L, Hoffken K (2007) Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. J Cancer Res Clin Oncol 133(12):945–950
77. Parmelee PA, Thuras PD, Katz IR, Lawton MP (1995) Validation of the cumulative illness rating scale in a geriatric residential population. J Am Geriatr Soc 43(2):130–137
78. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA (2009) Allostatic load and frailty in older adults. J Am Geriatr Soc 57(9):1525–1531
79. Seeman TE, McEwen BS, Rowe JW, Singer BH (2001) Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA 98(8):4770–4775
80. Balducci L (2007) Aging, frailty, and chemotherapy. Cancer Control 14(1):7–12
81. Fried LP, Tangen CM, Walston J et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56(3):M146–M156
82. Balducci L, Stanta G (2000) Cancer in the frail patient. A coming epidemic. Hematol Oncol Clin North America 14(1):235–250
83. Mohile SG, Xian Y, Dale W et al (2009) Association of a cancer diagnosis with vulnerability and frailty in older medicare beneficiaries. J Natl Cancer Inst 101(17):1206–1215
84. Balducci L, Extermann M (2000) Management of the frail person with advanced cancer. Crit Rev Oncol Hematol 33(2):143–148
85. Pal SK, Katheria V, Hurria A (2010) Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin 60(2):120–132
86. Koroukian SM, Murray P, Madigan E (2006) Comorbidity, disability, and geriatric syndromes in elderly cancer patients receiving home health care. J Clin Oncol 24(15):2304–2310
87. Greenfield S, Sullivan L, Dukes KA, Silliman R, D'Agostino R, Kaplan SH (1995) Development and testing of a new measure of case mix for use in office practice. Med Care 33(4 Suppl):AS47–AS55
88. Litwin MS, Greenfield S, Elkin EP, Lubeck DP, Broering JM, Kaplan SH (2007) Assessment of prognosis with the total illness burden index for prostate cancer: aiding clinicians in treatment choice. Cancer 109(9):1777–1783
89. Puts MT, Hardt J, Monette J, Girre V, Springall E, Alibhai SM (2012) Use of geriatric assessment for older adults in the oncology setting: a systematic review. J Natl Cancer Inst 104(15):1133–1163
90. Puts MT, Santos B, Hardt J et al (2014) An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol 25(2):307–315
91. Wildiers H, Heeren P, Puts M et al (2014) International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 32(24): 2595–2603
92. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 25(14):1824–1831
93. Ramjaun A, Nassif MO, Krotneva S, Huang AR, Meguerditchian AN (2013) Improved targeting of cancer care for older patients: a systematic review of the utility of comprehensive geriatric assessment. J Geriatr Oncol 4(3):271–281

94. Brunello A, Sandri R, Extermann M (2009) Multidimensional geriatric evaluation for older cancer patients as a clinical and research tool. Cancer Treat Rev 35(6):487–492
95. Extermann M (2003) Studies of comprehensive geriatric assessment in patients with cancer. Cancer Control 10(6):463–468
96. Girones R, Torregrosa D, Diaz-Beveridge R (2010) Comorbidity, disability and geriatric syndromes in elderly breast cancer survivors. Results of a single-center experience. Crit Rev Oncol Hematol 73(3):236–245
97. Safford MM, Allison JJ, Kiefe CI (2007) Patient complexity: more than comorbidity. The vector model of complexity. J Gen Intern Med 22(Suppl 3):382–390
98. Schaink A, Kuluski K, Lyons R et al (2012) A scoping review and thematic classification of patient complexity: offering a unifying framework. J Comorbidity 2:1–9
99. Nardi R, Scanelli G, Corrao S, Iori I, Mathieu G, Amatrian RC (2007) Co-morbidity does not reflect complexity in internal medicine patients. Eur J Intern Med 18(5):359–368
100. Lee L, Cheung WY, Atkinson E, Krzyzanowska MK (2011) Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. J Clin Oncol 29 (1):106–117
101. Edwards BK, Noone AM, Mariotto AB et al (2014) Annual report to the nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 120(9):1290–1314
