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2. Identify strategies to address comorbidities in cancer patients

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The Impact of Comorbidity on Cancer and Its Treatment

Diana Sarfati, MBChB, MPH, PhD1; Bogda Koczwara, BMBS, MBioethics2; Christopher Jackson, MBChB3,4

Comorbidity is common among cancer patients and, with an aging population, is becoming more so. Comorbidity potentially affects the development, stage at diagnosis, treatment, and outcomes of people with cancer. Despite the intimate relationship between comorbidity and cancer, there is limited consensus on how to record, interpret, or manage comorbidity in the context of cancer, with the result that patients who have comorbidity are less likely to receive treatment with curative intent. Evidence in this area is lacking because of the frequent exclusion of patients with comorbidity from randomized controlled trials. There is evidence that some patients with comorbidity have potentially curative treatment unnecessarily modified, compromising optimal care. Patients with comorbidity have poorer survival, poorer quality of life, and higher health care costs. Strategies to address these issues include improving the evidence base for patients with comorbidity, further development of clinical tools to assist decision making, improved integration and coordination of care, and skill development for clinicians. CA Cancer J Clin 2016;66:337-350. © 2016 American Cancer Society.

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Introduction

Chronic diseases are generally more common among the elderly than younger adults, and many of these are not life threatening in the short term. Consequently, many people live with, rather than die from, chronic health conditions. Cancer itself is a chronic disease with long-term consequences for health and quality of life and is more prevalent among older people. Comorbidity among cancer patients is therefore common. Data from Medicare beneficiaries in the United States (ie, for patients aged 65 years or older) indicate that four of ten patients with cancer have at least one other chronic condition recorded, and 15% have two or more, with the most common chronic conditions including cardiovascular illness, obesity and metabolic illness, mental health problems, and musculoskeletal conditions.1 The coexistence of cancer and other chronic conditions has substantial implications for treatment decisions and treatment outcomes for both cancer and chronic disease.2-6 Most guidelines of cancer treatment do not consider the complex interrelations between cancer and comorbidity and instead adopt a “single-disease” approach to management. With increasing subspecialization in medicine and surgery, providers are often not skilled in managing the wide spectrum of different diseases that may be present in individual patients with cancer, potentially negatively impacting patient outcomes.6

We have undertaken a Medline search of English language articles and relevant references for the period from 1948 to June 2015, using the search terms “cancer” or “neoplasms” and “comorbidity” or “multimorbidity” or “concomitant disease” to review current knowledge about the prevalence of comorbidity among cancer patients and to examine its impact on cancer diagnosis, treatment, and patient outcomes. This report offers an analysis of the available evidence and recommendations about directions for clinical practice and research in this area.

What Is Comorbidity?

Comorbidity is defined as the “coexistence of disorders in addition to a primary disease of interest.”7 In a setting of cancer, comorbidity is thus a construct relating to the presence, nature, and severity of health-related conditions that exist alongside...
cancer and is distinct from frailty and functional status (Fig. 1). The prevalence of comorbidity varies by patient factors. Like cancer itself, it increases with age, but older age and comorbidity do not necessarily coexist. Functional status, a measure of patients’ ability to perform everyday tasks, is related to both the presence and the consequences of chronic disease. 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.”8 Frailty is strongly related to increased age, although it has been observed in younger adult survivors of childhood cancers.8-10 Despite strong associations between them, comorbidity, functional status, and frailty are separate entities, and each has an independent effect on outcomes.7,8

There is no gold-standard approach to measuring comorbidity in the context of cancer.11 Many approaches have been proposed, including assessment of the impact of single conditions (such as diabetes or congestive heart failure),12-14 simple condition counts15-18 weighted indices,19-23 and organ-based systems.24-26 Any approach to summarizing comorbidity into a single metric, by necessity, results in loss of information.

