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Cancer survivorship research: State of knowledge, challenges and opportunities

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Abstract

Introduction. Seminal advances in early detection of and treatment strategies for cancer have led to burgeoning numbers of cancer survivors. While most therapeutic modalities for cancer are beneficial and lifesaving, they are associated with adverse long-term and late sequelae. *Materials and Methods.* Literature review using MEDLINE to identify studies examining adverse medical outcomes and post-treatment follow-up care among long-term survivors. Emerging concepts in survivorship research such as definitional issues, research paradigms and methodologic concerns were also examined. *Results.* Long-term or late adverse sequelae are more prevalent, serious, and persistent than expected in survivors of pediatric and adult cancer, but remain understudied especially among those diagnosed as adults. Follow-up care relevant to survivorship outcomes is neither standardized nor guideline or evidence based for most adult cancers, and optimal practices have yet to be defined. *Discussion.* Adverse sequelae contribute to burden of illness, health care costs, and decreased length and quality of survival. To-date, very few studies have compared survivor outcomes pre-and post diagnosis. It is critical to examine under-researched questions and understudied survivor groups. Regular follow-up care and monitoring of health status post cancer treatment should 1) permit the timely diagnosis and treatment of adverse outcomes; 2) enable timely diagnosis and treatment of recurrences; 3) facilitate screening and early detection of second cancer(s); 4) allow for detection and management of co-morbidities; and 5) provide the opportunity for preventive strategies such as lifestyle changes. Research findings to-date underscore the need for continued cancer survivorship research that will: inform our understanding of the mechanisms underlying adverse sequelae; lead to the design of less toxic treatments; test the effectiveness of interventions – medical, pharmacologic, and behavioral – that reduce adverse outcomes; test models of post-treatment follow-up care; develop an evidence base for optimal follow-up care practices; and inform survivor and provider decision making.

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 [1–4]. In the absence of other competing causes of death, 66% of adults diagnosed with cancer today can expect to be alive in 5 years [5]. Relative 5 year survival rates for those diagnosed as children (age <19 years) are even higher, with almost 79% of childhood cancer survivors estimated to be alive at 5 years, and 75% at 10 years [6–9]. Medical and socio-cultural factors such as psychosocial and behavioral interventions, active screening behaviors, and healthier lifestyles may also play an integral role in the length and quality of that survival [10,11].

Most therapeutic modalities for cancer are associated with a spectrum of late complications ranging from minor and treatable to serious or, occasionally, potentially lethal [3,4,12]. Thus, there is today a greater recognition of symptoms that persist after the completion of treatment and also those 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. 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. These concerns underscore the need to follow-up, monitor

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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 adverse outcomes [3,4].

The goal of survivorship research is to focus on the *health and life* of a person with a history of cancer *beyond* the acute diagnosis and treatment phase. Survivorship research seeks to examine the causes of, and to prevent and control the adverse effects associated with, cancer and its treatment, and to optimize the physiologic, psychosocial, and functional outcomes for cancer survivors and their families. A hallmark of survivorship research is its emphasis on understanding the integration/interaction of multi-disciplinary domains.

This paper will present definitional issues relevant to cancer survivorship, describe the evolving paradigm of cancer survivorship research, explore research needs of particular relevance to long-term cancer survivors, examine cancer survivorship as a scientific research area, provide a brief overview of medical sequelae of cancer diagnosis and treatment, assess the impact of these adverse sequelae on post-treatment follow-up care, and articulate gaps in knowledge and emerging research priorities in cancer survivorship research.

Definitional issues

Fitzhugh Mullan, a physician diagnosed with and treated for cancer himself, first described cancer survivorship as a concept [13]. Definitional issues for cancer survivorship encompass two related aspects: *1) What is cancer survivorship?* Mullan described the survivorship experience as similar to the seasons of 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 for facilitating an optimal transition into and management of survivorship; and *2) What is cancer survivorship research?* Cancer survivorship research seeks to identify, examine, prevent, and control 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 those for *long-term cancer survivorship* and *late versus long-term effects of cancer treatment*. Generally, *long-term cancer survivors* are defined as those individuals who are 5 or more years beyond the diagnosis of their primary disease and embody the concept of permanent survival described by Mullan. *Late effects* refer specifically to unrecognized toxicities that are absent or sub-clinical at the end of therapy and become manifest later with the unmasking of hitherto unseen injury due to any of the following factors: developmental processes; the failure of compensatory mechanisms with the passage of time; or, organ senescence. *Long-term effects* refer to any side effects or complications of treatment for which a cancer patient must compensate; also known as persistent effects, they begin during treatment and continue beyond the end of treatment. Late effects, in contrast, appear months to years after the completion of treatment. Some researchers classify cognitive problems, fatigue, lymphedema and peripheral neuropathy as long-term effects while others classify them as late effects [14–17].

