Background. Cancer is the leading cause of death by disease among U.S. children ages 1–14 years; however, over the last few decades there has been a dramatic increase in survival in these individuals. Although free of cancer, survivors are faced with a variety of chronic health problems including an increased risk of cardiovascular and metabolic abnormalities. The effect of cancer treatments on vascular structure and function in childhood cancer survivors (CCS) has not been examined. Procedure. Measures of carotid artery stiffness (compliance and distensibility) and thickness (IMT), brachial artery endothelial-dependent dilation (EDD), and endothelial-independent dilation (EID) were obtained from ultrasound imaging in 319 CCS (age: 14.6 ± 0.1 years; male/female: 112/96) who were >5 years from diagnosis and 208 (age: 13.6 ± 0.2 years; male/female: 171/148) siblings who had never been diagnosed with cancer. Participants were 9–18 years of age at examination. Results. Survivors of leukemia had lower carotid distensibility and compliance, indicating increased arterial stiffness, when compared to controls. There were no significant differences in measures of carotid stiffness or EDD in survivors of solid tumors and central nervous system (CNS) tumors compared to controls. EDD was lower in leukemia survivors than in controls, and EID was greater in survivors of CNS tumors than in controls. Conclusion. These results demonstrate that early in life, CCS have arterial changes indicating increased risk for premature atherosclerosis and cardiovascular disease. Therefore, it is reasonable to advocate that efforts should be directed at monitoring and managing cardiovascular risk factors in CCS. Pediatr Blood Cancer 2014;61:532–537. © 2013 Wiley Periodicals, Inc.

Key words: cancer survivors; children; compliance; distensibility; ultrasound

INTRODUCTION

Cancer is the leading cause of death by disease among U.S. children 1–14 years of age. Although the incidence of children diagnosed with all forms of cancer has remained somewhat constant over the last few decades the survival rate has increased dramatically from a 5-year survival rate of 58.1% in 1975–1977 to 83.1% in 2003–2009 [1] due to significant advances in treatment [2,3]. Although free of cancer, these childhood cancer survivors (CCS) are now at risk for a variety of chronic health problems including an increased risk of cardiovascular (CV) and related metabolic abnormalities [4].

High-resolution ultrasound imaging of the carotid IMT is the most widely used method to evaluate arterial structure. The IMT is often measured at the common carotid artery because this site has been linked to CV and metabolic risk factors [5]. Similarly, ultrasound imaging of the brachial artery during hyperemia is commonly used to assess vascular function and have been linked to a variety of CV and metabolic risk factors [5]. We have previously reported vascular dysfunction in young adult survivors of childhood acute lymphoblastic leukemia (ALL) who had received treatment 25 years before vascular testing and showed significant decline in vascular function compared to a healthy control group of similar age [6]. Whether this decline in vascular function occurs immediately as a result of the treatment or develops over time is not known. To date, most studies examining CV risk in cancer survivors have been done in adult survivors of childhood cancer [4,7,8]. Therefore, the primary objective of this study was to evaluate measures of carotid and brachial artery structure and function in a large population of CCS while they were still children and compare them to a control group of healthy sibling children.

METHODS

The study protocol was approved by the University of Minnesota Institutional Review Board (IRB): Human Subjects Committee at the University of Minnesota Medical Center and Children’s Hospital and Clinics of Minnesota. The study procedures adhered to the University of Minnesota’s IRB and the Health Insurance Portability and Accountability Act (HIPAA) guidelines. All subjects submitted written informed consent and assent (when appropriate) for study participation.