**Mechanisms of Interaction—Why Cancer and Comorbid Conditions Coexist**

There are many reasons why cancer may co-occur with chronic conditions. First, cancer and comorbid conditions share many common risk factors. Older age is associated with an increasing risk of cancer and of almost all other chronic conditions. Smoking, poor diet, lack of physical activity, obesity, and alcohol abuse are all risk factors for a range of common conditions as well as for many cancers.51 Second, the biological mechanisms associated with comorbidity may predispose to cancer. There are several chronic conditions that are causally associated with an increased risk of cancer, in particular chronic infections, diseases of the immune system, and diabetes mellitus. For example, hepatitis B can cause chronic liver disease, which is strongly associated with hepatocellular carcinoma, and patients with tuberculosis have an increased risk of lung cancer.52,53 Conditions associated with immune suppression (such as human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]) or dysregulation of the immune system (such as rheumatoid arthritis) are associated with several cancers, particularly hematological malignancies, the mechanisms for which are not completely understood.51,54,55 Diabetes is also associated with an increased risk of several cancers, including breast cancer,
colorectal cancer, endometrial cancer, pancreatic cancer, liver cancer, and intrahepatic cholangiocarcinoma. Although these associations may be related in part to common risk factors between diabetes and cancer (such as obesity), there are specific biological pathways that directly link diabetes with cancer. The most important mechanism is likely to be related to high circulating levels of insulin and other insulin-like growth factors, which promote cellular proliferation and affect programmed cell death (apoptosis), increasing the risk of cancer.56

However, there are examples where interaction between comorbidity and cancer is actually protective, with lower risk of cancers in some conditions. While patients with diabetes are at increased risk of several cancers, they may also have a lower risk of prostate cancer and possibly of lung cancer and Hodgkin lymphoma.56,59 It is postulated that this may be because of changes in hormone profiles, growth factors, and steroids.56 In addition, some treatments for diabetes, particularly metformin and thiazolidinediones, appear to have anti-neoplastic activity, which may act to reduce cancer incidence and slow its progression.56,57,60 Similarly, the use of nonsteroidal anti-inflammatory drugs used commonly in arthritis is associated with a reduced risk of colorectal cancer.61,62

Finally, there may be common genetic or physiological pathways between cancer and other chronic conditions. A possible example of this is the inverse relation between neurodegenerative disorders (such as Alzheimer and Parkinson disease) and cancer.63,64 This may be related to the genetically mediated balance between mechanisms that repair DNA and promote cell growth on one hand and those that inhibit cell growth, repair, and replication on the other.63,64

Impact of Comorbidity on Timing of Diagnosis of Cancer

Comorbidity may result in increased contact with health services resulting in more opportunities for screening and early diagnosis; or, conversely, comorbidity may distract either or both the patient and the health professional, resulting in delayed diagnosis.65-67 How these two mechanisms play out varies by cancer and comorbidity type, with studies in different populations reporting that, depending on the context, those with comorbidity may have their cancer diagnosed at an earlier,68-71 later,14,72-75 or at a similar stage as those without comorbidity.16 The impact of comorbidity on the diagnosis of cancer depends on factors that include those related to the type of cancer, the type and severity of comorbidity, and the health care system.

Type and Severity of Comorbidity

Higher frequency of physician visits has often been associated with earlier stage of cancer diagnosis.71,76 and with a higher likelihood of screening.77 Patients with comorbidity are likely to require more frequent physician visits and thus have greater opportunity to undergo screening or to have early symptoms of cancer investigated. However, counteracting this effect is that patients with comorbidity may have symptoms overlooked or may be less likely to be screened for cancer, as the management of the comorbidity may consume the health care provider’s attention. This is likely to be particularly true for those with unstable and/or life-threatening conditions. It may be reasonable to hypothesize that the balance of these two opposing mechanisms might favor the positive impact of frequent health care contact and thus earlier diagnosis for more mild or stable comorbidities, while the distracting effect of comorbidity might predominate for more severe or unstable conditions, a pattern that is seen in some,65,78,79 but not all studies.80 In addition to these general patterns, there may be biological interactions between specific comorbid conditions and cancer that may affect stage at diagnosis. For example, the pathophysiological effects of diabetes mellitus that result in an increased risk of cancer may also be associated with more rapidly growing cancers, which thus may tend to be diagnosed later. Siddiqui et al found that patients with uncontrolled type II diabetes (high hemoglobin 1c [HbA1c] levels before diagnosis) tended to have more advanced colorectal cancer diagnosed at a younger age than those with well controlled diabetes despite having similar sociodemographic characteristics and number of outpatient visits.61