The evolving paradigm of cancer survivorship research

Consistent with the shift in our perceptions of cancer as a chronic disease, new perspectives, and an emerging body of scientific knowledge must now be incorporated into Mullan's original description of the survivorship experience [2–4,13]. Mullan's comparison of cancer survivorship with "seasons of the year" had implied that the availability and widespread use of curative and effective treatments would lead to a low likelihood of recurrence and longer survival times. However, the potential impact of late and long-term adverse physiologic and psychosocial effects of treatment was not described. In addition, further advances in survivorship research over the past few years have necessitated the incorporation of other emerging concepts into the evolving paradigm of cancer survivorship research [2–4]. These include: the impact of comorbidities on a survivor's health status and their possible interaction with risk for or severity of late effects; the key role of lifestyle factors and health promotion in ameliorating adverse treatment and disease-related consequences; the effect of cancer on the family; and the need for incorporating a developmental and life-stage perspective in order to facilitate optimally a cancer patient's journey into the survivorship phase. A developmental/life-stage perspective is particularly important as it carries the

potential to affect and modify treatment decisions, the intensity of post-treatment follow-up care, the risk and severity of adverse sequelae of treatment, and the need for or use of technologies such as sperm banking (depending on the survivor's age at diagnosis and treatment) [2–4]. Data on late effects from studies conducted largely in childhood cancer survivors [18] have paved the way for and provided an implied "paradigm" for cancer survivorship research among adult survivors. Whether there is a consistent childhood cancer survivorship model requires examination. If this is so, we must explore whether and to what extent it 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.

It is of critical importance that we design and conduct cancer survivorship research with methodologic rigor. Confounders, effect modifiers, mediators, and moderators need to be assessed. Measurement issues are challenging and multifaceted. Not only must late and long-term medical effects be measured, attention also needs to be directed to the careful assessment of concurrent co-morbid conditions. The impact of late or long-term effects on the timing and severity of co-morbid conditions, and vice versa, needs to be examined rigorously. Health related quality of life needs to be assessed in conjunction with late effects and co-morbid conditions. Thus, these measurement issues are complex and encompass at least three inter-related aspects of cancer survivorship. All this needs to be carried out with an overall research/theoretical model that is capable of explaining the results and inferences observed [2–4].

Major portions of the published literature on cancer survivorship are descriptive (hypothesis generating) in nature. Survivorship research studies should now move towards analytic (hypothesis testing) study designs, clinical trials and interventions. Creative hybrid designs such as nested case-control or case-cohort studies are of great value in yielding quantitative data. Triangulation of methodologies, utilizing a combination of qualitative and quantitative approaches, is also immensely useful. There is a need for exploring models for interventions that are effective and can be disseminated into the community, and a need for education both for the provider and the survivor. Educational needs include the development of guidelines for optimal post-treatment follow-up care and monitoring of pediatric and adult cancer survivors, and the prevention, early detection, or management of late and long-term effects of cancer treatment. These guidelines must be evidence-based, and evaluated for effectiveness and impact.

The constantly evolving effect of a 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 significantly affects the cancer survivorship research paradigm of the new millennium. Cancer treatments today are increasingly used in the context of the survivor's life, striving toward minimal toxicity yet optimal effectiveness and with 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 [2–4]. Thus, our new, dynamic, and evolving paradigm of cancer survivorship research can be summarized as one that:

(a) Seeks to identify, examine, prevent and control adverse sequelae of cancer and its treatment;
(b) Manages, treats and prevents comorbidities;
(c) Incorporates health promotion and lifestyle interventions to optimize health after cancer treatment;
(d) Defines optimal follow-up care and surveillance strategies and guidelines for all survivors;
(e) Pays special attention to disparities in survivorship outcomes by age, income, ethnicity, geography or cancer site; and
(f) Explores the impact of the survivorship experience on the family (and vice versa).

This paradigm looks *beyond* treatment, representing a shift away from a medical deficit-dysfunction model, and towards a multi/inter disciplinary focus. Cancer survivorship research studies now rarely examine late effects in isolation, and are beginning to, and will continue to, incorporate the full domains of cancer survivorship research (physiologic, psychosocial, economic) in their conceptual models and research designs. There is a desire and a need to elucidate the underlying mechanisms, biology and bio-behavioral basis of sequelae, and the competing causes of morbidity and mortality. As such, cancer survivorship research today reflects the incredible successes in cancer treatment and early detection that have enabled the continued growth in numbers of cancer survivors and their expectation to lead rich and fruitful lives [2–4].

Long term cancer survivors: Research needs and issues in a growing yet understudied portion of the survivorship continuum

Despite the increasing number of cancer survivors living 5 years or more after a cancer diagnosis, a review of the literature indicates that most of what we know about cancer survivorship today focuses largely on the period between diagnosis and 2 years after treatment (the early survivorship phase). However, most late effects of cancer treatment have much longer latency periods, [3,9–13,19] and tend to occur during the extended survivorship years. Thus, while cancer survivors are living longer, we have limited knowledge and many questions about the health status, functioning, and quality of life for most of those who have been post-treatment for long periods of time: What are the most common late effects of treatment? Who is at risk and can they be protected? Can treatment-related injury to normal tissue be prevented or reversed? What proportion of survivors will experience recurrent or second malignancies? Who should be following these survivors for disease recurrence? What constitutes "optimal surveillance" and what is the cost of such follow-up care? Do medical, psychosocial, or behavioral interventions reduce morbidity in these populations? These questions, especially among those diagnosed with cancer as adults, underscore the need for continued research in this ever-growing portion of the cancer survivorship spectrum [9–11,13,21].

To date, the prevalence, incidence, relative risk, and genetic basis of late and long-term effects of cancer and its treatment among survivors diagnosed at least 5 years ago remains to be elucidated for the majority of cancer sites. Among adults, the largest body of knowledge comes from breast cancer survivors. Highly prevalent primary cancer sites such as colorectal, gynecologic, head and neck, prostate and lung continue to be understudied with respect to medical outcomes such as: cardiotoxicity [20,21], neurocognitive problems [22–25], premature menopause [26], sexual impairment [27,28], infertility [29,30], chronic fatigue [31,32], pain syndromes, and second malignancies [33].

