Survivors at Higher Risk for Adverse Late Outcomes Due to Psychosocial and Behavioral Risk Factors

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Abstract

Cancer survivors face significant morbidity and mortality associated with their disease and treatment regimens, some of which can be improved through modifying behavioral and psychosocial risk factors. This article examines risk factors for adverse late effects that contribute to morbidity and mortality in cancer survivors, provides a literature review on interventions to modify these risks factors, and summarizes the national recommendations and associated current practices for identifying and managing these risk factors. Finally, future directions for research and clinical practice are discussed.

Introduction

The estimated overall costs of cancer in 2010 were $263.8 billion, with $20.9 billion and $140.1 billion from indirect morbidity costs (lost productivity due to illness) and indirect mortality costs (lost productivity due to premature death), respectively (1). Indeed, cancer survivors are at risk for a number of health problems, disease recurrence and progression, and second primaries. Survivors are more likely to rate their health as fair or poor (2) and to report physical limitations and difficulties completing activities of daily living (2,3) than the general population. They also miss more than twice the number of days from work because of health problems and are more likely to have work limitations or be unable to work (2). To a certain degree, these health challenges may be addressable by modifying behavioral and psychosocial risk factors. The goals of this article are to examine behavioral and psychosocial risk factors for adverse late outcomes that contribute to morbidity and mortality in cancer survivors, provide a brief review of the literature on interventions to modify these risks factors, and summarize the national recommendations and associated current practices for identifying and managing these risk factors. Finally, future directions for research and clinical practice are discussed, with consideration of current health care and policy issues.

Behavioral Risk Factors for Adverse Late Effects

Smoking

A substantial percentage of cancer survivors continue to smoke after diagnosis. This is likely due to multiple factors, including lack of knowledge or denial about the connection between tobacco and cancer etiology (4, 5), limited knowledge about the adverse effects of smoking on treatment outcomes and survival, high nicotine dependence, and psychosocial factors such as negative affect and perceived stigma. Recent national data show that more than 15% of adult cancer survivors were smokers in 2008 (6). Smoking prevalence was about the same for cancer survivors and the U.S. general population among middle aged (45–64 years old, 23.6% vs. 22.3%) and older adults (65+, 8.6% vs. 9.4%), but in young adult cancer survivors (18–44 years), smoking prevalence was 70% higher than in the remaining population (40.4% vs. 24.6%). Prevalence of current smoking among lung cancer survivors is 20.9%, but it is approximately 85% higher (38.8%) among survivors of other smoking-related cancers. Of note, patients' self-reports of smoking status are often inaccurate. Kudrnova and colleagues (ref. 7; submitted for publication) identified a subset of head and neck cancer patients who consistently misrepresented weekly tobacco use (29.4%). In a general hospital sample, 25% underreported their smoking (8), showing this common problem and calling for biochemical verification of smoking status. Underreporting is likely due to fears of perceived blame or stigma about continued smoking (9–11).

There is a solid literature documenting the harmful effects of continued smoking following a cancer diagnosis and during treatment (summarized in Gritz and colleagues; ref. 12) These effects can be immediate (reduced treatment efficacy, increased side effects, and complications), as well as delayed and prognostic [increased rates
of recurrence and second primary tumors, poorer overall survival, and decreased quality of life (QOL). Reports are now emerging from in vitro studies that nicotine interferes with signaling pathways (13), affects DNA synthesis, and decreases drug-induced apoptosis (14, 15).

Exercise
Cancer diagnosis and treatment often result in decreased physical activity (16–18). Survivors may find that treatment leaves them feeling unwell or without the energy to exercise or that a demanding schedule of medical appointments leaves little time for their usual exercise routine. Even survivors who were not exercising before diagnosis may experience declines in their overall levels of household or occupational activities. In some studies, survivors who are farther from diagnosis have reported increases in physical activity in response to a cancer diagnosis (19–21). National surveys in the United States have shown that the percentage of cancer survivors who meet recommendations for aerobic exercise varies depending on cancer site, ranging from 21% to 43%; among those with no history of cancer, 36.6% were meeting recommendations. After controlling for potential confounding variables, cancer survivors were actually more likely to be physically active than those without cancer; however, most survivors were not sufficiently active according to public health guidelines (22).

