

Treatment, Behavioral, and Psychosocial Components of Cardiovascular Disease Risk Among Survivors of Childhood and Young Adult Cancer

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The incidence of childhood, adolescent, and young adult (AYA) cancers have been increasing since 1975.¹ In 2014, an estimated 10 450 and 5330 new cancers will be diagnosed among children aged birth–14 and adolescents aged 15 to 19 years old, respectively.² For young adults aged 20 to 34 years of age, nearly 40 000 new cases are diagnosed each year.³ As treatments have advanced, survival rates in children and young adults with cancer are increasing, with 5-year survival rates at $\approx 80\%$.^{2,4} The most recent survivorship estimates report that there are $\approx 400\,000$ survivors of childhood and adolescent cancers and $\approx 600\,000$ survivors of young adult cancers alive in the United States.^{2,5}

Though survival rates from cancer are increasing, there is growing evidence that childhood and AYA survivors are at competing risk of cardiovascular disease (CVD). In a study of 272 acute myeloid leukemia survivors in the Childhood Cancer Survivor Study (CCSS), the cumulative incidence of a cardiac event, defined as congestive heart failure or myocardial infarction, was 4.7% over 20 years of follow-up.⁶ In a larger study of 3306 survivors of childhood cancer performed in the United Kingdom, the cumulative incidence of cardiovascular events at 20 years of follow-up was 7.5% and 14.0% among those diagnosed at 0 to 14 and 15 to 29 years old, respectively. Importantly, these CVD event rates exceed expected rates of a general population. For example, a Finnish study of 16 769 survivors diagnosed prior to age 35 found a

nearly 2-fold higher risk of CVD among survivors compared to their cancer-free siblings.⁷ In the US CCSS cohort, an analysis including 20 483 survivors demonstrated a 7-fold higher risk for cardiac death among survivors compared to age-, year-, and sex-matched members of the general population.⁸ Similar results have been demonstrated in the Netherlands, France, and the United Kingdom.^{7,9,10}

Childhood and AYA cancer survivors are at risk for a variety of cardiovascular conditions (Table 1).

Survivors are more likely than cancer-free siblings to be diagnosed with congestive heart failure (hazard ratio [HR] 5.9, 95% CI 3.4 to 9.6), myocardial infarction (HR 5.0, CI 2.3 to 10.4), valvular abnormalities (HR 4.8, CI 3.0 to 7.6), or pericardial disease (HR 6.3, CI 3.3 to 11.9), at up to 30 years postdiagnosis.¹⁶ Increased risk of stroke has also been found in survivors of childhood and AYA cancers in the United States. Utilizing the CCSS cohort of 14 358 survivors and 4023 randomly selected sibling controls, Mueller et al found an age-adjusted stroke rate per 100 000 person years of 77 in survivors compared to 9.3 in controls, over a mean follow-up of 23.3 years.¹⁸ Similar results have been demonstrated in European populations. Kero et al compared risk of CVD separately in childhood and AYA cancer survivors over 30 years of follow-up from diagnosis with cancer-free siblings. Survivors aged 0 to 19 and 20 to 34 years at diagnosis, respectively, had significantly higher risks of cardiomyopathy (HR 13.5, CI 8.9 to 20.4 and HR 3.6, CI 2.8 to 4.6), myocardial infarction (HR 3.3, CI 1.7 to 6.5 and HR 1.8, CI 1.5 to 2.1), cardiac arrhythmia (HR 1.7, CI 1.2 to 2.6 and HR 1.4, CI 1.2 to 1.7), and stroke (HR 3.4, CI 2.3 to 5.1 and HR 1.7, CI 1.4 to 2.0).¹⁵

In the current review, we examine the potential contributors to the excess CVD risk among childhood and AYA cancer survivors. In particular, we discuss the treatment exposures, premature cardiac risk factor accumulation, and psychosocial components that put survivors at higher risk for CVD. Moreover, we discuss strategies to reduce CVD risk in this population as well as advocate for continued integration of surveillance and survivorship plans into clinical practice.