102. Hill S, Sarfati D, Blakely T et al (2010) Survival disparities in Indigenous and non-indigenous New Zealanders with colon cancer: the role of patient comorbidity, treatment and health service factors. J Epidemiol Comm Health 64:117–123
103. Stevens W, Stevens G, Kolbe J, Cox B (2008) Ethnic differences in the management of lung cancer in New Zealand. J Thorac Oncol 3(3):237–244
104. Baldwin L-M, Dobie SA, Billingsley K et al (2005) Explaining black-white differences in receipt of recommended colon cancer treatment. J Natl Cancer Inst 97(16):1211–1220
105. Coebergh JW, Janssen-Heijnen ML, Razenberg PP (1998) Prevalence of co-morbidity in newly diagnosed patients with cancer: a population-based study. Crit Rev Oncol Hematol 27 (2):97–100
106. Fleming ST, Pearce KA, McDavid K, Pavlov D (2003) The development and validation of a comorbidity index for prostate cancer among black men. J Clin Epidemiol 56(11):1064–1075
107. Gross CP, Guo Z, McAvay GJ, Allore HG, Young M, Tinetti ME (2006) Multimorbidity and survival in older persons with colorectal cancer. J Am Geriatr Soc 54(12):1898–1904
108. Hall WH, Jani AB, Ryu JK, Narayan S, Vijayakumar S (2005) The impact of age and comorbidity on survival outcomes and treatment patterns in prostate cancer. Prostate Cancer Prostatic Dis 8(1):22–30
109. Lemmens VE, Janssen-Heijnen ML, Verheij CD, Houterman S, Repelaer van Driel OJ, Coebergh JW (2005) Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg 92(5):615–623
110. Newschaffer CJ, Bush TL, Penberthy LT (1997) Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. J Clin Epidemiol 50 (6):725–733
111. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P (2004) In lung cancer patients, age, race-ethnicity, gender and smoking predict adverse comorbidity, which in turn predicts treatment and survival. J Clin Epidemiol 57(6):597–609
112. Yates JW (2001) Comorbidity considerations in geriatric oncology research. CA Cancer J Clin 51(6):329–336
113. Baldwin L-M, Klabunde CN, Green P, Barlow W, Wright G (2006) In search of the perfect comorbidity measure for use with administrative claims data: does it exist? Med Care 44 (8):745–753
114. Etzioni DA, El-Khoueiry AB, Beart RW (2008) Rates and predictors of chemotherapy use for stage III colon cancer. Cancer 113:3279–3289
115. Gross CP, McAvay GJ, Guo Z, Tinetti ME (2007) The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer 109(12):2410–2419

116. Stevens W, Stevens G, Kolbe J, Cox B (2007) Lung cancer in New Zealand: patterns of secondary care and implications for survival. J Thorac Oncol 2(6):481–493
117. Cronin DP, Harlan LC, Potosky AL, Clegg LX, Stevens JL, Mooney MM (2006) Patterns of care for adjuvant therapy in a random population-based sample of patients diagnosed with colorectal cancer. Am J Gastroenterol 101(10):2308–2318
118. Tammemagi C, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D (2005) Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294 (14):1765–1772
119. Velanovich V, Gabel M, Walker EM et al (2002) Causes for the undertreatment of elderly breast cancer patients: tailoring treatments to individual patients. J Am Coll Surg 194(1): 8–13
120. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285 (7):885–892
121. Bradley CJ, Dahman B, Anscher M (2014) Prostate cancer treatment and survival: evidence for men with prevalent comorbid conditions. Med Care 52(6):482–489
122. Redelmeier DA, Tan SH, Booth GL (1998) The treatment of unrelated disorders in patients with chronic medical diseases. N Engl J Med 338(21):1516–1520
123. Sarfati D, Gurney J, Lim B et al (2013) Identifying important comorbidity among cancer populations using administrative data: prevalence and impact on survival. Asia Pac J Clin Oncol. doi:10.1111/ajco.12130
124. Sarfati D, Gurney J, Stanley J et al (2014) Cancer-specific administrative data-based comorbidity indices provided valid alternative to Charlson and NHI indices. J Clin Oncol 67 (5):586–595