Survivors who are physically inactive after diagnosis are at risk for a number of problems, such as cancer-related fatigue, weight gain, poor QOL, and declines in physical functioning (23–28). Physically inactive cancer survivors also increase their risk of developing second cancers, other chronic diseases such as diabetes and cardiovascular disease, and disability from conditions such as arthritis (29). For some cancers (e.g., early-stage breast cancers), survivors are more likely to die of diseases such as heart disease or stroke than cancer (30). For certain cancers, physical inactivity may also increase the risk of recurrence and cancer-related death. Leisure-time physical activity levels after diagnosis are related to cancer recurrence, cancer-related mortality, and overall mortality for survivors of breast (31, 32) and colorectal cancer (33, 34). Among breast cancer survivors in the Nurse’s Health Study, those with at least 9 metabolic equivalent task (MET) hours per week of leisure-time physical activity (i.e., approximately 3 hours of brisk walking), had a 26% to 43% reduction in risk of recurrence, and a 40% to 50% reduction in risk of death from breast cancer (31). Colorectal cancer survivors in the same cohort needed approximately 18 MET hours per week of activity before seeing a benefit (33).

Diet and body weight
A recent survey of 9,105 survivors of breast, prostate, colorectal, bladder, and uterine cancer and melanoma found that only 15% to 19% of survivors were eating 5 fruits and vegetable servings per day (35), lower than the prevalence in the general population, where the estimate is 25% (36). Survivors’ eating behavior also may increase their risk of lasting adverse effects of cancer. Dietary patterns and body composition are both related to cancer risk, and recent studies have explored their effects on recurrence as well. In breast cancer patients, the Women’s Intervention Nutrition Study (WINS) and Women’s Healthy Eating and Living (WHEL) trials tested low-fat and high fruit and vegetable diets to determine the effect on disease recurrence. The WINS study found that a low-fat diet improved relapse-free survival by 24%, but the benefit seemed to be limited to women whose tumors were negative for estrogen and progesterone receptors (37). Furthermore, the survivors randomized to the low-fat diet also lost weight, which made it difficult to determine whether diet composition or weight loss influenced recurrence. The WHEL study intervention recommended consumption of a diet high in fruits, vegetables, and fiber and low in fat. The intervention produced high diet adherence but no effect on breast cancer event-free survival (38); secondary analyses to explore fruit and vegetable consumption in combination with exercise found that when both were high, risk of recurrence declined (39).

Diet can also have an impact on survivors’ QOL, primarily through its association with weight. Weight gain among breast cancer survivors is well documented (17, 40, 41), but evidence is emerging that weight gain is an issue for other cancer survivors as well, for example, testicular (42), prostate cancer treated with hormonal therapy (43), childhood brain tumors (44), or acute lymphoblastic leukemia treated with cranial radiation (45). In addition, for some cancers, obesity is a risk factor for developing the disease; therefore, survivors of these cancers are at an increased risk of obesity after diagnosis (26, 46). Studies have shown that obesity in cancer survivors is related to greater fatigue and poorer physical functioning and QOL (24, 26, 46–48).

Psychological Risk Factors for Adverse Late Effects
Psychological distress is common in cancer survivors, with prevalence rates for clinical levels of distress varying by disease site ranging from 43.4% in lung cancer to 29.6% for gynecologic cancers (49). Rates are likely higher if minor and subsyndromal distress levels are considered. Importantly, these rates are higher than the general population where epidemiologic data indicate that about 26.2% have a 12-month prevalence of a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) diagnosis (50), which includes substance use disorders not assessed when considering the prevalence rates for distress in cancer. Although some distress is normal, individuals presenting with even mild to moderate levels of distress may exhibit significant impairments in their functioning (51, 52) and require psychological treatment just as those with diagnosable disorders do (52). Early intervention may prevent “normal” adjustment reactions from progressing to diagnosable disorders.
Failure to manage psychological distress may compromise cancer treatment. For example, one study found that after controlling for neutropenia, smoking and elevated anxiety were significant predictors of chemotherapy dose delays and reductions in patients with advanced non–small cell lung cancer (53). Other studies have found that untreated depression increases noncompliance with difficult and complex chemotherapy and radiation treatment regimens (54, 55). Psychological distress has also been associated with noncompliance with some National Comprehensive Cancer Network (NCCN)-recommended cancer surveillance screening behaviors in long-term cancer survivors (56) and with engaging in health-enhancing behaviors such as exercise (57) and smoking cessation (58).

