Commentary

Breast cancer following childhood cancer—more to the story than we thought

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Advances in cancer biology, tested in clinical trials, and improvements in supportive care have contributed to an increasing number of individuals living many years following a cancer diagnosis. While this success has been realized across the age spectrum, it has been particularly evident in pediatric oncology, where overall survival rates approach, and in some cases exceed, 80% (1,2). As pediatric cancer survivors age, the health implications of prior cancer therapies become evident, elucidating a need for specialized long-term surveillance. The majority of childhood cancer survivors have at least one chronic health condition, many have multiple conditions, and these can be severe or disabling, affecting quality of life and contributing to pre-mature death (3,4). In fact, a recent report among a large cohort of Hodgkin lymphoma (HL) survivors uniquely outlined the multiplicity of cardiovascular conditions and the overall health burden experienced by these survivors (5). Many of the health issues identified among childhood cancer survivors might be expected in an older population, leading some investigators to suggest a potential mechanism for accelerated aging in this population (6).

Surveillance measures, initiated at an earlier age than might be routine, may be the first step to facilitate early detection and provide opportunities for preventive and ameliorative interventions to preserve health. Health care becomes a significant concern as these individuals move away from pediatric institutions and seek medical care from adult-focused providers in the community. Past medical histories and an understanding of long-term health risks do not necessarily transfer with the young adult survivor, nor are they uniformly appreciated by the primary care community. To address this need the Children's Oncology Group has meticulously developed guidelines to assist with the long-term management and screening of childhood cancer survivors (7). In addition to being regularly updated to reflect current research, these guidelines (survivorshipguidelines.org) are also being harmonized with guidelines from around the world in an effort to provide consistent recommendations for surveillance of common health conditions developing after treatment for childhood cancer (8).

Other than a primary recurrence, subsequent malignant neoplasms (SMN) are the leading cause of death among childhood cancer survivors. The risk of an SMN consistently increases over time, without plateau, and while elevated for all diagnoses, appears to be highest among survivors of HL (9). For female survivors, breast cancer is the most frequent neoplasm and is strongly associated with radiation exposure to the breast tissue. Numerous studies have elucidated this risk, reporting standardized incidence ratios (SIRs) ranging from 13.3 to 55.5 per 10,000 person years and a cumulative incidence of 13–20% by age 40–45 years (10). Using the Childhood Cancer Survivor Study (CCSS), Inskip and colleagues described a linear relationship between breast cancer and increasing radiation doses (OR, 7.1; 95% CI, 2.9–17 for 11.4–29.9 Gy; and 10.8; 95% CI, 3.8-31 for ≥30 Gy) (11). Importantly, survival from secondary breast cancer is inferior compared to a first breast cancer. Using population based data from the Surveillance, Epidemiology, and End Results program, HL survivors with a localized breast cancer had a 15-year overall survival rate

of 48% compared to 69% among patients with a *de novo* breast cancer and 33% *vs.* 43% among those with regional/distant disease (P value <0.0001) (12).

A recent report from Henderson *et al.* raises new questions concerning breast cancer following childhood cancer (13). Using the well-characterized CCSS cohort, risk of breast cancer was analyzed among 3,768 female survivors not previously exposed to chest radiotherapy. Forty-seven women reported a diagnosis of breast cancer (41 invasive cases and 6 ductal carcinomas *in situ*) with a median age at diagnosis of 38 years (range, 22–47 years). Twelve (26%) of these women were dead at last contact. The risk was 4-fold that of the general population (SIR, 4.0; 95% CI, 3.0–5.3) and notably elevated among sarcoma (SIR, 5.3; 95% CI, 3.6–7.8) and leukemia (SIR, 4.1; 95% CI, 2.4–6.9) survivors. Multivariable analyses identified associations with exposure to ≥250 mg/m^2 anthracyclines (rSIR, 3.8; 95% CI, 1.7–8.3) and high-dose alkylating agents (cyclophosphamide equivalent dose ≥18,000 mg/m^2; rSIR, 3.0; 95% CI, 1.2–7.7). Earlier studies have alluded to a potential breast cancer risk among survivors unexposed to chest radiation (14) but this is the first investigation to address this particular question with a sufficient number of cases to adequately characterize the risks.