There is growing appreciation of the role that socio-cultural and behavioral factors play in patient outcomes, decision-making, adherence to treatments, and willingness to adopt appropriate surveillance and health maintenance behaviors post-treatment. Psychosocial or behavioral interventions carry the potential to improve the health-related quality of life, functioning and even medical status of cancer survivors and their family members [34,35]. While we know that human behavior can have a profound impact on how cancer is managed and may also affect disease-free or overall survival, we are not currently using this information in the systematic delivery of care. We also know little about the best delivery of interventions, and we continue to need more data regarding psychosocial issues such as poor quality of life, fear of recurrence, poor self-esteem, anxiety and depression, job lock or loss, employment and insurance discrimination, body-image disturbances, relationship difficulties, and financial hardship [36–40].

Survivorship outcomes among medically underserved and ethno-culturally diverse cancer survivor populations, and family members or care-givers, represent another under-studied area [24,41,42]. Although more than 62% of cancer survivors are age 65 and older, and the median age at diagnosis is 67–68 years, only a fraction of research studies have examined the effect of cancer and its treatment on older individuals. This major segment of the cancer survivor population also tends to be affected by co-morbid health conditions which may interact with the cancer treatment itself, and may modulate the risk for, or severity of, persistent or late effects of cancer therapy [43].

Finally, while high quality follow-up care is a necessary fact of life for all cancer survivors, both for the prevention or early detection of physiological and psychosocial sequelae, and for the timely introduction of optimal treatment strategies to prevent or control late effects, to-date, there is no standardized model of service delivery applied consistently across cancer centers and post-treatment follow-up care programs. Nor has an attempt been made to examine the quality, content, and optimal frequency of follow-up care of cancer survivors delivered in the community setting by oncologists or by primary care providers [44].

Areas of emphasis and potential research questions in long-term cancer survivorship research are presented in Table IV.

Cancer survivors, health care utilization, and co-morbid conditions

Cancer survivors are high healthcare utilizers affecting distinct healthcare domains owing to therapeutic exposures, genetic predisposition and/or lifestyle risk factors [3,4,10,45–47]. While the threat of progressive or recurrent disease is at the forefront of health concerns for a cancer survivor, increased morbidity and decreased functional status and disability that result from cancer, its treatment or health-related sequelae also are significant concerns. The impact of chronic co-morbid conditions on cancer and its

treatment is heightened more so among those diagnosed as adults and those who are elderly at the time of diagnosis.

Presented below is a brief overview of some factors potentiating the risk for chronic co-morbid conditions among cancer survivors. A brief discussion of the major co-morbid illnesses observed among survivors is also presented.

Metabolic syndrome associated diseases – Obesity, diabetes and cardiovascular disease

Obesity is a well-established risk factor for cancers of the breast (post-menopausal), colon, kidney (renal cell), esophagus (adenocarcinoma), and endometrium, thus a large proportion of cancer patients tend to be overweight or obese at the time of diagnosis [48,49]. Additional weight gain also can occur during or after active cancer treatment, an occurrence that has been frequently documented among individuals with breast cancer, but recently has been reported among testicular and gastrointestinal cancer patients, as well [50,51]. Given data that obesity is associated with cancer recurrence in both breast and prostate cancer, and reduced QOL among survivors, there is compelling evidence to support weight control efforts in this population [14,15,52]. Gradual weight loss also has proven benefits in controlling hypertension, hyperinsulinemia, pain, dyslipidemia, and improving levels of physical functioning – conditions that reportedly are significant problems in the survivor population [14,15,21,53].

Obesity is a common manifestation of several metabolic disorders that are frequently observed among cancer survivors. These disorders are grouped under the umbrella term, "the metabolic syndrome," and also include diabetes and cardiovascular disease (CVD). Insulin-resistance is the underlying event associated with the metabolic syndrome and co-occurs with hyperinsulinemia and/or diabetes [54–56]. Diabetes may play an especially significant role in the increased number of non-cancer related deaths among survivors, however, its role in progressive cancer is still speculative [3,4].

Older breast cancer patients may derive a cardioprotective benefit from their diagnosis and/or associated treatments (most likely due to tamoxifen) [57]. Reports indicate that CVD is a major health issue among survivors, evidenced by mortality data which show that half of non-cancer related deaths are attributed to CVD [10]. Risk is especially high among men with prostate cancer who receive hormone ablation therapy, as well as patients who receive adriamycin, and radiation treatment to fields surrounding the heart [58].

Osteoporosis

Osteoporosis and osteopenia are prevalent health conditions in the general population, especially among women. Despite epidemiologic findings that increased bone density and low fracture risk are associated with an increased risk for breast cancer [59–62], clinical studies suggest that osteoporosis remains an important health concern among survivors [63,64]. Approximately 80% of older breast cancer patients have t-scores less than -1 and thus have clinically confirmed osteopenia at the time of their initial appointment. Other cancer populations, such as premenopausal breast and prostate cancer patients may possess good skeletal integrity at the onset of their disease, but are at risk of developing osteopenia which may ensue with treatment-induced ovarian failure or androgen ablation [10].