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Table 1. Incidence Rates and Relative Risks of Cardiovascular Outcomes Among Childhood and Young Adult Cancer Survivors

Cardiovascular Outcome	≤10 Years	>10 to 20 Years	>20 Years	≤10 Years	>10 to 20 Years	>20 Years
	Incidence Rate			Relative Risk		
General cardiac events	0.5% ¹¹	2.3% to 14.0% ^{6,11}	7.2% ¹¹	—	—	—
Left ventricular dysfunction	30.1% ¹²	12.0% to 23.9% ^{12,13}	9.8% to 30.3% ¹²	—	—	—
Cardiomyopathy	—	—	—	3.9 ¹⁴	—	3.6 to 13.5 ¹⁵
Congestive heart failure	0.4% ¹¹	1.2% to 1.9% ^{11,16}	3.1% to 4.1% ^{11,16}	—	12.7 ¹⁷	5.9 ¹⁶
Myocardial infarction	—	0.5% ¹⁶	1.5% ¹⁶	—	—	1.8 to 5.0 ^{15,16}
Pericardial disease	—	0.8% ¹⁶	3.0% ¹⁶	—	7.9 ¹⁷	6.3 ¹⁶
Valvular disease	—	0.3% to 0.7% ^{11,16}	1.7% to 4.0% ^{11,16}	—	3.2 ¹⁷	4.8 ¹⁶
Vascular disease	—	—	—	—	7.9 ¹⁷	1.7 to 3.4 ¹⁵
Stroke	1.1% to 4% ^{18,19}	8% ¹⁹	12.0% to 27% ^{18,19}	—	—	—

Why Are Childhood and Young Adult Cancer Survivors at CVD Risk?

Treatment

Anthracyclines

The cardiotoxicity of anthracyclines is well documented in the overall cancer literature,^{20,21} as well as among individuals diagnosed with childhood and AYA cancers.²² In a retrospective analysis of 14 358 5-year survivors from the CCSS, Mulrooney et al found that exposure to ≥ 250 mg/m² of anthracyclines increased the relative hazard of pericardial disease (HR 1.8, CI 1.1 to 3.0), congestive heart failure (HR 5.2, CI 3.6 to 7.4), and valvular disease (HR 2.3, CI 1.6 to 3.3) compared to survivors with no exposure to anthracyclines.¹⁶ Van der Pal et al evaluated the long-term risk of symptomatic cardiac events including congestive heart failure, cardiac ischemia, valvular disease, arrhythmia, and pericarditis among 1362 5-year childhood cancer survivors. Compared to non-anthracycline-based therapies, the 30-year cumulative incidence of cardiac events was significantly increased after treatment with anthracyclines (7.3%, CI 3.8% to 10.7%), with the risk of developing a cardiac event exponentially associated with anthracycline dose.¹¹ Results were similar in a European cohort of childhood cancer survivors, with risk of cardiac mortality significantly higher among patients who received cumulative anthracycline dose ≥ 360 mg/m² (relative risk 4.4, CI 1.3 to 15.3).¹⁰

Similar to studies in the adult cancer populations,²³ prior studies in childhood cancer have demonstrated a dose-dependent association between anthracyclines and cardiomyopathy.^{12–14,24} In a case-control study by Blanco et al, survivors exposed to the lowest doses (1 to 100 mg/m², odds ratio [OR] 1.65) up to the highest (>350 mg/m², OR 27.59) had elevated risks of developing cardiomyopathy compared to those not receiving anthracyclines.¹⁴ Moreover,

van der Pal et al found that left ventricular function was reduced with higher cumulative anthracycline dose among 514 5-year survivors of childhood cancer.¹² Of note, 1 prior study demonstrated that lower doses of anthracyclines (cumulative 180 to 240 mg/m²) were not found to be associated with clinical cardiotoxicity; however, subclinical cardiac abnormalities were found among 30% of the childhood acute lymphoblastic leukemia (ALL) survivors studied.²⁵ Finally, evaluating global left ventricular myocardial performance in adolescent and adult survivors of childhood cancer, Yu et al found that reduced left ventricular global 3-dimensional strain and global performance index were correlated with cumulative anthracycline dose.²⁶

