

Cancer Prevention after Cancer: Changing the Paradigm—a Report from the American Society of Preventive Oncology

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The increasing number of cancer survivors has led to a growing need to reorient a focus in the care of these individuals on health promotion. In 2010, there were an estimated 12.5 million cancer survivors, a figure projected to increase steadily over the next several years (1). Almost two-thirds of these survivors have lived with a cancer diagnosis for 5 or more years, and approximately 1.1 million cancer survivors will have lived with a cancer diagnosis for 25 or more years (2, 3). The numbers are even more impressive for childhood cancer survivors, where 10-year survival is approximately 75% (4). Because of earlier detection, improved diagnostic techniques, more effective treatment, and improved follow-up after treatment (3), more individuals will be living long-term with cancer; either cured of it or living with it as a chronic illness.

Survivors are also older and aging as they survive longer. Not only are they at risk for recurrence and new primary cancers, they are also at risk for a number of comorbid health conditions, such as cardiovascular disease, obesity/diabetes, osteoporosis, unique pain syndromes, functional declines, and poor quality of life. These may be exacerbated by a cancer diagnosis and/or treatment, but, notably, many of these health conditions can be modified by positive behaviors or lifestyle interventions that have been found to reduce health risks in the general population and in cancer survivors. In other words, a successful completion of cancer treatment does not infer an end to the disease and its effects.

For many cancer survivors, a new set of struggles begins posttreatment; consequently, there is a need to help control, and when possible, prevent cancer-related long-term and late occurring health outcomes. The transition from acute care to recovery represents a teachable moment in which health promotion interventions are

aimed at reducing the risk of cancer recurrence and subsequent comorbid conditions, promoting early detection of secondary cancers, and improving quality of life can be implemented. The growing number of cancer survivors calls for a shift in the cancer control paradigm from a limited view that places survivorship as one part of a linear continuum to one that recognizes survivorship issues more broadly, including the importance of prevention and early detection of second malignancies, as well as, the possibility of having treatment for second malignancies (Fig. 1; refs. 4, 5). Within this new paradigm, targeting cancer survivors at all points along the cancer control continuum is a prominent research priority.

The 2011 annual meeting of the American Society of Preventive Oncology (ASPO) held a survivorship special interest group (SIG) meeting to address the state of the cancer survivorship science on health promotion behaviors, examine knowledge gaps, and identify research directions to advance the field. Three crucial survivorship areas were discussed in this context: screening for second malignant neoplasms in adult childhood cancer survivors, smoking cessation among cancer survivors, and the role of energy balance in health of cancer survivors. This article summarizes those SIG meeting presentations and the recommended research directions for advancing the field.

Surveillance for Second Malignant Neoplasms in Adult Survivors of Childhood Cancer

Approximately 80% of children diagnosed with cancer today are expected to become long-term survivors (2, 6). Consequently, the population of survivors of childhood cancer continues to grow—in 2005, there were more than 325,000 childhood cancer survivors alive in the United States (7). Unfortunately, many of these survivors are at significant risk for morbidity or premature mortality as a result of their prior cancer or its therapy (8, 9). Even children or adolescents who survive for 5 years after their initial cancer diagnosis remain significantly more likely to die than the general population. Among 5-year survivors enrolled in the Childhood Cancer Survivor Study (CCSS), the cumulative incidence of mortality 30 years from diagnosis was 18%, which is almost 11 times greater than the similarly aged general population (8). The life expectancy of a child diagnosed with cancer at age 10 years who survives to age 15 years is reduced by an average of 10.4 years (10).

