

Commentary

Evidence-Based Nutrition Guidelines for Cancer Survivors: Current Guidelines, Knowledge Gaps, and Future Research Directions

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Cancer is one of the most prevalent chronic diseases in the United States and is the second leading cause of death (1). Approximately 1.48 million Americans were diagnosed with cancer in 2009, with prostate, lung, breast, and colorectal cancers being most common (2). Although only 3 million cancer survivors existed in the United States at the time of the National Cancer Act of 1971 (3,4), there are now nearly 12 million survivors (approximately 4% of the population), primarily due to increasing numbers of older Americans and advances in early cancer detection and treatment (5-8). The survivor population is comprised largely of individuals who have been diagnosed and treated for breast, prostate, and colorectal cancer because these are common cancers and have the best 5-year survival (9). Because cancer is a disease associated with aging, 60% of cancer survivors are age 65 or older (4).

Although survivorship should be celebrated, the impact of cancer is associated with several long-term health and psychosocial sequelae. Common late effects of cancer and its treatments include cardiovascular disease (CVD) (10), diabetes (11) and other endocrine disorders, and osteopenia/osteoporosis (12,13), some of which could be prevented or managed by nutrition interventions (14-20). However, our ability to develop evidence-based nutrition recommendations for cancer survivors is limited by the dearth of research in this area. This commentary reviews

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the current evidence-based diet and physical activity guidelines for cancer survivors, identifies current knowledge gaps, and describes the research needed to fill those gaps.

POTENTIAL IMPACT OF NUTRITION INTERVENTIONS AMONG CANCER SURVIVORS

Compared with the general population, cancer survivors die of noncancer causes at significantly higher rates, with almost one half of the deaths due to CVD (21-34). Cancer survivors have a twofold increased risk of functional limitations that may threaten their ability to live and work independently (35-47). In 2008, the US economic burden of cancer totaled more than \$228 billion. Although 41% of these costs involved direct cancer care, the majority of expenses were attributed to increased morbidity, lost productivity, and premature mortality (48). The vulnerability of cancer survivors and their unmet needs for adequate health care led to a 2005 Institute of Medicine report (49), which called for increased efforts in survivorship, including a need to improve nutritional status and lifestyle factors (eg, diet and physical activity).

Data on cancer survivors' lifestyle behaviors have been accumulating over the past 2 decades. Initial reports on select patient populations suggest that cancer survivors improve their lifestyle behaviors after diagnosis (50). However, data from larger subsequent population-based surveys with longer follow-up indicate that few health behavior differences may exist between cancer survivors and the general population (51-53). Given higher rates of comorbidity among survivors and the importance of diet and exercise for promoting overall health, these data support a need for lifestyle interventions that target this vulnerable population.

CURRENT RECOMMENDATIONS FOR CANCER SURVIVORS

In 1991, the American Cancer Society (ACS) first published nutrition and physical activity guidelines to reduce cancer risk, and in 2003 guidelines were issued specifically for cancer survivors. Both reports were updated in 2006 and are scheduled for reassessment this year (54-57). In developing these reports, the ACS assembles panels of experts who systematically review the available



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scientific evidence on diet and physical activity in relation to cancer risk reduction or for improving outcomes in cancer survivors.

Similarly, in 1997 the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) produced an extensive systematic review of the evidence linking foods, nutrition, and related factors to cancer (58). The updated 2007 report also addressed cancer survivors and concluded that the lack of sufficient research specifically among survivors precluded the development of evidence-based nutrition recommendations at this time (59). Thus, cancer survivors are encouraged to follow the recommendations for primary cancer prevention, which is consistent with the ACS recommendations.

The ACS and WCRF/AICR cancer prevention recommendations (Figure 1) both emphasize achieving and maintaining a healthy weight; encouraging regular physical activity; eating a diet rich in vegetables, fruit, and whole grains; and limiting meat and alcohol consumption. Furthermore, both sets of recommendations advocate food, rather than supplements, as the source of nutrients.

