Use and Correlates of Carotid Ultrasound in Survivors of Childhood Cancer: A report from the Childhood Cancer Survivor Study

Working Group: Cancer Control
                      Chronic Disease

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Background and Rationale:

Survivors of childhood cancer, especially those who are older, have a history of radiation therapy (RT), or are hypertensive, are at increased risk for stroke and recurrent stroke.[1,2] Among disease groups, survivors of Hodgkin lymphoma and pediatric brain tumors appear to be at highest risk, with incidence exceeding 250 cases per 100,000 person-years.[1,3] Evidence from the Childhood Cancer Survivor Study (CCCS) suggests that among survivors with a history of stroke, subsequent stroke is common; the 10-

Figure 1. Cumulative incidence of first stroke after cranial radiation therapy in pediatric cancer patients. [PMID 23623405]

year cumulative incidence of subsequent stroke was 21% overall and 33% among those with a history of ≥ 50 Gy of cranial RT. In that study, the median time from cancer diagnosis to first stroke was 10 years (interquartile range [IQR] 21 years) and the median time from cancer diagnosis to second stroke was 23 years (IQR 19 years).[2] In a separate retrospective study of 325 pediatric cancer survivors treated with cranial or cervical radiation, 19 had a first stroke (13 ischemic, 4 hemorrhagic, 2 unknown sub-type) at a median age of 24 years (IQR 17–33 years). The cumulative incidence of first stroke was 2% (95% confidence interval (CI): 0.01–5.3%) at 5
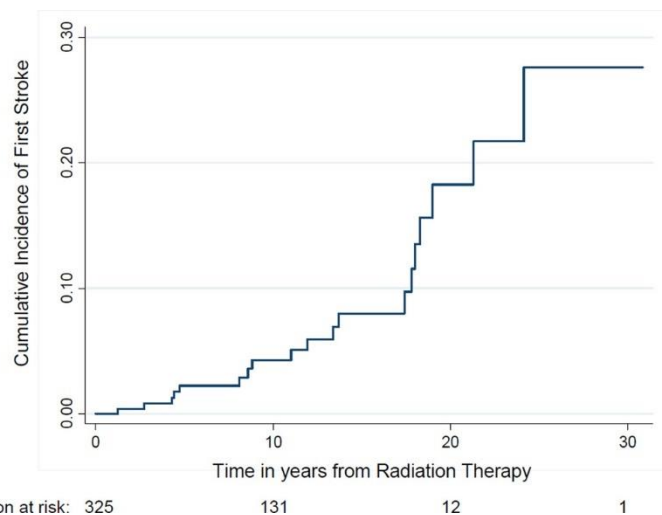
years and 4% (95% CI: 2.0–8.4%) at 10 years after irradiation. **Figure 1**) With each 1.0 Gy increase in the radiation dose, the stroke hazard increased by 5% (Hazard ratio = 1.05; 95% CI 1.01–1.09; p=0.02). Subsequent strokes were also observed at a median time of 15 months (IQR 6 months–3.2 years) from the first stroke; the cumulative incidence of subsequent stroke was 38% (95% CI 17–69%) at 5 years and 59% (95% CI: 27–92%) at 10 years after the first stroke.[4]

As a result of these observations, the European Society of Cardiology includes carotid ultrasound in a recommended comprehensive screening assessment for adults with a history of RT to the neck.[5] The North American Children's Oncology Group guidelines list ultrasound of the carotid vessels "as clinically indicated," as one of the "Potential considerations for further testing and intervention," and has recommended testing for those with a history of 40Gy or higher of radiation therapy to the neck ("Color Doppler US 10yrs after XRT as a baseline").[6]

In the general population, national guidelines recommend *against* screening asymptomatic adults for carotid artery stenosis with carotid ultrasound (or any other modality).[7] This recommendation is largely based on the fact that the prevalence of asymptomatic carotid artery stenosis in the general population is low, as is the risk of stroke. At the same time, the benefit of surgical revascularization is questionable in the face of modern medical management of atherosclerosis.[8,9]Therefore, carotid ultrasound should not be routinely performed in asymptomatic adults in the general population. However, carotid ultrasound is a safe, non-invasive, and inexpensive diagnostic tool. For adults with a history of stroke or other vascular event, and for childhood cancer survivors who are at risk, carotid ultrasound may have a role as part of routine surveillance.

