Cancer Survivorship Research: Challenge and Opportunity

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ABSTRACT With continued advances in strategies to detect cancer early and treat it effectively along with the aging of the population, the number of individuals living years beyond a cancer diagnosis can be expected to continue to increase. This paper reviews current prevalence data for cancer survivors; discusses definitional issues; examines cancer survivorship as a scientific research area; provides an overview of medical and psychosocial sequelae of cancer diagnosis and treatment experienced by survivors, gaps in knowledge and emerging research priorities; explores the role of weight, nutrition and physical activity as key variables carrying the potential to affect physiologic or psychosocial sequelae of cancer and its treatment; and discusses the evolving paradigm of cancer survivorship research. A large and growing community of cancer survivors is one of the major achievements of cancer research over the past three decades. Both length and quality of survival are important end points. Many cancer survivors are at risk for and develop physiologic and psychosocial late and long-term effects of cancer treatment that may lead to premature mortality and morbidity. Interventions—therapeutic and lifestyle—carry the potential to treat or ameliorate these late effects and must be developed, examined and disseminated if found effective. Diet, weight and physical activity interventions hold considerable promise for ameliorating multiple adverse sequelae of cancer and its treatment and should be investigated in larger populations of cancer survivors, those who are long-term survivors, those with understudied cancer sites and ethnocultural minority or medically underserved groups.

KEY WORDS: • cancer • survivorship • sequelae • research • paradigm

Once a virtual death sentence, cancer today is a curable disease for many and a chronic illness for most. With continued advances in strategies to detect cancer early and treat it effectively along with the aging of the population, the number of individuals living years beyond a cancer diagnosis can be expected to continue to increase. Statistical trends show that in the absence of other competing causes of death, 62% of adults diagnosed with cancer today can expect to be alive in 5 y (1). Relative 5-y survival rates for those diagnosed as children (age <19 y) are even higher, with almost 75% of childhood cancer survivors estimated to be alive at 5 y and 70% at 10 y (2). Prevalence proportions estimated from cancer incidence and follow-up data in the Surveillance, Epidemiology, and End Results (SEER) registry indicate that there are currently 8.9 million cancer survivors in the United States alone, representing ~3.3% of the entire U.S. population (3).

Although survival from cancer has seen dramatic improvements over the past three decades mainly as a result of advances in early detection, therapeutic strategies and the widespread use of combined modality therapy (surgery, chemotherapy and radiotherapy) (4–8), the important role of the interplay between medical and sociocultural factors must also be kept in mind. Sociocultural factors include psychosocial and behavioral interventions, active screening behaviors and healthier lifestyles (9). Cancers such as testicular cancer, childhood leukemia and Hodgkin’s disease are now considered amenable to cure; patients with common cancers such as breast or colorectal can look forward to a vastly improved disease-free and overall survival; and patients with potentially incurable disease can look forward to living for extended periods of time as a result of better disease control (10–12).

These therapeutic modalities, however, are associated with a spectrum of late complications ranging from minor and treatable to serious or, occasionally, potentially lethal (4). One fourth of late deaths occurring among survivors of childhood cancer during the extended survivorship period, when the chances of primary disease recurrence are negligible, can be attributed to a treatment-related effect such as a second cancer or cardiac dysfunction (13). Most frequently observed medical sequelae include endocrine complications, growth hormone deficiency, primary hypothyroidism and primary ovarian failure (10,13). Also included within the rubric of late effects are second cancers arising as a result of genetic predisposition (e.g., familial cancer syndromes) or the mutagenic effects of therapy. These factors may act independently or synergisti-
cally. Synergistic effects of mutagenic agents such as cigarette smoke or toxins such as alcohol are largely unknown (10).

Thus, there is today a greater recognition of symptoms that persist after the completion of treatment and that arise years after primary therapy. Both acute organ toxicities such as radiation pneumonitis and chronic toxicities such as congestive cardiac failure, neurocognitive deficits, infertility and second malignancies are being described as the price of cure or prolonged survival (10). The study of late effects, originally within the realm of pediatric cancer, is now germane to cancer survivors at all ages because concerns may continue to surface throughout the life cycle (10,11). These concerns underscore the need to follow-up and screen survivors of cancer for toxicities such as those mentioned and also to develop and provide effective interventions that carry the potential to prevent or ameliorate such adverse outcomes.

This paper reviews current prevalence data for cancer survivors; discusses definitional issues; examines cancer survivorship as a scientific research area; provides an overview of medical and psychosocial sequelae of cancer diagnosis and treatment experienced by survivors, gaps in knowledge and emerging research priorities; explores the role of weight, nutrition and physical activity as key variables carrying the potential to affect physiologic or psychosocial sequelae of cancer and its treatment; and discusses the evolving paradigm of cancer survivorship research.