WEIGHT CONTROL AND REGULAR PHYSICAL ACTIVITY

Excess body weight is a well-recognized risk factor for several types of cancers (59) and has been associated with higher mortality from all cancers combined, specifically for cancers of the breast, esophagus, colon and rectum, liver, gallbladder, prostate, and pancreas (60). Multiple biologic mechanisms may explain the association between excess body weight and cancer risk, including increased low-grade chronic inflammation, elevated levels of hormones and growth factors (for example, insulin, insulin-like growth factor-1, estrogens, and androgens), insulin resistance, adipokines (leptin, adiponectin), and signaling factors (phosphoinositol-3 kinase [PI3K], mammalian target of rapamycin [mTOR]) (59). Weight gain after diagnosis is associated with higher cancer-specific and/or all-cause mortality in women who have been diagnosed with breast cancer (61,62). A study of women with breast cancer found that women with normal body mass index (BMI; calculated as kg/m²) of 24.9 or less had significantly higher overall survival when compared with overweight (BMI 25.0 to 29.9) or obese (BMI ≥30) women (63). In another trial, women with BMI of 30 or more had higher all-cause mortality and higher risk for contralateral breast cancer and other primary cancers (64). Although the observational evidence is largely consistent, there has never been a clinical trial to determine whether weight loss and maintenance of that loss reduces recurrence risk or improves survival post-diagnosis. For colorectal and prostate cancer, available evidence suggests an unfavorable effect of increased adiposity on survival, although some inconsistencies exist (65).

Regular physical activity is a crucial determinant of weight control, and increasing evidence suggests that it exerts an important independent effect on survival after a breast or colorectal cancer diagnosis (66-69). The level of physical activity necessary to have beneficial effects on prognosis is still unclear. No clinical trials have yet reported the effect of physical activity on cancer recurrence or survival, though the Colon Health and Life-Long Exercise Change (CHALLENGE) trial is currently in progress (70). Several short-term studies

have demonstrated improvements in physical functioning and psychosocial factors with exercise (69). The American College of Sports Medicine has recently released consensus guidelines on exercise for cancer survivors (71), and now offers Certified Cancer Exercise Trainer (CET) certification (72).

DIET COMPOSITION

Few observational studies have reported associations between diet composition and cancer survival. These studies have been conducted largely in breast cancer survivors, although a few involve survivors of other types of cancer.

For breast cancer, evidence from observational cohort studies is mixed. Inverse associations have been found between fat intake and recurrence and/or survival, although these associations typically disappear with energy-adjustment (73-76). A U-shaped relationship between dietary fat intake and survival following the diagnosis of breast cancer was identified in one observational study (77), suggesting that extremes in fat intake may be associated with poorer outcomes. Intakes of vegetables, fruit, and related nutrients have been examined in relation to breast cancer recurrence and/or survival in 11 observational studies, with significant protective effects observed in four studies and suggestive findings in two others (73-75,78). Mixed findings from observational studies have been reported for fiber and meat.

Kroenke and colleagues (79) found that a prudent dietary pattern (high in fruits, vegetables, whole grains, legumes, poultry, and fish) was associated with a 15% reduction in relative risk of overall mortality, and death from causes other than breast cancer, when compared with a Western dietary pattern (characterized by refined grains, processed and red meats, desserts, high-fat dairy products, and french fries). In another cohort of breast cancer survivors, consumption of at least five servings per day of fruits and vegetables plus a level of physical activity equivalent to walking 30 minutes 6 days per week was associated with a 50% reduction in mortality over a 7-year follow-up (78), although neither of these factors was significantly protective alone. A study of 1,009 colon cancer survivors found that higher intake of a Western dietary pattern was associated with significantly higher risk of recurrence and mortality (80).

Two large randomized controlled trials (RCTs) have tested whether diet modification after the diagnosis of early-stage breast cancer affects cancer outcomes. The Women's Intervention Nutrition Study (WINS) tested a low-fat diet (≤15% of energy) in 2,437 postmenopausal women with early-stage breast cancer (81). Although on average the women in the intervention arm only decreased fat intake to 20% of energy at year 1, the intervention resulted in a 24% reduction in new breast cancer events. A stronger protective effect (42% reduction) was observed among women with estrogen receptor-negative tumors. Of note, women assigned to the low-fat diet arm lost an average of 6 pounds over the course of the study, thus confounding whether the reduction in breast cancer events was due to dietary fat restriction or lower body weight.