These findings raise important questions concerning potential cancer predisposition among these women. Limited by self-report, the authors acknowledge that sufficient family history data were not available to investigate familial correlations, though it is possible that at least some of these women may have carried a *BRCA1/BRCA2* mutation. While the study population did not receive chest-directed radiation, half of those studied, and 22 of the 47 women with breast cancer, were treated with radiation for their primary cancer. Investigators report calculating scatter radiation doses, though specific dosimetry is not reported, and even low level radiation exposure may increase the breast cancer risk among women with a germline *BRCA* mutation. Diagnostic radiation exposure before age 20 has been shown to increase the risk among carriers (HR, 1.62; 95% CI, 1.02–2.58) with doses ≥0.0066 Gy increasing the risk 3-fold (HR, 3.16; 95% CI, 1.19–8.36) (15). This could be significant among cancer patients not only receiving therapeutic radiation to non-chest regions but also receiving numerous diagnostic studies, particularly sarcoma survivors who may undergo multiple staging evaluations. Variants at 6q21 have also been associated with second cancer risk among HL survivors treated in childhood but not among those treated as adults (16). While this gene-exposure interaction was identified among irradiated survivors, it raises the possibility of interactions with chemotherapy, such as anthracyclines and/or alkylating agents that have yet to be investigated.

Breast cancer screening, shown to reduce death rates (17), has not been without controversy, and this study raises important questions about appropriate surveillance in this unique population. In the general population screening is based upon risk determined by age, clinical factors (age at menarche, first birth, history of benign breast disease, breast density, etc.), and family history. Weighing the benefits and harms, these factors help guide recommendations for optimal screening modalities and frequencies. Recognizing the high risk among previously irradiated women, guidelines have been developed recommending annual mammography and breast magnetic resonance imaging for women exposed to ≥20 Gy chest radiation starting at age 25 years or 8 years from exposure, whichever comes later (7). Unfortunately, women are not receiving this screening. Among 551 at risk women in the CCSS, 63.5% of those age 25–39 years and 23.5% of those 40–50 years had not had mammography within the last 2 years, in fact 47.3% of those 25–39 years had never had a mammogram (18). Women who reported a physician recommendation were three times more likely (PR, 3.0; 95% CI, 2.0–4.0) to report receiving a mammogram compared to those who did not receive such a recommendation. Guidelines for this population do not take into account non-irradiated survivors and that approach will not necessarily change from this initial study. However, future analyses need to consider factors beyond exposures typically expected as carcinogenic. Research is needed to fully characterized and understand the risks among cancer survivors with varying exposure histories.

Finally, breast cancer prevention medications have been studied in high-risk women in the general population and both the U.S. Preventive Services Task Force and the American Society of Clinical Oncology have issued guidelines for their use (19,20). Childhood cancer survivors clearly differ from the populations contributing to these recommendations, but perhaps the time has come to study such interventions in these high-risk individuals. Estrogen receptor (ER) modulators (tamoxifen and raloxifene) reduce the risk of invasive ER-positive breast cancer compared to placebo (RR, 0.70; 95% CI, 0.59–0.82 and 0.44; 95% CI, 0.27–0.71; respectively) (21). Similarly the aromatase inhibitor exemestane has been shown to reduce the risk for

invasive disease by 65% (HR, 0.35; 95% CI, 0.18–0.70) among postmenopausal women (22). Side effect profiles are not inconsequential (risk of endometrial cancer, bone health, thromboembolism, etc.) and long-term use among women at risk for a multiplicity of chronic health conditions needs to be considered, but this may be the population to benefit most from well-designed cancer prevention trials.

Henderson and colleagues have drawn attention to breast cancer, an important women's health issue, and the need for carefully tailored screening for women previously treated for a childhood cancer. The risk remains primarily driven by radiation; however, research considering exposures other than radiation and gene-environment interactions will further elucidate the pathophysiology contributing to this late effect of cancer therapy and help refine screening and preventive measures.

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Footnote

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