In addition to cardiac disease, vascular disease is also more common among childhood and young adult cancer survivors who were treated with anthracyclines. In a study of 96 long-term survivors of childhood cancers, Jenei et al found that those exposed to anthracycline treatment exhibited preclinical vasculopathy, marked by increased arterial stiffness and endothelial dysfunction.²⁷ Herceg-Cavrak et al also found increased arterial stiffness among children and young adults who had completed anthracycline treatment at least 1 year prior to the study.²⁸ Finally, in 2 separate studies assessing vascular endothelial function by brachial artery reactivity, those treated with anthracyclines had impaired vascular endothelial function compared to cancer-free children.^{29,30} Taken together, treatment with anthracyclines for childhood and young adulthood cancers can have detrimental effects on cardiac and vascular function, which can subsequently impact long-term cardiovascular risk.

Radiation

Exposure to radiation therapy has also been implicated in development of cardiac effects and late cardiac mortality among survivors of childhood and AYA cancers. In a study of 20 483 survivors from the CCSS, there was a 3.3-fold higher

risk of cardiac death over 30 years of follow-up in those treated with cardiac radiation (relative risk 3.3, CI 2.0 to 5.5).⁸ In an analysis of types of CVD associated with radiation therapy, Mulrooney et al assessed 14 358 5-year survivors from the CCSS, finding that exposure to cardiac radiation of ≥ 3.5 Gy increased the relative hazard of myocardial infarction (HR 3.6, CI 1.9 to 6.9), congestive heart failure (HR 4.5, CI 2.8 to 7.2), pericardial disease (HR 4.8, CI 2.8 to 8.3), and valvular disease (HR 5.5, CI 3.5 to 8.6) compared to survivors that were not exposed to radiation.¹⁶ This is supported by a study in a European cohort of childhood cancer survivors that demonstrated a higher risk of cardiac mortality among patients who received an average radiation dose that exceeded 5 Gy (relative risk 12.5, CI 1.4 to 116.1).¹⁰ Moreover, the long-term risk of symptomatic cardiac events including congestive heart failure, cardiac ischemia, valvular disease, arrhythmia, and pericarditis are maintained at 30 years after treatment with cardiac irradiation (4.0%, CI 0.5% to 7.4%). Importantly, the risk of developing a cardiac event was exponentially associated with cardiac irradiation dose.¹¹

Increased risk of vascular disease and stroke has also been associated with radiation therapy for childhood and AYA cancers. Brouwer et al performed vascular assessments among 277 adult survivors of childhood cancers, finding that, compared to other treatments, those who received radiation were more likely to show signs of endothelial damage, as measured by carotid-wall intima-media thickness.³¹ Additionally, in a study from the CCSS, Mueller et al found that risk of stroke was increased in a dose-dependent manner with cranial radiation therapy. Among survivors treated with the highest cranial radiation dose (50+ Gy), the cumulative stroke incidence was 1.1% at 10 years postdiagnosis and increased to 12% at 30 years postdiagnosis.¹⁸ This evidence is supported by a report from the Children's Oncology Group, stating that risk of stroke is increased among survivors of childhood cancers who received radiation to the brain and/or neck.³²

