Increased Risk of All Cardiovascular Disease Subtypes Among Childhood Cancer Survivors

Population-Based Matched Cohort Study

Key Words: anthracyclines ■ chemotherapy ■ diabetes mellitus ■ heart failure ■ hypertension ■ survivors of childhood cancer

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C hildhood cancer survivors are at risk for a range of cardiovascular diseases (CVD) as a consequence of their cancer therapy.1 However, most studies have focused on anthracycline-related heart failure (HF) only. To address these gaps, we evaluated the risks and predictors of HF, arrhythmias, pericardial disease, valvular disease, and coronary artery disease in a population-based cohort of childhood cancer survivors by leveraging health administrative data from Canada’s largest province, Ontario.

We used the provincial pediatric cancer registry, Pediatric Oncology Group of Ontario Networked Information System, to identify all 5-year cancer survivors diagnosed before age 18 years who were treated in a pediatric cancer center between 1987 and 2010. The registry provided detailed demographic, diagnosis, and treatment data. Each survivor was matched to 5 cancer-free individuals from the general population based on age, sex, and postal code. The index date was defined as 5 years from the survivor’s last pediatric cancer diagnosis.

All provincial residents receive coverage for medically necessary services. ICES, a nonprofit research institute that holds an array of Ontario’s health-related data, maintains various population-based health administrative databases that are linkable through encrypted, individual health card numbers. We identified cardiac events, diabetes, and hypertension using established algorithms based on combinations of hospital admission and physician billing codes. We used cumulative incidence estimates and cause-specific hazards ratios (HRs) to compare the risk of CVD between cohorts, accounting for matching and competing risks (other CVD subtypes, noncardiac death). Multivariable analyses, using proportional hazards models that accounted for clustering due to matching, were used to examine the association between baseline characteristics and cancer treatments with CVD rates among survivors. All predictors were checked for violations of model assumptions. The study was approved by the Research Ethics Boards of The Hospital for Sick Children and Sunnybrook Health Sciences Centre.

We studied 7289 5-year survivors (median age at diagnosis, 7 years; range, 0–17.9 years) and 36,205 matched cancer-free individuals with a combined median attained age of 24 years (range, 5–47 years) at the end of follow-up. Over a median follow-up of 10 years from index (range, 0–25 years), 203 survivors (2.8%) experienced one or more cardiac events compared with 331 (0.9%) controls ($P<0.001$). Survivors experienced 3.2 cardiac events per 1000 person-years (95% CI, 2.8–3.6) compared with 0.9 cardiac events per 1000 person-years in the general population (CI, 0.9–1.9). The Table presents the cumulative incidence and cause-specific HRs for each CVD subtype. Cause-specific HRs were significantly elevated in survivors compared with the general population for all CVD subtypes.
Correspondence models showed that among survivors, childhood relapse/subsequent cancer (HR, 1.7; CI, 1.1–2.7), exposure to ≥250 mg/m² of doxorubicin-equivalent anthracycline chemotherapy compared with <250 mg/m² or no anthracyclines (HR, 2.0; CI, 1.4–2.9), and diabetes mellitus preceding cardiac disease diagnosis (HR, 3.0; CI, 1.6–5.8) were associated with higher risks of CVD. Childhood relapse/subsequent cancer (HR, 2.0; CI, 1.1–3.7), exposure to ≥250 mg/m² of doxorubicinequivalent anthracycline chemotherapy (HR, 8.6; CI, 4.5–16.6), diabetes (HR, 4.3; CI, 1.8–10.7), and hypertension (HR, 3.1; CI, 1.3–7.9) were statistically significant predictors of HF. Because of the small number of non-HF events, we were unable to analyze predictors of other CVD subtypes with stable multivariable models. 

Even at relatively young ages, survivors experienced a 2- to 10-fold increased risk of CVD relative to the general population. Consistent with the literature, we found anthracycline dose predicted an increased risk of CVD overall and HF in particular. Although our univariate analyses demonstrated associations between chest-directed radiation and cardiac risk, this relationship was not significant in multivariable analyses. Because radiation-associated CVD can take 15 years or more to manifest, particularly with modern radiation techniques, and because our median length of follow-up was approximately 10 years, the relationship between radiation exposure and CVD may become more evident as the cohort ages.

Survivors diagnosed with diabetes mellitus were 3 times more likely to develop CVD and more than 4 times more likely to develop HF compared with nondiabetic survivors. Similarly, survivors diagnosed with hypertension were 3 times more likely to develop HF compared with nonhypertensive survivors. As suggested by the literature, cancer therapy can increase the risk of metabolic conditions such as diabetes, hypertension, and dyslipidemia. These modifiable risk factors appear to interact with cardiotoxic treatment exposures in a multiplicative manner to accelerate the progression of CVD and premature aging of the heart. Despite efforts to minimize cardiotoxic exposures during cancer treatment, many patients require these treatments to survive. Thus, modifiable risk factors provide alternative avenues for targeted intervention.

We were unable to assess behaviors such as smoking, physical activity, diet, or alcohol use using administrative data; however, these lifestyle factors might provide another target for reducing the incidence of CVD in survivors. Because the prevalence of CVD is expected to increase with age, this study reinforces the need for periodic CVD surveillance, and consideration of all CVD types, in childhood cancer survivors.

**ARTICLE INFORMATION**

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