Decreased functional status

Previous studies indicate that functional status is lowest immediately after treatment and tends to improve over time; however, the presence of pain and co-occurring diseases may affect this relationship [65]. In the older cancer survivor, regardless of duration following diagnosis, the presence of comorbidity, rather than the history of cancer per se correlates with impaired functional status [66]. Cancer survivors demonstrate almost a two-fold increase in having at least one functional limitation, and, in the presence of another co-morbid condition, the odds ratio increases to 5.06 (95% CI 4.47–5.72) [67]. These findings have been confirmed by other studies in diverse populations of cancer survivors [68–70].

Survivors of childhood cancer may experience an increased risk for functional limitations in physical performance and participation in activities of daily living. Compared with siblings, survivors are more likely to report performance limitations, restricted participation in personal care skills, problems with routine activities, and an adverse impact on the ability to attend work or school [71]. They also suffer from significantly elevated rates of *chronic* health conditions. Approximately 62.3% of 10 397 survivors in a recent study had at least one chronic, while 27.5% had a severe or life-threatening, condition. The cumulative incidence of a chronic health condition was 73.4%, and for a severe, disabling, or life-threatening condition was 42.4%, even as late as 30 years after diagnosis [72].

Among survivors diagnosed as adults, a seminal study utilizing the Nurses Health Study Cohort was the first to report that breast cancer results in persistent declines in multiple dimensions of func-

tional health status, and that socially isolated and younger women are an especially vulnerable group. These prospective data suggest that previous studies reporting no difference in physical function among breast carcinoma cases compared with disease free women underestimated the deleterious effect of the disease on function [73]. After adjustment for age, baseline functional health status, and multiple covariates, women who developed incident breast carcinoma were more likely to have experienced reduced physical function, role function, vitality, and social function and increased bodily pain compared with women who remained free of breast carcinoma. The risk of decline was attenuated with increasing time since diagnosis. Risk of decline in physical function was evident across all stages of breast carcinoma, even after adjustment for women undergoing treatment for persistent or recurrent disease. Compared with women $<$or$=$40 years without breast cancer, women with breast cancer experienced significant functional declines. Young (age $<$or$=$40) women who developed breast cancer experienced the largest relative declines in HRQoL (as compared with middle-aged and elderly women) in multiple domains including physical roles, bodily pain, social functioning and mental health [74]. Among socially isolated women, role function, vitality, and physical function were significantly lower compared to the most socially integrated women. Prediagnosis level of social integration was also shown to be an important factor in future HRQoL among breast cancer survivors [75].

Overview of physiologic sequelae of cancer and its treatment

Physiologic late effects

Late and long-term effects can be classified further as: *(a) system specific* (such as damage, failure or premature aging of organs, immunosuppression or compromised immune systems, and endocrine damage); *(b) second malignant neoplasms* (such as an increased risk of a certain cancer associated with the primary cancer and a second cancer associated with cytotoxic or radiological cancer therapies*); (c) functional changes* (such as lymphedema, incontinence, pain syndromes, neuropathies and fatigue); *(d) cosmetic changes* (such as amputations, ostomies and skin and hair alterations); and *(e) associated comorbidities* (such as osteoporosis, arthritis, scleroderma and hypertension) [1–4]. The risk of a recurrence of the primary malignancy also must be kept in mind.

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 [20]. 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. Combinations of chemotherapy and radiation therapy are more often associated with late effects. 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. Organs or tissues most susceptible have high cell proliferation rates and include the 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 cytosine arabinoside; bone injury may be caused by methotrexate; and cardiac sequelae can occur after treatment with adriamycin. 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 [1–4]. The *most frequently observed medical sequelae* include endocrine complications, growth hormone deficiency, primary hypothyroidism, primary ovarian failure, cardiac dysfunction, neurocognitive deficits and second cancers. Risk factors for late effects may act independently or synergistically.

Issues unique to certain cancer sites. The examination of late effects for childhood cancers such as leukemia, Hodgkin's lymphoma and brain tumors have provided the foundation for this area of research. A body of knowledge on late effects of radiation and chemotherapy is also now appearing for adult cancer sites such as *breast cancer*. 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 [3,9–11,33,34]. We now have preliminary support for the hypothesis that the epsilon 4 allele of APOE may be a potential genetic marker for increased vulnerability to chemotherapy-induced cognitive decline [76]. 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 [3,20,35,36]. The side effects of radiotherapy, both alone and with chemotherapy, have been reported fairly comprehensively for childhood cancer sites associated with good survival rates. 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.

Issues unique to specific therapeutic exposures. The use of *anthracyclines* for cancer treatment is associated with cardiotoxic effects among survivors of both childhood and adult cancer. The result is cardiomyopathy and potentially irreversible congestive heart failure. Anthracycline-induced cardiotoxicity is characterized by reduced left ventricular wall thickness and mass, indicating decreased cardiac muscle and depressed left ventricular contractility. Risk factors include high cumulative doses, high dose intensity, and radiotherapy. Among survivors of breast cancer, *Herceptin* and *radiotherapy* have both been shown to exert cardiotoxic effects. Cardiomyopathy disease progression can be delayed in adults by using angiotensin-converting enzyme inhibitors such as enalapril. Studies in long-term survivors of pediatric cancer have shown that enalapril has significant benefits in preventing cardiac functional deterioration on a short-term basis, but this is not sustained. Dexrazoxane may significantly reduce cardiotoxicity associated with anthracyclines in adult patients, and is possibly efficacious among children and adolescents as well. Significantly fewer dexrazoxane-treated patients (21%) had elevated serum cardiac troponin (a biomarker of acute myocardial injury) levels than patients treated with chemotherapy alone (50%; $p < 0.001$). Dexrazoxane has been shown to have no effect on the event-free survival rate at 2.5 years, emphasizing that it does not detrimentally affect the efficacy of anthracycline therapy [77–80]. However, its long-term impact on the risk for second cancers remains to be elucidated. In terms of health-related quality of life, important differences have been reported between breast cancer survivors treated with chemotherapy compared to local therapy alone, suggesting that long-term QOL may vary depending on the type of treatment and diagnosis [81].