Interestingly, the impact of radiation is not limited to cardiac disease. Chow et al examined the prevalence of cardiometabolic traits among survivors of childhood and young adult ALL. Those treated with total body irradiation based hematopoietic cell transplantation were significantly more likely to meet criteria for metabolic syndrome compared to non-hematopoietic cell transplantation survivors (23.1% versus 4.2%, $P=0.02$). Cranial radiation exposure also increased the risk of exhibiting cardiometabolic traits.³³ Oeffinger et al performed a similar study among 118 survivors of childhood ALL, finding that survivors had a significantly increased prevalence of insulin resistance compared to controls from the Dallas Heart Study cohort. Overall, there was no difference in number of CVD risk factors in male survivors and controls, but women treated with cranial

radiation were 6 times more likely (OR 5.96, CI 2.15 to 16.47) than controls to have 3 or more risk factors (including adiposity measures, cholesterol, lipids, insulin, C-reactive protein).³⁴ Brouwer et al assessed body mass index by treatment type among 985 ≥ 5 year survivors of childhood cancer. Cranial/craniospinal radiation was associated with greater odds of being overweight (OR 2.23, CI 1.17 to 4.26), compared to age-matched controls. This association was not seen among those treated with anthracyclines or platinum.³⁵ Similarly, in separate studies of survivors of childhood brain tumors and childhood ALL, cranial irradiation was associated with greater risks of overweight/obesity.^{36,37} Finally, Oeffinger et al found significantly increased body mass index among young adult survivors of childhood ALL treated with cranial irradiation compared to those treated with chemotherapy alone ($P=0.039$).³⁸ This is supported by a separate study demonstrating significantly higher odds of obesity among females (OR 2.59, CI 1.88 to 3.55) and males (OR 1.86, CI 1.33 to 2.57) treated with cranial radiation doses ≥ 20 Gy, compared to sibling controls.³⁹

Premature Accumulation of CVD Risk Factors

In addition to the impact of treatment on CVD risk, survivors of childhood and young adult cancers are more likely than their cancer-free peers to take on a variety of unhealthy behaviors. Alcohol use and smoking have also been evaluated among different cohorts of childhood and young adult cancer survivors. In a Swiss cohort of 1049 childhood cancer survivors, Rebholz et al found that survivors were more likely than controls to consume alcohol frequently (OR 1.7, CI 1.3 to 2.1) and to binge drink (OR 2.9, CI 2.3 to 3.8).⁴⁰ In the CCSS, 16% of survivors reported risky drinking and 8% reported heavy drinking. Seventeen percent reported current smoking; however, the frequency of smoking initiation was significantly lower among survivors compared to the general population (observed-to-expected ratio 0.72, CI 0.69 to 0.75).⁴¹ Utilizing data from the Behavioral Risk Factor Surveillance System, Tai et al identified 4054 AYA cancer survivors, finding that, compared to respondents without a history of cancer, survivors were significantly more likely to be current smokers.⁴² These findings may differ by geographic region. In a Hawaiian cohort, Wada et al found significantly lower rates of alcohol and tobacco use among survivors compared to controls.⁴³

Physical activity levels have been demonstrated to be lower among childhood and young adult cancer survivors than controls and to decrease in survivors after treatment relative to prediagnosis physical activity. In the Swiss Childhood Cancer Survivor Study, survivors had higher odds of not engaging in sports (OR 1.3, CI 1.1 to 1.7) compared to controls.⁴⁴ In a separate study in the same cohort, Rueegg

et al found that, compared to siblings, survivors had higher odds (OR 5.5, CI 2.9 to 10.4) of reporting physical performance limitations that hindered ability to participate in sports.⁴⁵ In the CCSS, it was shown that 53% of survivors of childhood ALL did not meet recommendations for time spent in physical activity and that 23% were inactive, which was significantly higher than the general population.⁴¹ A more recent CCSS study, assessing multiple cancer types, found that about 30% of survivors did not meet physical activity recommendations and this was significantly higher than the percent of sibling controls who did not meet physical activity recommendations (23%, $P<0.0001$).⁴⁶ Wampler et al assessed physical activity levels among adult survivors of childhood lower-extremity sarcoma from the CCSS, finding that only 41% of survivors met national physical activity guidelines. Furthermore, survivors were more likely than the general population (prevalence ratio 1.12, CI 1.10 to 1.15) to fail to meet recommended activity levels.⁴⁷ Hocking et al evaluated physical activity levels in young adult survivors of childhood cancer and healthy controls. Compared to healthy controls, survivors reported participating in moderate to vigorous physical activity 2.1 fewer times per week ($P=0.02$).⁴⁸ In a Hawaiian cohort, Wada et al found that 44% of survivors <18 years old and 29% of survivors ≥ 18 years old failed to meet national guidelines for time spent in physical activity.⁴³ Lastly, in a study of 74 survivors of AYA cancers, Murnane et al found a significant reduction in average minutes spent in physical activity after treatment, compared to prediagnosis (219 versus 148, $P<0.0005$).⁴⁹