**Prevalence data for cancer survivors**

The most frequently cited estimate for the number of cancer survivors in the United States today, broadly defined as those presently alive after a diagnosis of cancer, is 8.9 million (3,14). This number is based on prevalence proportions estimated from cancer incidence and follow-up data from the Connecticut SEER registry, 1940–1994, projected onto 1997 U.S. Census Bureau figures. Nonmelanoma skin cancer and in situ diseases are excluded from this estimate. The proportion of cancer survivors who may be cured, in remission, in active treatment for or dying from cancer is unknown. The SEER database can provide frequencies of second malignancies but is unable to link frequency to the primary cancer diagnosis for a given individual. As a result, adjustments to the reported prevalence rates are needed so that only first-time cancers are included (3).

*Estimated prevalence of persons alive in the United States diagnosed with cancer in the past 20 y, by current age.* Survivors ≤19 y old comprise 1% of the cancer survivor population; 6% of survivors are aged 20–39 y, 33% are aged 40–64 y and 60% (more than half) are aged ≥65 y. These percentages are based on SEER January 1998 prevalence estimates applied to January 1998 U.S. census population estimates. The number of invasive or first primary cases only estimated by this method is 7.4 million survivors (3).

It is important to note that 60% of cancer survivors are >65 y old, emphasizing that cancer remains a disease associated with aging (3). Because most individuals today can expect to have a long life expectancy, it is reasonable to assume that the number joining the ranks of cancer survivors has the potential to grow correspondingly. This assumption is supported by current population trends estimating that ~20% of Americans will be ≥65 y old by 2035 and the estimate that 12.6% of Americans were ≥65 y old as of July 1, 2000 (3).

*Estimated number of persons alive in the United States diagnosed with cancer in the past 20 years, by site and gender.* Breast cancer survivors are the largest constituent group within the overall population of cancer survivors (22%), followed by prostate cancer survivors (19%) and colorectal cancer survivors (11%) (3). Gynecological and other genitourinary cancers each account for 9% of cancer survivors, followed by hematological cancers and lymphoma (7%) and lung cancer (4%). Other cancer sites account for much smaller percentages and together are responsible for 19% of the total number of survivors. In terms of stratification by gender, more than two thirds (69%) of all female cancer survivors have a history of breast (41%), gynecological (17%) or colorectal (11%) cancer. For male survivors, two thirds (66%) have a history of prostate (39%), other genitourinary (such as testicular or renal) (14%) or colorectal (13%) cancer. (All percentages are based on SEER January 1998 prevalence estimates applied to January 1998 U.S. census population estimates, yielding 7.4 million individuals diagnosed with invasive or first primary cancer) (3).

*Estimated number of persons alive in the United States diagnosed with cancer, by time from diagnosis and gender.* Male cancer survivors account for a greater proportion of survivors who are within 5 y of diagnosis (3). This trend is consistent with the larger number of males who are diagnosed annually with cancer. The mean time since diagnosis by gender is 72 mo for males and 87 mo for females. (These data are based on prevalence estimates of invasive and first primary cases for 1999 from 9 SEER registries applied to January 1, 1999, population estimates, yielding 8.9 million survivors) (3). Additionally, data from the Connecticut SEER registry indicate that 13% of the 8.9 million estimated survivors had been diagnosed >20 y previously (3). Given the mean age at diagnosis and length of time projected for survival, it is reasonable to assume that chronic comorbid conditions and diseases will be an issue for most cancer patients, either at diagnosis or later during the survivorship years.

*Estimated number of persons alive in the United States diagnosed with cancer, by race and ethnicity.* African-Americans (n = 565,882) are 8% of the cancer population in the SEER database (3). Men with prostate cancer are the largest constituent group among African-American cancer survivors (25%; n = 141,345) followed by African-American women with breast cancer (21%; n = 120,943). The reverse is seen in the Caucasian population in which women with breast cancer are the largest constituent group among Caucasian cancer survivors (22%; n = 1.4 million) followed by Caucasian men with prostate cancer (18%; n = 1.1 million). Colorectal cancer is the third most prevalent cancer for both African-American male and female cancer survivors (12%; n = 68,590). Survival data from the SEER registry (1988–1997), stratified by race and ethnicity and adjusted by age and stage at diagnosis, show poorer survival for African-Americans than Caucasians in the database for female breast cancer, male prostate cancer and male and female colorectal cancer (3). Possible explanations for these race and ethnicity survival differentials include differential access to screening, optimal treatment or both; variations in screening rates resulting in lead-time bias (greater survival but no change in total life time) and length bias (screening detects slow-growing tumors with better prognosis); and clustering of socioeconomic status and race and ethnicity data (e.g., a delay in treatment or underuse of screening because of low income) (3). Finally, the importance of diverse cultural factors (beliefs, attitudes and knowledge) in influencing prevention and treatment choices must be considered (15).

Benefits of current knowledge about state-of-the-art cancer care are not shared equally by all members of our society (16). Although the 3-y relative survival rate for all cancers combined in all races of ~62% reflects an increase from 49% in
1974–1976 and 51% in 1980–1982, significant differences exist across ethnic minority and medically underserved populations for both risk of developing and dying from cancer. For all cancer sites combined, African-Americans are more likely to develop and die from cancer than persons of any other racial or ethnic group. They are also at greater risk of dying from the 4 most common types of cancer (breast, prostate, colon and lung cancer) than any other minority group (1).