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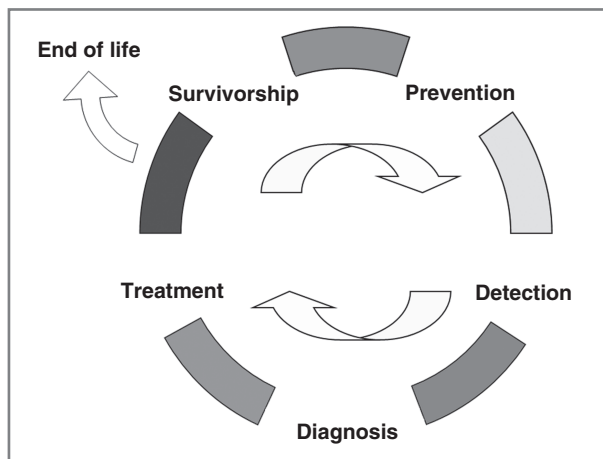


Figure 1. Cancer control continuum-revisited (Courtesy of the National Institutes of Health).

After recurrence of the original cancer, the development of a second malignant neoplasm (SMN) is the leading cause of mortality in childhood cancer survivors, accounting for approximately 20% of deaths and 45% of

nonrecurrence deaths (11). Among 14,359 survivors in the CCSS cohort, the 30-year cumulative incidence of a SMN was 7.9%, with a further 9.1% having developed a non-melanoma skin cancer (Fig. 2; ref. 12). Among 17,981 survivors in the British Childhood Cancer Survivor Study (BCCSS), 5% of survivors had developed an SMN by age 38 years, whereas it took until age 54 years for 5% of the general population to develop an SMN (13). Furthermore, childhood cancer survivors are at risk of developing not just one, but multiple SMNs over their lifetime (14).

The risk for development of a SMN varies by original cancer diagnosis. Survivors of Hodgkin lymphoma are particularly vulnerable to developing a SMN (12), as are survivors of Ewings' sarcoma (12) and hereditary retinoblastoma (13). Radiation therapy is likely the most important risk factor for the development of a SMN. Women treated with chest radiation during childhood or adolescence are at significantly increased risk for developing a subsequent breast cancer, and this risk does not plateau with age (15). By 25 to 30 years after chest radiation therapy, 12% to 26% of female survivors will develop a breast cancer. This risk is similar to that observed in the *BRCA1*- and *BRCA2*-positive populations. Similarly, children treated with