Lack of physical activity among childhood and young adult survivors translates into loss of cardiorespiratory fitness (VO_{2max}), a key prognostic marker of survival.⁵⁰ De Caro et al performed maximal exercise testing among 84 asymptomatic childhood cancer survivors and 79 controls. Significant differences in VO_{2max} were found among males <13 years old, with survivors obtaining a VO_{2max} of $33.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ compared to 40.8 in controls. No other significant differences were noted.⁵¹ Miller et al also measured VO_{2max} utilizing a treadmill stress test among 72 childhood cancer survivors and 32 siblings. Differences between female survivors and controls were demonstrated (VO_{2max} : 19.8 versus $23.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P=0.03$), while no difference was seen in males (VO_{2max} : 28.5 versus $30.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P=0.08$).⁵² Jarvela et al measured VO_{2max} by cycle ergometry among 21 long-term survivors of childhood ALL, finding a significant reduction in survivors compared to controls ($-5.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, CI -9.4 to -1.9 , $P=0.01$).⁵³

Not surprisingly, change in health behaviors and loss of fitness leads to an accumulation of cardiometabolic risk factors among childhood and AYA cancer survivors. Steinberger et al evaluated 319 survivors of childhood cancers, and found compared sibling controls, survivors had greater

adiposity (waist girth 73.1 versus 71.1 cm, $P=0.02$) and percent fat (28.1 versus 25.9%, $P=0.007$). After adjustment for adiposity, survivors had significantly higher total cholesterol ($P=0.004$), triglycerides ($P=0.03$), and were less insulin sensitive ($P=0.002$) than sibling controls.⁵⁴ Moreover, in a study of 8599 childhood cancer survivors from the CCSS, Meacham et al found survivors were more likely to take medications for hypertension (OR 1.9, CI 1.6 to 2.2), diabetes (OR 1.7, CI 1.2 to 2.3), or dyslipidemia (OR 1.6, CI 1.3 to 2.0) compared to sibling controls.⁵⁵

Psychosocial—Depression

Psychological late effects cannot be overlooked when reviewing CVD risk among survivors of childhood and AYA cancers, as poor mental health and depression are strongly associated with such CVD risk factors as weight gain and physical inactivity.^{56–58} Deyell et al measured antidepressant use in a Canadian cohort of childhood and AYA cancer survivors. After adjustment for sociodemographic factors, survivors were more likely than controls to have filled a prescription for antidepressants (OR 1.21, CI 1.09 to 1.35).⁵⁹ In the CCSS, Hudson et al found that compared to sibling controls, survivors were more likely to report adverse mental health (OR 1.8, CI 1.6 to 2.1).⁶⁰ In a study focused on long-term survivors of childhood leukemia, Hodgkin's and non-Hodgkin's lymphoma, Zebrack et al found that compared to sibling controls, survivors were significantly more likely to report symptoms of depression.⁶¹

Multiple studies have assessed risk of post-traumatic stress disorder among survivors of childhood and young adult cancers. Kwak et al found that at 6 and 12 months postdiagnosis, 39% and 44%, respectively, of adolescent and young adult cancer survivors experienced moderate to severe levels of post-traumatic stress symptoms.⁶² In a report from the CCSS, Stuber et al found that survivors, compared to sibling controls, had more than a 4-fold higher risk of post-traumatic stress disorder (OR 4.14, CI 2.08 to 8.25).⁶³ Importantly, there are established connections between post-traumatic stress disorder and CVD risk factors, with post-traumatic stress disorder symptoms found to be associated with heart rate variability,⁶⁴ obesity,^{65–67} as well as CVD incidence and mortality.^{68–70}

What Can Be Done to Mitigate CVD Risk Among Childhood and Young Adult Cancer Survivors?