Special considerations when primary diagnosis and treatment occurs in childhood. Cancer therapy during childhood may interfere with physical and musculoskeletal development [82–86], neurocognitive and intellectual growth [87,88], and pubertal development [89]. These effects may be most notable during the adolescent growth spurt. Prevention of second cancers is also a key issue [11,13].

Premature menopause is a frequent and significant after effect of cancer treatment. It has now been shown that childhood cancer survivors who retain ovarian function after completing cancer treatment are at increased risk of developing premature menopause (cessation of menses before age 40 years). Risk factors for such nonsurgical premature menopause include attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent score (based on number of alkylating agents and cumulative dose), and a diagnosis of Hodgkin lymphoma. Those treated with alkylating agents plus abdominopelvic radiation are at particularly high risk (cumulative incidence approaching 30%) [90]. Defined as the loss of ovarian function within 5 years of diagnosis, acute ovarian failure is known to develop in a subset of survivors of pediatric and adolescent cancers. Risk factors for acute ovarian failure include: older age at diagnosis, Hodgkin's lymphoma, and, abdominal or pelvic radiotherapy in doses of at least 1 Gy. Increasing doses of ovarian irradiation, exposure to procarbazine, and exposure to cyclophosphamide at ages 13–20 years have also been reported as independent risk factors [91].

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 [3]. 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 [92].

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 [3,11,20]. 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 [93]. 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. 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 [3,9,10].

Although *older patients (aged 65 years or more)* 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. The combination of late effects of cancer or its treatment and age-related health problems and co-morbidities add to the vulnerability of older survivors. In one study, older or long-term survivors who had chemotherapy and survivors with more types of treatment reported significantly more symptoms both during treatment and currently. Women and African Americans appear to be at special risk for more symptoms and greater functional difficulty. Pain was the most commonly reported symptom, with 21% attributing it to cancer [94]. 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 and the subsequent course of cancer or the comorbid condition. It is also not known 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 [52].

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) [1–4]. Within 20 years, survivors of childhood cancer have an 8 – 10% risk of developing a second cancer [1–4]. 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 [1–4]. The risk of malignancy with normal aging may be a result of cumulative cellular mutations. 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; solid tumors, including breast, bone and thyroid cancer in radiation fields; and bladder cancer after cyclophosphamide. Second cancers may also occur in the same organ site (e.g., breast, colorectal); thus there is a clear need for continued surveillance [3,9,10,73].

Follow-up care for late and long-term effects

Optimal follow-up of survivors includes both an ongoing monitoring and assessment of persistent and late effects of cancer treatment, and the successful introduction of appropriate interventions to ameliorate these sequelae [44]. The achievement of this goal is challenging and inherent in that challenge is the recognition of the importance of preventing premature mortality from the disease and/or its treatment, and the prevention or early detection of both the physiologic and psychologic sources of morbidity. The prevention of late-effects, second cancers, and recurrences of the primary disease requires watchful follow up and optimal utilization of early detection screening techniques. Physical symptom management is as important in survivorship as it is during treatment and effective symptom management during treatment may prevent or lessen lasting effects [1–4,44,95].

Regular monitoring of health status post cancer treatment is recommended since this should 1) permit the timely diagnosis and treatment of long-term complications of cancer treatment; 2) enable timely diagnosis and treatment of recurrent cancer; 3) facilitate screening for, and early detection of, a second cancer; 4) allow the detection, and referral for management, of co-morbid conditions; and 5) provide the opportunity to institute preventive strategies such as diet modification, tobacco cessation and other life style changes [1–4,44,104,105].

Quality continuing care for cancer survivors spans a broad spectrum of medical domains ranging from surveillance to genetic susceptibility [1–4,44,96, 104,105]. Health promotion, since it addresses modifiable factors, is a key concern of survivors once acute management of their disease is complete. Increasingly, cancer survivors are looking to their oncology care providers for counsel and guidance with respect to lifestyle change that will improve their prospects of a healthier life, and possibly a longer one as well. While complete data regarding lifestyle change among cancer survivors have yet to be determined, and there remains an unmet need for behavioral interventions with proven efficacy in various cancer populations [97], the oncologist can nonetheless make use of extant data to inform

practice and also should be attentive to new developments in the field.

Follow-up care and monitoring for late effects is usually done more systematically and rigorously for survivors of childhood cancer while they continue to be part of the program or clinic where they were treated. The monitoring of adult cancer sites for the development of late effects, particularly outside the oncology practice, is neither thorough nor systematic. It is important that survivors of both adult and childhood cancers be monitored for the late and long-term effects or treatment discussed in preceding sections, at regular intervals.