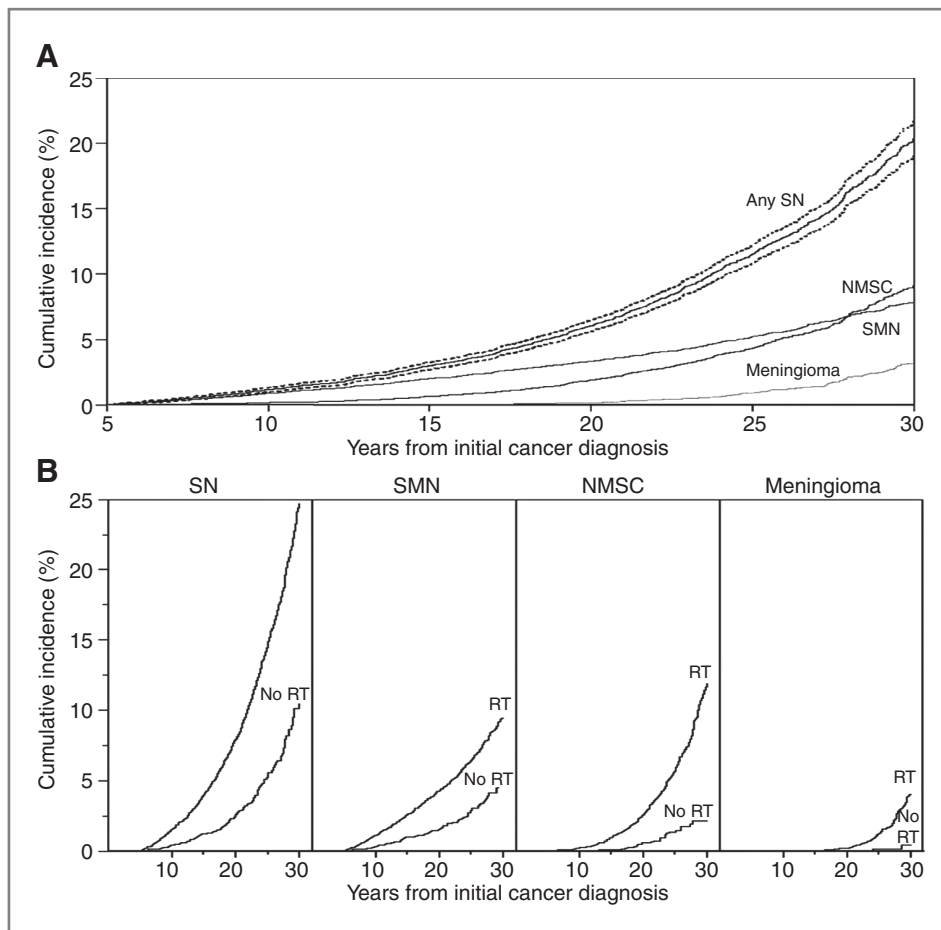


Figure 2. Cumulative incidence of second neoplasms (SN) among 14,359 five-year survivors of childhood cancer in the CCSS cohort. A, cumulative incidence of any second neoplasm (SN), non-melanoma skin cancer (NMSC), second malignant neoplasm (SMN), and meningiomas. B, SN stratified by radiation therapy treatment (RT) or no RT (Reprinted with permission of Oxford University Press).

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cranial radiation for a brain tumor have an increased risk for the development of subsequent meningiomas and gliomas, with increasing radiation doses portending a greater risk (16). The most frequent SMNs reported by the CCSS are cancers of the breast and thyroid, as well as soft tissue sarcomas. As the survivor population ages, the spectrum of SMNs observed may change. In the BCCSS cohort, gastrointestinal and genitourinary tract cancers account for more than one-third of the absolute excess risk of cancer among survivors older than 40 years (13).

Because SMNs cause considerable morbidity and mortality in childhood cancer survivors, it is essential that all at-risk survivors undergo routine surveillance with the goal of detecting SMNs early enough in their development to improve outcome. Several organizations have published comprehensive guidelines for the long-term follow-up of survivors of childhood and adolescent cancers. Recently, an international group of survivorship experts has been convened to harmonize these guidelines. The North American Children's Oncology Group's (COG) guidelines (17) include recommendations for surveillance for breast, colorectal, skin, and thyroid cancers, among others. For example, it is recommended that women treated with more than 20 Gray (Gy) of radiation to a field that involves the chest should receive annual imaging (by mammogram \pm MRI) starting at age 25 years or 8 years after their initial cancer therapy, whichever occurs last. Similarly, survivors who have received more than 30 Gy to a field that involves the colon or rectum should have a colonoscopy every 5 years starting at age 35 years or 10 years after radiation, whichever occurs last. Unfortunately, the evidence for the impact of these surveillance recommendations on outcomes in childhood cancer survivors is limited, and because childhood cancer is a rare event, the rationale for the specific guidelines is usually based on expert review of guidelines in other populations at increased risk for cancer (such as women with *BRCA1* or *BRCA2* mutations, or individuals with a family history of colorectal cancer).

Although survivors are generally compliant with cancer screening guidelines published for the general population by groups such as the American Cancer Society or the United States Preventive Services Task Force, compliance with the COG surveillance guidelines for survivors at increased risk for specific cancers as a result of their prior therapy is poor. Among survivors at increased risk for breast, colorectal, or skin cancer as a result of their prior therapy, only 46%, 12%, and 27%, respectively, were compliant with the COG guidelines for SMN surveillance (18). The reasons for these concerning surveillance rates are poorly understood, but seem to be due to a lack of knowledge among survivors and their health care providers, rather than a lack of motivation. Adherence to surveillance is better among survivors who receive their follow-up care at a cancer center compared with those cared for by primary care clinicians. However, less than 15% of long-term survivors continue to be followed at a

cancer center and this proportion decreases as survivors age. Although most primary care clinicians will treat many survivors of adult cancer, very few have more than a handful of childhood cancer survivors in their practice. Thus, survivors must be educated about and empowered to advocate for appropriate cancer surveillance. Such interventions must be implemented and subsequently evaluated to establish their effectiveness.