Medical Therapy

Cardioprotective drugs combined with chemotherapy agents are important tools for early prevention of CVD among

childhood and young adult cancer survivors. Dexrazoxane has been identified as a potential cardioprotectant for children treated with doxorubicin, a chemotherapeutic agent associated with development of late cardiac effects (Table 2).

In a randomized trial of the effectiveness of dexrazoxane, Lipshultz et al found that the drug provided long-term cardioprotection among children treated for ALL without compromising the oncological effectiveness of doxorubicin. Specifically, dexrazoxane offered protection against change in mean left ventricular fraction shortening and end-systolic dimension.⁷¹ Similarly, in a Korean cohort of pediatric cancer patients, Kang et al found that dexrazoxane protected against cardiotoxicity during anthracycline treatment.⁷² Furthermore, in a study assessing the effect of dexrazoxane use on biomarkers associated with cardiomyopathy, among pediatric patients being treated for ALL, Lipshultz et al found that after treatment, children receiving dexrazoxane in addition to doxorubicin had significantly lower levels of cardiac biomarkers, compared to children receiving doxorubicin alone.⁷³

In a synthesis of the current data on dexrazoxane use in children receiving anthracyclines, Wu et al propose that dexrazoxane use is safe, tolerable, and effective in the pediatric cancer setting, and called for further studies with larger sample sizes and longer follow-up times.⁷⁹ However, the use of dexrazoxane in children remains controversial, with a 2011 statement from the Food and Drug Administration restricting dexrazoxane use to the adult setting among patients who had reached a certain threshold of anthracycline dose and noted that any pediatric use would be considered “off-label.”⁸⁰ Limited data have found that dexrazoxane use in the pediatric setting may increase the risk of a second malignancy. Combining 2 Pediatric Oncology Group studies

with a total of 578 pediatric Hodgkin’s disease patients, Tebbi et al found that dexrazoxane was associated with an increased risk of secondary malignancies.⁸¹ However, in a Cochrane review of all published studies in children and adults, dexrazoxane showed efficacy in preventing heart damage and no evidence for a lower response rate or negative overall survival.⁸² Furthermore, in a 2015 study of 15 532 pediatric patients, Seif et al found no increased risk of secondary acute myeloid leukemia associated with the use of dexrazoxane.⁸³ Given the ongoing debate, the use of dexrazoxane varies significantly across geographic region and institution.⁸⁴ While dexrazoxane is the most widely studied agent, additional therapies to reduce myocardial injury have been tested and discussed in more detail in other reports.^{85–88}

Behavioral Interventions

After treatment, behavioral interventions are important tools for modifying CVD risk factor burden as well as introducing positive lifestyle behaviors at an early age. Valle et al utilized a Facebook-based intervention to increase moderate to vigorous physical activity among young adult cancer survivors. Participants received pedometers to track activity and received weekly Facebook messages (over the course of 12 weeks) with specific guidance on physical activity and behavioral strategies. Participants increased their moderate to vigorous physical activity levels by 67 minutes per week and lost 2.1 kg.⁸⁹ Jarvela et al assessed the effectiveness of a home-based exercise program on metabolic risk factors and cardiorespiratory fitness levels among young adult survivors of ALL. Subjects were given specific strength-training

Table 2. Cardioprotectant Effects of Dexrazoxane in Pediatric Patients Treated With Anthracyclines