Whether carotid ultrasound is routinely used in childhood cancer survivors, as either a way to identify survivors with atherosclerosis of the carotid arteries or to diagnose carotid stenosis after a vascular event, is unknown. This study proposes to describe the use of carotid ultrasound in the CCSS cohort, comparing survivors to siblings, with a goal of better understanding its engagement and role in this setting.

Specific Aims:
1. **Compare prevalence of self-reported carotid US use between childhood cancer survivors and siblings (controls) in the CCSS.**
2. **Evaluate factors potentially associated with use of carotid ultrasound including:**
   a. **demographics, socioeconomic and treatment-related variables,**
   b. **history of stroke or other vascular disease, and traditional cardiovascular risk factors.**
   c. **Carotid artery surgeries, including endarterectomy**

Analysis Framework:

Subject population:

We will include all survivors diagnosed between 1970 and 1999 and siblings who completed the Follow-up 5 (2014) CCSS questionnaire.

Outcome(s) of interest:

The primary outcome is <u>ultrasound of the carotid arteries</u> from the Follow-up 5 (2014) questionnaire,

      a. Follow-up 5 (2014), C1h: When was the last time you had an ultrasound of the carotid arteries (blood vessels in the neck)?

         Answers will be dichotomized into never/ever.

            Responses: Never; Ever (Less than 1 year ago/1-2 years ago/More than 2 but less than 5 years ago/5 or more years ago/I had one, but I don't recall when/I don't know if I ever had one)

      b. Follow-up 5 Sibling (2014), C1h: When was the last time you had an ultrasound of the carotid arteries (blood vessels in the neck)?

         Answers will be dichotomized into never/ever.

            Responses: Never; Ever (Less than 1 year ago/1-2 years ago/More than 2 but less than 5 years ago/5 or more years ago/I had one, but I don't recall when/I don't know if I ever had one)

Explanatory variables:

<u>Demographics (see table for categories):</u>

Age

Age at diagnosis

Body mass index (FU5 – A1 and 2)

Race

Ethnicity

Gender

Insurance (FU5 – A10)

Marriage (FU5 – M2)

Education (FU5 – A4)

Employment (FU5 – A5)

Tobacco (never; former; current – by FU5)

Alcohol typical (none/moderate/heavy; FU5 – N1-3)

        Moderate: any amount of consumption ≤1 drink on a typical day for women and ≤ drinks on a typical day for men

Heavy: >1 drink per typical day for women and >2 drinks per typical day for men

Alcohol binging (none/binging/drinking but not binging; FU5 – N1 and N4)

Binging: ≥ 4 drinks in one day for women and ≥ 5 drinks in one day for men

Physical activity (active/inactive; FU5 – N15 through N21)

Active defined as ≥ 75 minutes/week of vigorous activity or ≥ 150 minutes/week of moderate intensity activity

Cancer treatment variables:

Diagnosis

Anthracyclines (yes/no)

Alkylating agents (yes/no)

Radiation therapy to neck, cranium, chest, or total body (yes/no)

Body region dosimetry for brain, neck, and chest, i.e., maximum target dose (maxTD) Gy

Carotid artery surgery (FU5 – J40; free text response)

Cardiovascular risk factors or history of stroke. (ever):

Hypertension (FU5 - F5)

Arrhythmia (FU5 – F3)

Heart failure (FU5 - F1)

Coronary artery disease (FU5 – F4)

Myocardial infarction (FU5 – F2)

Stroke (FU5 – K14)

Medications (current as per FU5):

Statins (FU5 – C2.6)

Anti-hypertensive medications (FU5 – C2.5)

Other heart medications (FU5 – C2.7 and free text response)

Other Guideline-Related Testing (ever, as per FU5)

Mammogram

Colonoscopy

Echocardiogram

Skin exam

Health Services Variables (as of FU5)

Visit to primary care clinician (FU5 – B1b)

Last routine checkup with tests for problems from cancer (FU5 – B4)

Last visit with a cancer specialist (FU5 – B4c)

Last visit to a special clinic for cancer survivors (FU5 – B4d)

Survivorship Care Plan – Survivor (FU5 – B2)
Survivorship Care Plan – Primary Care Provider (FU5 – B8)

Statistical Approach:

Aim 1. We will summarize the categorical responses to Follow-up 5, C1h survey question using frequencies and percents. We will also define a binary variable for *ever received an ultrasound* by using response "never" to indicate never ultrasound and combining the following responses to indicate ever ultrasound: less than 1 year ago/1-2 years ago/more than 2 but less than 5 years ago/5 or more years ago/I had one, but I don't recall when/I don't know if I ever had one.