The psychoneuroimmunological literature consistently documents reduced immune function and dysregulated hypothalamic-pituitary axis and noradrenergic stress response activity in depressed individuals (59), including those facing cancer (60). For example, in a sample of ovarian cancer patients, depressed and anxious mood were associated with greater immune impairments both in peripheral blood and in the tumor microenvironment (61). Studies indicate that patients with even mild to moderate levels of depression have reduced natural killer cell activity (62). Fortunately, cancer survivors receiving psychosocial interventions have shown improved immune function (63–65) and lower recurrence rates (66, 67). The impact of such interventions on survival remains inconclusive (68).

Several meta-analyses have examined the association between depression and mortality in cancer survivors. For example, Satin and colleagues concluded that depressive symptoms were consistently associated with a significant but small increase in mortality, independent of other known risk factors. Patients endorsing depressive symptoms and those diagnosed with major depression had 26% and 39% greater mortality, respectively (69), which further underscores that all distress levels be managed. Similarly, a recent and more comprehensive meta-analysis concluded that the effect of depression on mortality is independent of disease stage and site (70). Depression may enhance mortality risk because of its effect on neuroendocrine and immunologic functions and its potential effects on adherence to screening, cancer treatment, and health recommendations (71).

Interventions for Modifying Risk Factors

**Smoking**

The diagnosis and treatment of cancer offer a “teachable moment” for smoking cessation interventions (9, 72, 73). Success rates are higher when treatments are offered closer to diagnosis, likely because of the medical impact on the disease and treatment. Patients with smoking-related cancers have the highest quit rates, but relapse can be substantial even after a year of abstinence (74, 75). The few randomized controlled trials with cancer patients have encountered challenging methodological issues, including low eligibility, low smoking rates, distance barriers, multiple languages, comorbidities (depression and alcohol use), and medical contraindications to pharmacotherapy (76). Of the intervention studies identified to date, most did not show significant between-group differences, or sustained differences at long-term follow-ups. The highest quit rates (70.2% continuous abstinence at 1 year, across conditions) involved a sample of head and neck cancer patients given a physician-delivered intervention of personalized advice and tailored materials and monthly booster sessions compared with advice alone (72). Other studies highlight the complexity and importance of targeting multiple risk behaviors and specialized populations (77–79). In-depth study reviews of smoking cessation trials with cancer survivors are available (12, 80).

**Exercise**

Exercise interventions have been shown to improve cancer survivors’ physical fitness, functional QOL, fatigue, anxiety, and self-esteem (81). Many of these studies have used structured, supervised exercise interventions, but there is an emerging evidence that exercise interventions delivered via distance-based methods that do not require in-person contact can also increase physical activity and improve QOL (82–84). Although supervised exercise approaches may be appropriate for certain populations and forms of exercise (see Schmitz and colleagues; refs. 85, 86 for trials on weight training for women with or at risk for lymphedema), interventions that can be delivered to survivors in their own homes have greater potential for dissemination at lower cost. Successful interventions to increase cancer survivors’ exercise behavior include telephone counseling (82), provision of pedometers and print material (87), and tailored print material, with and without telephone counseling (83, 84).

