Editorial

Cancer Survivorship Research: Opportunities and Future Needs for Expanding the Research Base

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The National Cancer Institute has determined that there are >10 million people alive today in the United States who have been diagnosed with cancer, and nearly two thirds have survived >5 years after their initial diagnosis (1). With the current advances in early detection and treatment, certain types of cancer that were once uniformly fatal, such as large majority of pediatric cancer, testicular cancer, and Hodgkin lymphoma, are now potentially curable. Additionally, patients with other common neoplasms, such as breast and colorectal cancers, enjoy improved disease-free and overall survival as a result of adjuvant therapy.

The number of cancer survivors in the United States has tripled since 1971 and is growing at the rate of 2% every year (2). It is therefore imperative to focus on the health and well-being of this large and ever-increasing population of cancer survivors. Cancer survivors represent a remarkably diverse group, characterized by a wide range of cancer diagnoses, clinical/biological features of their primary cancer, treatment exposures, social and demographic characteristics, and other comorbid health conditions. For example, whereas breast, prostate, and colorectal cancer account for >50% of all cancer survivors, >5 million survivors have been diagnosed and treated for other forms of cancer (Fig. 1). Furthermore, cancer is largely a disease of older persons, and thus, the majority of cancer survivors are older than 65 years (3). Thus, survivorship for the vast majority of cancer survivors occurs in a background setting of comorbid conditions, with a potentially greater effect on the health status of elderly cancer survivors (3).

Current Survivorship-Based Research. In recent years, research on quality of life in cancer survivors has increased steadily, consistent with the increasing recognition that end points other than disease-free survival are important to consider when evaluating the effectiveness of long-term survival (reviewed by Ayanian and Jacobsen; ref. 4). Contributing to this expansion of research has been the efforts of the National Cancer Institute Office of Cancer Survivorship. As summarized in Table 1, much of the increasing body of literature on treatment-related morbidities has come from research involving childhood cancer survivors (5, 6). Thus, although research in childhood cancer survivors has conclusively shown that chronic health conditions are more prevalent, serious, and persistent in cancer survivors, when compared with age- and sex-matched siblings (7), the substantially larger population of survivors of adult-onset cancers remain understudied (8).

The vast majority of cancer outcomes described in the adult cancer survivors has depended upon registry data, clinical trials data, or has been drawn from small convenience samples. One of the more reliable sources of treatment-related events is the randomized trial because it allows for capture of protocol-specified therapeutic exposures. However, many individual trials conducted in the adult cooperative group setting are small, with very low participation rates and lack sufficient statistical power to detect the very rare or low incidence treatment-related events. For this reason, data on the frequency and severity of treatment-related adverse events in the adult cancer population often comes from registry studies. These studies are subject to various biases that may underestimate or overestimate the association between treatment exposure and adverse events. For example, a large dropout rate from follow-up may overestimate the true incidence of adverse event, whereas serious underreporting of the event of interest due to lack of follow-up by the participating sites may underestimate the true incidence. In addition, information on family history or underlying comorbidities, such as hypertension, diabetes, and smoking are not assessed in many of these studies, and therefore, the effect of these factors on the risk of treatment-related toxicity is unknown. Thus, some of the critical questions about cancer outcomes in the adult cancer populations will require research involving large patient populations—populations that are representative of the cancer survivor community, and have been followed for long periods of time, with a greater range of patients than is offered by adults treated on cooperative group clinical trials or at smaller cancer centers.

As previously noted, cancer survivors are a very heterogeneous population. The risk for adverse events usually depends on therapeutic exposures, when those treatments were delivered (because regimens and techniques change over time), the length of time that has elapsed since those exposures, and underlying risk factors independent of the primary cancer or its treatment. Moreover, cancer is largely a disease of the elderly, so determining late effects from unrelated comorbid conditions during childhood cancer treatment, as well as other factors (such as genetic predisposition, environmental exposures, family history, and lifestyle) may all contribute to the development of chronic conditions later in life. Therefore, although much has been learned about the treatment-related morbidities in childhood cancer survivors, much more remains to be learned about cancer survival in adulthood.
conditions can be difficult. Outcomes research in cancer survivors therefore represents several challenges unique to this field. Additionally, the outcomes are relatively infrequent, requiring assembly of large, relatively uniform cohorts. The events occur after a latency of several years, sometimes decades, necessitating long and complete follow-up of these large populations. Finally, the study population needs to be well-characterized in terms of sociodemographic characteristics, detailed therapeutic exposures as well as comorbidities and family history. Having these data available when assessing long-term outcomes allows for adjustment for potential confounding and/or the ability to investigate the relationship between these variables and adverse events.