Study Population

The CCS subjects for this study were selected from Pediatric Oncology databases at the University of Minnesota/Fairview-University Medical Center and Children’s Hospitals and Clinics of Minneapolis and St. Paul. We identified 723 living subjects, who were >9–18 years old in 2006, who were treated for cancer either at the University of Minnesota/Fairview-University Medical Center (N = 313), or at the Children’s Hospitals and Clinics of Minneapolis and St. Paul (N = 410) and who have survived for ≥5 years after diagnosis of leukemia, lymphomas, CNS tumors, and sarcomas. Of these, 66 could not be located. The remaining 657 were contacted and consent for participation was obtained from 322 (49%). Three CCS were determined to be ineligible after consent, leaving the final study population of 319 CCS (Table I). In order to establish a contemporary control group, siblings were informed of the study by their parents and if they agreed to participate they were evaluated at the same time as the CCS. From the 322 families enrolled...
TABLE I. Demographic Characteristics of Study Population

<table>
<thead>
<tr>
<th>Race/ethnicity, N (%)</th>
<th>Control (N = 208)</th>
<th>All CCS (N = 319)</th>
<th>Leukemia (N = 110)</th>
<th>CNS (N = 82)</th>
<th>Solid tumors (N = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>P-value</td>
<td>Mean ±SE</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.6 ±0.2</td>
<td>14.6 ±0.1</td>
<td>&lt;0.0001</td>
<td>14.4 ±0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>112/96</td>
<td>171/148</td>
<td>0.93</td>
<td>65/45</td>
<td>0.37</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>194 (93)</td>
<td>274 (86)</td>
<td>0.0008</td>
<td>94 (85)</td>
<td>0.02</td>
</tr>
<tr>
<td>Others</td>
<td>14 (7)</td>
<td>45 (14)</td>
<td></td>
<td>16 (15)</td>
<td></td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>4 (2)</td>
<td>4 (1)</td>
<td></td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (1)</td>
<td>14 (4)</td>
<td></td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7 (4)</td>
<td>27 (9)</td>
<td></td>
<td>10 (9)</td>
<td></td>
</tr>
<tr>
<td>Tanner Stage</td>
<td>3.4 ±0.1</td>
<td>3.6 ±0.1</td>
<td>0.05</td>
<td>3.5 ±0.1</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Values presented are mean (±standard error) or N (%) where indicated; CNS, survivors of central nervous system tumors; CCS, childhood cancer survivors.

Measurements

Anthropometric and blood pressure assessments. Measurements for height and weight were taken at the start of the visit using a digital stadiometer. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters-squared (m²). Seated blood pressure was obtained in the right arm using an automatic blood pressure monitor (Model BP-8800C; Colin PressMate, San Antonio, TX). Tanner stage was assigned according to pubic hair development in boys and breast and pubic hair development in girls. Dual-energy X-ray absorptiometry (DXA) measurements were obtained with a Lunar Prodigy scanner (software version 9.3; General Electric Medical Systems, Madison, WI). Fat mass was expressed as a percent of fat mass (PFM), and lean body mass (LBM) was expressed in kilogram.

Vascular assessments. All vascular testing was performed in the Vascular Biology Laboratory in the University of Minnesota Clinical and Translational Science Institute in a quiet, temperature-controlled environment (22–23°C). Artery images were measured by a non-invasive ultrasound with subjects in the supine position. All images were digitized and stored on a personal computer for later off-line analysis of arterial compliance and distensibility. Electronic wall-tracking software was used for the analysis (Vascular Research Tools 5, Medical Imaging Application, LLC, Iowa City, IA).