125. Gonzalez EC, Ferrante JM, Van Durme DJ, Pal N, Roetzheim RG (2001) Comorbid illness and the early detection of cancer. South Med J 94(9):913–920
126. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP (1999) Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993–1996. J Clin Epidemiol 52(12):1131–1136
127. Cronin-Fenton DP, Norgaard M, Jacobsen J et al (2007) Comorbidity and survival of Danish breast cancer patients from 1995 to 2005. Br J Cancer 96(9):1462–1468
128. Iversen LH, Norgaard M, Jacobsen J, Laurberg S, Sorensen HT (2009) The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006–a population-based cohort study. Dis Colon Rectum 52(1):71–78
129. Janssen-Heijnen MLG, Houterman S, Lemmens VEPP, Louwman MWJ, Maas HAAM, Coebergh JWW (2005) Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 55(3):231–240
130. Janssen-Heijnen MLG, Smulders S, Lemmens VEPP, Smeenk FWJM, van Geffen HJAA, Coebergh JWW (2004) Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer. Thorax 59(7):602–607
131. Miller DC, Taub DA, Dunn RL, Montie JE, Wei JT (2003) The impact of co-morbid disease on cancer control and survival following radical cystectomy. J Urol 169(1):105–109
132. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D (2011) The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 103(14):1101–1111
133. Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H (1999) A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. J Clin Epidemiol 52(2):137–142
134. Malenka DJ, McLerran D, Roos N, Fisher ES, Wennberg JE (1994) Using administrative data to describe casemix: a comparison with the medical record. J Clin Epidemiol 47 (9):1027–1032
135. Sarfati D, Hill S, Purdie G, Dennett E, Blakely T (2010) How well does routine hospitalisation data capture information on comorbidity in New Zealand? NZ Med J 123 (1310):50–61

136. van Doorn C, Bogardus ST, Williams CS, Concato J, Towle VR, Inouye SK (2001) Risk adjustment for older hospitalized persons: a comparison of two methods of data collection for the Charlson index. J Clin Epidemiol 54(7):694–701
137. Harlan LC, Klabunde CN, Ambs AH et al (2009) Comorbidities, therapy, and newly diagnosed conditions for women with early stage breast cancer. J Cancer Surviv 3(2):89–98
138. Zeber JE, Copeland LA, Hosek BJ, Karnad AB, Lawrence VA, Sanchez-Reilly SE (2008) Cancer rates, medical comorbidities, and treatment modalities in the oldest patients. Crit Rev Oncol Hematol 67(3):237–242
139. Smith AW, Reeve BB, Bellizzi KM et al (2008) Cancer, comorbidities, and health-related quality of life of older adults. Health Care Finan Rev 29(4):41–56
140. Hewitt M, Rowland JH, Yancik R (2003) Cancer survivors in the United States: age, health, and disability. J Gerontol A Biol Sci Med Sci 58(1):82–91
141. Repetto L, Venturino A, Vercelli M et al (1998) Performance status and comorbidity in elderly cancer patients compared with young patients with neoplasia and elderly patients without neoplastic conditions. Cancer 82(4):760–765
142. Piccirillo JF, Costas I, Claybour P, Borah A, Gorove L, Jeffe D (2003) The measurement of comorbidity by cancer registries. J Reg Mgmt 30(1):8–14
143. Driver JA, Yung R, Gaziano JM, Kurth T (2010) Chronic disease in men with newly diagnosed cancer: a nested case-control study. Am J Epidemiol 172(3):299–308
144. Jorgensen TL, Hallas J, Friis S, Herrstedt J (2012) Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Cancer 106(7):1353–1360
145. Cho H, Mariotto A, Mann B, Klabunde CN, Feuer E (2013) Assessing non-cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. Am J Epidemiol 178(3):339–349
146. Chamberlain J, Sarfati D, Cunningham R, Koea J, Gurney J, Blakely T (2013) Incidence and management of hepatocellular carcinoma among Māori and non-Māori New Zealanders. Aust N Z J Public Health 37:520–526
147. Robson B, Harris R (eds) (2007) Hauora: maori standards of health IV. A study of the years 2000–2005. Te Ropu Rangahau Hauora a Eru Pomare, Wellington
