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Premature Carotid Artery Disease in Pediatric Cancer Survivors Treated With Neck Irradiation

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Abstract

Background—While carotid artery disease and strokes have been documented in adult cancer patients treated with neck irradiation, little information is available on pediatric patients. The purpose of this study is to determine if carotid disease is more prevalent among pediatric cancer survivors treated with neck irradiation than among healthy controls.

Procedure—Thirty pediatric cancer survivors who received neck irradiation (2,000–6,660 cGy) and 30 healthy subjects underwent bilateral carotid ultrasounds. Study outcome measures were common carotid intima-media thickness (IMT) and plaque (present or absent). Multivariate methods were used to compare cases and controls and to identify risk factors related to carotid disease in childhood cancer survivors.

Results—IMT was greater for cancer survivors than controls (0.46mm (SD 0.12) vs. 0.41mm (SD 0.06), $P < 0.001$). Plaque was present in 18% of irradiated vessels and 2% of non-irradiated vessels ($P < 0.01$). Among cancer survivors, IMT was positively associated with female gender ($P < 0.05$), nonwhite ethnicity ($P < 0.01$), positive family history of stroke/heart attack ($P < 0.05$), BMI ($P < 0.001$), total cholesterol ($P < 0.01$), cancer relapse ($P < 0.001$), and years off treatment ($P < 0.0001$). Plaque was positively associated with relapse ($P < 0.05$) and C-reactive protein ($P <$

0.01). There was no significant relationship between radiation dose at levels $\geq 2,000$ cGy and IMT or plaque.

Conclusions—Carotid artery disease was more prevalent among cancer survivors treated with neck irradiation than among controls. Due to the high risk of stroke associated with advanced carotid disease, larger prospective studies are needed to better define disease risk in these long-term survivors.

Keywords

carotid artery disease; childhood cancer survivors; late effects; neck irradiation; radiation therapy

INTRODUCTION

Childhood cancer survivors treated with neck irradiation are at risk of developing a number of late effects, including xerostomia, esophageal stricture, subcutaneous fibrosis and muscle wasting in the radiation field, dental problems, dysphagia and thyroid abnormalities [1]. While studies in adult head and neck cancer patients have found that therapeutic irradiation to the neck also increases survivors' risk of carotid artery disease and stroke [2,3], these radiation-related late effects have only recently been documented in young adult survivors of childhood cancer [4–7].

Carotid artery disease is a progressive vascular disease in which a build-up of atherosclerotic plaque leads to the gradual narrowing of the lumina of the carotid arteries, eventually resulting in decreased blood flow to the brain. Patients with carotid disease are often asymptomatic during the early stages, and stroke and transient ischemic attacks are often the first symptoms of advanced disease [8]. Carotid artery disease is an adult-onset disease that rarely occurs symptomatically in individuals younger than 50 years of age [9].

Radiation therapy can damage the endothelial lining of the arteries, inducing a series of inflammatory responses [10]. Radiation-induced vascular injury is characterized by endothelial cell proliferation, intimal thickening, medial scarring, lipid deposits and adventitial fibrosis [11]. The current theory is that radiation accelerates atherosclerosis in adult patients and induces atherosclerosis in younger patients [12,13].

Current understanding of radiation-related carotid artery disease is based primarily on adult studies. Dorresteijn et al. [3] found a 10-fold increase in carotid-related strokes among head and neck cancer patients treated with high-dose neck irradiation compared with the general population. In cross-sectional studies, 12–40% of adult cancer patients treated with neck irradiation had significant carotid artery stenosis [14–18]. Significant increases in carotid intima-media thickness (IMT) have been documented in adult patients 1-year post-radiation therapy [19,20]. Furthermore, adult prospective studies have demonstrated that carotid stenosis progresses at a faster rate in irradiated patients than in non-irradiated patients [21,22]. Correlates of radiation-related carotid disease include increasing age and time from radiation therapy [2,3]. Associations between radiation-induced carotid artery disease and established cardiovascular risk factors, such as smoking, hypertension and

hypercholesterolemia have been inconsistent [2,5,13,14,16]. These types of follow-up studies have not been conducted in survivors of childhood cancer.