Smoking Cessation among Cancer Survivors

An astonishing 15% of cancer survivors were classified as cigarette smokers in 2008 and even among patients with lung or head-and-neck cancer, current smoking rates range from 37% to 60% (19–21). Rates of current smoking remain high at the time of cancer diagnosis and during treatment. There is a growing body of literature that points to significant adverse effects of continued tobacco use on the effectiveness of cancer treatment (i.e., surgery, radiation, and chemotherapy) and the exacerbation of treatment-related side effects (Fig. 3). However, cancer patients who stop smoking can experience physical benefits (e.g., pulmonary, wound healing, immune system, and metabolic functioning improvements), greater treatment efficacy, decreased risks of treatment complications and second primary tumors, and improved quality of life and survival rates (22–25). As more data on the survival benefits of smoking cessation and adverse effects of continued smoking on treatment become available, it will make a more compelling case to health care providers to encourage smoking cessation in their patients who have a personal history of cancer. For more details on the adverse effects of continued smoking on cancer treatment, state of the science in this area and the MD Anderson Cancer Center's Tobacco Treatment Program please see the article by Carmack, Basen-Engquist and Gritz (26) in this issue of *Cancer Epidemiology Biomarkers & Prevention*, and Gritz and colleagues (19).

The discussion of ASPO SIG meeting on tobacco cessation for cancer survivors included a call for further investigations that focus on development and testing of

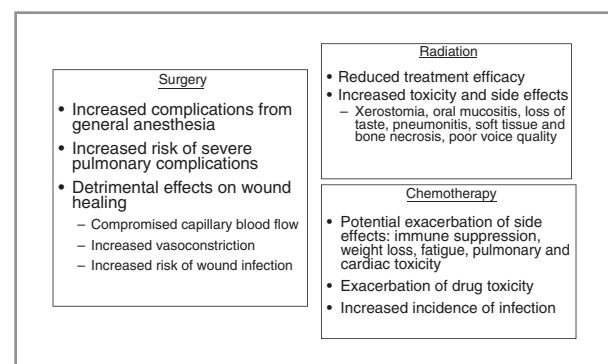


Figure 3. Adverse effects of continued smoking on treatment outcomes for cancer (Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved. Gritz, E et al: *Cancer Prevention*: p. 1–26).

interventions that link patients with cessation efforts, as well as mechanisms underlying effective interventions for relapse prevention, the use of nicotine replacement, and tobacco use assessment in clinical trials and other clinical settings. At the University of Texas MD Anderson Cancer Center, every cancer patient completes a smoking assessment at registration, which is entered into the electronic medical record of patient made available to healthcare providers on his/her medical team. Patients are assessed for tobacco use at each visit through nursing assessment procedures. Patients who respond that they are using tobacco are automatically referred through an electronic system to the comprehensive cessation services offered by the Tobacco Treatment Program as needed. In addition, providers can refer patients to the program or the patient may self-refer. Such a systematic approach to identification and referral of survivors who smoke to cessation services is not currently offered at the majority of funded clinical or comprehensive cancer centers of National Cancer Institute (NCI).

