TITLE: Subsequent malignant neoplasms in childhood cancer survivors with a history of cardiovascular events

WORKING GROUPS:
Chronic Disease (primary), Subsequent Neoplasms (secondary), Epidemiology and Biostatistics (secondary)

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Background

Subsequent cancers and cardiovascular disease are two frequently occurring late effects of treatment for a childhood cancer.[1-3] Both share multiple risk factors including radiotherapy and some chemotherapy agents such as anthracyclines, and many childhood cancer survivors ultimately develop both a subsequent cancer and cardiovascular disease.[4-6] Female survivors treated with chest radiation and/or anthracyclines, in particular, have high risks of both breast cancer and cardiovascular disease as a result of these prior therapies.[7-10] Previous analyses of childhood cancer survivors have looked broadly at the risk of multiple comorbidities, but the specific co-occurrence of subsequent cancers and cardiovascular disease, and especially breast cancer and cardiovascular disease, has not previously been detailed.

In adults with de novo cancers, it is well-recognized that patients can have increased risks of cardiovascular disease as a result of their cancer therapies as well.[11,12] In particular, women with a history of breast cancer are at an increased risk of cardiovascular disease due to the breast cancer treatments and lifestyle factors that may change following a breast cancer diagnosis.[13] Recently, though, several studies have pointed to the possibility that associations may run in the opposite direction as well, and that major cardiovascular events may predispose patients to develop cancer.[14-17]

In a large case-control study, Hasin et al. showed that patients with newly diagnosed heart failure had a 60% increased risk of developing cancer relative to matched controls without heart failure.[15] Among the cancers observed in patients with heart failure were digestive system, hematologic, male reproductive, breast, and respiratory cancers. Furthermore, they found that mortality was higher among patients who developed cancer after heart failure relative to those who developed cancer without heart failure.

These results were followed by mouse studies looking at the possible mechanisms involved. Meijers and colleagues studied mice prone to precancerous intestinal tumors.[17] In a series of experiments, they found a more than 2-fold increased intestinal tumor burden in mice with heart failure relative to mice without myocardial infarctions and that severity of cardiac dysfunction was associated with increased tumor growth. Studying human patients, they also identified elevated levels of cardiac biomarkers of heart failure that were associated with an increased risk of colorectal cancer. Koelwyn and colleagues showed in mouse models that myocardial infarctions induce systemic alterations that accelerate breast tumor growth.[16] Specifically, they found that myocardial infarctions are associated with a systemic response whereby pathways regulating immune and inflammatory responses are affected. Bone marrow myeloid cells are reprogrammed to be immunosuppressive and monocytosis is induced. Breast tumors take advantage of these changes leading to tumor growth. In separate studies of women with early stage breast cancer participating in prospective cohort studies, cardiovascular events (including myocardial infarction, stroke, coronary artery disease, and heart failure) were found to be associated with an increased risk of breast cancer recurrence and breast cancer-specific mortality.

In light of this recent work, we propose to assess whether childhood cancer survivors who have major cardiovascular events have an increased risk of subsequent malignant neoplasms (SMN) and whether outcomes after SMNs differ between survivors who have had a grade 3-5 cardiovascular event and those who have not.

Aims

1. **To evaluate whether major cardiovascular events are risk factors for SMNs in childhood cancer survivors after accounting for childhood cancer treatment.** We will evaluate whether self-reported myocardial infarctions, coronary heart disease, heart failure, and stroke are associated with subsequent pan-cancer incidence and different SMNs individually after controlling for radiation therapy (including but not limited to chest radiation therapy) and cardiotoxic chemotherapy.
   Hypotheses: We hypothesize that cardiovascular events will be associated with an increased risk of SMNs. Specifically, we hypothesize that there will be substantially increased risks of subsequent breast cancer, and potentially other cancers, after heart failure and myocardial infarctions after controlling for other key shared risk factors.

2. **To evaluate whether cancer-specific mortality is elevated in childhood cancer survivors who have SMNs and have had major cardiovascular events.** In childhood cancer survivors who have

an SMN, we will evaluate whether having had a cardiovascular event either prior or subsequent to the SMN is associated with an increased risk of cancer-specific mortality across all SMNS and for different SMNs individually.