The purpose of this study is to determine if carotid artery disease is more prevalent among pediatric cancer survivors treated with neck irradiation than among healthy control participants matched on gender and age. We further sought to identify risk factors associated with carotid artery disease among cancer survivors.

METHODS

Subjects

Patients were eligible for this study if they had been diagnosed with cancer before the age of 20 years, had received radiation $\geq 2,000$ cGy to at least one side of the neck and were off-treatment and disease-free for at least 5 years. Patients with a history of stroke or known carotid disease were excluded. We identified 49 eligible patients using the cancer registry, radiation therapy database and the long-term follow-up clinical database at Childrens Hospital Los Angeles (CHLA). An invitation letter explaining the study was mailed to all potential subjects and a follow-up telephone call answered questions and determined the patient's interest in the study. Thirty of the 49 eligible cancer survivors (61%) participated in the study. Reasons for non-participation were lost-to-follow-up ($n = 10$), not interested ($n = 3$) and interested but missed multiple appointments (passive refusals) ($n = 6$). Non-participants were younger than participants ($P = 0.05$) and their time off-treatment was shorter ($P < 0.01$). Participants and non-participants did not differ in gender, ethnicity, age at diagnosis and radiation dose delivered to the neck.

We recruited 30 healthy control subjects matched in ethnicity, gender and age. Ten participating patients (33%) identified a relative (sibling, cousin) or friend who participated as a control. The other 20 control participants were recruited with flyers placed at CHLA and the University of Southern California. All participants were paid 25 dollars for their participation.

Informed consent was obtained from all participants. Study procedures were approved by the Research Committees at the University of Southern California and CHLA, in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services.

Study Evaluation

Clinical and laboratory measures—Participants underwent a clinical assessment that included height (cm), weight (kg), waist and hip measurements (cm) and two sitting blood pressures measured 5 minutes apart. Eight hour fasting blood samples were collected and the following laboratory studies obtained: complete blood count, glucose, high-sensitivity C-reactive protein (hs-CRP), homocysteine, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), thyroid stimulating hormone (TSH) and free thyroxine (free T4).

Subjects completed a questionnaire that collected information on demographics, smoking behaviors, comorbidities and family history of heart attack and stroke. Diagnosis and treatment information were abstracted from patients' medical records. The total radiation dose (cGy) delivered to the right and to the left neck were abstracted from the patient's radiation oncology chart.

Carotid measurements—The primary outcome measures used in this study are carotid intima media thickness (IMT) and plaque. Carotid IMT and plaque are validated markers of subclinical atherosclerosis that predict future cerebrovascular and cardiovascular events [23–25]. It has been suggested that elevated IMT may be a precursor to plaque development.

Images of the common carotid arteries were acquired from three independent complete cardiac cycles by using a 15L8-MHz ultrasound (US) transducer. IMT was measured on the images of each cycle that depicted the narrowest and widest vessel diameters, and at the R wave of the electrocardiogram (ECG). All studies were performed by the same technologist using a US scanner (Acuson Sequoia 512; Siemens Medical Solutions) and a high-frequency 15L8-MHz linear-array transducer, following a predetermined standardized scanning protocol. The participants were studied in the supine position with the head turned slightly away from the side that was examined. Images of the arterial wall were obtained from the posterior walls of both common carotid arteries 1 cm below the carotid bulb (bifurcation) during three complete and independent cardiac cycles.

An automated computerized edge detection software package (version 1.0, 2002; Siemens Medical Solutions) was used to determine IMT values in the frames of each cycle that depicted the narrowest and widest vessel diameters. All examinations were digitally stored and analyzed by the same technician, who was blinded to the participants' case/control status [26]. The average IMT of the minimum and maximum diameters of each carotid artery was calculated. The reproducibility of the IMT measurements has been reported previously as high (coefficient of variation (CV) = 3.3%) [26]. A single radiologist {MN}, blinded to participants' case/control status, reviewed ultrasound images for plaque in the common, bulb, internal and external segments of the carotid artery. Presence or absence of plaque deposits was recorded.