Adult-Onset Cancers: Expanding the Scope of Survivorship Research. Survivorship research should be expanded to include large multidisciplinary initiatives consisting of observational cohort studies and programmatically aligned projects (e.g., program projects). The National Cancer Institute–funded (CA 55727) Childhood Cancer Survivor Study (CCSS) is a well-established model for such research, enrolling >14,000 participants who have survived at least 5 years after treatment for childhood cancer (9). Survival rates for many of the childhood and adolescent cancers improved at a remarkable pace beginning in the early 1970s. With this success came the need and responsibility to consider the long-term morbidity and mortality associated with the treatments responsible for the increases in survival. To varying degrees, it had been shown that long-term survivors were at risk of developing a spectrum of adverse outcomes including premature death, second neoplasms, organ dysfunction (e.g., cardiac, pulmonary, gonadal), reduced growth and development, decreased fertility, impaired cognitive function, difficulties obtaining employment and insurance, and overall reduction in quality of life. Because of the young age of these cancer survivors, and thus the potential longevity, the delayed consequences of therapy may have a greater effect on their lives, families, and on society at large, than the acute complications of the cytotoxic therapies they have already experienced. Although single-institution studies, some limited consortia, and, occasionally, cooperative clinical trials groups, pursued investigation of late sequelae, it became increasingly clear that there were limitations inherent in these approaches. Single institution investigations provided many of the initial observations on selected sequelae occurring at relatively high frequencies or associated with severe morbidity. However, many of these single institution investigations and limited consortia were restricted by a small sample size and were often derived from patient populations that were treated in a similar fashion. Thus, accurate quantification of a complete range of risk was often impossible. Some studies of long-term survivors had been carried out within established consortia or cooperative clinical trials groups but with varied success. The pediatric cooperative groups had a primary objective of conducting therapeutic clinical trials and, although questions of health-related outcomes were of interest, the resources did not always exist to provide the necessary support to successfully conduct such nontherapeutic studies. Thus, it was determined that there was a critical need for an infrastructure, such as CCSS, for late-effects research that would overcome these limitations and move the field forward.

The case can be made that the status of survivorship research among adult-onset cancers is not dissimilar to the situation of childhood cancer survivorship research at the time the CCSS was proposed. Thus, investment in large-scale, multidisciplinary research initiatives among survivors of adult-onset cancers should be made.

The CCSS represents an outstanding example of a retrospective cohort study established to capture data on childhood cancer survivors; such information has proven to be extremely valuable in establishing the true incidence of, and quantifying relative-risk for, a broad range of adverse events within childhood cancer survivors. The CCSS has been successful because of the size and diversity of the cohort, which is extremely well-characterized in terms of therapeutic exposures and because of the very high participation rates of the cohort members—with follow-ups extending into decades. Because of these characteristics, the CCSS has been able to answer a wide spectrum of questions (Table 2) and represents a unique resource for research that is made available to the broader scientific community.

Recognizing these strengths, it is important to acknowledge the fact that the CCSS relies on self-report of outcomes and certain questions remain to be answered; these are detailed in Table 2. For example, the study design precludes understanding the natural course of asymptomatic cardiac dysfunction or the nature of hepatic dysfunction or the prevalence of osteoporosis—because all of these outcomes are asymptomatic until they are fairly advanced in their disease course. These limitations notwithstanding, the CCSS has enriched the childhood cancer survivorship literature in unprecedented ways and has been adopted as a model to study childhood cancer survivorship by several other countries. Through the Cancer Care Outcomes Research and Surveillance Consortium and the Cancer Research Network, the National Cancer Institute has already made substantial investments in assembling research cohorts of adults with newly diagnosed cancer identified from

![Figure 1. Estimated number of persons alive in the United States diagnosed with cancer by site (n = 10.5 million).](image-url)
population-based registries and large health care systems (10, 11). The infrastructure developed for these projects may provide platforms for expanded research on cancer survivors, although these might take some time to mature because of the prospective nature of the cohorts.