Health Service Factors

The organization and funding of health services may impact on how comorbidity influences stage of diagnosis, particularly in the context of screen-detected cancers. Cancers that are effectively screen-detected are more amenable to early diagnosis than other cancers, an effect that will be most pronounced in the context of widespread screening. For example, in the US contexts, where colorectal cancer screening is widespread and funded (for example, in the Veterans Health Administration system), comorbidity has been associated with earlier stage at diagnosis.69,71 Those with comorbidity are likely to be regularly accessing services and thus may be more likely to undergo screening (or to have early signs and symptoms recognized), particularly where screening coverage rates are related to health service funding or to quality indicators that may encourage the screening of those with high levels of comorbidity.77,82 Many studies (but not all83,84) have shown that screening rates among those with comorbidity in the context of widespread screening are similar to those without comorbidity. In fact, several authors have noted that screening is often carried out inappropriately among those with severe comorbidity and limited life expectancy.82,85-87
Interactions Between Cancer and Comorbidity

There may also be interactions between specific cancers with specific comorbid conditions. For example, Taneja and colleagues found that, among patients on renal dialysis for end-stage renal disease, colorectal cancer tended to be diagnosed earlier, whereas prostate cancer was diagnosed later. They demonstrated that this group of patients tended to undergo higher rates of lower endoscopy than the general population, probably because both anemia and benign gastrointestinal disturbances are common among patients with endstage renal disease. These investigations are likely to increase the incidental finding of early colorectal cancer. In contrast, patients on dialysis do not produce urine; therefore, urinary symptoms that may indicate prostate cancer may not be noticed, resulting in later diagnosis.

Impact of Comorbidity on Treatment Choice and Uptake

Patients with comorbidity are generally less likely to receive curative treatment for their cancer than those without comorbidity. This phenomenon has been reported across different health settings, cancer sites, and treatment types. Taking colorectal cancer as an example, numerous studies have found that the offer and uptake of chemotherapy among colorectal cancer patients is lower among patients with comorbidity independent of age. The relation between comorbidity and surgery is less clear, with some studies reporting no association and others showing an inverse relation between increasing comorbidity and decreasing likelihood of surgery or reduced quality of surgical care for those with comorbidity.

Although most studies find that those with comorbidity receive less treatment than those without, a few have reported findings suggesting overtreatment of those with comorbidity in certain circumstances. For example, Bradley et al found that, among those with high levels of comorbidity and low-risk prostate cancer, treatment did not affect survival, which was primarily driven by comorbidity, indicating the overtreatment of patients in this category.

Vignette-based studies that ask clinicians to consider decisions in hypothetical patients have consistently found that surgeons and oncologists are less likely to recommend treatment for cancer patients with comorbidity. In the context of multidisciplinary meetings, in which many cancer treatment decisions are made, recommendations for curative-intent therapy are less likely to be made for cancer patients with comorbidity, and these decisions are less likely to be concordant with clinical guidelines.

There are several reasons that may explain the impact of comorbidity on treatment uptake. Clinicians may be concerned that concomitant conditions will increase the toxicity and side effects of treatment, that treatments may be less effective in these groups, or that the life expectancy of these patients is insufficient to justify the use of potentially toxic agents. It is also possible that these patients themselves are more likely to decline treatment.

While it seems clear that cancer patients with comorbidity are generally less likely to be offered and to receive curative treatment, it is also clear that there is substantial inconsistency in clinical decisions relating to those with comorbidity. This is not surprising given the lack of high-level evidence relating to cancer therapies that includes those with comorbidity. Randomized controlled trials (RCTs) frequently exclude older patients and/or those with comorbidity, which results in evidence that is not necessarily directly applicable to the majority of cancer patients. To assist clinicians in helping patients with their treatment choices, decision aids have been developed that incorporate the impact of chronic disease on survival or life expectancy.