Another discussion point was whether oncology care settings have implemented evidence-based special relapse prevention programs for cancer survivors who resume smoking after stopping for treatment. The MD Anderson Cancer Center Tobacco Treatment Program supports long-term abstinence in this population through continued availability of cessation services, following relapse. Clinicians should be attentive to delayed relapse in cancer patients, which can occur as long as 1 to 6 months postsurgery (27). However, this delayed relapse also presents an opportunity for more time to deliver relapse prevention to these individuals. Education about the link between cancer and smoking, and the benefits of quitting should also be a fundamental component of cessation treatment. Patients who relapse tend to be highly nicotine dependent and will likely require more formal intervention to encourage adoption of smoking cessation as part of their passport of health, in addition to guidance about diet, physical activity, and cancer screening and surveillance. In these at-risk populations, particular emphasis must be placed on preventing relapse and promoting sustained abstinence throughout the survivorship period. The need for further research to identify effective evidence-based cessation interventions in diverse cancer survivor populations was highlighted.

Finally, there was discussion with regard to the use of nicotine replacement therapy during and after cancer treatment in light of the recent laboratory evidence documenting the role of nicotine in carcinogenesis. It was noted that there is not yet convincing evidence on whether treatment efficacy is decreased by nicotine or tobacco and the carcinogens that are present in smoke and smokeless tobacco. Nonetheless, there is evidence documenting that the short-term benefit of nicotine replacement is worthwhile because of its established efficacy in boosting smoking cessation (28). This should be an important motivation for clinicians to push forward on all aspects of smoking cessation. Further research on the develop-

ment and testing of disseminable interventions targeted at providers is needed. Considering the known and potential adverse effects of smoking on the effectiveness of cancer treatments, it was additionally discussed that smoking status should be considered as a covariate in analysis of clinical trials. Thus, tobacco exposure data should be systematically collected as core data in all oncology clinical trials, and at routine points across the trajectory of care, including posttreatment. In addition, there is evidence supporting use of objective measures of abstinence validation, such as cotinine measurements. Such systematic assessment of tobacco use in clinical trials and the study of its effects on therapeutic outcomes is expected to yield an even more compelling case for the importance of widespread adoption of smoking cessation during cancer treatment and for long-term survival benefits.

Energy Balance: Its Role in Cancer Survivors' Health

Research indicates that physical activity not only helps prevent cancer (29, 30), it also confers mortality benefits for cancer survivors (31, 32). Yet, current cancer therapies do not address the association of lifestyle factors on prognosis and survivorship, despite the fact that obesity, weight gain, and physical inactivity are common in cancer patients before and after a cancer diagnosis (33). There is a strong association between having a higher body mass index (BMI) before cancer diagnosis and mortality from different cancer types. For instance, uterine cancer survivors who had a prediagnosis BMI greater than 35 have a 6-fold increase risk of mortality compared with survivors who had a prediagnosis BMI less than 25 (34). In early-stage breast cancer, a BMI greater than or equal to 40 is associated with at least a 5-fold increase of mortality risk compared with BMI less than 25 (35). Furthermore, a higher BMI may explain up to 14% and 20% of all deaths from cancer in men and women, respectively (34). Physical activity can enhance weight loss, but unfortunately, physical activity levels of cancer survivors tend to decline before diagnosis to within 1 year after diagnosis, and approximately 50% of survivors maintain these decreased levels 3 years after diagnosis (33).

Physical activity has been shown to improve multiple aspects of quality of life and functional health of survivors (36). More recently, observational studies point to its role in cancer progression and survival. Investigators with the Nurses' Health Study found that breast cancer survivors who reported physical activity levels of more than 9 MET-hours per week 2 years after diagnosis had an approximate 50% decreased risk of cancer recurrence, breast cancer death, and total death (31). In the Women's Healthy Eating and Living (WHEL) study (37), the combination of high physical activity (~3 h/wk) and a high vegetable/fruit diet (>5 daily servings per day) was associated with higher breast cancer survival rates than