Impact of Expanding the Agenda of Survivorship Research. The population of cancer survivors is growing at the rate of 2% per year, and there is, therefore, a sense of urgency, as well as a moral obligation, to understand the health-related challenges faced by this seemingly vulnerable group of individuals to optimize their long-term care. Comprehensive and well-designed survivorship research can be translated into clinical practice through development of evidence-based clinical care guidelines and through development, testing, and implementation of intervention strategies designed to prevent or minimize the effect of treatment-related adverse outcomes (Fig. 2). Currently, follow-up care relevant to survivorship outcomes is neither standardized nor guideline- or evidence-based for most adult-onset cancers, and optimal practices have yet to be defined. The American Society of Clinical Oncology Cancer Survivorship Expert Panel chose two of the most common, well-known, and well-studied late effects—cardiac and pulmonary dysfunction—to provide the evidence to form the basis for the evidence-based clinical practice guidelines. Yet, after rigorous evaluation of the evidence, it was concluded that the evidence was not sufficient to support evidence-based guidelines (12). There is therefore insufficient evidence on which to base evaluation for and management of these relatively common problems.

Although evidence on which to base management of cancer survivors may not be currently available, consensus guidelines from an expert panel can serve as a starting point by standardizing care. It then becomes possible to study the effect of the guidelines on care delivered, thereby gaining the evidence needed to create subsequent iterations of the guidelines. Through this process, the critical accumulation of data will then form the basis of truly evidence-based guidelines. In the meantime,

| Table 1. Summary of selected treatment-related adverse events in cancer survivors |
|--------------------------------|----------------------------------|
| Exposure | Potential adverse events |
| Surgery | Impaired cognition, motor and/or sensory neurologic sequelae |
| Head and neck surgery | Difficulty swallowing, impaired speech, cosmetic, psychosocial morbidity |
| Lymph node dissection | Lymphedema, retrograde ejaculation in testicular cancer |
| Abdominal surgery | Intestinal obstruction, hernia |
| Pelvic surgery | Sexual dysfunction, incontinence, hernia, intestinal obstruction |
| Splenectomy | Impaired immune function—increased risk of sepsis |
| Amputation, Limb-sparing procedures | Cosmetic, psychosocial morbidity, arthritis, phantom/neuropathic pain, functional impairment |
| Lung resection | Impaired pulmonary functions, fatigue |
| Prostatectomy | Urinary incontinence, sexual dysfunction |
| Orchietomy | Premature menopause, infertility |
| Ostomy | Infertility, testosterone deficiency |
| Bowel obstruction, nausea/constipation/anorexia, fatigue, poor body image |
| Chemotherapy | Therapy-related myelodysplasia/acute myeloid leukemia (t-MDS/AML), gonadal failure, premature menopause, infertility, bladder cancer, bladder fibrosis (hemorrhagic cystitis), congestive heart failure (high-dose cyclophosphamide) |
| Anthracyclines | Cardiomyopathy, cardiac arrhythmias, t-MDS/AML |
| Bleomycin | Pulmonary fibrosis |
| Platinum compounds | Hearing loss, t-MDS/AML, impaired renal function, neuropathies |
| Corticosteroids | Osteoporosis, avascular necrosis, cataracts |
| Trastuzumab | Congestive heart failure |
| Taxanes | Congestive heart failure, neurophy |
| Carmustine | Pulmonary fibrosis |
| Topoisomerase II inhibitors | t-MDS/AML |
| Vinca alkaloids | Neupathy |
| Tamoxifen | Hot flashes, stroke, uterine cancer, blood clots |
| Aromatase inhibitors | Osteoporosis |
| Radiation therapy | Second cancers |
| Site of radiation | Atrophy, cosmetic, fibrosis, avascular necrosis |
| Bone and soft tissue | Coronary artery disease, congestive heart failure, pericarditis |
| Heart | Dental caries, xerostomia |
| Cranial radiation | Hypopituitarism, neurocognitive dysfunction |
| Thyroid | Hypothyroidism, thyroid cancer |
| Gonads | Hypogonadism, infertility, premature menopause |
| Gastrointestinal tract | Intestinal strictures, malabsorption |
| Lymph nodes | Lymphedema |
| Eye | Cataracts |
| Lung | Interstitial pneumonitis, pulmonary fibrosis |
| Kidney | Renal impairment |