Following 15 minutes of quiet rest in the supine position, vascular images were obtained of the carotid artery using a conventional ultrasound scanner (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc., Mountain View, CA) with a 15-8 MHz linear array probe held at a constant distance from the skin and at a fixed point over the imaged artery. The transducer was held at a constant distance from the skin and at a fixed point over the common carotid artery, approximately 1-cm proximal from the carotid bifurcation bulb, to capture the left common carotid artery’s lumen diastolic and systolic diameters. Depth and gain settings were set to optimize images of the lumen/arterial wall interface. Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer during the 10-second carotid measurements. The ultrasound scanning system was interfaced with a standard personal computer equipped with a data acquisition card for attainment of radio frequency ultrasound signals from the scanner. Images were collected at 20 frames per second for 10 seconds (200 frames) to ensure the capture of full arterial diameter change during a cardiac cycle. To measure carotid elasticity properties, the following formulas for distensibility and compliance were used: Diameter distensibility (DD, %) is defined as \[
\frac{[\text{maxDiamM} - \text{minDiamM}] \times 100\%}{\text{minDiamM}};\]
Cross-sectional distensibility (CSD, %) is defined as \[
\frac{\sigma\left(\frac{\text{maxDiamM}}{2}\right)^2 - \sigma\left(\frac{\text{minDiamM}}{2}\right)^2}{\sigma\left(\frac{\text{maxDiamM}}{2}\right)^2};\]
Compliance (DC, mm/mmHg) is defined as \[
\frac{[\text{maxDiamM} - \text{minDiamM}] \times 100\%}{\Delta P};\]
Cross-sectional compliance (CSC, mm²/mmHg) is defined as \[
\frac{\sigma\left(\frac{\text{maxDiamM}}{2}\right)^2 - \sigma\left(\frac{\text{minDiamM}}{2}\right)^2}{\sigma\left(\frac{\text{maxDiamM}}{2}\right)^2};\]
Incremental elastic modulus (IEM, mmHg) is defined as \[
3\left[1 + \frac{\sigma\left(\frac{\text{maxDiamM}}{2}\right)^2}{\sigma\left(\frac{\text{minDiamM}}{2}\right)^2}\right]/\frac{\text{CSC}}{\text{IEM}};\]
Pulse pressure (\(\Delta P\)) is calculated as the difference between systolic and diastolic pressures. Also, max-DiamM denotes maximum diameter measurement, and minDiamM denotes minimum diameter measurement.

Assessment of flow-mediated endothelial-dependent dilation (EDD) was performed by imaging the left brachial artery at the distal third of the upper arm using techniques previously described by our laboratory and others [9,10]. After measuring resting artery diameter, a blood pressure cuff was inflated below the elbow (distal to imaged artery segment) to a pressure of 200 mm Hg maintained for 5 minutes to induce muscle ischemia. Brachial artery diameter was measured continuously for a 3-minute period immediately after cuff release during reactive hyperemia to determine peak EDD (the greatest percent change from resting baseline brachial artery diameter following reactive hyperemia during the 3-minute collecting period). After a 15-minute rest, 0.3 mg sublingual nitroglycerin (NTG) was administered and the diameter of the brachial artery was continuously measured for a 15-minute period.
post NTG administration. Peak NTG-mediated EID was defined as the highest percent change from resting baseline brachial artery diameter following NTG administration during the 15-minute collection period. Reproducibility of the carotid IMT and EDD techniques in our laboratory have shown a mean difference of 0.02 ± 0.03 mm and 0.39 ± 0.65%, respectively for analysis separated by 1 week in healthy young adults.

**Statistical analysis.** Descriptive statistics are expressed as frequencies, percent or mean ± standard error (SE), as appropriate. For unadjusted comparisons among CCS groups but not controls, P-values are from a t-test or Fisher’s exact test; for unadjusted comparisons involving CCS groups and controls, P-values are from generalized estimating equations (GEE) with robust SEs, accounting for clustering by sibship of cases and controls. Multivariable linear regression models were used to compare groups according to adjusted mean outcome measures, with adjustments for age, sex, race, and Tanner stage unless noted otherwise. Adjusted means were evaluated at the average levels of covariates included in the analysis. GEE was also used to test the association between diagnosis and vascular measures. All analyses used the SAS system (v. 9.2; SAS Institute, Cary, NC).

**RESULTS**

The demographic characteristics of the study population are described in Table I. There were no significant differences in Tanner stage and gender distribution between CCS and controls. A higher fraction of white, non-Hispanic participants were present in the controls compared to CCS, and although CCS were slightly older, Tanner stage of pubertal development was not different from the controls. Measures of body composition can be found in Table II. All measures were adjusted for at the study, sex, race, and Tanner score. There were no significant differences between CCS and controls in weight, BMI, or BMI percentile; however, CCS were significantly shorter and had significantly higher percent body fat and significantly lower LBM (Table II).