adherence to only one healthy behavior (i.e., diet or physical activity) or no healthy behaviors. Increased physical activity levels are found to be associated with reduced mortality in other cancer populations as well, such as nonmetastatic colorectal cancer. In this latter study, survivors who engaged in more than 18 MET-h/wk of physical activity (~5 h/wk) postdiagnosis, compared with those who engaged in less than 3 MET-h/wk (<1 h/wk), had reduced cancer-specific mortality and overall mortality (32). Interestingly in this study, which also drew upon the Nurses' Health Study, prediagnosis levels of physical activity were not associated with mortality. Yet, those who increased their levels of physical activity after diagnosis, compared with women who did not change their levels, had decreased cancer-specific mortality and overall mortality 2 years after diagnosis. These findings point to the importance of encouraging survivors to return to exercise, if they were active prior to diagnosis, and educating inactive survivors that it is never too late to increase activity levels to affect survival or recurrence risk.

To put in perspective how important this lifestyle behavior is, based on reported studies, physical activity is associated with a reduction in risk of recurrence by 30% to 50%, an effect comparable with chemotherapy and hormonal therapy; however, many patients and clinicians may not appreciate its benefit on survival. This may be due to the fact that much of the exercise and dietary data come from observational studies, rather than from randomized clinical trials. The Women's Intervention Nutrition Study (WINS; ref. 38), a 5-year multicenter randomized trial, showed that a reduced dietary fat

intervention in a breast cancer population was associated with a 24% lower risk of relapse events compared with women in the control group. This effect seemed to be strongest for women with hormone receptor-negative cancer. To parse out the mechanisms elucidating the benefits of exercise and diet on survival, more clinical trials in various cancer populations are needed.

Another plausible explanation for survival benefits associated with energy balance interventions is the reduction in total caloric intake that occurs with reducing fat intake and increasing fruits and vegetables. Body fat is a likely primary mechanism of how energy balance interventions affect cancer survival, as it is related to insulin and insulin-like growth factors (IGF), adipokines, inflammatory pathways, immune function, and sex hormones (Fig. 4; ref. 39). Many of these hormones and proteins cause cell proliferation; therefore, reducing levels could decrease tumor growth. The role of these is gaining recognition and more research is needed to determine mechanisms related to mortality risk that will help elucidate targets for reducing this risk.

A growing number of randomized controlled exercise trials have been conducted showing that exercise favorably influences various biomarkers associated with cancer outcomes in survivors, in particular insulin and IGF levels (40, 41). These findings are encouraging, considering that insulin may be an important link between obesity and breast cancer, and is strongly associated with recurrence and mortality (35). In fact, reducing insulin levels by 25% may improve 5-year disease-free survival by 5%, again, comparable with adjuvant therapies (35, 42). Overall, energy balance interventions hold