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Table 2. Current literature on long-term outcomes of interest in cancer survivors—strengths and limitations of a CCSS paradigm

<table>
<thead>
<tr>
<th>Outcome of interest</th>
<th>CCSS</th>
<th>Current literature in outcomes after adult-onset cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsequent malignant neoplasms (except t-MDS/AML)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of risk with accuracy</td>
<td>Yes (14, 15)</td>
<td>Registry data with risk of underreporting (16)</td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (14, 15)</td>
<td>Yes</td>
</tr>
<tr>
<td>Relationship with chemotherapy dose</td>
<td>Yes (14, 15)</td>
<td>Registry data—limited information regarding radiation exposures</td>
</tr>
<tr>
<td>Identification of radiation dose response</td>
<td>Yes (17)</td>
<td>Registry data—limited information linked to comorbidities</td>
</tr>
<tr>
<td>Modification of risk with comorbidities, life-style exposures, family history</td>
<td>Yes (15)</td>
<td>Clinical trials—selection bias, follow-up issues, small sample</td>
</tr>
<tr>
<td>Examination of role of genetic susceptibility</td>
<td>Yes (18)</td>
<td>Lack of infrastructure to correlate biospecimens with outcomes</td>
</tr>
<tr>
<td>Therapy-related myelodysplasia/acute myeloid leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of risk, demographic and clinical risk factors, relationship with chemotherapy dose</td>
<td>No: study design precludes study of events in first 5 y of diagnosis with high fatality rates</td>
<td>Yes: extremely short latency, limited “at risk period”—conducive to studies using clinical trial (19) or registry data (20)</td>
</tr>
<tr>
<td>Studies to identify predictors/biomarkers before occurrence of subsequent malignant neoplasm (SMN)</td>
<td>No: study design precludes longitudinal data collection before occurrence of event of interest</td>
<td>No: lack of infrastructure for conduct of such studies</td>
</tr>
<tr>
<td><strong>Cardiovascular and pulmonary complications</strong> (congestive heart failure, coronary heart disease, stroke, pulmonary compromise)</td>
<td>Yes: self-report (risk of misclassification if no validation; refs. 21-23)</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size (24); small convenience samples (25-28); registry data (29, 30)</td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (21, 22)</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td>Relationship with chemotherapy dose</td>
<td>Yes (21, 22)</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td>Relationship with radiation dose</td>
<td>Yes (21, 22)</td>
<td>Registry data — with limited information regarding radiation details</td>
</tr>
<tr>
<td>Modification of risk with comorbidities, life-style exposures, family history</td>
<td>Yes (21)</td>
<td>Lack of infrastructure to correlate biospecimens with outcomes</td>
</tr>
<tr>
<td>Examination of role of genetic susceptibility</td>
<td>Yes (21)</td>
<td>Small studies—conflicting results</td>
</tr>
<tr>
<td>Type of pulmonary compromise</td>
<td>No: self-report precludes identification of specific types</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td>Asymptomatic cardiac dysfunction</td>
<td>No</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td>Progression of disease with serial follow-up</td>
<td>No</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special education needs, return to work</td>
<td>Yes (31)</td>
<td>Yes (32)</td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (31)</td>
<td>Yes (33)</td>
</tr>
<tr>
<td>Relationship with chemotherapy dose</td>
<td>Yes (31)</td>
<td>Small samples preclude association with specific therapeutic agents</td>
</tr>
<tr>
<td>Impact on specific domains</td>
<td>No: study design precludes testing</td>
<td>Small samples, nonstandardized instruments, conflicting results</td>
</tr>
<tr>
<td>Natural course of cognitive function</td>
<td>No: study design is cross-sectional</td>
<td>Small samples</td>
</tr>
<tr>
<td><strong>Endocrine</strong> (hypothyroidism, hypogonadism, infertility, premature menopause, obesity, diabetes)</td>
<td>Yes: self-report (risk of misclassification if no validation; refs. 34, 35)</td>
<td>Yes (limited to certain cancer sites; refs. 36, 37)</td>
</tr>
<tr>
<td>Magnitude of risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (34)</td>
<td>Yes</td>
</tr>
<tr>
<td>Relation with chemotherapy/radiation dose</td>
<td>Yes (34)</td>
<td>Limited information regarding chemotherapy/radiation details</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 2. Current literature on long-term outcomes of interest in cancer survivors—strengths and limitations of a CCSS paradigm (Cont’d)