Impact of Comorbidity on Cancer Treatment Outcomes

Impact on Treatment Toxicity and Effectiveness

The extent to which comorbidity affects how well treatments are tolerated will necessarily relate to the type and severity of comorbidity and the specific treatment. For example, patients with severe chronic airways disease are unlikely to tolerate pneumonectomy for lung cancer but may tolerate treatment that does not affect the lung; and patients with severe renal impairment are unlikely to tolerate nephotoxic chemotherapy but may tolerate other chemotherapy drugs. Several authors have reported that comorbidity does not increase the frequency or severity of treatment complications in some circumstances. For example, LoConte et al identified 242 cancer patients representing 27 cancer types who were enrolled in RCTs for phase 1 chemotherapy within their institution. They did not find that comorbidity was predictive of dose-limiting toxicity in either univariate or multivariate analyses. In correspondence after publication of the first RCT focused on the provision of chemotherapy among elderly or frail cancer patients, Seymour and colleagues reported that there was no evidence of additional cardiotoxicity among patients with preexisting cardiovascular disease (having excluded those with unstable or poorly controlled disease) despite the possible cardiotoxicity of the fluorouracil-based regimens evaluated.

In contrast, other studies have reported higher rates of complications among cancer patients with comorbidity. For example, in their review of the literature relating to the impact of comorbidity on chemotherapy use for solid tumors, Lee et al reported that, among the 10 studies that reported on the tolerability of chemotherapy,
5 reported a higher rate of grade 3 or 4 toxicity among those with comorbidity, but there were no differences in hospitalization rates or overall complications at 1 year.27 Higher rates of complications after cancer surgery (including longer length of stay and in-hospital mortality) have been reported in several settings.1,4,124-127

Studies that assess evidence relating to whether treatment has a positive impact on outcomes for patients with comorbidity given their potentially higher risk of complication typically report that patients with comorbidity who are treated have better survival outcomes than those who are not.74,96,98,104,128-130 The interpretation of these findings is complicated by the finding that most cancer clinical trials exclude patients with substantial comorbidity, which makes the assessment of both toxicity and treatment effectiveness among these patients difficult.114 Comparing the cancer outcomes of cancer patients with and without comorbidity within observational studies is also problematic because of the possibility of confounding by other unmeasured factors that impact both the decision to treat and potential outcomes.

A few studies have attempted to address the problem that healthier patients are more likely to be given treatment and thus have better outcomes, even within a particular stratum of comorbidity using propensity scores.98,104,129,130 Propensity scores predict the likelihood that a given individual would receive treatment based on a range of factors regardless of whether or not they actually received treatment.131 Patients with similar propensity scores can then be compared in relation to their outcomes, depending on whether or not they actually received treatment. Bradley and colleagues investigated whether treatment had an impact on survival among older prostate cancer patients with and without comorbidity, dividing their sample into men with high-risk, intermediate-risk, and low-risk prostate cancer.104 They specifically focused on men with congestive heart failure, diabetes, and chronic airways disease. They calculated propensity scores for the likelihood of receiving treatment for each man based on demographic characteristics, the presence or absence of a large number of specific comorbid conditions, health service use before diagnosis, and measures of functional status. They found that, among men with intermediate-risk or high-risk prostate cancer, those who were treated had a substantially better survival compared with those who were not, regardless of comorbidity status. Similarly, Gross et al used propensity scores to adjust for background likelihood of receiving adjuvant chemotherapy for older patients with stage III colorectal cancer.98 They also found lower likelihood of receipt of chemotherapy among patients with comorbidity, but that those with comorbidity who were treated had a clear and consistent survival advantage over those who were not. These findings suggest that some patients with comorbidity have potentially curative treatment unnecessarily modified.