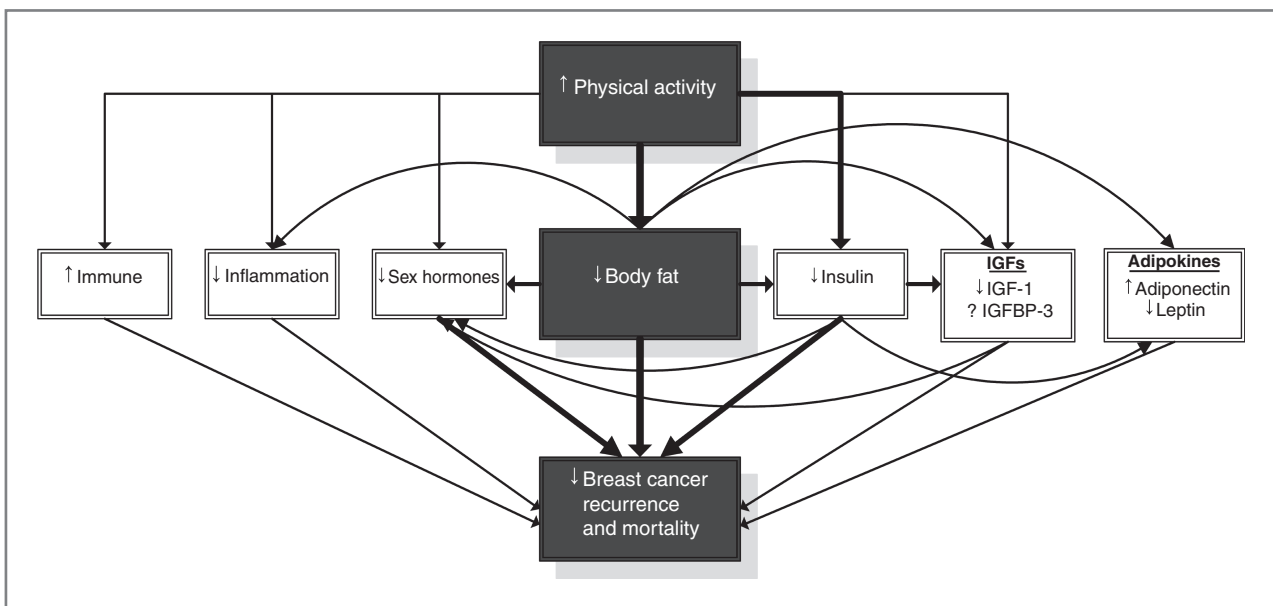


Figure 4. Hypothesized mechanisms mediating an effect of physical activity on breast cancer outcomes (With kind permission from Springer Science +Business Media: The biological mechanisms by which physical activity might have an impact on outcome/prognosis after a breast cancer diagnosis. In: Saxton J, Daley A, Editors. *Exercise and Cancer Survivorship*. New York: Springer; 2010. p. 97–112, Irwin, M).

promise for reducing treatment side effects (e.g., BMD and weight gain) and for reducing the risk of cancer recurrence and mortality.

Over the last 10 years, there has been a growing volume of literature focusing on energy balance interventions and cancer. Much of the early research has focused on quality of life and now the field is moving into examining the mechanisms and the role of such interventions in cancer morbidity and mortality. The direction for future energy balance research is to address novel endpoints that are more downstream and closer to recurrence and survival, such as tumor tissue markers, interactions with genetic and molecular markers, and personalization of recommendations. The Transdisciplinary Research on Energetics and Cancer (TREC) initiative is a NCI-funded research effort aimed at reducing cancer risk and death linked

with obesity, poor diet, and low levels of physical activity (43). At present, several studies are being pursued at the 4 funded TREC sites. As more clinical trials come forward with evidence that cancer survivors who engage in healthy behaviors have lower overall morbidity and, importantly, better survival outcomes, cancer survivors will be empowered to demand and cancer care providers to design and deliver survivorship care that recognizes the need of this diverse population, not just for cancer surveillance, but also for tailored and targeted health promotion.

Summary

The state of cancer survivorship science has made significant advances, yet there still remain knowledge

Surveillance for second malignant neoplasms in adult survivors of childhood cancer

- *Four of every 5 children diagnosed with cancer will become long-term survivors.*
- *Second malignant neoplasms (SMN) are a significant cause of morbidity and early mortality in childhood cancer survivors.*
- *Surveillance guidelines for the detection of SMN in childhood cancer survivors have been published by several groups, including the North American Children's Oncology Group (COG).*
- *Compliance with these surveillance recommendations is poor, and research is needed to improve the uptake of these guidelines.*

Smoking cessation among cancer survivors

- *Up to 30% to 50% of patients who are smoking at the time of their cancer diagnosis do not quit or relapse after initial quit attempts.*
- *There are significant adverse effects of continued tobacco use on the effectiveness of cancer treatment and the exacerbation of treatment-related side effects.*
- *Cancer patients who stop smoking experience physical and psychological benefits, greater treatment efficacy, decreased risks of treatment complications and second primary tumors, and improved survival rates.*
- *Research relating to tobacco and tobacco-related diseases is severely underfunded relative to its public health burden of death and disease.*