The Women's Healthy Eating and Living (WHEL) Study tested the effect of a diet very high in vegetables, fruit, and fiber and low in fat (20% of energy intake) on

American Cancer Society Recommendations ^a	World Cancer Research Fund/American Institute for Cancer Research Recommendations ^b
<p>Maintain a healthy weight throughout life</p> <ul style="list-style-type: none"> ● Balance caloric intake with physical activity ● Avoid excessive weight gain throughout the lifecycle ● Achieve and maintain a healthy weight if currently overweight or obese <p>Adopt a physically active lifestyle</p> <ul style="list-style-type: none"> ● Adults: engage in at least 30 minutes of moderate-to-vigorous physical activity, above usual activities, on five or more days of the week (45-60 minutes of intentional physical activity are preferable). ● Children and adolescents: engage in at least 60 minutes/day of moderate-to-vigorous physical activity at least 5 days per week. Limit screen time (TV, computer, games) to no more than 2 hours per day. <p>Consume a healthy diet, with an emphasis on plant sources</p> <ul style="list-style-type: none"> ● Choose foods and beverages in amounts that achieve and maintain a healthy weight. ● Eat five or more servings of a variety of vegetables and fruits each day. ● Choose whole grains in preference to processed (refined) grains. ● Limit consumption of processed and red meats. <p>If you drink alcoholic beverages, limit consumption</p> <ul style="list-style-type: none"> ● Drink no more than one drink/day for women or two drinks/day for men. 	<p>Be as lean as possible within the normal range of body weight</p> <ul style="list-style-type: none"> ● Ensure that body weight through childhood and adolescent growth projects toward the lower end (<22.9) of the normal BMI^c range at age 21 ● Maintain body weight within the normal range from age 21 ● Avoid weight gain and increases in waist circumference throughout adulthood <p>Be physically active as part of everyday life</p> <ul style="list-style-type: none"> ● Be moderately physically active, equivalent to brisk walking, for at least 30 minutes each day ● As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day ● Limit sedentary habits such as watching television <p>Limit consumption of energy-dense foods; avoid sugary drinks</p> <ul style="list-style-type: none"> ● Consume energy-dense foods sparingly ● Avoid sugary drinks ● Consume fast foods sparingly, if at all <p>Eat mostly foods of plant origin</p> <ul style="list-style-type: none"> ● Eat at least five portions/servings (at least 400 g or 14 oz) of a variety of non-starchy vegetables and of fruits every day ● Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal ● Limit refined starchy foods ● People who consume starchy roots or tubers as staples also should ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes) <p>Limit intake of red meat and avoid processed meat</p> <ul style="list-style-type: none"> ● People who eat red meat should consume less than 500 g (18 oz) a week, very little if any should be processed <p>Limit alcoholic drinks</p> <ul style="list-style-type: none"> ● If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women <p>Limit consumption of salt; avoid moldy cereals (grains) or pulses (legumes)</p> <ul style="list-style-type: none"> ● Avoid salt-preserved, salted, or salty foods; preserve foods without using salt ● Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day ● Do not eat moldy cereals (grains) or pulses (legumes)
<p>^aCopyright 2006 American Cancer Society. This material is reproduced with permission of Wiley-Blackwell, a subsidiary of John Wiley & Sons, Inc (57). ^bThis material has been adapted from the 2007 WCRF/AICR Report <i>Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective</i>, www.wcrf.org and www.aicr.org (59). ^cBMI=body mass index.</p>	

Figure 1. American Cancer Society 2006 Guidelines on Nutrition and Physical Activity for Cancer Prevention (57) and the World Cancer Research Fund/American Institute for Cancer Research Recommendations for the Prevention of Cancer, 2007 (59).

cancer outcomes in 3,088 pre- and postmenopausal breast cancer survivors who were followed up for an average of 7.3 years (82). At baseline, study participants reported a high average intake of vegetables and fruit (7.3 servings/day). At 6 years, the intervention group had increased to an average of 9.2 servings per day, whereas the control group averaged 6.2 servings per day. Recurrence-free survival did not differ between the two study arms (83).

However, serum estrogens at baseline were independently associated with poor prognosis, and a protective effect of the diet was observed in the subgroup of women who did not report hot flashes at enrollment (84). These findings suggest that reproductive hormonal status may determine whether a high-vegetable, fruit, and fiber diet affects prognosis. In addition, longitudinal exposure to carotenoids was associated with breast cancer-free sur-

vival regardless of study group assignment (85). Thus, diet before the diagnosis of cancer and over the long-term may be more important than short-term dietary change post-diagnosis.

