Challenges Predicting the Cardiovascular Future for Survivors of Childhood Cancer

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ABSTRACT

Cardiovascular disease (CVD) risk stratification relies on assessment of nonmodifiable (age, sex, family history) and modifiable (weight, tobacco, physical activity, blood pressure, glucose/lipid levels) risk factors. Cancer therapy, itself a potential risk factor, may alter metabolism in long-term survivors of childhood cancer resulting in premature acquisition of age-related modifiable CVD risk factors. For survivors exposed to cardiotoxic therapies, the risk for CVD is significantly augmented by obesity, diabetes, dyslipidemia, and hypertension. An understanding of these risks may not be well communicated as survivors return to primary care and general population screening practices may be insufficient. Lipshultz and colleagues recruited childhood cancer survivors to return to their treating institution for a comprehensive clinical assessment. Interestingly, compared with a noncancer age-, sex-, and race/ethnicity-matched National Health and Nutrition Examination Survey population, cardiometabolic profiles were largely similar. However, cancer survivors had a higher prevalence of prehypertension/hypertension (38.4% vs. 30.1%, $P = 0.04$) and a lower prevalence of the metabolic syndrome (11.9% vs. 18.7%, $P = 0.05$). Applying general population CVD risk calculators and a cancer-specific model from the Childhood Cancer Survivor Study, risk estimates were notably higher when cardiotoxic cancer treatment exposures were included.

See related article by Lipshultz et al., p. 536

With some variability across diagnoses, 5-year survival rates for children diagnosed with cancer have consistently improved over the last five decades. However, the persistent health impacts of a cancer diagnosis and its treatment, particularly the influence of anthracycline exposures on the cardiovascular system contribute to substantial morbidity and premature mortality for this young adult population (1). Prevention efforts have included modifications of cardiotoxic exposures, the introduction of protective agents such as dexrazoxane, and long-term health surveillance.

Risk prediction modeling, mathematical formulas applied to clinical data to estimate health outcomes, have been used across medical subspecialties to foretell a variety of outcomes such as the development of disease, treatment responses, adverse events, and prognosis, as well as applied to resource utilization and care coordination (2). Accurate categorization can guide clinical decision-making and direct surveillance or interventions toward patients or populations at the highest risk. Focused identification of and interventions for high-risk groups may alleviate costs and reduce unneeded expenditures for low-risk populations. Many healthcare agencies and medical societies have developed risk-stratified screening guidelines, and these are particularly prominent in oncology and cardiology, with the goal of reducing the burden on healthcare systems and improving quality of life and life expectancy.

The analysis by Lipshultz and colleagues reports provocative findings comparing a select cohort of adult survivors of childhood cancer with a general population sample while simultaneously highlighting a paradox with standard cardiovascular disease (CVD) risk calculators applied to survivors of childhood cancer. Investigators compared the cardiometabolic profiles of 164 survivors participating in the Children's Oncology Group (COG) study 'Health Effects After Anthracycline and Radiation Therapy' (ALTE11C2) to a noncancer, age-, sex-, and race/ethnicity-matched population from the National Health and Nutrition Examination Survey (NHANES) database. The primary aim of ALTE11C2 is to determine whether patients treated on legacy COG protocols [P9404, P9425, P9426, DFCI 95–01 (leukemia/lymphoma survivors), and P9754 (osteosarcoma survivors)] randomized to dexrazoxane cardio-protection have decreased markers of heart failure compared with patients not treated with dexrazoxane. Eligibility for ALTE11C2 includes being alive, in first complete remission, without a history of progressive disease, hematopoietic cell transplant, or a subsequent malignant neoplasm requiring cardiotoxic therapy (chest radiation and/or anthracycline exposure). Results from this study have recently been published (3). The current analysis published in this issue of *Cancer Epidemiology, Biomarkers & Prevention* reports specifically on survivors enrolled on ALTE11C2 between 2014 and 2019 [median age 28 years (range: 16–38) and median time from diagnosis 17.5 years (13–22)] who returned to a COG institution for a history and physical examination, fasting laboratory panel [glucose, lipid panel, and glycosylated hemoglobin (HgbA1c)], and 2-dimensional echocardiography. The aim was to assess the burden of modifiable cardiovascular risk factors (obesity, diabetes, dyslipidemia, and hypertension) compared with population controls.

Rates of obesity, diabetes, and dyslipidemia did not differ, and fasting glucose, mean waist circumference, and HgbA1c were statistically lower among survivors, albeit within normal ranges for both groups. Mean systolic and diastolic blood pressures, also within normal parameters, were higher among survivors. The prevalence of diabetes was low in both groups (1.2% vs. 1.4%, $P = 0.99$) and fewer survivors had evidence of prediabetes (a fasting glucose of 100–125 mg/dL or HgbA1c of 5.7%–6.4%) compared with controls (9.9% vs. 15.8%, $P = 0.06$, respectively). Notably, however, prehypertension/hypertension was higher among survivors compared with the NHANES group (38.4% vs. 30.1%, $P = 0.04$). The metabolic syndrome (≥3 of the criteria set by the National Cholesterol Education Program's Adult Treatment Panel

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III) was present in 11.9% of survivors versus 18.7% of controls ($P = 0.05$). Fortunately, survivors were more likely to meet activity guidelines [OR 2.7, 95% confidence interval (CI), 1.9–3.9] and less likely to have smoked (OR 0.5, 95% CI, 0.3–0.7) or currently use tobacco (OR 0.4, 95% CI, 0.3–0.6).