Statistical Analysis

The primary outcome measures in this study were common carotid IMT (continuous) and the presence/absence of carotid plaque (dichotomous). An average systolic and diastolic blood pressure was calculated using the two sitting blood pressures. Neck irradiation dose was analyzed as both a continuous and categorical variable. Three radiation exposure (dose) groups were created: no radiation (controls), radiation < 3,000 cGy and radiation ≥ 3,000 cGy.

Chi-square (categorical variables) and *t*-test (continuous) were used to compare cases and controls. Our analyses of IMT and plaque included right and left measures from all participants except for the five cancer survivors who received unilateral irradiation. These patients contributed carotid measurements only from the treated side. Our final analyses included carotid measurements from 55 irradiated vessels (cases) and 60 non-irradiated

vessels (controls). We used generalized estimating equations (GEE) that accommodate repeated measures within subjects, to identify independent correlates of IMT (linear regression with GEE) and plaque (logistic regression with GEE). We developed multivariate models for carotid IMT and plaque for survivors. Variables with P -values < 0.20 from our univariate analyses were included in our multivariate regression analyses. Age was included in all final models because of its strong relationship with cardiovascular disease. Furthermore, since IMT among controls was greater for the left carotid than the right ($P < 0.05$), multivariate models also were adjusted for side [left or right carotid]. All P -values reported are two-sided. Data analyses were conducted using SAS statistical software (Version 9.0) (SAS Institute; Cary, NC).

RESULTS

Subjects

In our comparison of cases and controls, we found that body mass index (BMI [kg/m^2]) and diastolic blood pressure were significantly higher for controls than cases ($P = 0.05$; Table I). No significant group differences were found for age, ethnicity, gender, education, work status, income, marital status, smoking, family history of stroke, heart attack or diabetes, systolic blood pressure, waist-hip ratio, platelets, triglycerides, total cholesterol, LDL, HDL, glucose, homocysteine, hs-CRP, freeT4 or thyroid stimulating hormone (TSH) (not all data shown).

Cancer survivors ranged in age from 14 to 47 years (mean age 27.5, standard deviation (SD) 10.7). More than half of the survivors had been diagnosed with Hodgkins Disease (Table II). Average age at diagnosis was 10.4 years (SD 5.2, range 2–20 years). Twentyfive patients (83%) were treated with bilateral neck irradiation; five received radiation to only one side of the neck. Average radiation dose delivered to the left neck was 3,794 cGy (SD 1,456) (range = 1,800–6,660 cGy); average dose delivered to the right neck was 3,634 cGy (SD 1,440 cGy) (range = 2,100–6,660 cGy). There was a high correlation between the radiation doses delivered to the left and right neck ($r = 0.94$). Survivors were off-treatment for an average of 15 years (SD 8.7, range 6–35 years).

Carotid Disease

Common carotid IMT was significantly higher for survivors than controls (survivors 0.46mm (SD 0.12) vs. 0.41mm (SD 0.06); mean difference 0.05 mm, unadjusted P -value < 0.01 ; age adjusted P -value < 0.001). When we categorized survivors as receiving low dose (1,800–3,000 cGy) or high dose ($> 3,000$ cGy) neck irradiation and compared them to controls who had received no neck irradiation, we found that IMT increased with higher doses of radiation therapy (trend $P < 0.0001$; Table III).