An important factor that impacts on cancer treatment uptake and completion is interaction with other drugs. Those with comorbidity are likely to be on several prescribed, over-the-counter, or alternative medications, which can interact with each other and with chemotherapeutic agents, potentially leading to increased toxicity, reduction in the effectiveness of a therapeutic regime, or reduction in compliance.132-134 Despite this, a 2009 review identified fewer than 10 articles investigating the frequency of drug-drug interactions in oncology.132 The few studies that have been done suggest that about one-third of cancer patients are exposed to potential interactions,135,136 around one in ten unplanned hospitalizations among cancer patients are because of adverse drug reactions, and polypharmacy is associated with an increased risk of toxicity of chemotherapeutic agents.137,138

In summary, while there is evidence that some cancer patients with comorbidity may be at increased risk of post-therapeutic complications, this is not a consistent finding. The extent to which treatments are tolerated will depend, of course, on several complex interacting factors, including the cancer treatment and the number, type, and severity of the specific comorbidities involved. However, what is clear is that there is substantial inconsistency in treatment decisions based on comorbidity and a lack of consensus on what should be done. It is possible or even likely that the lack of demonstrable differences in treatment tolerability in many studies between patients with and without comorbidity, as well as the demonstrated effectiveness of treatment among those with comorbidity in several studies, suggests that the large differences in treatment recommendation and uptake between these groups may not always be justifiable.

Impact on Survival

Comorbidity has consistently been found to have an adverse impact on cancer survival.2,5,27 The magnitude of the association is variable, depending on how comorbidity is measured, the measure of survival used, the cancer studied, and the population included.

The impact of comorbidity tends to increase with increasing severity of comorbidity, although not necessarily in a linear fashion.2,96,139 The most common way of assessing the role of comorbidity is to categorize comorbidity into two or three categories and compare each with a “no comorbidity” category. The typical pattern is for ratio measures of association between comorbidity and all-cause mortality (risk ratios, odds ratios, or hazard ratios) to be in the range from 1.0 to 2.5 for each category of comorbidity compared with the lowest category in cancer populations. When multiple categories of comorbidity are assessed in this way, very high levels of comorbidity are often associated with considerably higher risk of death compared with
no comorbidity, with ratio estimates sometimes extending to 4.0 to 5.0 or beyond.\(^2\) The impact of comorbidity on cancer-specific survival is less consistent than the impact on all-cause survival and is likely to vary, depending on the prognosis of the cancer, the stage, the impact of treatment, and the severity of the comorbidity.\(^1,5\)

The (relative) impact of comorbidity tends to be greater for cancers with a better prognosis.\(^1,140-143\) This is because those who have cancer associated with a high mortality rate will be more likely to die from their cancer regardless of other concomitant disease compared with patients who have a less severe prognosis. For example, Piccirillo et al found that, when they compared hazard ratios for mortality among patients who had severe comorbidity versus those with none, these varied from a high of 9.2 for prostate cancer to 1.5 for lung cancer.\(^142\) The impact of comorbidity is greater for early stage cancer compared with advanced cancer for similar reasons.\(^1,16\)

There are several reasons why comorbidity impacts survival. The most obvious is the direct, independent impact of concomitant disease on noncancer mortality. This difference in mortality would be observed in any population in which patients with and without comorbidity were compared, all else being equal. This mechanism will affect non-cancer and all-cause survival. Cancer-specific survival is also sometimes found to be reduced among those with comorbidity. One possible explanation for this is that it is caused by artifact, where those with cancer who die of unrelated comorbid conditions are incorrectly categorized as dying from their cancer.\(^144\) This is difficult to entirely discount and is likely to play a role in the excess cancer-specific mortality observed among cancer patients with comorbidity. However, it is unlikely to entirely account for the associations observed. As detailed above, there is consistent evidence that those with comorbidity receive less active treatment than those without, and this impacts their survival probabilities. Those with comorbidity may also suffer higher levels of toxicity from cancer treatments, which may also detrimentally impact their cancer-specific survival.\(^27\) A third mechanism is through a direct impact of comorbidity on cancer progression. For example, Meyerhardt et al investigated the prognosis of patients with and without diabetes within an RCT for adjuvant therapy for colon cancer in which treatment protocols were strictly standardized.\(^13\) They found that patients with diabetes had a 21% increased risk of recurrence even after adjusting for a range of other factors. The authors concluded that this higher risk of recurrence was because of the hyperinsulinemia of diabetes, resulting in more rapid tumor progression. Consistent with this, in their study of 17,712 cancer patients, Piccirillo et al found that the likelihood of developing a recurrence of cancer increased with increasing level of comorbidity (hazard ratio, 1.18 for mild, 1.37 for moderate, and 1.54 for severe relative to none adjusted for extent of disease and treatment).\(^142\) In contrast, Kiderlan found that, among breast cancer patients, those with diabetes had lower relapse rates than those without, which they suggested might be because of the favorable impact of metformin outweighing the unfavorable impact of diabetes itself.\(^145\)