Study	Population	Summary of Cardioprotectant Effect
Lipshultz et al ⁷¹	Pediatric ALL (n=205)	Fractional shortening (girls only) Left ventricular dimension
Kang et al ⁷²	Pediatric cancer patients (n=258)	Fractional shortening Left ventricular ejection fraction
Lipshultz et al ⁷³	Pediatric ALL (n=205)	Cardiac biomarkers: cTnT and NT-proBNP
Choi et al ⁷⁴	Pediatric patients with solid tumors (n=89)	Fractional shortening Left ventricular dimension Congestive heart failure 5-year cardiac event-free survival
Elbl et al ⁷⁵	Pediatric hematological malignancies (n=108)	Fractional shortening Left ventricular ejection fraction
Lipshultz et al ⁷⁶	Pediatric ALL (n=101)	Cardiac biomarkers: TnT
de Matos Neto et al ⁷⁷	Pediatric osteosarcoma (n=55)	Fractional shortening
Elbl et al ⁷⁸	Pediatric hematological malignancies (n=75)	Fractional shortening Exercise tolerance

ALL indicates acute lymphoblastic leukemia; cTnT, cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide; TnT, troponin T.

regimens and were encouraged to participate in aerobic activities of their choice. Over the 16-week intervention, participants showed significant improvement in metabolic risk factor profile, including improvements in fasting plasma insulin, waist circumference, fat percent, waist-to-hip ratio, and diastolic blood pressure. Cardiorespiratory fitness (VO_{2max}) also improved by 5% ($P=0.01$).⁹⁰

Importantly, quality of life in childhood and young adult cancer survivors is positively impacted when survivors adopt healthier exercise patterns. In a cohort of 215 survivors of childhood cancer, Paxton et al found a significant linear association between leisure time physical activity and overall health-related quality of life.⁹¹ Similarly, Murnane et al found that adolescent and young adult cancer survivors who met public health physical activity guidelines had significantly higher quality of life measurements compared to survivors not meeting physical activity guidelines.⁴⁹ Moreover, increasing daily walking, as measured by pedometer, decreased fatigue symptoms among adult survivors of childhood cancer, with symptom improvement demonstrated throughout the study's 36 weeks of follow-up.⁹²

Smoking cessation programs have also been tested among childhood and AYA cancer survivors. Emmons et al found that smoking cessation was higher among childhood cancer survivors assigned to a peer-counseling telephone and mail intervention group compared to those who received educational materials but not counseling (15% versus 9%, $P=0.01$).⁹³ In a follow-up study, equal effectiveness was demonstrated between printed educational materials and web-based educational interventions, with about 15% of survivors in each group reporting smoking cessation.⁹⁴ Klesge et al assessed the efficacy of a tobacco quitline in combination with nicotine replacement therapy among adult survivors of childhood cancer. After 12 months of follow-up, it was found that intervention did not influence long-term smoking cessation rates.⁹⁵ Interestingly, Ford et al assessed health risk perceptions among childhood and AYA survivors, finding that current smokers did not endorse the belief that they were at higher risk of heart problems.⁹⁶ Furthermore, de Moor et al found that only 3% of participating institutions assessed smoking status of childhood cancer survivors at every health visit, and that only 25% of sites had cessation services available to survivors.⁹⁷

Surveillance Strategies and Education

The Children's Oncology Group Late Effects Committee and Nursing Discipline have developed risk-based guidelines for pediatric cancer survivors that take into consideration treatment, cancer type, existing medical conditions, and behavioral risk factors. The committee recommends that those who were exposed to anthracyclines, or site-specific radiation undergo a

baseline echocardiogram, or comparable imaging to assess cardiac function and anatomy, at entry into long-term follow-up, with periodic echocardiograms based on age at treatment, cumulative anthracycline dose, and radiation dose. A baseline ECG is also recommended and is to be repeated as clinically indicated.^{98,99} The International Late Effects of Childhood Cancer Guideline Harmonization Group was initiated in 2010 to establish an evidence-based strategy for surveillance of late effects and to facilitate dissemination and implementation of recommendations. Work is continuing to be done, with cardiomyopathy guidelines pending publication.¹⁰⁰