Hypotheses: We hypothesize that survivors who have had a major cardiovascular event either prior to or after developing an SMN will have an increased risk of cancer-specific mortality.

Analysis Framework

A. Study Population
   All CCSS participants

B. Outcomes
   1. Subsequent neoplasms excluding non-melanoma skin cancers
   2. Malignant neoplasms
      a. Breast
      b. Gastrointestinal
      c. Leukemia
      d. Lymphoma
      e. Lung
   3. Cancer (SMN)-specific mortality
   4. Dates for all of the above

C. Independent variables

   1. Birthday (medical records)
   2. Primary cancer diagnosis (medical records)
   3. Date of primary cancer diagnosis (medical records)
   4. Age at primary cancer diagnosis (medical records)
   5. Race (self-reported)
   6. Ethnicity (self-reported)
   7. Sex (medical records)
   8. BMI at primary cancer diagnosis (medical records)
   9. BMI over time (FU2 Q6 & Q7, FU4 A1 & A2, FU5 A1 & A2, FU6 A1 & A2, FU7 A1 & A2)
   10. Smoking over time (original Baseline N.1 & N.1a, FU2 L.1 & L.2, FU4 N7 & N8, FU5 N7 & N8, FU7 M7 & M8, expansion Baseline O1 & O2 & O3)
   11. Radiation exposure and dose where available (any, brain, chest, abdomen, pelvis, neck, TBI, limb) (medical records)
   12. Chemotherapy exposure and dose (medical records)
      a. Any
      b. Anthracyclines
      c. Alkylating agents

13. Diabetes, presence and age at occurrence (Chronic Conditions dataset). We will consider diabetes yes/no regardless of whether/how it is controlled, but then also take into consideration whether it is controlled with diet or controlled with pills or tablets (Grade 2) or controlled with insulin shots (Grade 3).
14. Hypertension, presence and age at occurrence (Grade 2+, Chronic Conditions dataset).
15. Dyslipidemia, presence and age at occurrence (Grade 2+, Chronic Conditions dataset).
16. Heart failure, presence and age at first occurrence (Grade 3+, Chronic Conditions dataset)
17. Coronary artery disease/myocardial infarction, presence and age at first occurrence (Grade 3+, Chronic Conditions dataset)
18. Stroke, presence and age at first occurrence (Grade 3+, Chronic Conditions dataset)

D. Statistical analysis

Aim 1: To evaluate whether major cardiovascular events are risk factors for SMNs in childhood cancer survivors we will use several different analyses. We will use cause-specific Cox proportional hazards models with time at-risk starting at 5 years post-primary cancer diagnosis, age as the time scale, and cardiovascular events treated as time-dependent variables. We will initially fit univariable models and then look at models that adjust for whether radiotherapy was used, the region of the body that was exposed to radiation, and potentially the dose where available. Similarly, we will look at models that adjust for exposure to anthracyclines and the cumulative dose of anthracyclines, and models that adjust for alkylators and the cumulative cyclophosphamide equivalent dose.

We will consider interaction terms between treatment variables and cardiovascular events to explore the inter-relationships between treatment and both health conditions of interest. Potentially depending on the results of the interaction analyses, we may also stratify the analysis by treatment to further help disentangle the associations of treatment with both health conditions.

We will also evaluate whether adjusting for other potentially important variables change the key estimates of interest, the regression coefficients associated with cardiovascular events. These variables include sex, race/ethnicity, primary cancer diagnosis, and age at primary cancer diagnosis. Other participant-related factors such as obesity, smoking, diabetes, hypertension, and dyslipidemia are also important factors to consider and we will aim to include these as well, treated them as time-dependent factors in the models. The primary analysis will combine all cardiovascular events into one composite variable and use the time of the first cardiovascular event for the time-dependent variable. Secondarily, if there are a sufficient number of each event, we will separate out the different events. In this analysis, individuals with more than one cardiovascular event will contribute to each analysis corresponding to the event they had. Further, if there are a sufficient number of people with synchronous cardiovascular events, we may look whether the number of cardiovascular events is associated with the risk of SMNs. For all these analyses, model assumptions, including proportional hazards, will be evaluated.