<table>
<thead>
<tr>
<th>Outcome of interest</th>
<th>CCSS</th>
<th>Current literature in outcomes after adult-onset cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcomes</td>
<td>Yes (38, 39)</td>
<td>Yes (limited to certain cancer sites; ref. 40)</td>
</tr>
<tr>
<td><strong>Health status of cancer survivors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison with noncancer population</td>
<td>Yes (41)</td>
<td>Limited data</td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (43)</td>
<td>Limited data</td>
</tr>
<tr>
<td>Survivors’ knowledge about cancer, treatment</td>
<td>Yes (44)</td>
<td>Limited data</td>
</tr>
<tr>
<td>Health-related screening</td>
<td>Yes (45)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and hepatic dysfunction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identification of specific types of renal compromise (glomerular vs tubular defect)</td>
<td>No: self-report precludes</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td>Identification of specific types of hepatic dysfunction (cirrhosis vs chronic active hepatitis), association with hepatitis B or C</td>
<td>No: self-report precludes</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size</td>
</tr>
<tr>
<td><strong>Psychosocial outcomes</strong> (health-related quality of life, fatigue, sleep disturbance, depression, anxiety, stress)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of risk</td>
<td>Yes (46)</td>
<td>Yes (reviewed in refs. 4, 47-49)</td>
</tr>
<tr>
<td>Demographic and clinical risk factors</td>
<td>Yes (46)</td>
<td>Yes (reviewed in ref. 4)</td>
</tr>
<tr>
<td>Relation with chemotherapy/radiation dose</td>
<td>Yes (46)</td>
<td>Yes</td>
</tr>
<tr>
<td>Trajectory of recovery after diagnosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Patterns of healthcare use</td>
<td>Yes (50)</td>
<td>Yes (51)</td>
</tr>
<tr>
<td>Burden of morbidity</td>
<td>Yes (7)</td>
<td>Limited data</td>
</tr>
<tr>
<td>Cause-specific late mortality</td>
<td>Yes (53)</td>
<td>Data limited to specific populations (25, 54, 55)</td>
</tr>
<tr>
<td>High risk behaviors</td>
<td>Yes (56)</td>
<td>Clinical trials—selection bias, follow-up issues, limited sample size; registry data—with limited information linked to high-risk behaviors</td>
</tr>
</tbody>
</table>

Figure 2. Survivorship issues—future direction.

Consensus guidelines can educate the health care provider about the unique needs of cancer survivors and prevent overutilization or underutilization of screening tests. The Children’s Oncology Group has developed such guidelines for the long-term follow-up of childhood cancer survivors (13). However, the underpinnings of the Children’s Oncology Group Long-term Follow-up Guidelines is the large body of evidence in the literature.
describing the magnitude of risk of the adverse events, clear associations between specific therapeutic exposures and the adverse events, and finally identifying those at highest risk of the adverse events described by their sociodemographic, clinical, and therapeutic exposure characteristics. Creation of similar follow-up guidelines for the adult cancer survivors will require research endeavors that assist in describing the magnitude of risk and associated risk factors for the late-occurring adverse events in this population—an issue that needs to be addressed with a clear sense of urgency.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
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