The above statistics notwithstanding, the outlook for minority cancer survivors is far from grim. Incidence and mortality rates for all cancers combined decreased more among African-American men than for any other racial or ethnic group between 1992 and 1998 (1). Additionally, cancer incidence rates decreased by 2%/y among Hispanics, 1.7%/y among African-Americans, 1.2%/y among Caucasians and remained relatively stable among American Indians/Native Alaskans and Asian/Pacific Islanders (1). Similarly, the mortality rate for all sites has decreased annually by 1.3% among African-Americans, 1.2% among Asian/Pacific Islanders, 1.1% among whites, 0.9% among Hispanics and leveled off for American Indians/Native Alaskans (1). Although comparisons of cancer rates among racial and ethnic groups should be interpreted with caution because of the potential for misclassification of race on medical records, death certificates and the census, the decreased mortality rates support the fact that the cancer survivor population is growing across all racial and ethnic categories (1,15).

Ethnicity has been reported as an important prognostic factor in various studies. However, the independent effect of ethnicity on survival is still being established. Some studies suggest that socioeconomic status may be a more critical determinant than ethnicity or race. It is argued that the poorer overall and disease-free survival of minority and medically underserved populations is a consequence of or is compounded by the effects of low income and education. Poorer and less well-educated cancer patients often have inadequate access to care, adverse prognostic factors at diagnosis (e.g., advanced disease stage), suboptimal treatment, inadequate follow-up care and monitoring, and poorer overall health status as a result of comorbidities or lifestyle (17–22). As stated earlier, cultural beliefs and attitudes may further contribute to the survival disadvantage of minority patients (23). The effect of cultural beliefs, mores and norms on the quality of a person's survivorship experience is a virtually unexplored area.

**Definitional issues**

Cancer survivorship was first described as a concept by Fitzhugh Mullan, a physician diagnosed with cancer (24). Definitional issues for cancer survivorship encompass three related aspects: 1) Who is a cancer survivor? Philosophically, anyone who has been diagnosed with cancer is a survivor, from the time of diagnosis to the end of life (National Coalition of Cancer Survivors). Caregivers and family members are also cancer survivors (secondary survivors). 2) What is cancer survivorship? Mullan (24) described the survivorship experience as being similar to the seasons the year. He recognized three seasons or phases of survival: acute (extending from diagnosis to the completion of initial treatment, encompassing issues dominated by treatment and its side effects), extended (beginning with the completion of initial treatment for the primary disease, remission of disease, or both; dominated by watchful waiting, regular follow-up examinations and, perhaps, intermittent therapy) and permanent survival (not a single moment; evolves from extended disease-free survival when the likelihood of recurrence is sufficiently low). An understanding of these phases of survival is important vis-à-vis an optimal transition into and management of survivorship. 3) What is cancer survivorship research? Cancer survivorship research seeks to identify and examine adverse cancer diagnosis and treatment-related outcomes (such as late effects of treatment, second cancers and quality of life); provide a knowledge base regarding optimal follow-up care and surveillance of cancer survivors; and optimize health after cancer treatment.

Other important definitions include long-term cancer survivorship and late and long-term effects of cancer treatment. Generally, long-term cancer survivors are defined as 5, 10, 15 or 20 y beyond the diagnosis of their primary disease and embody the concept of permanent survival described by Mullan (24). Late effects refer specifically to unrecognized toxicities that are absent or subclinical at the end of therapy but manifest later with the unmasking of hitherto unseen injury to immature organs by developmental processes or as a result of failure of compensatory mechanisms because of the passage of time or organ senescence (4,11). Long-term effects refer to any side effects for which a cancer patient must compensate; also known as persistent effects (4,10), they begin during treatment and continue beyond the end of treatment. Late effects, in contrast, appear months to years after the completion of treatment (4,25). Some researchers classify cognitive problems, fatigue, lymphedema and peripheral neuropathy as long-term effects. Patients with late or long-term effects may have to undergo major adjustments to a lifestyle for which they are unprepared (26–29).

**Implications of the data**

Most survivors can expect to cross the 5-y mark, and for many, cancer has become a chronic illness. However, although our understanding of the causes of differences in cancer incidence and mortality in diverse populations is growing rapidly, the effect of diagnosis and treatment on those who continue to survive and live with their disease is less clear. Survival disparities exist across ethnocultural minority and medically underserved groups. The demography of cancer survivorship is changing and many sequelae of the disease and its treatment are as yet uncharted.

Although research on the biology, treatment and cure of cancers has flourished, relatively modest efforts have addressed outcomes of cancer and its treatment in general or long-term survivorship outcomes in particular. This is in sharp contrast to the body of evidence increasingly demonstrating that most people treated for cancer need preemptive medical and psychosocial management to address the medical, emotional, social and economic effects of their illness. These effects of cancer and its treatment are multifaceted and interrelated (30).