Among cancer survivors, we found a positive association between carotid IMT and age ($P < 0.0001$), BMI ($P < 0.0001$) and years since diagnosis ($P < 0.0001$). IMT was higher for nonwhite participants than white ($P < 0.05$). Additionally, we found a negative relationship between IMT and TSH ($P = 0.02$), homocysteine ($P = 0.02$) and age at diagnosis ($P < 0.01$; Table IV). No significant relationships were found for gender, total cholesterol,

triglycerides, hs-CRP, cancer diagnosis, radiation dose, adriamycin or relapse. The following factors were significant in a multivariate model of carotid IMT: female gender ($P < 0.05$), nonwhite ethnicity ($P < 0.01$), positive family history of stroke/heart attack ($P < 0.05$), cancer relapse ($P < 0.001$), total cholesterol ($P < 0.01$), BMI ($P < 0.001$) and years off treatment ($P < 0.0001$; Table V). The positive relationship between carotid IMT and time off treatment is illustrated in Figure 1. In this multivariate model, we found no significant relationship between radiation dose at levels $\geq 2,000$ cGy and IMT ($P = 0.94$ [radiation dose as a continuous variable]; $P = 0.72$ [radiation dose as a categorical variable]).

Plaque was present in 10 of the 55 irradiated vessels (survivors = 18%) and in one of the 60 non-irradiated vessel (controls = 2%; Table III). Childhood cancer survivors treated with neck irradiation were 12 times more likely to have plaque deposits in the carotid arteries than controls (adjusted OR = 11.81, 95% CI = 1.29–108.34).

Among cancer survivors, carotid IMT was significantly greater among those with plaque (0.54mm (SD 0.12)) than those without plaque (0.45mm (SD 0.12); $P = 0.02$). In our univariate analyses, plaque was associated with higher levels of hs-CRP (OR 1.20, 95% CI = 1.04–1.40) and cancer relapse (OR 7.94, 95% CI = 2.02–31.18; Table IV). The multivariate model for plaque included hs-CRP (OR 1.22, 95% CI = 1.09–1.37) and relapse (OR 7.14, 95% CI = 1.68–30.45; Table VI). There was no significant relationship between plaque and the other disease/treatment factors, including years off treatment and radiation dose. Interestingly, four of the ten survivors with plaque (40%) received radiation doses between 2,000 and 3,000 cGy.

DISCUSSION

On carotid ultrasound, we found an increase in carotid disease in a relatively young group of asymptomatic cancer survivors who were treated with neck irradiation. Common carotid IMT was greater and plaque deposits were more common among these survivors than among age/gender matched control subjects. Our study findings for pediatric cancer survivors are consistent with those reported for older adult cancer survivors [13,15,19,22,26,27].

While our ultrasound results are similar to those reported by King et al. [7], the only other study to assess carotid artery disease in childhood/young adult cancer survivors treated with neck irradiation, our study is the first to identify significant demographic and disease-related risk factors associated with the development of radiation-related carotid disease in survivors of childhood cancer (e.g., longer time from treatment, history of relapse, female gender). Furthermore, participants in our study received a wide range of radiation doses (2,000–6,660 cGy), allowing us to examine the relationship between radiation dose and risk of carotid disease. This dose-response relationship has not been explored previously in survivors of pediatric cancer.

Among cancer survivors who received neck irradiation ($\geq 2,000$ cGy), we found no significant relationship between radiation dose and carotid IMT or plaque. Both survivor groups, those who received lower doses (1,800–3,000 cGy) and those who received higher

doses (>3,000 cGy) of radiation, had significantly higher IMT and more plaque deposits than controls. While animal studies have demonstrated a dose response relationship between radiation and vascular injury [28], findings from adult cancer studies have been inconsistent [26,29]. As a result of these inconclusive findings, current recommendations for ultrasound screening of adult patients treated with neck irradiation are not based on radiation exposure, that is, dose [30]. In contrast, the screening guidelines for pediatric patients published by the Children's Oncology Group identify as high risk only those who received radiation doses 4,000 cGy [31]. Our study suggests that children/adolescents treated with lower doses of neck irradiation (i.e., 1,800–3,000 cGy) are also at higher risk of developing carotid disease.

In this study, female gender was an independent risk factor for IMT. While this finding is inconsistent with results seen in the general population [32], it is consistent with the pediatric oncology literature on late effects. A recent review of pediatric survivorship studies suggests that females have a higher risk of developing several long-term radiation-related adverse outcomes, including cognitive dysfunction, primary hypothyroidism and obesity [33]. Cardiovascular late effects also are more common among female cancer survivors than males [34]. While several theories for these gender differences have been proposed, including male/female differences in endogenous hormones and brain development, the underlying mechanisms are unknown. These gender differences in treatment-related late effects among pediatric cancer patients clearly need further study.