**Impact on Quality of Life**

Noncancer studies find that comorbidity is associated with poorer quality of life.\(^146-149\) There are few studies that specifically investigate the impact of comorbidity on the quality of life of cancer patients. In a cohort of patients with advanced nonsmall cell lung cancer, Gronberg et al found that all patients had poor quality of life and that this did not vary much by comorbidity status.\(^117\) Studies of patients with early-stage prostate cancer have suggested that those with comorbidity have lower quality of life throughout the diagnosis and treatment period but that all patients report a similar magnitude of reduction in quality of life over that period.\(^150,151\) This may be because, for some patients, the relative contribution of cancer and its treatment to their overall perception of quality of life may be so great that it will “overshadow” the impact of comorbidities. Nevertheless, higher burden of disease is associated with greater health care needs, greater likelihood of disability, increased cost of care, higher likelihood of financial burden, and resulting socioeconomic disadvantage. All these can be associated with impaired quality of life.\(^152-154\)

**Impact of Cancer on Comorbidity Outcomes**

In addition to the impact of comorbidities on cancer outcome, it is worth noting that cancer itself or, more specifically, cancer treatment may impact comorbidity outcomes. Cancer therapies can increase the risk of cardiovascular, metabolic, musculoskeletal, and other conditions and can worsen preexisting comorbidities. For example, metabolic changes associated with hormonal treatment for cancer may lead to worsening of diabetic control and greater risk of diabetic complications,\(^155\) anthracyclines and antihuman epidermal growth factor receptor 2 (anti-HER2) therapies are associated with development of cardiac failure,\(^156\) androgen-deprivation therapy for prostate cancer is associated with greater risk of cardiovascular problems and worsening of preexisting cardiac disease,\(^157,158\) and hormonal treatment for breast and prostate cancer is known to lead to greater likelihood and greater severity of osteoporosis.\(^159,160\) These impacts are likely to be greatest among patients at high risk of developing—or with preexisting—comorbid disease. In addition to these direct effects, it is likely that, in the course of cancer treatment, there may be a lack of attention to chronic disease management by both patients and clinicians; for example, there may be less emphasis on routine blood sugar management in diabetes,
which, in turn, may have a detrimental impact on outcomes. Little is known about how much cancer and its treatment impacts comorbidity outcomes, partly because patients with significant comorbidities are usually excluded from clinical trials and partly because most data for cancer patients are focused on cancer-specific outcomes rather than outcomes related to other conditions.

Impact of Comorbidity on Care Delivery
The presence of comorbidity poses substantial challenges for traditional models of care. Because of the complexity of health needs that must be addressed, a greater diversity of expertise is required for optimal management. Delivery of care to patient with multiple problems requires significant care coordination within the cancer setting as well as within the broader health care context, including community care. It is likely that the resulting complexity of care is associated with greater costs of care for patients as individuals and for society and the health system.\textsuperscript{161,162} There are very few studies that have investigated this specifically. Taplin and colleagues studied patients with colon, breast, and prostate cancers and found that comorbidity was associated with higher health system costs for these groups of patients.\textsuperscript{163} While there are well established models of care to manage chronic conditions, these often do not include cancer and thus little is known about how well these apply to patients with cancer.\textsuperscript{164}

Addressing the Problem of Comorbidity in Cancer—Call to Action
The multitude of challenges related to coexistence of comorbidity and cancer require a multilevel approach to address them with solutions spanning both clinical practice and research. Below, we propose a list of key strategies that offer a promise of progress in this field.