Issues facing the cancer survivor are not extensions of the issues facing the cancer patient in treatment. There is a diversity of sequelae encompassing physical and psychologic sequelae that require medical management on one hand and societal and interpersonal issues including changed lifestyle, disruption of home and family roles and the fear of recurrence on the other (31,32). Research also shows that cancer survivors live with compromise and uncertainty and face challenges resulting from changes in strength, endurance, reproductive capacity and body image. These adverse medical, psychosocial and economic outcomes carry tremendous potential to cause physical, psychological social morbidity. They often manifest as related and concurrent issues for the cancer survivor (30,32).
Issues of particular importance to cancer survivors include the risk of recurrence; follow-up care and surveillance for the adverse sequelae of treatment and the development of new cancers, reproductive issues and sequelae in offspring; and quality of life and psychosocial adjustment beyond acute treatment (30,32). Not only do these issues occupy a central core of importance in and of themselves, they also can influence infrastructure systems such as databases, follow-up requirements for clinical trials, new therapeutic approaches, surveillance recommendations and the cancer research agenda itself (10,33–35).

Decisions concerning needs for specific follow-up care benefit from information derived from studies of the medical and psychological outcomes of both the cancer experience and therapy. Providing information, education and other forms of intervention during active cancer treatment and beyond may have implications for the prevention of future illness and for the overall quality of life of survivors. Cancer survivors are also a rich source of information on consequences of the cancer diagnosis and treatment, such as second cancers and potential comorbidities. (4,10,30)

**Physiologic late effects**

Few current cancer therapies are benign, but debilitating side effects may diminish in the future as more targeted therapies are developed. Most cancer treatments carry substantial risk of adverse long-term or late effects, including neurocognitive problems, premature menopause, cardiac dysfunction, sexual impairment, chronic fatigue and pain syndromes, and second malignancies for both adult and childhood cancer survivors (4,10,11,13). One fourth to one third of breast and lymphoma survivors who receive chemotherapy may develop detectable neurocognitive deficits, and late clinical cardiotoxicity, often life threatening, may occur in 5–10% of long-term pediatric cancer survivors even 5–10 y after therapy (13). The most frequently observed medical late effects, however, include endocrine complications, growth hormone deficiency, primary hypothyroidism and primary ovarian failure (10,11,13).

Late effects can be classified further as system specific (such as damage, failure or premature aging of organs; immunosuppression or compromised immune systems; and endocrine damage), second malignant neoplasms (such as an increased risk of recurrent malignancy, a certain cancer associated with the primary cancer and a second cancer associated with cytotoxic or radiological cancer therapies) and functional changes (such as lymphedema, incontinence, pain syndromes, neuropathies and fatigue); cosmetic changes (such as amputations, ostomies and skin and hair alterations); and associated comorbidities (such as osteoporosis, arthritis, scleroderma and hypertension) (4,10,11,30). The spectrum of late and long-term complications ranges from minor and treatable to serious and lethal (11,13).

**Generalizations.** Certain types of late effects can be anticipated from exposure to specific therapies, age of the survivor at the time of treatment, combinations of treatment modalities and dosage administered (36). Susceptibility differs for children and adults. Generally, chemotherapy results in acute toxicities that can persist, whereas radiation therapy leads to sequelae that are not immediately apparent (11,36). Combinations of chemotherapy and radiation therapy are more often associated with late effects (36). Toxicities related to chemotherapy, especially those of an acute but possibly persistent nature, can be related to proliferation kinetics of individual cell populations because these drugs are usually cell-cycle dependent (36). Organs or tissues most susceptible have high cell proliferation rates and include skin, bone marrow, gastrointestinal mucosa, liver and testes. The least susceptible organs and tissues replicate very slowly or not at all and include muscle cells, neurons and connective tissue. However, neural damage may be caused by commonly used chemotherapeutic drugs such as methotrexate, vinca alkaloids and cytotoxic arabinoside; bone injury may be caused by methotrexate; and cardiac sequelae can occur after treatment with adriamycin (36). Injuries in tissues or organs with low repair potential may be permanent or long lasting. Risk of late death from causes other than recurrence is greatest among survivors treated with a combination of chemotherapy and radiotherapy (13).

**Issues unique to certain cancer sites.** The examination of late effects for childhood cancers such as leukemia, Hodgkin’s disease and brain tumors have provided the foundation for this area of research (11). A body of knowledge on late effects of radiation and chemotherapy is also now appearing for adult cancer sites such as breast cancer (10). For example, neurocognitive deficits that may develop after chemotherapy for breast cancer are an example of a late effect that was initially observed among survivors of childhood cancer receiving cranial irradiation, chemotherapy or both (37–40). Late effects of bone marrow transplantation have been studied for both adult and childhood cancer survivors as have sequelae associated with particular chemotherapeutic regimens for Hodgkin’s disease and breast cancer (4,10,11,36). The side effects of radiotherapy, both alone and with chemotherapy, have been reported fairly comprehensively for most childhood cancer sites associated with good survival rates (36). Most cancer treatment regimens consist of chemotherapy in conjunction with surgery or radiation, and multidrug chemotherapeutic regimens are the rule rather the exception. As such, the risk of late effects must always be considered in light of all other treatment modalities to which the patient has been exposed.