An important but not surprising finding among our cancer survivors was that carotid IMT increased with longer follow-up. In the Childhood Cancer Survivor Study (CCSS), investigators found that a number of treatment-related late effects increased with time (e.g., cardiac, pulmonary, and musculoskeletal) with no indication of a plateau [35]. In the general population, carotid occlusive disease increases with age [36]. Furthermore, follow-up studies with adult cancer patients treated with neck irradiation demonstrate an increase in carotid stenosis and stroke risk with longer follow-up [2,3,9,37]. This positive relationship with time and the young age of our study population (80% < 40 years of age) clearly demonstrates the need for life-long surveillance of patients treated with neck irradiation. Long-term follow-up studies are needed to understand how the normal aging process impacts treatment-related late-effects. For example, with this survivor population, the interval between radiation therapy and the development of significant occlusive stenosis and symptoms is unknown [13].

Survivors who relapsed had higher IMT and more plaque deposits than those who did not relapse. While relapse patients tend to receive more intensive treatments and experience more late effects [38], we found that the relapsed and non-relapsed patients did not differ significantly on most factors, including neck radiation dose, total anthracycline dose, age at diagnosis, BMI, time off treatment and lipid levels. However, we did find an increase in smoking among relapsed patients. Fifty percent of the relapsed patients (3/6) were current smokers compared to 4% of the non-relapsed patients (1/24). While our numbers are small, this positive relationship with smoking, a well established cardiovascular risk factor in the general population [39], illustrates how poor health behaviors have the potential to increase further the cancer survivor's risk of late effects. In addition to smoking, we found a positive relationship between IMT and cholesterol and BMI. These relationships, which also are

present in the general population [39], further suggest that interventions aimed at reducing modifiable cardiovascular risk factors are important and may have added value for this population of survivors [3,11,36].

Using healthy controls as a comparison group is a limitation of this study. The study's cross sectional design does not rule out the possibility that group differences in carotid disease were present before radiation therapy was administered to our cancer patients. It is possible that factors other than radiation therapy are responsible for these group differences. Some adult cancer studies have used different control groups to address this limitation. Cheng et al. [21] conducted a prospective study that included cancer patients who had neck irradiation and controls who were matched on degree of carotid artery stenosis and had not received radiation. At 3 years follow-up, carotid disease progressed more rapidly among irradiated patients than non-irradiated patients ($P < 0.05$). In another prospective study with adult cancer patients who received unilateral neck irradiation [22], IMT was significantly greater in the irradiated vessels than non-irradiated vessel 1 year after radiation ($P < 0.05$). These adult studies suggest that radiation plays a key role in disease promotion. While these adult follow-up studies provide valuable information it is unknown if these findings apply to the pediatric survivor population. Prospective longitudinal studies such as these have not been and need to be conducted with survivors of childhood cancer. It also would be informative to compare patients with similar diagnoses who were and were not treated with neck radiation.

This is the first study to identify risk factors associated with radiation-related carotid disease in pediatric cancer survivors. Further research is needed, as the prevalence, natural history and genetic susceptibility of this late effect are unknown. In view of the potential risk of stroke associated with carotid disease [3,6,8] and its asymptomatic nature, the value and cost-effectiveness of monitoring these young at-risk patients with serial carotid duplex ultrasonography needs to be determined. Furthermore, this study highlights the need to explore treatment and clinical management options for this subset of cancer survivors who have an increased risk of premature carotid artery disease.

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Fig. 1.
Carotid IMT by years off treatment.