**Diet and body weight**

Because of relationships between obesity and symptoms, interventions to improve QOL in cancer survivors should address eating patterns, particularly those that can lead to weight gain. Dietary interventions in the WINS (37) and WHEL (38) trials were quite intensive. The WINS study provided in-person counseling by registered dieticians in 8 biweekly sessions followed by contact (either in-person or by phone) every 3 months. In addition, the study provided optional monthly dietary group sessions. The WHEL intervention consisted of telephone counseling, monthly cooking classes (in the first year of participation), and newsletters; on average, participants received 31 calls, 48 newsletters, and attended 4 cooking classes. Although these trials showed that significant dietary behavior change could be achieved with these intensive methods, subsequent research has investigated methods that can be implemented at a lower cost and over wide geographic areas. The FRESH START study evaluated the use of tailored print materials for promoting dietary behavior change (increased fruit and vegetable consumption and...
decreased fat intake) and increased physical activity. Participants in the tailored materials group received a workbook and 7 newsletters at 6-week intervals. Feedback provided in the newsletters was tailored on the basis of information from brief surveys completed by participants. The tailored intervention participants had greater increases in diet quality and fruit and vegetable consumption and greater decreases in fat intake at the end of the 1-year intervention than those receiving standard print materials, and improvements were sustained at 2 years (88). Overall, studies show that behavioral interventions can improve diet quality in cancer survivors; however, additional studies, similar to FRESH START, are needed to test easily disseminated interventions. Furthermore, the literature base is fairly limited to breast cancer survivors; thus, studies in other cancer sites are warranted.

Interventions to support weight loss have been tested primarily in breast cancer survivors, who are at an increased risk of gaining weight, particularly if they receive chemotherapy (89). The most successful interventions address dietary changes, increases in physical activity, and behavioral modification. Several intervention studies have tested cognitive behavioral interventions that involve group and/or individual counseling to modify diet and increase physical activity (90–92) and found this approach successful in reducing weight in the intervention group. In addition, the WINS study intervention, which used a combination of individual in-person and telephone counseling, resulted in weight loss in the intervention group that was 6 pounds more than the control group. However, although interventions requiring face-to-face contact are effective in encouraging weight loss, they can be costly and require participants to travel to where the intervention is provided and thus have a difficult time reaching survivors who live outside the major metropolitan areas or have transportation difficulties. Distance-based approaches involving tailored print material and telephone counseling may be effective and more accessible to a broader range of survivors. For example, Morey and colleagues tested the RENEW intervention in 641 elderly long-term survivors of breast, colorectal, and prostate cancer who were overweight or obese. The participants in the tailored intervention arm lost an average of 2.06 kg, compared with 0.92 kg in the wait-list control. They also had greater increases in fruit and vegetable consumption, greater decreases in fat consumption, and increases in strength exercise (84). Distance-based approaches show promise, but additional research is needed to determine whether they are effective for other populations of cancer survivors and to optimize methods to maximize their reach and effectiveness.

**Psychological distress**

Several reviews indicate that survivors accrue multiple benefits from psychosocial interventions (93–97), with a meta-analysis indicating positive effects on emotional adjustment, functional adjustment, and treatment- and disease-related symptoms. Interventions are typically delivered face-to-face, either individually or to a group, although increasingly, distance-based approaches are being used (98–103).

The types of interventions vary, should be chosen on the basis of the desired clinical outcomes, and include cognitive-behavioral programs (66, 104–108), educational/informational programs (109, 110), peer support and discussion programs (109, 110), supportive-expressive group therapy (111–116), and expressive disclosure programs (117). A meta-analysis suggests that no specific therapeutic approach is more effective than another (97). Although Helgeson and colleagues found that education groups are more effective than peer discussion groups (118), they also show that peer discussion groups are effective for those lacking emotional support (119). Other research indicates that patients who have more psychological symptoms (113, 120, 121), low optimism, and limited social support (119, 121, 122) benefit more from psychosocial interventions. Limiting psychosocial clinical trials to those most in need will “...likely yield findings of greater relevance to clinical practice” (123).

**National Guidelines and Current Practices for Identifying and Managing Risk Factors**

**Smoking**

The evidence base for smoking cessation treatments is summarized and updated periodically in the USPHS Clinical Practice Guideline, Treating Tobacco Use and Dependence (124). Although there is no separate section for cancer, it is commented upon as a medical comorbid condition in the context of the teachable moment. It is suggested that chronic disease management programs be utilized to integrate tobacco dependence interventions into medical treatment.