While it is now recognized that cancer survivors may experience various late physical and psychological sequelae of treatment, and that many health care providers may be unaware of the adverse outcomes [98], until recently, there were no clearly defined, easily accessible risk-based guidelines for cancer survivor follow-up care. Such clinical practice guidelines can serve as a guide for doctors, outline appropriate methods of treatment and care, address specific clinical situations (disease-oriented) or use of approved medical products, procedures, or tests (modality-oriented). In response to this growing mandate, the Children's Oncology Group has developed and published its guidelines for long-term follow-up for Survivors of Childhood, Adolescent, and Young Adult Cancers [99]. These risk-based, exposure-related clinical practice guidelines are intended to promote earlier detection of and intervention for complications that may potentially arise as a result of treatment for pediatric malignancies, and are both evidence-based (utilizing established associations between therapeutic exposures and late effects to identify high-risk categories) and grounded in the collective clinical experience of experts (matching the magnitude of risk with the intensity of screening recommendations). Importantly, they are intended for use beginning 2 or more years following the completion of cancer therapy, and are not intended to provide guidance for follow-up of the survivor's primary disease.

Of great significance to survivors of adult cancer, using the best available evidence, ASCO's expert panels have also identified and developed practice recommendations for post-treatment follow-up of specific cancer sites (breast and colorectal; source: www.asco.org). In addition, ASCO has also created an expert panel tasked with the development of follow-up care guidelines geared towards the prevention or early detection of late effects among survivors diagnosed and treated as adults.

It is critical, if we are to develop effective research priorities and recommendations for clinical care, education, and policy related to care for survivors of cancer, that we note two key points: (a) the population of cancer survivors consists of individuals with varying needs and issues – those cured of their disease and no longer undergoing active treatment, as well as patients with recurrences or resistant disease requiring ongoing treatment; and (b) regardless of disease status, any survivor may experience lasting adverse effects of treatment [100].

Survivors of cancer have significantly poorer health outcomes on multiple burden-of-illness measures than do people without a history of cancer, and these health decrements may occur or continue many years after diagnosis [1–4,44]. Co morbid conditions are another major issue for many diagnosed with cancer, yet little is known about the quality of the non-cancer-related care receive by these survivors [101]. Compared with matched controls with no history of cancer, it has been reported that it is more likely that survivors would not receive recommended care across a broad range of chronic medical conditions (e.g., angina, congestive heart failure, and diabetes) [5]. Quality-of-life issues in long-term survivors of cancer differ from the problems they face at the time of diagnosis and treatment [102,103]. Thus, interventions with the potential to treat or ameliorate these many and varied late and chronic effects of cancer and its treatment must be developed, evaluated for efficacy, and disseminated.

The larger scientific community has begun to champion the need for cancer survivorship research, and to call for solutions that will lead to both increased length and quality of life for all cancer survivors. This demand is reflected in the language of several Institute of Medicine (IOM) and President's Cancer Panel reports, Progress Review Group (PRG) documents, and National Cancer Institute priorities. The IOM Report on cancer survivors diagnosed as adults articulates key areas for research and care delivery, especially with respect to the development of a formal care plan for survivors that integrates, within one document, key treatment relevant variables, exposures, late effect risks, and management/follow-up care needs [104]. The recent IOM report on childhood survivorship cites the need to create and evaluate standards and alternative models of care delivery, including collaborative practices between pediatric oncologists and primary care physicians as well as hospital-based long-term follow-up clinics [105]. Another IOM Report, *Ensuring Quality Cancer Care*, recognized that attributes of high quality care could be linked to optimal outcomes such as enhanced length and quality of survival, and that continued medical follow-up of survivors should include basic standards of care that address the specific needs of long-term survivors.

Survivors of cancer who have completed initial therapy generally require significant amounts of follow-up care during the first 2 years of diagnosis. The frequency and intensity of monitoring diminishes each year thereafter, a dramatic decrease occurring 2–5 years post-treatment. Conversely, the risk of late effects and the impact of long-term effects increases with time. This progressive fall-off in cancer and non-cancer related medical visits may reflect either a failure of the medical system to convey the risk for adverse treatment-related sequelae, or a manifestation of system driven barriers (unequal access, disparities in receipt of quality care). Patient driven factors (fear of recurrence or of findings) are also critical. Not all survivors may be aware of the late effects they may be at risk for. Thus treating physicians and institutions must provide survivors with a discharge summary detailing key treatment/exposure and baseline health information that may be relevant if or when late effects become manifest. They must also develop a tailored follow-up care plan that reflects elevations in risk due to previous therapeutic exposures.

To facilitate optimal follow-up during the post-treatment phase, the patient's age at diagnosis, side effects of treatment reported or observed during treatment, calculated cumulative doses of drugs or radiation, and an overview of late effects most likely for a given patient given the treatment history, should be summarized and kept on file. A copy of this summary should be provided to the patient, or parent of a child who has undergone treatment for cancer. The importance of conveying this detailed treatment history to primary care providers should be clearly communicated, especially if follow-up will occur in the primary/family care setting. Finally, screening tests that may help detect subclinical effects that could become clinically relevant in the future should be listed.

The majority of cancer survivors return to their primary care providers for medical follow-up once treatment ends, many of whom may be unaware of the additional health risks of cancer treatment. Provider education and training is thus necessary. Extant published international long term follow-up care guidelines provide a logical basis for informed practice, but are not truly evidence based and must be updated regularly and communicated optimally to providers and survivors to be truly effective and useful [106,107].

Due to the potential health vulnerability and complexity of medical needs, attention may shift away from important health problems not related to cancer, or, surveillance may become over vigilant. The lack of evidence base that can help tailor optimal care strategies needs to be addressed. The relative roles of primary care providers and specialists in the care of cancer survivors are not clear. Developing and testing interventions that examine outcomes among groups of survivors managed under different follow-up care settings is a critical need. We must add to the growing knowledge base of cancer survivorship and to facilitate the development of evidence based follow-up care and surveillance strategies in this health vulnerable group of individuals.