TABLE I

Characteristics of Participants

	Cancer survivors, N (%)	Healthy controls, N (%)	<i>P</i> -value ^a
Total	30 (100)	30 (100)	
Age			
13–19	8 (27%)	8 (27%)	0.93
20–29	11 (37%)	10 (33%)	
30–39	5 (17%)	7 (23%)	
40–47	6 (20%)	5 (17%)	
Ethnicity			
White	14 (47%)	14 (47%)	1.00
Black/Hispanic	16 (53%)	16 (53%)	
Gender			
Male	19 (63%)	18 (60%)	0.79
Smoking			
Ever (yes)	5 (17)	6 (20)	0.74
Family history of heart attack/stroke			
Yes	8 (27%)	6 (20%)	0.39
	Cancer survivors, Mean (SD)	Healthy controls, Mean (SD)	<i>P</i> -value ^b
Platelets (K/μl)	272.4 (77.8)	248.9 (62.4)	0.20
BP diastolic (mm Hg)	68.0 (8.6)	73.6 (10.9)	0.03
BP systolic (mm Hg)	112.1 (13.5)	117.6 (11.7)	0.10
BMI	22.3 (4.8)	25.1 (5.5)	0.04
Triglycerides (mg/dl)	93.4 (48.7)	100.3 (75.1)	0.67
Cholesterol (mg/dl)	173.9 (33.9)	165.4 (28.7)	0.30
LDL (mg/dl)	100.3 (29.7)	89.5 (23.9)	0.13
HDL (mg/dl)	54.9 (12.1)	55.7 (17.1)	0.83
Glucose (mg/dl)	89.4 (7.6)	92.6 (9)	0.14
Homocysteine (mmol/L)	8.2 (2.2) ^c	8.9 (2.7) ^d	0.34
HS-CRP*(mg/dl)	1.79 (3.2)	1.96 (3.5)	0.83
Free T4 (ng/dl)	0.92 (0.22)	0.95 (0.16)	0.59
TSH (μl U/ml)	7.4 (26)	1.9 (0.66)	0.26

^aChi-square;^b*t*-Test;^cn = 28;^dn = 29;

hs-CRP, high sensitivity C-reactive-protein (see P. 2).

TABLE II

Cancer Survivors: Disease and Treatment Factors

Disease and treatment factors	N (%)
Total	30 (100)
Diagnosis	
Hodgkins	17 (57%)
Rhabdomyosarcoma	6 (20%)
Other	7 (23%)
Age at diagnosis (years)	
2–5	4 (13%)
5–9	10 (33%)
10–14	8 (27%)
15–20	8 (27%)
Chemotherapy	
Yes	28 (93)
Treated with Adriamycin	
Yes	17 (57)
Neck irradiation	
Unilateral	5 (17)
Bilateral	25 (83)
Average dose (SD)	3,716 cGy (1,437)
Range	1,800–6,660 cGy ^a
Relapse	
Yes	6 (20%)
Time off treatment (years)	
6–10	8 (27)
10–19	12 (40)
20–35	10 (33)

^aOne subject received 1,800 cGy to one side of the neck and more than 2,000 cGy to the other side of the neck.

TABLE III

Carotid Artery Disease: Cancer Survivors Compared to Healthy Controls

		IMT		Plaque	
	Neck Irradiation	Carotid arteries, N = 115 ^a	Mean (SD) (mm)	Adjusted <i>P</i> -value ^b	Adjusted <i>P</i> -value ^c
Healthy controls	No radiation	60	0.41 (0.06)	Reference group	Reference group
Cancer survivors	1,800–2,900 cGy	21	0.43 (0.09)	<0.01	<0.001
Cancer survivors	3,000–6,660 cGy	34	0.48 (0.14)	<0.0001	<0.001
			Trend <i>P</i> -value	<0.0001	<0.01

^aThirty control subjects representing 60 non-irradiated carotid arteries and 30 cancer survivors representing 55 irradiated carotid arteries;

^bMultiple linear regression adjusted for age, BMI, total cholesterol, triglycerides, LDL and side (right or left carotid artery);

^cMultiple logistic regression adjusted for age, BMI, total cholesterol, triglycerides, LDL and side.