Smoking cessation with cancer survivors requires tailoring interventions on a number of dimensions. Survivors need education about the link between cancer and smoking (and continued smoking), which may not be apparent. Critically important is the dissemination of current knowledge on the adverse effects of continuing to smoke after a cancer diagnosis, irrespective of whether the tumor is smoking related (12). For example, smoking compromises wound healing after reconstructive plastic surgery, a major issue for breast cancer patients (125). Furthermore, cancer and its treatment impose physical limitations, and certain types of pharmacotherapy for smoking cessation are contraindicated. Finally, psychological issues such as negative affect (anxiety and depression), stress, guilt, and comorbid alcohol/substance use may be important factors that require attention and management.

The National Cancer Institute (NCI) convened a conference in 2009 on treating tobacco dependence at NCI cancer centers. The conference established the need for cancer centers to develop systems to identify smokers and refer them for treatment, use standardized treatment...
guidelines (124), and address barriers to implementation. American Society of Clinical Oncology (126), American Association for Cancer Research (5), and Oncology Nursing Society (127) support tobacco dependence treatment for oncology patients and the Joint Commission is working toward including tobacco assessment, treatment, and follow-up as a quality indicator (128). At MD Anderson, a model tobacco treatment program that incorporates key assessment, treatment, and follow-up elements is available at no cost to patients, spouses/partners, and employees (129, 130). Established in 2006 and seeing almost 600 patients per year, this clinical service offers 12 to 16 weeks of behavioral counseling and pharmacotherapy. At the 1-year follow-up, 30% to 50% of patients were abstinent (7-day point prevalence), which compares favorably with highly motivated populations of healthy smokers treated with pharmacotherapy (130). This program sets a standard for health care settings in terms of serving a cancer patient population during and following treatment.

Exercise
Because of the emerging evidence on the benefits of exercise for cancer survivors, the American College of Sports Medicine (ACSM) convened an expert roundtable to review the literature and make exercise recommendations for survivors (131). The panel concluded that exercise is safe for cancer survivors both during treatment and in the posttreatment period. Furthermore, because of the documented benefits of exercise, cancer survivors should avoid inactivity, return to exercising as soon as possible after surgery (after healing is complete), and exercise during chemotherapy and radiation treatment if possible. With a few exceptions (e.g., adaptations for patients with metastatic disease, increased fracture risk from hormonal treatment, or at risk for lymphedema), the panel concluded that the age-appropriate exercise recommendations for the general population (aerobic exercise 30–60 minutes per day on 5 or more days per week, strength exercises 2 days per week, and balance exercise for older adults; ref. 132) are also appropriate for cancer survivors. However, the panel cautioned that research on safety and benefits of strength building and flexibility activities in cancer patients and survivors is currently somewhat limited. Efforts are underway to make exercise programming more accessible to cancer survivors, such as the Livestrong at the Y program and the ACSM’s cancer exercise specialist certification. However, there has not been systematic information gathered to describe current cancer center and community practices to help cancer survivors adopt exercise programs.

Diet and body weight
The American Cancer Society published its most recent dietary guidelines for cancer survivors in 2006 (133). These recommendations, in addition to reinforcing the importance of physical activity, advise maintaining a healthy weight throughout life, eating 5 or more servings of a variety of vegetables and fruits each day, choosing whole grains, limiting consumption of processed and red meats, and limiting alcoholic beverages to no more than 1 drink per day for women and 2 drinks per day for men. The World Cancer Research Fund/American Institute of Cancer Research developed dietary guidelines for cancer prevention; they determined that there was not sufficient evidence related to cancer survivors specifically and recommended that cancer survivors follow the cancer prevention guidelines (134). These guidelines are similar to those of the American Cancer Society but are more specific with regard to certain recommendations. For example, they recommend consuming less than 500 g of red meat per week and less than 6 g of processed foods with added salt per day, and limiting refined starchy foods. They also recommend staying as lean as possible within the body mass index (BMI) range of a healthy body weight range (BMI $\geq 18.5$ and $<25$ kg/m²). Many cancer centers have dietitian services available, but it is not known whether these services are widely available in all types of oncology settings. Furthermore, often these services are oriented toward helping patients with feeding problems specific to cancer or treatment toxicities; it is uncertain whether these dietitians are available for providing evidenced-based interventions for adopting a healthier diet as well.