**Special considerations when primary diagnosis and treatment occurs in childhood.** Cancer therapy during childhood may interfere with physical and musculoskeletal development (41–45), neurocognitive and intellectual growth (46,47) and pubertal development (48). These effects may be most notable during the adolescent growth spurt (11). Prevention of second cancers is also a key issue.

**Special considerations when primary diagnosis and treatment occurs during adulthood.** Some late effects of chemotherapy may assume special importance depending on the adult patient’s age at the time of diagnosis and treatment (4). Diagnosis and treatment during the young adult or early reproductive years may call for a special cognizance of the importance of maintaining reproductive function and the prevention of second cancers. Cancer patients diagnosed and treated in their 30s and 40s may need specific attention for premature menopause; issues relating to sexuality and intimacy; use of estrogen replacement therapy; prevention of neurocognitive, cardiac and other sequelae of chemotherapy; and prevention of coronary artery disease and osteoporosis (4,10,49). Sexual dysfunction may persist after breast cancer treatment and may include vaginal discomfort, hot flashes and alterations in bioavailable testosterone, luteinizing hormone and sex hormone binding globulin (49). Menopausal symptoms such as hot flashes, vaginal dryness and stress urinary incontinence are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy in these patients (50). The normal life expectancy of survivors of early-stage cancers during these years of life underscores the need to address their long-term health and quality-of-life issues.
Although older patients (aged ≥ 65 y) bear a disproportionate burden of cancer, advancing age is also associated with increased vulnerability to other age-related health problems, any of which could affect treatment choice, prognosis and survival. Hence, cancer treatment decisions may have to consider preexisting or concurrent health problems (comorbidities). Measures that can help to evaluate comorbidities reliably in older cancer patients are warranted. Little information is available on how comorbid age-related conditions influence treatment decisions, the subsequent course of cancer or the comorbid condition, how already compromised older cancer patients tolerate the stress of cancer and its treatment and how comorbid conditions are managed in light of the cancer diagnosis (51).

**Second cancers.** Second cancers may account for a substantial number of new cancers. A second primary cancer is associated with the primary malignancy or with certain cancer therapies (e.g., breast cancer after Hodgkin’s disease or ovarian cancer after primary breast cancer) (52).

Within 20 y, survivors of childhood cancer have an 8–10% risk of developing a second cancer (53,54). This can be attributed to the mutagenic risk of both radiotherapy and chemotherapy, which is further compounded in patients with genetic predispositions to malignancy. The risk of a second cancer induced by cytotoxic agents is related to the cumulative dose of drug or radiotherapy (10,11,36).

The risk of malignancy with normal aging may be a result of cumulative cellular mutations (10). The interaction of the normal aging process and exposure to mutagenic cytotoxic therapies may result in an increased risk of second malignancy, particularly after radiotherapy and treatment with alkylating agents and podophyllotoxins. Commonly cited second cancers include leukemia after alkylating agents and podophyllotoxins (55,56); solid tumors, including breast, bone and thyroid cancer in radiation fields (57); and bladder cancer after cyclophosphamide. Second cancers may also occur in the same organ site (e.g., breast, colorectal); thus there is definite need for continued surveillance (4,10,11).

**Psychosocial outcomes**

The psychosocial effect of cancer has been well studied during the past few years (58–61). Despite this, surprisingly few studies examine psychosocial or quality-of-life outcomes in women from diverse backgrounds or survivors of cancer other than breast cancer. Psychosocial and quality-of-life sequelae incorporate aspects of survivorship relating to adaptation of the patient to the personal consequences of cancer diagnosis and treatment (issues of self-concept, body image, personal autonomy, coping strategies, intimacy, interpersonal and family interactions and living with uncertainty) and adjustment to the social consequences of cancer (societal and familial perceptions and expectations; altered interpersonal relationships, family roles and functions; and issues of financial stability, job security, health insurance, job lock or discrimination) (30,62).

Persons who have cancer experience the effect of the disease in many different ways and at different times. These issues in turn exert an effect on perceived quality of life and contribute to the meaning of cancer for the patient. The person’s age and the degree to which the disease and treatment effects threaten life goals and activities modify the meaning of cancer for an individual. At any age, disruption of function, even when temporary, becomes disturbing if it involves valued life activities or forces a change in goals (30,58).

For most, cancer is a new experience, perhaps filled with false notions, and thus likely to engender fear and psycholog-
a tremendous paucity of information regarding physiologic and psychosocial outcomes among survivors of colorectal, head and neck, hematologic or lung cancers (3,4,10,30,70). This must be addressed, especially because these cancer sites account for a significant portion of the percentage of annual incident cancers and overall proportions of survivors (3).