Both the categorical and binary variables will be summarized for each of the survivor and sibling cohorts and, for the survivors within diagnosis specific groups. Prevalence will be calculated along with 95% confidence intervals. Prevalence of ultrasound use will be compared between the survivors and siblings using multivariable Poisson regression models with robust variance estimates, adjusted for sex and current age.

Aim 2. We will use multivariable Poisson regression with robust variance estimates to determine whether any explanatory variables are associated with the binary outcome of ultrasound receipt, separately for survivors and siblings (if there are sufficient numbers of events among the siblings for modelling)[10] All independent variables that are significant at the P ≤ 0.15 level in univariate models will be included in the multivariate model. To assess whether there is a differential effect of factors by history of stroke and the presence of cardiovascular risk factors (defined below), we will test for interaction between those variables and covariates significant in the univariate model and included in the multivariate model. Missing covariate data will be imputed using fully conditional specification;[11] analyses based on imputed data will be checked for similarity to results from those participants with complete data.   If the same variables are risk factors for ultrasound for both siblings and survivors, we will evaluate whether they have similar magnitude of associations by including all subjects together in a full multivariable model to test for interactions between survivor/sibling status and the risk factor of interest.

Table 1. Demographics and cancer treatment variables for survivors (diagnosed 1970-1999) and siblings in the Childhood Cancer Survivor Study

	Survivors		Siblings	
	N	%	N	%
Age at time of study, years				
18-24				
25-29				
30-34				
35-39				
40-44				
45-49				
≥ 50				
Male				
Race/ethnicity				
White non-Hispanic				
Minority				
Body mass index (kg/m^2)				
< 18.5				
18.5-21.9				
22.0-24.9				
25.0-29.9				
30.0-34.9				
≥35				
Physical activity				
Inactive lifestyle				
Active lifestyle				
Tobacco use				
Current				
Ever				
Never				
Alcohol use				
Married				
Education				
Less than high school				
High school				
More than high school but less than college				
College				
More than college				
Currently employed				
Health insurance				
Yes				
No				
Cancer diagnosis				
Leukemia				

Brain tumor				
Hodgkin lymphoma				
Other				
Age at diagnosis, years				
0-4				
5-9				
10-14				
15-20				
Anthracyclines				
Alkylating agents				
Cranial radiation therapy, maximum dose, Gy				
None				
0.01-18.9				
19-29.9				
30-49.9				
≥ 50				
Indirect				
Unknown				
Any neck radiation				
Yes				
No				
Unknown				
Radiation to neck or brain				
Direct neck, no direct brain radiation				
Direct brain radiation				
No neck or direct brain radiation				
Unknown				
Surgery to neck				
Cardiovascular risk factors prior to carotid ultrasound				
Hypertension				
Arrythmia				
Heart failure				
Coronary artery disease				
Myocardial infarction				
Stroke				
More than one stroke				
Family history of heart disease or stroke				
Medications prior to carotid ultrasound				
Aspirin				
Statin				
Anti-hypertensive medications				
Other heart medications				
Other guideline-related testing (ever)				
Mammogram				
Colonoscopy				
Echocardiogram				

Skin exam				
Health services				
Visit to a survivor program				
Visit to a cancer center				
Physician visit				
Survivorship care plan – survivor				
Survivorship care plan – primary care provider				

Table 2. Factors associated with ultrasound of the carotid arteries among survivors (diagnosed 1970-1999) and siblings in the Childhood Cancer Survivor Study, univariate analysis.