Based upon overall similarities in therapeutic exposures, CCS were grouped into three major diagnostic groups: leukemia (n = 110), central nervous system (CNS) tumors (n = 82), and solid tumors (n = 127). Of the 110 participants in leukemia group 102 participants were diagnosed with ALL and 8 were diagnosed with Hodgkin’s lymphoma. CNS survivors were significantly more likely to receive focal brain radiation than solid tumor survivors, who in turn were significantly more likely to receive focal brain radiation than leukemia survivors (Table III). The length of follow-up (time from diagnosis to study evaluation) was not different between the cancer groups (P = 0.50) (Table III). Further analyses were adjusted for age at study, sex, race, and Tanner stage. The physical characteristics of the CCS, divided according to diagnosis, are described in Table II. There were no significant differences in body weight or BMI between control subjects and the three cancer survivor groups. Survivors of CNS tumors and leukemia were significantly shorter and had higher percent fat than controls. Leukemia survivors were also significantly shorter than survivors of solid tumors. LBM was significantly lower in leukemia survivors than in controls.

**Vascular Assessment**

**Brachial vascular measures.** Measures of systolic and diastolic blood pressure as well as brachial artery EDD and EID are displayed in Table IV. All measures were adjusted for age at study, sex, race, Tanner score, and PFM. There were no significant differences in systolic and diastolic blood pressure between controls and CCS as a whole or individual diagnosis groups. Although there were no differences in EDD between CCS as a whole and controls, leukemia survivors had significantly lower EDD compared to controls. There were no significant differences in EDD between the other cancer groups and the controls (Table IV). EID was not significantly different between controls and CCS as a whole or individual diagnosis groups.

**Carotid vascular measures.** Measures of carotid IMT as well as carotid artery function (i.e., carotid compliance and distensibility) are displayed in Table V. All measures were adjusted for age at study, sex, race, Tanner score and PFM. Carotid IMT did not differ significantly between CCS and controls, though carotid IMT was significantly (P = 0.02) greater in CNS survivors compared to leukemia survivors. Carotid IMT did not differ between leukemia and solid tumor survivors or controls (Table V).

**Carotid diameter distensibility (DD) and carotid cross-sectional distensibility (CSD) were significantly lower in CCS than in the controls.**

**TABLE II. Comparison Body Composition Measures Between CCS Groups and Sibling Controls; Mean (±Standard Error)**

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 208)</th>
<th>All CCS (N = 319)</th>
<th>Leukemia (N = 110)</th>
<th>CNS (N = 82)</th>
<th>Solid tumors (N = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
<td>Mean ±SE</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.9 ± 0.7</td>
<td>158.2 ± 0.6</td>
<td>156.4 ± 1.0</td>
<td>156.2 ± 1.0</td>
<td>158.7 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.1 ± 1.2</td>
<td>57.2 ± 1.1</td>
<td>55.4 ± 1.7</td>
<td>58.1 ± 2.0</td>
<td>55.4 ± 1.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.8 ± 0.4</td>
<td>22.4 ± 0.3</td>
<td>22.2 ± 0.5</td>
<td>23.1 ± 0.6</td>
<td>21.8 ± 0.5</td>
</tr>
<tr>
<td>BMI percentile (%)</td>
<td>66.1 ± 2.4</td>
<td>67.5 ± 2.0</td>
<td>68.0 ± 2.8</td>
<td>71.0 ± 3.2</td>
<td>64.6 ± 3.6</td>
</tr>
<tr>
<td>Percent fat mass (%)</td>
<td>25.9 ± 0.9</td>
<td>28.1 ± 0.8</td>
<td>28.6 ± 1.1</td>
<td>29.9 ± 1.2</td>
<td>26.3 ± 1.4</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>39.9 ± 0.6</td>
<td>38.4 ± 0.5</td>
<td>37.0 ± 0.9</td>
<td>37.3 ± 0.9</td>
<td>38.6 ± 0.8</td>
</tr>
</tbody>
</table>

CNS, survivors of central nervous system tumors; CCS, childhood cancer survivor; BMI, body mass index; LBM, lean body mass. Measures adjusted for age at study, sex, race, and Tanner score.
controls. Leukemia survivors also had significantly lower carotid diameter compliance (DC), cross-sectional compliance (CSC), and incremental elastic modulus (IEM) compared to controls. Both CSD and DD were significantly lower in the CNS group compared to controls. There were no significant differences in DD, CSD, DC, CSC, and IEM between the other cancer groups and the control subjects (Table V).