For prostate cancer, dietary factors associated with reduced risk for recurrence include fish, tomato sauce, and monounsaturated fat intakes (86,87), whereas worse outcomes are observed with high levels of saturated fat (but not total fat) (88). In the single study that examined diet and survival after the diagnosis of ovarian cancer, increased consumption of vegetables, especially cruciferous, was associated with longer survival (89). No clinical trials of diet modification with sufficient follow-up have been reported for other cancer types.

Epidemiologic evidence has consistently linked alcohol intake to risk for several specific cancers, supporting the recommendation to limit alcohol intake for primary cancer prevention (56). However, only a limited number of studies have evaluated the association between alcohol use after a cancer diagnosis and survival or disease recurrence. Observational evidence suggests worse prognosis for individuals with head and neck cancer who report higher (vs lower) alcohol consumption after diagnosis (90,91). In contrast to the consistent positive association between alcohol intake and risk for primary breast cancer, findings conflict regarding alcohol intake and breast cancer recurrence (73,92,93). Small sample sizes, differences in study design and data collection, and correlations between alcohol intake and other lifestyle factors (eg, smoking) or comorbid conditions may be responsible for the conflicting results reported thus far. Recognizing the potential cardioprotective effects of alcohol on overall survival (94), the ACS report advises tailored guidance that considers other risk factors and comorbid conditions (57).

Micronutrients may play different roles in different stages of the cancer continuum, as is commonly demonstrated with the case of folate. Data from prospective observational cohort studies suggest that folate status is inversely associated with cancer initiation, due to its role in maintaining DNA stability and integrity (95). However, once cancer is initiated, folate may enhance cancer proliferation (96). Mason and colleagues (97) hypothesized that the increased rates of colorectal cancers observed around the time of mandatory folate fortification of enriched grain products in the United States may be due to increased folate exposure promoting the growth of undetected cancers. Similarly, pharmacologic doses of micronutrients may enhance progression of clinically undetectable cancers, including those remaining after cancer treatments, increasing the risk of relapse (98).

DIETARY SUPPLEMENTS

Dietary supplement use is reported by 52% of US adults (99), and studies report ranges between 64% and 81% among cancer survivors (100,101). A recent systematic review indicates that 14% to 32% of cancer survivors initiate supplement use after their diagnosis (100). Breast cancer survivors report the highest prevalence of supplement use, whereas prostate cancer survivors report the lowest (100).

However, evidence from both observational studies and clinical trials suggests that dietary supplements are not

likely to improve prognosis or overall survival after the diagnosis of cancer, and may actually increase mortality. A 2006 meta-analysis found no association between antioxidant or retinol supplementation and all-cause mortality among cancer patients, although the authors noted that this report was limited by the small number of trials, particularly those of high-quality (102). The use of multivitamins or vitamins E or C were not associated with protection from cancer death in a cohort of 77,719 Washington state residents followed up over a 10-year period (103). A randomized clinical trial of 540 head and neck cancer patients receiving radiotherapy, in which participants were randomly assigned to either 400 IU/day vitamin E or placebo, found that supplement use was associated with significantly higher cause-specific and all-cause mortality (104).

Both the ACS and the WCRF/AICR advise cancer survivors to meet nutrient needs through food, although the ACS endorses the use of standard multivitamin/mineral supplements during and after cancer treatment for those who are unable to meet their needs through diet alone or who demonstrate specific deficiencies (57).

KNOWLEDGE GAPS TO BE ADDRESSED

Although results from research on the nutritional needs of cancer survivors is beginning to accumulate, several gaps in the knowledge base need to be addressed before evidence-based recommendations can be formulated specifically for cancer survivors. The focus of nutrition-related cancer survivorship research to date has largely focused on interventions to decrease risk of cancer recurrence; however, data are also needed on the ability of nutrition interventions to address non-cancer endpoints and healthcare costs. In addition, optimal timing and methodology of nutrition interventions need to be identified.

Need to Address Both Cancer and Noncancer Endpoints

Cancer survivorship research commonly focuses on survival and cancer recurrence as the primary outcomes of interest. However, data indicate that 60% to 75% of cancer patients have at least one comorbid condition (105,106) and are significantly more likely to die of non-cancer causes than the general population (21-34). Therefore, nutrition interventions aimed at prevention or management of comorbidities and functional impairment, and at improving quality of life, may be as important as length of life to the individual survivor. In addition, research is needed to determine whether nutrition interventions can decrease health care costs among cancer survivors.