	Survivors N =		Siblings N =	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age at time of study, years				
18-24				
25-29				
30-34				
35-39				
40-44				
45-49				
≥ 50				
Male				
Race/ethnicity				
White non-Hispanic				
Minority				
Body mass index (kg/m^2)				
< 18.5				
18.5-21.9				
22.0-24.9				
25.0-29.9				
30.0-34.9				
≥35				
Physical activity				
Inactive lifestyle				
Active lifestyle				
Tobacco use				
Current				
Ever				
Never				
Alcohol use				
Death				
Married				
Education				
Less than high school				
High school				
More than high school but less than college				
College				
More than college				
Currently employed				

Health insurance				
Yes				
No				
Cancer diagnosis			NA	
Leukemia				
Brain tumor				
Hodgkin lymphoma				
Other				
Age at diagnosis, years			NA	
0-4				
5-9				
10-14				
15-20				
Anthracyclines			NA	
Alkylating agents			NA	
Cranial radiation therapy, maximum dose, Gy			NA	
None				
0.01-18.9				
19-29.9				
30-49.9				
≥ 50				
Indirect				
Unknown				
Any neck radiation			NA	
Yes				
No				
Unknown				
Radiation to neck or brain			NA	
Direct neck, no direct brain radiation				
Direct brain radiation				
No neck or direct brain radiation				
Unknown				
Surgery to neck			NA	
Cardiovascular risk factors prior to carotid ultrasound				
Hypertension				
Arrythmia				
Heart failure				
Coronary artery disease				
Myocardial infarction				
Stroke				
Medications prior to carotid ultrasound				

Statin				
Anti-hypertensive medications				
Other heart medications				
Other guideline-related testing (ever)				
Mammogram				
Colonoscopy				
Echocardiogram				
Skin exam				
Health services				
Visit to a survivor program			NA	
Visit to a cancer center			NA	
Physician visit				
Survivorship care plan – survivor			NA	
Survivorship care plan – primary care provider			NA	

Table 3. Factors associated with ultrasound of the carotid arteries among survivors (diagnosed 1970-1999) and siblings in the Childhood Cancer Survivor Study, multivariate analysis.*

	Among Survivors		Among Siblings	
	HR (95% CI)	P	HR (95% CI)	P
Age at time of study, years				
18-24				
25-29				
30-34				
35-39				
40-44				
45-49				
≥ 50				
Male				
Race/ethnicity				
White non-Hispanic				
Minority				
Body mass index (kg/m^2)				
< 18.5				
18.5-21.9				
22.0-24.9				
25.0-29.9				
30.0-34.9				
≥35				
Physical activity				
Inactive lifestyle				
Active lifestyle				
Tobacco use				
Current				
Ever				
Never				
Alcohol use (typical)				
None				
Moderate				
Heavy				
Alcohol use (binging)				
Married				
Education				
Less than high school				
High school				
More than high school but less than college				
College				

More than college				
Currently employed				
Health insurance				
Yes				
No				
Cancer diagnosis			NA	
Leukemia				
Brain tumor				
Hodgkin lymphoma				
Other				
Age at diagnosis, years			NA	
0-4				
5-9				
10-14				
15-20				
Anthracyclines			NA	
Alkylating agents			NA	
Cranial radiation therapy, maximum dose, Gy			NA	
None				
0.01-18.9				
19-29.9				
30-49.9				
≥ 50				
Indirect				
Unknown				
Any neck radiation			NA	
Yes				
No				
Unknown				
Radiation to neck or brain			NA	
Direct neck, no direct brain radiation				
Direct brain radiation				
No neck or direct brain radiation				
Unknown				
Surgery to neck			NA	
Cardiovascular risk factors prior to carotid ultrasound				
Hypertension				
Arrythmia				
Heart failure				
Coronary artery disease				
Myocardial infarction				
Stroke				

Medications prior to carotid ultrasound				
Statin				
Anti-hypertensive medications				
Other heart medications				
Other guideline-related testing (ever)				
Mammogram				
Colonoscopy				
Echocardiogram				
Skin exam				
Health services				
Visit to a survivor program			NA	
Visit to a cancer center			NA	
Physician visit				
Survivorship care plan – survivor			NA	
Survivorship care plan – primary care provider			NA	

*All independent variables that are significant at the P ≤ 0.15 level will be included in each multivariate model (survivor and sibling models).

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