**DISCUSSION**

To our knowledge, this is the first study to evaluate endothelial function as well as carotid structure and stiffness in a large sample of children who had survived cancer. Endothelial function and carotid IMT are important early markers of subclinical atherosclerosis and increased CV disease risk [5,11,12,13]. In the present study we observed that leukemia survivors had significantly decreased lower measures of vascular function in both the brachial and carotid arteries and that carotid IMT was increased in survivors of CNS tumors compared to leukemia survivors.

Current cancer therapies typically employ multi-modal treatments, which include surgery, radiation therapy, and/or multi-agent chemotherapy. Determining the impact of any individual therapeutic exposure is a complex issue that requires a large number of subjects who have received each agent. In the present study, we grouped the CCS into three major diagnostic groups: leukemia, central nervous system tumors, and solid tumors. As in our previous study in adult survivors of childhood ALL [6], we observed reduced vascular function in survivors of leukemia. In the same study [6], we measured vascular function in the brachial artery using flow- and NTG-mediated dilation some 25 years after these individuals had undergone chemotherapy alone or combined with cranial radiation and observed that vascular function was not impacted by addition of cranial radiation to chemotherapy. In a similar study, Chow et al. [14] examined the short term (<60 months) effects of chemotherapy on endothelial-dependent function in 14 child, adolescent, and young adult (age 7–21 years) cancer patients with a variety of diagnoses (e.g., T-cell ALL, Ewing sarcoma, osteosarcoma, primitive neuroectodermal tumors, acute myelogenous leukemia, abdominal sarcoma, or lymphoma) examined between 2 and 60 months after cancer treatment. The authors reported a significant decline in endothelial-dependent dilation among patients compared to a control group of healthy individuals. Due to the small number of patients studied and the variety of diagnoses, it was not possible to determine whether chemotherapy and/or radiation was responsible for this acute decline in vascular function.

In the present study, similar to our earlier findings [6], we observed that leukemia survivors had a decline in endothelial function when measured by ultrasound imaging during brachial

**TABLE IV. Comparison of Brachial Vascular Measures Between CCS Groups and Sibling Controls; Mean (± Standard Error); P-values**

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 208)</th>
<th>All CCS (N = 319)</th>
<th>Leukemia (N = 110)</th>
<th>CNS (N = 82)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>P-value</td>
<td>Mean ± SE</td>
<td>P-value</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>110.5 ± 1.0</td>
<td>0.59</td>
<td>110.8 ± 1.3</td>
<td>0.84</td>
<td>109.8 ± 1.3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>57.5 ± 0.7</td>
<td>0.22</td>
<td>58.6 ± 0.9</td>
<td>0.10</td>
<td>57.8 ± 0.9</td>
</tr>
<tr>
<td>EDD (%)</td>
<td>8.20 ± 0.36</td>
<td>0.047</td>
<td>7.55 ± 0.38</td>
<td>0.016</td>
<td>8.13 ± 0.47</td>
</tr>
<tr>
<td>EID (%)</td>
<td>25.06 ± 0.57</td>
<td>0.04</td>
<td>26.05 ± 0.63</td>
<td>0.08</td>
<td>26.68 ± 0.68</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; EDD, endothelial-dependent dilation; EID, endothelial-independent dilation; CNS, survivors of central nervous system tumors; CCS, childhood cancer survivors. All measures adjusted for age-at-study, sex, race, Tanner score and percent fat mass.