**Health disparities.** A recent detailed review of the extant literature attempting to describe cancer survivorship outcomes (physiologic, psychosocial), health services and quality of care, and health-promoting behaviors and lifestyles among cancer survivors belonging to ethnoculturally diverse and medically underserved groups demonstrated the disturbing paucity of research addressing these questions (15). The review was conducted in an effort to understand both the similarities and differences in the survivorship experience of different ethnic groups and to examine the potential role of ethnicity in influencing the quality and length of survival from cancer. Although the few studies identified emphasize the significant lack of knowledge in this critical area, some potentially important findings across all of the a priori selected survivorship outcome categories were identified. Research examining ethnic or minority differences in cancer survivorship outcomes is limited largely to epidemiologic analyses of differences in cancer risk and survival; little effort has been made to extend findings related to differential risk of developing, being diagnosed with, and being treated for or dying of cancer to address their effect on individuals living with this disease. This represents a wide-open and timely area for inquiry for future investigators (15).

**Follow-up care and surveillance.** High quality follow-up care is necessary for all cancer survivors, both for the early detection of late effects and the timely introduction of optimal treatment strategies to prevent or control late effects. No evaluative data have been gathered or published on the effectiveness of follow-up care clinics in preventing or ameliorating long-term effects of cancer and its treatment; no consistent, standardized model of service delivery for cancer related follow-up care is applied uniformly across cancer centers and community oncology practices; and little attempt has been made to examine the quality, content and optimal frequency of follow-up care for cancer survivors in the community setting by oncologists or by primary care providers. Developing an understanding of these issues is critical.

**Economic sequelae.** The economic effect of cancer for the survivor and family and the health and quality-of-life outcomes resulting from diverse patterns of care and service delivery settings must be examined (3,30).

**Family and caregiver issues.** Cancer is not a disease affecting only the survivor. It is a chronic condition affecting family members, caregivers, friends and coworkers (3,10,30). This aspect of cancer survivorship has not been well addressed and is an increasingly important and fruitful area of research.

**Instrument development.** Instruments capable of collecting valid data on survivorship outcomes and developed specifically for survivors beyond the acute cancer treatment period are warranted because many currently in use were developed for the cancer patient in treatment.

**Diet, weight and physical activity in cancer survivorship research**

A number of lifestyle factors increase an individual’s risk of developing cancer. These include high energy intake, sedentary lifestyle, tobacco use, alcohol consumption, sexual activity and exposure to environmental toxins (71). Less clear is whether changing these behaviors once cancer is diagnosed affects disease-free or overall survival and prevents or ameliorates long-term effects, late effects and comorbidities. Research on possible differences in such outcomes as a result of positive lifestyle changes by ethnic or cultural group is virtually nonexistent (15).

Conducting survivorship research and successfully introducing appropriate interventions that could improve the care and management of cancer survivors as well as lead to better quality of life and favorable long-term survival is indeed a challenge. Inherent in that challenge is the recognition of the importance of preventing premature mortality from the disease and its treatment and the prevention or early detection of both the physiologic and psychological sources of morbidity. Second cancers must be prevented and also recurrences of the primary disease. The prevention of future morbidity in long-term survivors of cancer is largely unaddressed, and strategies that focus not only on the control or eradication of disease but also on restoration of function and maintenance of psychological well-being are appropriate (4,10,11,30). Diet, weight, and physical activity interventions carry tremendous potential to affect length and quality of survival in a positive manner and prevent or control morbidity associated with cancer or its treatment.

It is plausible that exercise and physical activity may reduce the risk of second cancers by physiologic mechanisms such as decreased lifetime exposure to estrogen or other hormones, reduced body fat, enhanced gut motility, improved antioxidant defenses and stimulation of antitumor immune defenses. However, the exercise or activity dosage required for optimal protection is unclear (72), and the effect of such interventions in the prevention or control of comorbidities among adult survivors must be examined (73). Physically active men are at a significantly lower risk of death from cancer than are sedentary men (74,75).

Physical activity may help cancer patients build up their physical condition; decrease the number of comorbid conditions; reduce drug interactions; help cancer patients cope with treatment; restore good health; improve quality of life during and after treatment; and help cancer patients and survivors maintain independence as long as possible (76).

Physical rehabilitation programs similar to those for cardiac rehabilitation may be effective in managing, controlling or preventing adverse medical and psychosocial outcomes manifested during cancer survivorship (4,10,11,30). For example, exercise programs are being developed as interventions to improve the physical functioning of persons who have problems with mobility as a result of therapy, and are also being shown to be efficacious for weight control after breast cancer treatment, lessen the effects of chronic fatigue, improve quality of life, prevent or control osteoporosis as a result of premature menopause, and prevent or control future or concurrent comorbidities (4,10,11,30,36). The effect of nutrition interventions on second cancer risk reduction or modulation (10,30) is also being examined.

Weight gain and obesity among women who have undergone adjuvant chemotherapy for breast cancer is a consistently reported finding (71). Evidence exists that postdiagnosis weight gain may adversely affect disease-free or overall survival among breast cancer survivors, and obesity at the time of breast cancer diagnosis is an established negative prognostic factor that may be associated with a higher risk of cardiovascular disease, diabetes and other comorbid conditions (71).