It is imperative that we achieve an evidence based understanding of the frequency, content, setting and experiences of follow-up care received by the broader population of cancer survivors in order to develop standards for such care with a view towards preventing, detecting early, or ameliorating the adverse outcomes [1–4,44]. Findings from methodologically rigorous studies will improve our understanding of the nature and extent of the burden of illness carried by cancer survivors, yield key information regarding follow-up care, and facilitate future efforts focusing on the development of standards or best practices for such care, especially when notable health disparities might exist.

Potential late effects of cancer and its treatment are summarized by organ system and by exposure to chemotherapy, radiation, or surgery, in Table I. Suggested follow-up care and monitoring strategies and guidelines for the prevention, early detection, or optimal management of late effects, are presented in Table II.

Discussion

Cancer survivorship research continues to provide us with a growing body of evidence regarding the unique and uncharted consequences of cancer and its treatment among those diagnosed with this disease. It is becoming an acknowledged fact that most cancer treatment options available and in use today will affect the future health and life of those diagnosed with this disease. Adverse cancer treatment-related sequelae thus carry the potential to contribute to the ongoing burden of illness, health care costs, and decreased length and quality of survival [2,44].

Given the current gaps in our knowledge, it is especially critical that we expand and accelerate our potential to address the impact of survival from cancer in particular with respect to:

1) *Research questions addressing specific gaps in our knowledge*: such as the incidence of and risk factors for late and long-term effects of cancer and its treatment, role of socio-cultural and behavioral factors in modulating treatment out-

Table I. Possible late effects of radiotherapy & chemotherapy.

Organ System	Late Effect/Sequelae of Radiotherapy	Late Effect/Sequelae of Chemotherapy	Chemotherapeutic drugs responsible
Bone and Soft Tissues	Short stature; atrophy, fibrosis, osteonecrosis	Avascular necrosis	Steroids
Cardiovascular	Pericardial effusion; pericarditis; CAD	Cardiomyopathy; CCF	Anthracylines Cyclophosphamide
Pulmonary	Pulmonary Fibrosis; Dec. Lung Volumes	Pulmonary fibrosis Interstitial pneumonitis	Bleomycin, BCNU Methotrexate, Anthracyclines
CNS	Neuropsychological Deficits, Structural Changes, Haemorrhage	Neuropsychological Deficits, Structural changes; Hemiplegia; seizure	Methotrexate
Peripheral Nervous System	–	Peripheral neuropathy; hearing loss	Platinum analogues, Vinca alkaloids
Hematological	Cytopenia, myelodysplasia	Myelodyplastic syndromes	Alkylating agents
Renal	Dec. creatinine clearance; Hypertension	Dec creatinine clearance; Inc. creatinine; Renal F Delayed Renal F	Platininum analogues Methotrexate Nitrosoureas
Genitourinary	Bladder fibrosis, contractures	Bladder fibrosis; Hemorrhagic cystitis	Cyclophosphamide
Gastrointestinal	Malabsorption; stricture; Abnormal LFT	Abnormal LFT; Hepatic fibrosis; cirrhosis	Methotrexate, BCNU
Pituitary	Growth hormone deficiency; pituitary deficiency	–	–
Thyroid	Hypothyroidism; nodules	–	–
Gonadal	Men: risk of sterility, Leydig cell dysfunction.	Men: sterility	Alkylating agents
	Women: ovarian failure, early menopause	Women: sterility, prem menopause	Procarbazine
Dental/oral health	Poor enamel & root formation; dry mouth	Tooth decay	multiple
Opthalmological	Cataracts; retinopathy	Cataracts	Steroids

comes, impact of survivorship on health care utilization, role of co-morbidity in outcomes, appropriate follow up care and surveillance for survivors, and the effect on families of living with a cancer history in a loved one; and

2) *Research among understudied survivor groups*: such as those treated for colorectal, gynecologic, or hematologic malignancies, and those belonging to underserved populations (e.g. adult, elderly, rural, low education/income, and diverse racial and ethnic populations) [2].

The goal of cancer survivorship research is to examine questions and develop interventions or strategies that will lead to a decrease in physiologic and psychologic morbidity and mortality associated with post-treatment survival from cancer. While there is a critical need for additional data on adult cancer survivors, innovative studies addressing gaps in research among survivors of childhood cancer, especially those who are 5 years or more beyond diagnosis, are also important. The next generation of survivorship studies will need to use appropriately valid and reliable measures of both physiologic and psychosocial variables. Furthermore, as the number of new therapies for cancer with as yet undocumented sequelae continue to increase, we will need research models and trained researchers poised to explore and address these [1,2,4].

Cancer survivorship research domains are presented in Table III and examples of research questions of particular relevance to long-term cancer survivorship are summarized in Table IV.

Conclusion

As the number of survivors with long overall or disease-free survival periods increase, long-term health issues are fast emerging as a public health concern. Research on the chronic or delayed complications of cancer and its treatment or care is needed, and will: inform our understanding of the biology of the disease; lead to the design of novel, less toxic treatments; test the effectiveness of interventions – medical, pharmacologic, and behavioral – to reduce adverse physiological and quality of life outcomes; guide follow-up care practices; and inform patient and provider treatment-related decision making.

Table II. Follow-up care and surveillance for late effects.