*Pediatr Blood Cancer* DOI 10.1002/pbc
artery flow-mediated dilation. We did not find endothelial dysfunction among survivors of CNS or solid tumors. In addition, in the leukemia survivors we also observed reduced arterial compliance and distensibility indicating increased arterial stiffness. Observing both functional and mechanical dysfunction in more than one vascular bed suggests that the vascular derangements in leukemia patients are most likely systemic. Furthermore, the results of this study suggest that vascular dysfunction in survivors occurs early after treatment.

While the exact mechanism by which chemotherapy causes endothelial dysfunction is unknown, both in vitro and in vivo studies have shown that doxorubicin causes apoptosis of vascular endothelial cells [15,16]. Apoptosis has been associated with reduced endothelial cell density and a decrease in endothelial function as determined by acetylcholine infusions [17]. Therefore, it may be possible that administration of chemotherapy increases apoptosis resulting in permanent damage to endothelial cells lining the vessel wall. In support of this, Herceg-Cavrak et al. [18] examined pulse wave velocity, a marker of arterial stiffness, in 53 children and adolescents who as part of their cancer therapy had undergone anthracycline treatment at least 12 months prior to testing. Pulse wave velocity was significantly increased in the cancer survivors compared to an age-and sex-matched control group, consistent with an increase in arterial stiffness. This study was limited because doxorubicin, epirubicin, and daunorubicin were administered as part of various chemotherapy protocols in a total dose of 75–375 mg/m² (212 ± 93 mg/m²). In addition, in some cases cyclophosphamide, another possibly cardiotoxic drug [19,20,21,22,23], was administered.

Another important finding in the present study was the increased carotid IMT observed in the survivors of CNS tumors. Although they did not have the same level of vascular dysfunction observed in the survivors of leukemia, the structural aspect of the carotid artery showed significant differences. Although the carotid IMT values of survivors of CNS tumors was well below what would be considered an abnormal value in young patients (> 1.00 mm) it should be noted that the mean difference of 0.02 mm was equal to the estimated annual progression of carotid IMT (0.02–0.05 mm) and atherosclerosis [24]. The use of carotid IMT is beneficial in predicting increased risk in patients without document coronary artery disease and can be an important tool in guiding intensity treatment if the carotid IMT continues to progress [25].

While it is not possible to determine the factors responsible for this increase in carotid IMT, in the CNS tumor survivors compared to the leukemia survivors, it should be noted that CNS tumor survivors received more radiation overall and specifically to the head and neck region. Recent studies have shown that carotid IMT is increased after radiotherapy to the head and neck [26,27] and that this finding is related to the radiation dose [28]. Thus, it is likely that in the current cohort the increase in carotid IMT is a result of the acute damage to the endothelium caused by radiotherapy. This endothelial damage results in endothelial proliferation [29] as well as chronic fibrosis of the media and occlusive changes of the vaso vasorum of the adventitia [30].

Previously in this same population we have reported that survivors of CNS tumors and leukemia had a higher burden of CV risk factors (obesity, cholesterol, insulin resistance) than survivors of solid tumors [31]. The higher incidence of CV risk factors in survivors of CNS tumors and leukemia may also play a role in the vascular structural and functional declines observed in the present study. Further studies will be required to identify specific exposures that have a higher propensity to induce vascular structure and functional declines.

Given that there is a substantial body of evidence that regular physical activity can be protective against obesity, CV disease, diabetes, hypertension, osteoporosis, and some cancers [32,33] one might hypothesize that the declines in vascular structure and function may be due to lower physical activity levels in the CCS population. In support of this a review [34] of physical activity levels in CCS reported that most studies have found low levels of physical activity among CCS than healthy controls. We have previously reported in this population [35] that weekly minutes of physical activity did not differ between CCS and their sibling controls. Therefore, in the present study the observed differences in vascular structure and function in CCS population cannot be explained by lower levels of physical activity.