This may hold true for survivors of other cancer sites as well, especially those that are hormone dependent. Chemotherapy-induced weight gain is distinct in that patients lose muscle as they gain adipose tissue, thus calling for interventions that promote exercise (71). Demark-Wahnefried et al. (71) showed
that breast cancer survivors, even when weight stable, demonstrate trends toward decreasing lean body mass. Whether this is also an issue among survivors of other adult cancers, especially male and female reproductive tract cancers, is an important and timely research area that warrants further investigation.

Long-term survivors of childhood cancer (especially female) may also have chronic problems with obesity/high body mass index (71,77,78), significantly greater mean body fat, decreased total energy expenditure, decreased levels of physical activity, reduced energy expenditure with low intensity exercise, reduced stroke volume and increased heart rate compared with control subjects (79–81). Reduced exercise capacity may account in part for the decreased levels of physical activity and excess adiposity (82,83) observed in this population. An increased risk of death from cardiovascular disease, probably a result of obesity, insulin resistance, hyperinsulinemia, glucose intolerance, hypertension and dyslipidemia (metabolic syndrome) (84) has been reported among childhood cancer survivors. This may hold true for survivors of adult cancer as well, and larger, well-designed studies with the capacity to generate definitive findings continue to be needed.

Health-related beliefs and behaviors of long-term survivors of childhood cancer are important because of vulnerability to adverse late effects of their cancer and its treatment. Areas of concern to be targeted for educational interventions and other appropriate monitoring include alcohol and tobacco use, diet, exercise, sleep, dental habits and other lifestyle influences on health status and cancer risk. A study of health-related behaviors of survivors of childhood cancer showed that >80% of parents and 60% of young adult survivors believed that it was more important for the survivor to remain healthy than for most other people (85). However, this shared belief in increased vulnerability was inconsistently expressed in the survivors’ health behaviors.

Late onset of congestive heart failure has been reported during pregnancy and rapid growth or after the initiation of vigorous exercise programs in adults treated for cancer during childhood or young adulthood (4,10,11). This may occur as a result of increased afterload and the effect of the additional myocardial work of pregnancy or growth or the additional work of the heart muscle resulting from the additional stress of the exercise program. A study of physical activity interventions with young adult survivors of childhood cancer showed that >80% of survivors believed that they would have preferred exercise intervention before diagnosis and treatment (86,87). Cancer treatment can also alter sexual function directly, making the patient feel less attractive and diminish sexual desire and suppress gonadal function resulting in ovarian failure and the development of osteoporosis. Exercise and nutrition interventions may be effective in ameliorating such potential adverse health consequences and warrant further research.

Only limited studies of physical activity and organized fitness programs have been done with adult cancer patients, and fewer still have been done for survivors of childhood cancer. Physical activity has been shown to reduce fatigue and other somatic complaints and improve several scores of psychological distress (obsessive-compulsive traits, fear, interpersonal sensitivity and phobic anxiety) associated with cancer treatment or tumor burden (88). It may also improve physical performance and decrease the duration of neutropenia or thrombocytopenia, severity of diarrhea, severity of pain and duration of hospitalization (89,90).

Research has focused largely on the role of diet, weight and physical activity as factors relevant to risk of developing cancer, not on the prevention or control of late and long-term sequelae of survivorship, comorbidities and recurrence. Health behavior and lifestyle interventions such as exercise and weight reduction to enhance physical health and quality of life of those already diagnosed with cancer is a timely, exciting and emerging research area. Such interventions have the potential to exert effects on multiple body systems and could thus play a role in ameliorating diverse adverse consequences of cancer diagnosis and treatment (91,92).

The possible negative effect of strenuous exercise programs on those with compromised cardiac function or lymphedema has to be examined carefully (4,11). Pediatric cancer survivors may require special consideration because of the cardiovascular complications of treatment. Other survivor subpopulations (categorized by age, menopause status, working status) may also require modified diet, weight or physical activity interventions. The nature of that modification and indeed the need for such modifications should be researched and documented.

Cancer has been considered a reachable moment by some investigators because of the particular motivation for change resulting from the diagnosis and its potential effect on both the survivor and the survivor’s family (9). Diet, weight or physical activity interventions may thus be able to harness this motivation for positive change. Research questions of particular interest include the examination of motivators of health behaviors after cancer; multiple risk factor interventions; optimal timing of interventions; optimal type and dose of exercise; clinical variables that influence the response to exercise; and patients who will respond most favorably to diet, weight or physical activity interventions (93).

The evolving paradigm of cancer survivorship research

New perspectives and an emerging body of scientific knowledge must be incorporated into Mullan’s original description of the survivorship experience as similar to the climactic seasons of the year (24). A combination of factors such as curative and effective treatments, a low likelihood of recurrence, chronicity and the potential for late and long-term adverse effects of cancer or its treatment (both physiologic and psychosocial) were implicit in Mullan’s description of the survivorship experience (24). However, advances in survivorship research over the past few years have necessitated the incorporation of additional concepts into the evolving paradigm of cancer survivorship research, i.e., lifestyle and health promotion, the effect of comorbidities, family issues and the incorporation of a developmental and life-stage perspective.