Work has already been done to evaluate the effectiveness of the current screening guidelines. Abosoudah et al assessed the yield of the surveillance echocardiogram guidelines laid out in the Children's Oncology Group's *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer Survivors*. In a cohort of children treated with anthracyclines at a single institution, it was found that about 80% of eligible survivors completed at least 1 echocardiogram following treatment, with 17% of results coming back as abnormal.¹⁰¹ Armstrong et al compared the current recommended method of screening for cardiomyopathy in childhood cancer survivors, 2-dimensional echocardiography, to cardiac magnetic resonance imaging. It was found that cardiac magnetic resonance identified a high prevalence of cardiomyopathy in those without a previous diagnosis of cardiac disease, and that 2-dimensional echocardiographic screening may not achieve the same level of accuracy as cardiac magnetic resonance.¹⁰² Three-dimensional speckle-tracking echocardiography also has demonstrated high accuracy in assessing global left ventricular performance among high-risk survivors of childhood cancer.²⁶ Further work is needed to determine whether these early detection strategies actually impact survival and prevention of cardiovascular events, and to determine the most effective imaging strategies.

Although screening guidelines are in place, patient and provider knowledge of long-term risks and proper surveillance can be a barrier to guideline adherence. In a study assessing knowledge and perception of risks of late effects of cancer therapy among young adult survivors and parents of childhood survivors, it was found that participants had a low perceived likelihood of developing a late effect and many incorrect perceptions surrounding risk of specific late effects. Forty-two percent of participants believed that developing a late effect was not likely or only slightly likely.¹⁰³ Oeffinger et al mailed a 1-page survivorship plan with surveillance recommendations to Hodgkin's lymphoma survivors from the CCSS who had not had a screening echocardiogram for at least 2 years. It was found that reception of the survivorship information did not raise anxiety levels, and 20% of survivors reported undergoing an echocardiogram within 6 months of receiving the survivorship plan.¹⁰⁴

In addition to lack of knowledge of long-term health risks, there are several other barriers to follow-up care that must be addressed in order to maximize cardiovascular health among survivors of childhood and young adult cancers. Multiple studies have found that cost and loss of health insurance were the biggest barriers to survivors receiving follow-up medical care.^{105–107} Emotional barriers exist as well, with perceived stigma of a cancer history and continued psychological trauma related to cancer diagnosis and treatment cited as reasons for childhood and young adult cancer survivors to avoid continued follow-up care.^{107,108} Institutionally, barriers to continued follow-up care for survivors of childhood and young adult cancer include lack of time dedicated to program development and perceived lack of knowledge of the clinician taking over care from the primary oncologist.¹⁰⁹

Long-Term Survivorship Care

On a larger scale, standardization of survivorship care centers that incorporate appropriate screening, focus on treatment specific CVD risks, and modification of behavioral risk factors are important components towards preventing CVD incidence and mortality among childhood and young adult cancer survivors. In a document on childhood cancer survivorship from the Institute of Medicine and National Research Council National Cancer Policy Board, the authors state that the focus of survivorship care programs should be educating survivors regarding their specific long-term risks; applying preventive approaches to abstinence from tobacco, sun protection, limited alcohol use, recommended physical activity, healthy weight maintenance, and diet quality; providing psychosocial support; and providing genetic counseling for survivors with hereditary cancer and their family members. Although these general recommendations are in place, there is no consensus on the specifics of follow-up care, and each institution has tended to define their own protocols and programs. As a result, studies are needed to assess the effectiveness of established follow-up programs in terms of improved quality of life and reduced morbidity and mortality.¹¹⁰

Conclusions

The incidence of childhood and young adult cancers is increasing, as are survival rates. Survivors of childhood and young adult cancers have a long lifespan ahead, but the health implications of their cancer diagnosis and treatment cannot be ignored. Treatment-related cardiac insults, health behaviors, and the psychological impact of a cancer diagnosis all contribute to the increased risk of CVD incidence and death in this population, with risks not mitigated with time from diagnosis. Survivors need to be educated to their particular

risks and transitioned into a survivorship care plan that focuses on modifying CVD risk factors.

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Disclosures

None.

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