148. Robson B, Purdie G, Cormack D (2010) Unequal impact: maori and non-maori cancer statistics by deprivation and rurality 2002–2006. Ministry of Health, Wellington
149. Knaul F, Frank J, Shulman L (2011) For the global task force on expanded access to cancer care and control in developing countries. Closing the cancer divide: a blueprint to expand access in low and middle income countries. Harvard Global Equity Initiative, Boston, MA
150. Coleman MP (2014) Cancer survival: global surveillance will stimulate health policy and improve equity. Lancet 383(9916):564–573
151. Steinberg ML (2008) Inequity in cancer care: explanations and solutions for disparity. Semin Radiat Oncol 18(3):161–167
152. Valery PC, Coory M, Stirling J, Green AC (2006) Cancer diagnosis, treatment, and survival in Indigenous and non-Indigenous Australians: a matched cohort study. Lancet 367 (9525):1842–1848
153. Centers for Disease Control (2013) CDC health disparities and inequalities report—United States. MMWR 62(Suppl 3):1–187
154. King M (2011) Chronic diseases and mortality in Canadian aboriginal peoples: learning from the knowledge. Prev Chronic Dis 8(1):A07
155. Moore SP, Green AC, Bray F et al (2014) Survival disparities in Australia: an analysis of patterns of care and comorbidities among indigenous and non-indigenous cancer patients. BMC Cancer 14(1):1
156. Schrijvers CTM, Coebergh JWW, Mackenbach JP (1997) Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer 80(8):1482–1488
157. Louwman WJ, Aarts MJ, Houterman S, Van Lenthe FJ, Coebergh JWW, Janssen-Heijnen MLG (2010) A 50 % higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. Br J Cancer 103(11):1742–1748

158. Sheppard AJ, Chiarelli AM, Marrett LD, Nishri ED, Trudeau ME (2011) Stage at diagnosis and comorbidity influence breast cancer survival in first nations women in Ontario Canada. Cancer Epidemiol Biomark Prev 20(10):2160–2167
159. Martin JH, Coory MD, Valery PC, Green AC (2009) Association of diabetes with survival among cohorts of Indigenous and non-Indigenous Australians with cancer. Cancer Causes Control 20(3):355–360
160. Putt M, Long JA, Montagnet C et al (2009) Racial differences in the impact of comorbidities on survival among elderly men with prostate cancer. Med Care Res Rev 66(4):409–435
161. Allard JE, Maxwell GL (2009) Race disparities between black and white women in the incidence, treatment, and prognosis of endometrial cancer. Cancer Control 16(1):53–56
162. Braithwaite D, Tammemagi CM, Moore DH et al (2009) Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. Int J Cancer 124(5):1213–1219
163. Holmes L Jr, Chan W, Jiang Z, Ward D, Essien EJ, Du XL (2009) Impact of androgen deprivation therapy on racial/ethnic disparities in the survival of older men treated for locoregional prostate cancer. Cancer Control 16(2):176–185
164. Yang R, Cheung MC, Byrne MM et al (2010) Do racial or socioeconomic disparities exist in lung cancer treatment? Cancer 116(10):2437–2447
165. Cook LS, Nelson HE, Cockburn M, Olson SH, Muller CY, Wiggins CL (2013) Comorbidities and endometrial cancer survival in Hispanics and non-Hispanic whites. Cancer Causes Control 24(1):61–69
166. Curtis E, Quale C, Haggstrom D, Smith-Bindman R (2008) Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? Cancer 112(1):171–180
167. Coker AL, Eggleston KS, Du XL, Ramondetta L (2009) Ethnic disparities in cervical cancer survival among Medicare eligible women in a multiethnic population. Int J Gynecol Cancer 19(1):13–20
168. Hines RB, Shanmugam C, Waterbor JW et al (2009) Effect of comorbidity and body mass index on the survival of African-American and Caucasian patients with colon cancer. Cancer 115(24):5798–5806
169. Adami HO, Hunter D, Trichopoulos D (eds) (2008) Textbook of cancer epidemiology, 2nd edn. Oxford University Press, New York
170. Wu C-Y, Hu H-Y, Pu C-Y et al (2011) Pulmonary tuberculosis increases the risk of lung cancer: a population-based cohort study. Cancer 117(3):618–624