A metabolic pattern among cancer survivors that is not significantly worse, or potentially better, than the general population is reassuring. Estimates of lifestyle parameters and metabolic abnormalities have varied across studies, often varying by diagnostic groups and exposures as well as comparison groups (i.e., siblings, community controls, or the general population; refs. 4–10). Recently, investigators from the Icahn School of Medicine at Mount Sinai reported similar findings among survivors of adult cancers participating in NHANES (mean age 55 $\pm$ 0.14 years; ref. 11). No statistical differences were noted on total cholesterol, high-density lipoprotein cholesterol, smoking status, overweight/obesity among participants with and without a history of cancer. However, more cancer survivors had a systolic blood pressure in the prehypertensive >120–129 mmHg (64%) or hypertensive ranges >130 mmHg (36%), as defined by Lipshultz and colleagues, than those without a cancer history (56% and 33%, respectively). These frequencies were higher than that found in the childhood cancer survivor cohort, 18.9% and 19.5%, respectively, likely due to differences in attained age (55 vs. 28 years). These investigators applied the Pooled Cohort Equation to estimate the 10-year risk for an atherosclerotic event. Mean scores were 8.3 $\pm$ 0.4% and 5.1 $\pm$ 0.1%, respectively, among those with and without a cancer history. Thirty-five percent of those with a cancer history had an elevated risk of a CVD event in the next 10 years compared with 23% of those without a cancer history ($P < 0.001$), suggesting unaccounted factors that may elevate the risk in patients with cancer.

Given the young age of childhood cancer survivors and the need for a longer-term risk perspective, Lipshultz used the Framingham 30-year risk calculator for a cardiovascular event. The hard model defines events as a composite of coronary death, myocardial infarction, and stroke (fatal and nonfatal). The full model includes coronary death, myocardial infarction, coronary insufficiency, angina pectoris, stroke, transient ischemic attack, intermittent claudication, and congestive heart failure (12). Mean risk scores were lower for survivors compared with controls (Hard model: 3.8 $\pm$ 3.5% vs. 4.8 $\pm$ 5.3%, $P = 0.03$; Full model: 7.6 $\pm$ 5.5% vs. 9.2 $\pm$ 8.3%, $P = 0.02$), though the frequencies of survivors with elevated scores were not reported. Applying risk prediction models developed within the Childhood Cancer Survivor Study (CCSS) cohort incorporating cancer therapeutic variables (13, 14), 30% of survivors were considered at moderate risk for myocardial ischemia and nearly all at either moderate (47%) or high (50%) risk for heart failure. The incidence of ischemic heart disease or heart failure was estimated at 9% to 12% by age 50 years. The inclusion of cardiotoxic cancer exposures, provides a risk estimate higher than the general population Framingham model and higher than the more favorable cardiometabolic profile in these cancer survivors might suggest.

This important discrepancy is not entirely unexpected. Risk stratification is common in both primary and subspecialty cardiovascular care, and multiple prediction models have been developed and tested across various populations, countries, and health systems. Traditional CVD risk factors (age, weight, lipids, diabetes, and blood pressure) are commonly accepted, though some models incorporate a variety of other factors such as family history, serum biomarkers, and/or imaging studies among others. In fact, over 360 prognostic models exist (15). Many, including the Framingham 30-year risk calculator used by Lipshultz and colleagues, are heavily weighted on age. The details of the models applied in this manuscript are described in Supporting Table 2, and the hazard ratios are highest for age (ranging from 1.98 to 3.63). Given the young age of childhood cancer survivors and the low prevalence of risk factors identified, it is not unexpected that these models might estimate a lower CVD risk. The CCSS models' incorporation of cancer therapy–related variables is an important advance, offering fair predictive capability with AUCs for heart failure 0.74 (C-statistic 0.76) and ischemic heart disease 0.70 (C-statistic 0.70).

It is important to consider the limitations of this analysis. The convenience sample was largely composed of anthracycline-exposed leukemia and lymphoma survivors with very few survivors from the sole osteosarcoma study ($n = 9$). Other, potentially high-risk groups, such as relapsed and/or stem cell transplant survivors were excluded. The participation rate (35%) was suboptimal, 0.7% refused but most eligible survivors were either not identified or failed to respond, significantly limiting generalizability of the study. Given the morbidity associated with CVD, the most impaired survivors may not have been capable of participating, thus overestimating the cardioembolic profiles and underestimating the risk calculations.

The participation rate highlights the inherent difficulties of following and validating outcomes in a transient young adult population with a high health burden moving from childhood to adulthood. Investigators attempted to offset this limitation by comparing demographic characteristics between those who chose and did not choose to participate as well as examining differential enrollment across participating sites. Survivors from high accruing COG sites had fewer cardiometabolic risk factors; potentially healthier and more likely to participate. The implications of these limitations should be considered when translating the results to clinical practice.

Following a population of anthracycline-exposed cancer survivors at high risk for CVD, particularly at a young age, with a cardiometabolic profile similar to the general population presents a clinical challenge. Prediction models incorporating therapeutic variables might be useful, not only for cardiovascular care but also for monitoring the development of other chronic health conditions. International efforts to harmonize surveillance recommendations for childhood cancer survivors are ongoing, and recommendations have been made for heart failure and coronary artery disease surveillance (16, 17). Implementation of cancer-specific models and recommendations into standard primary care for cancer survivors will be needed to truly move beyond 5-year survival rates to life-long sustained health.

Authors' Disclosures

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