The present study has some limitations. The population was predominantly white non-Hispanic so the findings may not generalize to other racial/ethnic groups. Despite adjusting for gender in the analyses, gender differences in outcomes were not

**TABLE V. Comparison of Carotid Vascular Measures Between CCS Groups and Sibling Controls; Mean (± Standard Error); P-values Are for Comparison to Control**

<table>
<thead>
<tr>
<th>CSS divided according to diagnosis</th>
<th>Control (N = 208)</th>
<th>All CCS (N = 319)</th>
<th>Leukemia (N = 110)</th>
<th>CNS (N = 82)</th>
<th>Solid tumors (N = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>DD</td>
<td>15.10 ± 0.26</td>
<td>14.32 ± 0.21</td>
<td>14.02 ± 0.34</td>
<td>14.30 ± 0.35</td>
<td>14.61 ± 0.28</td>
</tr>
<tr>
<td>CSC</td>
<td>0.63 ± 0.02</td>
<td>0.60 ± 0.01</td>
<td>0.59 ± 0.02</td>
<td>0.61 ± 0.02</td>
<td>0.61 ± 0.01</td>
</tr>
<tr>
<td>DC</td>
<td>1.65 ± 0.04</td>
<td>1.61 ± 0.03</td>
<td>1.55 ± 0.05</td>
<td>1.65 ± 0.05</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td>CSD</td>
<td>32.70 ± 0.61</td>
<td>30.72 ± 0.48</td>
<td>30.09 ± 0.79</td>
<td>30.77 ± 0.79</td>
<td>31.24 ± 0.67</td>
</tr>
<tr>
<td>IEM</td>
<td>885.3 ± 20.9</td>
<td>923.0 ± 18.2</td>
<td>952.9 ± 31.3</td>
<td>904.3 ± 27.8</td>
<td>911.0 ± 26.7</td>
</tr>
<tr>
<td>LD</td>
<td>5.95 ± 0.05</td>
<td>5.92 ± 0.04</td>
<td>5.85 ± 0.06</td>
<td>5.96 ± 0.07</td>
<td>5.93 ± 0.05</td>
</tr>
<tr>
<td>IMT</td>
<td>0.44 ± 0.003</td>
<td>0.44 ± 0.003</td>
<td>0.44 ± 0.004</td>
<td>0.45 ± 0.007</td>
<td>0.44 ± 0.003</td>
</tr>
</tbody>
</table>

DD, diameter distensibility, %; CSD, cross-sectional distensibility, %; DC, diameter compliance, mm/mmHg; CSC, cross-sectional compliance, mm²/mmHg; IEM, incremental elastic modulus, mmHg; LD, lumen diameter, mm; IMT, intima-medial thickness, mm. Adjusted averages are adjusted for age-at-study, sex, race, Tanner score and percent fat mass.
monitoring CV risk factors in CCS of all ages. early in the course of survivorship, indicating the importance in declines in vascular structure and function are likely established by 45 or more years from diagnosis [37]. Time since diagnosis has CCS [36], with CV deaths accounting for 26% of the absolute cancers, since no patients receive specific therapies in isolation. The total impact of combination therapy for various childhood are present relatively soon after treatment. It also provides data on CCS have differences in both vascular structure and function that specifically addressed due to lack of power for statistical analyses by gender within each diagnostic category. In addition, because of differences in treatment protocols we are unable to attribute the changes in vascular structure and function to a specific chemother-apy agent. Strengths of the study include its relatively large sample size and representation of many different groups of cancer survivors and treatment types.

In summary, this study shows that compared to sibling controls, CCS have differences in both vascular structure and function that are present relatively soon after treatment. It also provides data on the total impact of combination therapy for various childhood cancers, since no patients receive specific therapies in isolation. Several studies have described adverse CV events among adult CCS [36], with CV deaths accounting for 26% of the absolute excess risk of death (second only to second primary cancers 51%) by 45 or more years from diagnosis [37]. Time since diagnosis has no effect on any outcome variable, which further suggests that the declines in vascular structure and function are likely established early in the course of survivorship, indicating the importance in monitoring CV risk factors in CCS of all ages.

REFERENCES