Improving the Evidence Base From Which to Make Cancer Treatment Decisions for Those With Comorbidity
RCTs frequently exclude older patients and/or those with comorbidity. This results in evidence that may not be directly applicable to the majority of patients.\textsuperscript{113,114} For those running clinical trials, there is a tension between providing evidence that can be directly generalized to the patient population and optimizing the internal validity of their studies by including patients who are most likely to complete the trials and for whom the benefit:harm ratio may be most positive. In their recent report on high-quality cancer care, the Institute of Medicine recommends that US researchers evaluate interventions and technologies in populations that reflect the age distribution and health-risk profile of patients with cancer. To reflect the likely additional cost and risk to the pharmaceutical companies, they also suggest an amendment to patent law providing extensions for companies that conduct clinical trials of cancer treatments in older patients or patients with comorbidities.\textsuperscript{6} Similarly, research funding bodies could require cancer treatment studies to be carried out within relevant populations.

Improving the Measurement of Comorbidity Among Cancer Patients
To better understand the relation between comorbidity and cancer outcomes, comorbidity must be measured more accurately. Cancer minimum data sets generally do not routinely report on comorbidities and noncancer outcomes. The recent Report to the Nation provided a useful exception to this, delivering a snapshot of the prevalence and impact of comorbidity in the United States.\textsuperscript{1} Such reporting provides a vehicle to assess changing trends in relation to cancer and comorbidity and allows the assessment of the impact of specific combinations of comorbid conditions and cancers. There are two elements to this. The first and most important is the acknowledgment of comorbidity as an important variable to consider as a moderator of cancer outcomes. Second, careful consideration about how best to measure comorbidity is required. No one approach is optimal for all purposes; the choice of measure depends on whether study questions are focused on assessment in the clinical setting or for population-based monitoring. Some guidelines exist to assist in this choice.\textsuperscript{11,165} The impact of comorbidities in cancer care and outcomes needs to be examined both from the perspective of those affected by cancer (such as the impact of comorbidity on survival, disability, and individual costs of care) and from the perspective of the health system (such as overall cost of care and health care utilization).

Improving Integration and Coordination of Care
The management of patients with multiple, diverse health problems can result in fragmented care. The coordination of care has been previously identified as fundamental both to

| Strategies to Address Comorbidity Among Cancer Patients |
|--------------------------------------------------------|
| • Improving the evidence base from which to make cancer treatment decisions for those with comorbidity |
| • Improving the measurement of comorbidity among cancer patients |
| • Improving integration and coordination of care |
| • Preventing the occurrence of new comorbidities and limiting exacerbations of existing conditions |
| • Developing better tools for clinicians |
| • Facilitating skill development for clinicians |
| • Building research collaborations |
effective delivery of cancer care and to effective care for those with multiple chronic conditions.\textsuperscript{166,167} It is essential to ensure that care coordination and integration extend beyond the cancer domain and include other needs of patients. There are many approaches that may be helpful in improving the coordination of care for cancer patients within and outside cancer care services, including increasing collaboration with primary care services, more effectively using health information technology to facilitate coordination, shared medical appointments, promotion of care plans, and increasing the use of community-based cancer care.\textsuperscript{6,167,168} It is likely that the utility of each model will depend on context and setting, and more work is needed on evaluating which models are most useful and cost effective in the cancer care setting.

The use of comprehensive geriatric assessments in geriatric oncology provides an excellent example of integrating care. Comprehensive geriatric assessments provide data on patient functional status, comorbidity, polypharmacy, existence of geriatric syndromes, nutritional status, social support, and psychological status. A large number of studies show that incorporating such an assessment to the care of older people with cancer can be useful to predict complications of care, estimate mortality or survival, and assist in treatment decision making for older people.\textsuperscript{169-176} Only a few studies have incorporated full assessments as part of a cancer care pathway, with explicit multidisciplinary care plans developed to address issues identified and explicit evaluation of the intervention on outcomes.\textsuperscript{177-179} These studies have generally demonstrated positive results. For example, a recent interventional study found that older cancer patients who had already been selected to receive chemotherapy and then underwent comprehensive geriatric assessment experienced lower treatment toxicity, more treatment completions, and fewer treatment modifications compared with controls.\textsuperscript{177} However, such studies have been small and limited to older populations. More work is needed to assess whether such broad-based interventions are beneficial in general (including to nongeriatric patients and comorbidity) and whether they are cost effective.