Follow-up Visit	Content of Clinic Visit	Suggested Evaluative Procedures and ancillary actions
Chemotherapy/Radiotherapy Treatment Completion	1. Review Complete Treatment History	Develop late Effect Risk profile
	2. Calculate cumulative dosages of drugs	Summarize all information in previous column
	3. Document Regimen(s) administered and Radiation ports, dosage, machine	Provide copy to patient (or parent if minor child)
	4. Document patient age at diagn/Trt	Instruct that this summary should be provided to primary care or other health care providers
	5. Assess side effects during treatment	
	6. Identify likely late effects	
	7. Perform Baseline "grading" of late effects (CTCAEv.3.0, Garre, SPOG, others)	Keep copy of summary in patient chart
General Measures at every visit	1. Detailed history	Evaluate symptomatology, patient reports of issues
	2. Complete Physical exam	Review any intercurrent illnesses
	3. Review systems	Evaluate for disease recurrence, second neoplasms
	4. Meds, maint., prophylactic antibiotics	Systematic Evaluation of long term(persistent) and late effects (See Specific Measures)
	5. Education: GPA, school performance	
	6. Employment history	Grade long term & late effects: Garre or SPOG criteria and note changes
	7. Menstrual status/cycle	
	8. Libido, sexual activity	CBC; Urinalysis; Other tests depending upon exposure History and late effect risk profile
	9. Pregnancy & outcome	
Specific Measures to evaluate late effects	Growth: Includes issues such as short stature, scoliosis, hypoplasia	Monitor growth (growth curve); sitting height, parental heights, nutritional status/diet, evaluate scoliosis, bone age, growth hormone assays, thyroid function, endocrinologist consult; orthopaedic consult (if appropriate)
Relevance differs by:		
1. Age at diagnosis/Treatment	Cardiac	EKG, Echo, afterload reduction, cardiologist consult
2. Specific drugs, regimens		Counsel against isometric exercises if high risk, advise OB/Gyn risk of cardiac failure in pregnancy
3. Combinations of Treatment modalities	Neurocognitive	History and Exam
4. Dosages administered		Communicate: School, Family, Special education
5. Expected Toxicities (based on mech of action of cytotoxic drugs (cell cycle dependent; proliferation kinetics).		Compensatory Remediation Techniques
		Neuropsych consult; CT or MRI; CSF; basic myelin protein
		Written instructions, appointment cards
6. Exceptions occur to the theoretical assumption that least susceptible organs/tissues are those that replicate slowly or not at all (Platinum analogues, methotrexate, anthracyclines).	Neuropathy	History/Exam: Neurolog exam, sensory ch hands/ feet, paresthesias, bladder, gait, vision, muscle strength
		Neurologist consult
7. Combinations of radiation/ chemotherapy more often associated with late effects.	Gonadal toxicity	History for primary vs. secondary dysfunction, gonadal function (menstrual cycle, pubertal development/delay, libido); hormone therapy; interventions (bromocriptine)
		Premature menopause: hormone replacement unless contraindicated; DXA scans for osteoporosis; calciumEndocrinologist consult
		Reproductive Technologies
	Pulmonary	Chest X-ray; Pulmonary function tests; Pulmonologist consultation
	Urinary	Urinalysis; BUN/Creatinine; Urologist if hematuria
	Thyroid	Annual TSH; thyroid hormone repl; Endocrinologist
	Weight History	Evaluate Dietary intake (Food diary)/Physical Activity
		Nutritionist and/or Endocrinologist consult
	Lymphedema	History/ Exam: swelling, Sensations of heaviness/fullness
	Fatigue	Rule out hypothyroidism; anemia, cardiac/pulm sequelae,
		Evaluate sleep habits;
		Evaluate physical fitness and activity levels
		Regular physical activity unless contra-indicated
	Surgical Toxicity	Antibiotic prophylaxis (splenectomy)
	Gastrointestinal/Hepatic	Liver function, hepatitis screen, Gastro-enterologist consult

Table II (*Continued*)

Follow-up Visit	Content of Clinic Visit	Suggested Evaluative Procedures and ancillary actions
Screening for Second Malignant Neoplasms	Screening guidelines differ by age	Follow guidelines for age appropriate cancer screening (mammogram, pap smear, FOBT/ Flex Sig)
	Oncologist Consult	Mammog at age 30 if hx of mantle radiation for hodgkins Screen for associated cancers in HNPCC family syndrome Screen for ovarian cancer if hx of Breast ca and BRCAI II
Assess/Manage Co-morbidities	Osteoporosis; Heart Disease; Arthritis, etc.	History/Exam; Be Cognizant of risk; Appropriate Consult

To-date, few studies have examined and compared survivor outcomes pre-and post diagnosis. Inferences such as those from the Nurse Health Study need to be examined among other populations of survivors (e.g. colorectal, prostate, gynecologic, etc). Future studies also need to be cognizant of and utilize a life stage framework. The special vulnerability among older or long-term survivors is an important issue researchers and clinicians need to address. To improve overall health and to prevent or control long term or late effects, many cancer survivors may need to initiate and maintain diet, exercise and other lifestyle changes soon after diagnosis, and strategies that will facilitate these changes need to be tested and disseminated.

Not only do the late and long-term consequences of cancer and its treatment occupy a central core of importance in and of themselves, they also can influence infrastructure systems such as databases, follow-up requirements in clinical practice settings or clinical trials, new therapeutic approaches, surveillance recommendations, and the cancer research agenda itself.

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