Need for Risk-Based Nutrition Recommendations

Although all cancers share the characteristic of uncontrolled growth and proliferation, there are more than 100 different types of cancer, each with different etiology, rates of progression, recommended treatment regimens, response to treatment, and prognosis. Substantial heterogeneity in treatment regimens used to treat different cancer types contribute to the heterogeneity in health status and health concerns among cancer survivors. Better information about the relative effectiveness of specific

	Diagnosis	≥5 Years After Diagnosis	
	Initial Treatment	Early Post-treatment	Long-term Cancer Survivorship
Potential nutrition-related health issues	Side effects of treatment (nausea, vomiting, diarrhea, mucositis, taste changes) Fatigue, pain Anorexia, treatment-related cachexia Immunosuppression Weight/body composition changes	Fatigue Pain Endocrine disorders Weight/body composition changes Cognitive deficits Dental caries/complications	Weight changes Osteoporosis Endocrine disorders Cardiovascular complications Cognitive deficits Dental caries/complications
Nutrition research challenges	Competing research protocols Need for individualized nutrition interventions; difficult to standardize for study Demands on patient, ie, time, travel, and burden of cancer and its treatment may impede patient's ability to attend to lifestyle interventions	Patients may want a hiatus from interacting with health care providers/system Transition to care of providers outside the system	Identification and recruitment of eligible study participants
Potential outcomes of interest for nutrition research	Ability to adhere to scheduled treatment Infectious complications Quality of life Weight/body composition management Disease progression Survival	Fatigue Quality of life Functional status Weight/body composition management Disease recurrence Second primary cancers Survival	Late-effects of treatment Functional status Quality of life Weight/body composition management Disease recurrence Second primary cancers Survival Cost of care

Figure 2. Stages of cancer survivorship and the corresponding nutrition and research issues.

nutrition interventions in managing these cancer- and treatment-specific effects will allow nutrition services and resources to be better allocated. Risk-based, treatment-specific monitoring guidelines have been developed for pediatric cancer survivors (107), but these guidelines do not include nutrition recommendations, and similar guidelines for adults do not yet exist.

Need to Identify Optimal Timing and Method for Promoting Health Behavior Change

Despite efforts by the ACS and WCRF/AICR to encourage cancer survivors to follow diet and lifestyle recommendations for cancer prevention, evidence suggests that few cancer survivors are doing so (108,109). Further research is needed to determine the optimal method and timing of interventions to promote healthy lifestyle behaviors among cancer survivors.

Figure 2 summarizes the stages of cancer survivorship, common nutrition issues, and challenges. For many patients, the treatment period is overwhelming as patients cope with their treatment, treatment-related side effects, and other life demands. Patients also may be approached to participate in competing research studies that may prohibit participation in nutrition-related trials. Nutrition interventions during this stage need to be highly individualized and symptom-focused. Research to date

has largely focused on the effect of medical nutrition therapy on short-term outcomes, such as ability to maintain lean body mass, minimize weight loss, or improve quality of life (110-113). Until recently, the lack of standardization in oncology nutrition training and the lack of controlled studies have complicated efforts to compare findings across studies during treatment (114).

Readiness to adopt long-term health behaviors may be enhanced after the completion of treatment. However, transition of health care to providers outside the cancer care facility may complicate recruitment for nutrition intervention studies, especially for individuals who are years beyond treatment. Outside of large urban areas, low population density and barriers involving travel and time also can be a challenge in recruiting sufficient numbers of participants. Alternatives to traditional face-to-face nutrition interventions, such as telephone counseling and written materials, have been successful in achieving dietary behavior change among broad-based groups of cancer survivors (115,116).

CONCLUSION

Cancer survivorship research is still in its infancy, and the scientific evidence supporting nutrition recommendations for cancer survivors is currently limited. However, the increasing number of cancer survivors augments the impor-

tance of identifying appropriate nutrition interventions to improve outcomes, prevent or manage chronic health issues, improve quality of life, and decrease health care costs. Further research is needed to support the development of evidence-based nutrition guidelines for cancer survivors.

STATEMENT OF POTENTIAL CONFLICT OF INTEREST:

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