Novel models of care, which are increasingly used for patients with multiple chronic conditions, may offer opportunities for greater care integration and delivery of more holistic care for cancer patients with complex needs. In particular, self-care management has been found to be helpful among those with chronic conditions.\textsuperscript{167} There has been substantial interest in these approaches during the survivorship phase of cancer care but less focus on whether they might also be helpful during the active treatment phase.\textsuperscript{180}

**Preventing the Occurrence of New Comorbidities and Limiting Exacerbations of Existing Conditions**

New comorbidities can emerge during or after cancer treatment, and cancer treatment can exacerbate underlying conditions. To date, most research has focused on the management of comorbid conditions among cancer survivors\textsuperscript{181,182} whereas there is very little about the impact of careful management of comorbidity and polypharmacy in the active treatment phase. For example, to our knowledge, no study has investigated ideal glycemic control for diabetic patients undergoing chemotherapy. Furthermore, research has shown that polypharmacy and adverse drug reactions are important causes of unplanned hospitalization and higher toxicity rates,\textsuperscript{135-138} yet the studies that have been carried out to date are small and usually single-institution studies or small series. There remains a substantial gap in the evidence base regarding the frequency, severity, and impact of drug-drug interactions and regarding whether intervention to reduce polypharmacy among cancer patients receiving noncancer medications and chemotherapy would be helpful.\textsuperscript{132,138,183-186}

**Developing Better Tools for Clinicians**

There are limited point-of-care resources available to clinicians to assist them in managing multiple health care problems that patients with comorbidity encounter or to provide accurate prognostic information with regard to outcomes of interaction of cancer and coexisting conditions. Some decision aids have been developed either in the context of geriatric oncology or that incorporate the impact of chronic disease on survival or life expectancy, and these may be useful in assessing treatment decisions for people with comorbidity.\textsuperscript{115,116} While the final decision on how these are weighed will necessarily lie with the patient, their family, and the health providers looking after them, clinical guidelines and decision aids that explicitly address coexisting conditions could be helpful.

**Facilitating Skill Development for Clinicians**

Most physician training schemes focus on the development of specialist rather than generalist knowledge and skills. Specialist knowledge is clearly required in highly specialized areas of cancer management. However, new models of care delivery require new skills for health care providers, and work is needed to build skills and capabilities of providers among cancer care professionals as well as outside of cancer. The skills include not just understanding of risk, prevalence, and management of comorbidities in cancer but also skills of achieving care integration, communication across providers, and empowering the patient to be an active participant in their care delivery. Again, these are skills that are recognized as important for those working with complex patients in general.\textsuperscript{187}

**Building Research Collaborations**

Many of the proposed strategies are currently at the very early stage of development and are not yet ready to be
adapted into routine clinical practice. Research is needed in the area of epidemiology of comorbidities in cancer, their mechanisms, and models of care delivery and their implementation. To really accelerate research work in this area, it is essential that we build strong research collaborations in this field that link efforts across countries and regions as well as across the diverse disciplines required to address these issues, including epidemiology, biology, cancer medicine, population health, and health services research.

Summary

With an aging population and increasing numbers of patients diagnosed with cancer, comorbidity management is set to play an increasing role in modern health services. To address this growing challenge, we need to move beyond the present single-disease model of studying cancer and embrace the complexities of studying and managing people with complex medical conditions. The recommendations we have proposed align with the recommendations of the recent report by the Institute of Medicine as well as with recent reports regarding the care of patients with multimorbidity.6,167 The Institute of Medicine report recognizes that the important drivers behind the “crisis” in cancer care relate to population ageing and the complex care needs of cancer patients that go beyond cancer alone. Addressing the challenges of comorbidity in cancer is a central challenge if we are to avert this impending crisis.

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