We will also estimate standardized incidence ratios (SIRs) using age-, sex-, and calendar year-specific rates of cancer from SEER. SIRs will be presented separately by whether someone had a cardiovascular event or not for all SMNs combined and then separately for different SMNs. For participants with a cardiovascular event, their post-cardiac event SIR will be estimated starting at the time period after the cardiovascular event. To estimate the non-cardiovascular SIR, all participants without a cardiovascular event will be included starting at 5-years after their childhood cancer diagnosis; participants with cardiovascular events will also contribute to this analysis, restricted to the time before they had a cardiovascular event. SIRs will be presented together with 95% confidence intervals.

Aim 2: To evaluate whether cancer-specific mortality is elevated in childhood cancer survivors who have SMNs and have previously had major cardiovascular events, we will restrict the analysis to CCSS participants with SMNs. Our primary goal here is to look at cancer-specific mortality. Several different analyses will be done.

First, focusing on survivors with a cardiovascular event prior to an SMN diagnosis, cumulative incidence curves for cancer-specific mortality treating death from causes other than cancer as a competing risk will be estimated nonparametrically using SMN diagnosis as the time origin and time from SMN diagnosis as the time scale separately for participants with a previous cardiac event and for those with no previous cardiac event. Death from cardiovascular causes (including a cardiovascular event after the SMN) will be treated as a competing risk in this analysis.

In addition, cause-specific Cox models will be used to test for differences in cancer-specific mortality associated with cardiac events, adjusting for other variables such as prior treatment exposures. Causes of death, including from cardiovascular events occurring after the SMN, will be censored in this analysis. Cardiovascular events will be included in the models as time-dependent variables. As above, we will consider interaction terms between treatment variables and cardiovascular events to explore the inter-relationships.

Because CCSS has cancer specific deaths (from NDI) among people for whom an SMN was not reported and for whom an SMN diagnosis time is not available, this group will be excluded from the analysis. This will be mentioned in the limitations section of the manuscript as a potential source of bias.

References

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Table 1. Cohort description

Characteristic	Total (n=)	SMNs (n=)			
		Any (n=)	Breast (n=)	GI (n=)	Respiratory (n=)
Sex					
Male					
Female					
Race/ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Other					
Age at diagnosis with primary childhood cancer, years					
<5					
5-9					
10-14					
15+					
Primary cancer diagnosis					
Acute lymphoblastic leukemia					
Acute myeloid leukemia					
Other leukemia					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Astrocytoma					
Medulloblastoma/primitive neuroectodermal tumor					
Other central nervous system tumor					
Wilms tumor					
Osteosarcoma					
Ewing sarcoma					
Other bone cancer					
Neuroblastoma					
Rhabdomyosarcoma					
Radiotherapy					
Chest-directed					
Other than chest-directed field					
None					
Chemotherapy					
Anthracyclines					
Alkylating agents					
Other					
Maximum radiation treatment dose to the chest, Gy					
< 10					

10 to < 20					
20 to < 30					
30 to < 40					
40 to < 50					
50+					
Maximum radiation treatment dose to the abdomen/pelvis, Gy					
< 10					
10 to < 20					
20 to < 30					
30 to < 40					
40 to < 50					
50+					
Anthracycline dose, mg/m^2					
None					
0-100					
101-299					
300+					
Cyclophosphamide equivalent dose, mg/m^2					
None					
1-3999					
4000-7999					
8000+					
Attained aged at time of analysis among those last known to be alive, years					
< 20					
20-29					
30-39					
40-49					
50-59					
60-69					
70+					
Cardiovascular events					
Any					
Myocardial infarction					
heart failure					
Coronary artery disease					
Stroke					
Vital status					
Alive					
Dead					

Table 2. Risk of subsequent malignant neoplasm following cardiovascular events

	Any subsequent cancer			Breast cancer			Gastrointestinal cancer			Respiratory cancer		
	No. events	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**
Any cardiovascular event												
Myocardial infraction												
Heart failure												
Coronary artery disease												
Stroke												

Table 3. Risk of cancer-specific death following subsequent malignant neoplasm by cardiovascular event status

	Any subsequent cancer			Breast cancer			Gastrointestinal cancer			Respiratory cancer		
	No. events	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**	**No. events**	**HR (95% CI)**	**p**
Any cardiovascular event												
Myocardial infraction												
Heart failure												
Coronary artery disease												
Stroke												