TABLE IV

Cancer Survivors: Factors Associated with Carotid Disease

	IMT		Plaque	
	Linear regression estimate (SE)	P-value ^a	OR (95% CI) ^b	P-value ^c
Age	0.006 (0.002)	<0.0001	1.05 (0.99–1.11)	0.11
Female gender	0.05 (0.03)	0.14	0.34 (0.07–1.62)	0.18
Black/Hispanic Ethnicity ^d	0.06 (0.03)	0.04	2.05 (0.58–7.53)	0.28
Smoking (yes)	0.01 (0.06)	0.88	1.56 (0.25–9.87)	0.64
BMI	0.009 (0.002)	<0.0001	0.96 (0.85–1.09)	0.55
Family history heart attack/stroke	0.07 (0.04)	0.08	2.01 (0.42–9.63)	0.38
BP diastolic	0.001 (0.002)	0.63	1.04 (0.96–1.12)	0.32
BP systolic	−0.0001 (0.001)	0.91	1.03 (0.98–1.08)	0.23
Triglycerides	0.0004 (0.0003)	0.09	1.00 (0.98–1.01)	0.56
Cholesterol	0.0007 (0.0004)	0.07	1.00 (0.98–1.02)	0.87
LDL	0.0005 (0.0005)	0.35	1.00 (0.98–1.02)	0.84
HDL	0.002 (0.001)	0.21	1.01 (0.97–1.06)	0.58
Glucose	−0.002 (0.002)	0.35	1.05 (0.97–1.13)	0.26
Homocysteine	−0.01 (0.005)	0.02	1.14 (0.91–1.43)	0.27
Free T4	−0.006 (0.06)	0.92	0.65 (0.04–11.15)	0.77
TSH	−0.0004 (0.0002)	0.02	0.99 (0.97–1.01)	0.32
Platelets	0.0001 (0.0002)	0.57	0.99 (0.98–1.01)	0.31
hs-CRP	0.008 (0.006)	0.18	1.20 (1.04–1.40)	0.02
Hodgkins		Reference		Reference
Rhabdomyosarcoma	−0.006 (0.05)	0.89	1.51 (0.28–8.22)	0.63
Other	0.02 (0.04)	0.50	1.34 (0.38–6.54)	0.71
Age at diagnosis	−0.007 (0.003)	<0.01	0.89 (0.78–1.02)	0.11
Radiation dose (per 1,000 cGy)	0.005 (0.01)	0.65	1.00 (0.65–1.55)	0.99
Chemo (yes)	−0.02 (0.07)	0.77		—
Adriamycin (yes)	0.03 (0.03)	0.39	1.97 (0.45–8.67)	0.37
Relapse	0.08 (0.04)	0.07	7.94 (2.02–31.18)	<0.01
Years since diagnosis	0.008 (0.002)	<0.0001	1.00 (0.89–1.14)	0.95

^aLinear regression adjusted for age and side (right or left carotid artery);^bOdds ratio (OR), confidence interval (CI);^cLogistic regression adjusted for age and side (right or left carotid artery);^dReference group = white.

TABLE V

IMT: Multivariate Model for Cancer Survivors

	Estimate (SE)	<i>P</i> -value ^a
Age	0.002 (0.001)	0.08
Female gender	0.04 (0.02)	<0.05
Black or Hispanic ethnicity	0.04 (0.02)	<0.01
BMI	0.006 (0.002)	<0.001
Cholesterol	0.0009 (0.0003)	<0.01
Relapse	0.08 (0.02)	<0.001
Years off treatment	0.007 (0.001)	<0.0001
Positive family history of stroke/heart attack	0.05 (0.02)	<0.05

SE, standard error.

^aMultiple linear regression model, adjusted for side (right or left carotid artery).

TABLE VI

Plaque: Multivariate Model for Cancer Survivors

	OR (95% CI)	<i>P</i> -value ^a
Age	1.05 (0.98–1.12)	0.17
hs-CRP	1.22 (1.09–1.37)	<0.01
Relapse	7.14 (1.68–30.45)	<0.05

OR, odds ratio; CI, confidence interval.

^aMultiple logistic regression model, adjusted for side (right or left carotid artery).