Psychological distress
Multiple and sometimes differing sources of distress emerge throughout the cancer trajectory of diagnosis, treatment, survivorship, and end of life; thus, distress requires ongoing assessment and monitoring (135). The Institute of Medicine (IOM; ref. 136) has established a standard of care that includes evaluating the psychosocial status of all cancer patients and making it standard to care for the “whole” patient. The National Comprehensive Cancer Network (NCCN) has established Standards of Care for Distress Management, which includes recognizing, monitoring, documenting, and promptly treating distress (135). The standards also establish an expectation that treatment of distress become institutionalized within the mainstream of cancer care. Leading researchers in psycho-oncology are proposing the routine practice of making distress the sixth vital sign (137), which is already gaining acceptance in oncology care in Canada (138, 139).

Although some practice groups in the United States have instituted routine screening in their patients (140), most NCCN member institutions are not following the NCCN guidelines for distress management, with only 20% screening all patients as the guidelines recommend (141). A survey of oncologists from the American Society of Clinical Oncology found that 24.9% of patients reported being “somewhat familiar” with NCCN guidelines (142). It is important to note, however, that screening alone is insufficient for improving patient QOL (143) or psychosocial well-being (144). Adequate follow-up must include
tracking patterns of referral and treatment of patients and direct intervention (145–147).

In 2003, the National Breast Cancer Centre and the National Cancer Control Initiative in Australia systematically reviewed existing randomized controlled trials and established recommendations for various psychosocial interventions in Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer (148). Cognitive-behavioral and psychoeducational interventions are recommended for treating anxiety and depression in cancer patients. For actual implementation, research needs to focus more on how to increase patient access to these evidence-based psychosocial interventions (123).

Future Opportunities

Significant future opportunities exist to reduce late adverse outcomes in cancer survivors by modifying behavioral and psychosocial risk factors. Depending on the risk factor, survivors may have higher risks than the general population, which adds to the importance of targeting this population, who by virtue of their disease are already at an increased risk for morbidity and mortality. Such risk factors may even be higher in special populations of survivors who are more vulnerable to behavioral and psychosocial risk factors including individuals of low socioeconomic status, certain ethnic/racial groups, immigrants, and lesbian, bisexual, gay, and transgendered (LBGT) individuals. Unfortunately, these populations have received limited research attention.

Of particular importance is considering the development of evidence-based programs that can be easily integrated into standard clinical practice. Although research supports the efficacy of a number of behavioral and psychosocial interventions, questions arise about the generalizability of the findings, as most studies include primarily white, educated participants receiving treatment in large cancer centers (109, 110, 112, 115, 149). Such demographics likely reflect who has access and ability to attend such interventions, excluding those residing in rural areas or areas distant from their care center, with limited resources and/or transportation problems, language and literacy barriers, and physical limitations that make travel difficult. Thus, employing interventions that can be widely disseminated is critical to advancing science and providing equal access for disparate populations. Technology, such as the telephone, Internet, smart phones, and videoconferencing, allows for remote counseling/interventions and thus more widespread dissemination of psychosocial and behavioral programs (150). Although research on the development of cost-effective and easily disseminated programs for improving the QOL of cancer survivors progresses, change in the health care system is needed to integrate these programs into cancer treatment plans. Reimbursement is key to stimulating health care system change. Fortunately, some changes are on the horizon. For example, the Obama administration will expand Medicaid coverage of smoking cessation services, including coverage for quitlines (151). It is a matter of policy for cancer leadership organizations, including survivor groups, to recognize the key role behavioral and psychosocial factors play in health, morbidity, and mortality among cancer survivors. The oncology community needs to further educate its professional practitioners and their allied health care team members to regard behavioral and psychological factors as key elements in all care and to provide referral to appropriate services for all cancer survivors.

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References


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