171. Hensel M, Goetzenich A, Lutz T et al (2011) HIV and cancer in Germany. Dtsch 108 (8):117–122
172. Chen Y-J, Chang Y-T, Wang C-B, Wu C-Y (2011) The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. Arthritis Rheum 63(2):352–358
173. Extermann M (2007) Interaction between comorbidity and cancer. Cancer Control 14(1): 13–22
174. Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 50(7):1365–1374
175. Bartosch-Harlid A, Andersson R (2010) Diabetes mellitus in pancreatic cancer and the need for diagnosis of asymptomatic disease. Pancreatology 10(4):423–428
176. Tabares-Seisdedos R, Dumont N, Baudot A et al (2011) No paradox, no progress: inverse cancer comorbidity in people with other complex diseases. Lancet Oncology 12(6):604–608
177. Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. Diabetes Care 33(7):1674–1685
178. Dantal J, Hourmant M, Cantarovich D et al (1998) Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet 351(9103):623–628
179. Gallagher MP, Kelly PJ, Jardine M et al (2010) Long-term cancer risk of immunosuppressive regimens after kidney transplantation. J Am Soc Nephrol 21(5):852–858

180. Hernández Vallejo G, Jiménez Romero C, De Vicente JC (2005) Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 56(1 SPEC. ISS.):87–99
181. Jensen P, Hansen S, Moller B et al (1999) Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 40(2 I):177–186
182. Din FVN, Theodoratou E, Farrington SM et al (2010) Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 59(12):1670–1679
183. Flossmann E, Rothwell PM, British Doctors Aspirin T, The UKTIAAT (2007) Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 369(9573):1603–1613
184. Huls G, Koornstra JJ, Kleibeuker JH (2003) Non-steroidal anti-inflammatory drugs and molecular carcinogenesis of colorectal carcinomas. Lancet 362(9379):230–232
185. Kasznicki J, Sliwinska A, Drzewoski J (2014) Metformin in cancer prevention and therapy. Ann Trans Med 2(6):57
186. Suissa S, Azoulay L (2012) Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 35(12):2665–2673
187. Haugnes HS, Aass N, Fossa SD et al (2007) Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol 18(2):241–248
188. Smith LA, Cornelius VR, Plummer CJ et al (2010) Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 10:337
189. Carver JR, Shapiro CL, Ng A et al (2007) American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 25(25):3991–4008
190. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD (2011) Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 13(3):R64
191. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G (2007) Prospective case-control study of nonfatal cancer preceding the diagnosis of Parkinson's disease. Cancer Causes Control 18(7):705–711
192. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G (2008) Parkinson disease and risk of mortality: a prospective comorbidity-matched cohort study. Neurology 70(16 Pt 2):1423–1430
193. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T (2007) A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. Cancer Epidemiol Biomarkers Prev 16(6):1260–1265
194. Olsen J, Friis S, Frederiksen K, McLaughlin J, Mellemkjaier L, Moller H (2005) Atypical cancer pattern in patients with Parkinson's disease. Br J Cancer 92:201–205
195. Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC (2005) Alzheimer disease and cancer. Neurology 64(5):895–898
196. Roe CM, Fitzpatrick AL, Xiong C et al (2010) Cancer linked to Alzheimer disease but not vascular dementia. Neurology 74(2):106–112
197. West AB, Dawson VL, Dawson TM (2005) To die or grow: Parkinson's disease and cancer. Trends Neurosci 28(7):348–352
198. Yashin AI, Ukraintseva SV, Akushevich IV, Arbeev KG, Kulminski A, Akushevich L (2009) Trade-off between cancer and aging: what role do other diseases play? Evidence from experimental and human population studies. Mech Ageing Dev 130(1–2):98–104