A developmental and life-stage perspective is important because it carries the potential to affect and modify treatment decisions, follow-up care, adverse sequelae of treatment, the making of optimal transitions into survivorship and the use of technologies (such as sperm banking) depending on the survivor’s age at diagnosis and treatment (4). Data on late effects from studies conducted largely in childhood cancer survivors (11,36) have paved the way for and provided a relative format for adult cancer survivorship research. Whether there is a consistent childhood cancer survivorship model requires examination; if this is so, we must explore whether it also holds true for adult and elderly survivors, the distribution, determinants and health implications of late effects among adults, and...
similarities or differences in outcomes of cancer and its treatment between pediatric and adult cancer survivors.

A research shift in the past 5–10 years encompasses a move away from descriptive (hypothesis generating) to analytic (hypothesis testing) investigations, an increased emphasis on clinical trials and interventions, a need for exploring psychosocial models for interventions that are effective and can be disseminated into the community, a need for education both for the provider and the survivor and the constantly evolving effect of a potential philosophical shift in cancer treatment from a primarily seek-and-destroy mindset toward one reflecting the importance of both curing the disease and controlling its attendant adverse sequelae. Cancer treatments today are increasingly used in the context of the survivor’s life, striving toward minimal toxicity yet optimal effectiveness and with a recognition of the importance of interdisciplinary care and management. This philosophy must be communicated to researchers and care providers across diverse settings to promote its incorporation into the design of the next generation of cancer survivorship investigations.

The new and evolving paradigm of cancer survivorship research can be summarized as one that seeks to identify, examine, prevent and control adverse sequelae of cancer and its treatment; manages, treats and prevents comorbidities; incorporates health promotion and lifestyle interventions to optimize health after cancer treatment; defines and incorporates optimal follow-up care and surveillance for all survivors; pays special attention to disparities in survivorship outcomes by age, income, ethnicity, geography or cancer site; and incorporates the effect on the family within its rubric. This paradigm looks beyond treatment, representing a shift away from descriptive (hypothesis generating) to analytic (hypothesis testing) investigations, an increased emphasis on clinical trials and interventions, a need for exploring psychosocial models for interventions that are effective and can be disseminated into the community, a need for education both for the provider and the survivor and the constantly evolving effect of a potential philosophical shift in cancer treatment from a primarily seek-and-destroy mindset toward one reflecting the importance of both curing the disease and controlling its attendant adverse sequelae. Cancer treatments today are increasingly used in the context of the survivor’s life, striving toward minimal toxicity yet optimal effectiveness and with a recognition of the importance of interdisciplinary care and management. This philosophy must be communicated to researchers and care providers across diverse settings to promote its incorporation into the design of the next generation of cancer survivorship investigations.

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In conclusion, a large and growing community of cancer survivors is one of the major achievements of cancer research over the past three decades. Both length and quality of survival are important end points. Many cancer survivors are at risk for and develop physiologic and psychosocial late and long-term effects of cancer treatment that may lead to premature mortality and morbidity. As in the past when treatments were modified to decrease the chance of toxicities in childhood cancer survivors, the goal of future research and treatment should also be to evaluate these adverse consequences systematically and further modify toxicities without diminishing cures. Interventions and treatments that can ameliorate or manage effectively both persistent and late medical or psychosocial effects of treatment should be developed and promoted for use in this population. Oncologists, primary care physicians and ancillary providers should be educated and trained to effectively monitor, evaluate and optimize the health and well-being of a patient who has been treated for cancer.

Additional research is required to provide adequate knowledge about symptoms that persist after cancer treatment or arise as late effects and interventions that are effective in preventing or controlling them. Prospective studies that collect incidence data on late effects are warranted because most of the current literature relevant to this domain is derived from cross-sectional studies in which it is not clear whether the symptom began during treatment or immediately post-treatment. Continued, systematic follow-up of survivors will result in information about the full spectrum of damage caused by cytotoxic and radiation therapy and possible interventions that may mitigate the effects.

Interventions, both therapeutic and lifestyle, that carry the potential to treat or ameliorate these late effects must be developed. Diet, weight and physical activity interventions hold considerable promise for ameliorating multiple adverse sequelae of cancer and its treatment and should be investigated in larger populations of cancer survivors, those with understudied cancer sites and ethnic-cultural minority or medically underserved groups.

The relative lack of knowledge that currently exists about the physical health and quality-of-life outcomes of cancer survivors represents a clear area of challenge. It is also one for exciting opportunity and growth. Cancer is expected to become the leading cause of death in the future as a result of our aging population, reduced death rates from cardiovascular disease, and efficacious treatment and screening methodologies. Effective strategies to prevent and delay treatment-related physiologic and psychosocial sequelae must be developed, tested and disseminated to achieve not only the goal of higher cancer cure rates but also a decreased risk of adverse health and social outcomes.

LITERATURE CITED