Energy balance: It's role in cancer survivors' health

- *Obesity, weight gain, and physical inactivity are common among cancer survivors and a higher BMI is associated with increased mortality risk.*
- *Increasing physical activity is associated with decreased risk of cancer recurrence and reduced cancer-specific and overall mortality risk.*
- *The role of insulin and IGFs, adipokines, inflammatory pathways, immune function, and sex hormones are gaining recognition for their role in effective energy balance interventions.*
- *Future research should target endpoints that are closer to recurrence and survival, and increase focus on the personalization of recommendations.*

Figure 5. Highlights of the annual ASPO 2011 cancer survivorship special interest group.

gaps (Fig. 5). First, there is an overall need to continue establishing a robust evidence base. In childhood cancer survivorship, research is needed that shows the effectiveness of the screening and surveillance guidelines developed, how best to inform adult childhood cancer survivors of these guidelines, and ways to improve patient-provider communication about this care. In tobacco cessation, more research is needed to examine and document the adverse effects of tobacco use on cancer treatment and survival, particularly, mechanisms underlying effect of tobacco on chemotherapy and other emerging modalities. In addition, more research is needed on the effectiveness of cessation programs tailored to different types of cancer survivors (by disease, age, and gender) and the effective timing of such interventions. Finally, in the area of energy balance, more randomized controlled trials are needed to elucidate the mechanisms by which diet, weight, and physical activity are associated with recurrence and survival, and to examine more downstream processes, such as the direct effects on and interactions with genetic, epigenetic, and molecular markers.

Survivorship issues in diverse populations (e.g., low income status, rural geographic locations, or ethnic minority populations) remain a largely unexplored area in cancer survivorship science. A potential area of disparity research in childhood cancer survivorship would be the effectiveness and uptake rates of the screening and surveillance guidelines in rural and other underserved geographic locations, where access to healthcare professionals that are knowledgeable of these guidelines may be particularly scarce. Important diversity issues in tobacco research may include the effects of continued smoking on cancer treatment in different ethnic minority populations, such as African Americans who have a higher incidence of more advanced head and neck squamous cell carcinoma and poorer survival (44, 45). Finally, energy balance research on effective interventions for underserved populations would increase the generalizability of survival benefits; for instance, among African American breast and colorectal cancer survivors with high mortality (46).

For cancer survivorship science to continue advancing, transdisciplinary research is critical. New advances in genomics and questions of gene-environment interactions can help inform survivorship science of the most

effective interventions in different survivor populations and lead to personalization of these to produce the most successful outcomes. Furthermore, we need to build our capacity to deliver effective interventions more broadly if we are to significantly reduce the incidence of cancer recurrence and second cancers, and enhance quality of life. The first step would be educating physicians about effective interventions, such as the importance of prioritizing attention to tobacco cessation among cancer patients and survivors, and the need for special cancer screening guidelines for specific subsets of adult survivors of childhood cancers. In the area of energy balance, as more evidence of survival benefits comes forth, these interventions could be readily prescribed to overweight or obese cancer survivors, just as cardiac rehabilitation is prescribed for cardiovascular patients. Finally, design of evidence-based interventions that can be readily incorporated into standard clinical and community settings will lead to wider dissemination that will help improve the lives of more cancer survivors.

The increasing prevalence of cancer survivors underscores a need for clinicians and public health professionals to provide health promotion interventions in this population. We need to continue to expand the evidence base with regard to the following: (i) healthy behaviors to reduce risk for new or recurrent cancers, maintain or improve health and quality of life, and (ii) early detection or guidelines for childhood cancer survivors to increase likelihood of survival with new or recurrent cancers. It is never too late for cancer survivors—or their healthcare providers—to make these changes.

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No potential conflicts of interest were disclosed.

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