CCSS Research Concept Proposal

Title: Accelerated aging and risk of subsequent neoplasms in survivors of childhood cancer

Primary Working group: SMN

Secondary Working Group: Epidemiology & Biostatistics

Investigators:

Amy Berkman
Kendrick Li
Cindy Im
Wendy Leisenring
AnnaLynn Williams
Adam Esbenshade
Samah Hayek
Eric Chow
Lucie Turcotte
Joseph Neglia
Michael Arnold
Deokumar Srivastava
Vikki Nolan
Kiri Ness
Gregory Armstrong
Melissa Hudson

Background:

Survivors of childhood cancer are at risk for many treatment-related late effects, including subsequent neoplasms (SNs).[1] A subset of these, subsequent malignant neoplasms (SMNs) represent one of the most serious of these late effects.[2] Early data from the Childhood Cancer Survivor Study (CCSS) reported a cumulative incidence of SMNs of 3.2% at 20-years of follow-up.[2] Similarly, a study from the Dutch Childhood Cancer Oncology Group – Long-Term Effects after Childhood Cancer cohort found that the cumulative incidence of SMNs at 25-years post-diagnosis was 3.9%.[3] A follow-up study from the CCSS found that, at 55 years of age, the cumulative incidence of new SMNs occurring in survivors after the age of 40 years was 16.3%,[4] indicating that SMNs are an important health risk for aging survivors. Additionally, while survivors are more likely than the general population to die from several different health-related causes, this risk is highest for SMNs.[5]

Studies to date have focused on identifying sociodemographic and treatment-related factors associated with increased risk of SNs among survivors of childhood cancer. Sociodemographic factors associated with increased risk include female sex, older age at diagnosis (≥15 years), and treatment in earlier eras, compared with male sex, younger age at diagnosis, and treatment in more recent eras, respectively.[6] Exposure to radiation therapy is an important treatment-related risk factor for SNs, and among those treated with radiation the cumulative burden of SMNs exceeds 50 per 100 survivors by 65 years of age.[6,7] Specifically, cranial radiation is associated with risk of subsequent CNS tumors, radiation field involving the

neck is associated with risk of subsequent thyroid cancer, chest radiation is associated with subsequent lung and female breast cancers, abdominopelvic radiation is associated with subsequent GI tumors, and there is a risk of skin cancers and sarcomas for tissues within the radiation field.[8] Certain chemotherapies are also associated with risk of SNs. Exposure to alkylating agents, particularly at high cumulative doses, is associated with risk of subsequent sarcomas, GI, lung, thyroid, breast, and bladder cancers.[3,8,9] Finally, anthracycline exposure exceeding 200 mg/m^2 doxorubicin-equivalent dose is associated with risk of subsequent female breast cancer.[10]

Importantly, while these studies have identified survivors who need increased attention to SMN surveillance, these risk factors are not modifiable, and aside from altering up-front therapy, do not offer a target for SN prevention efforts. Given that cancer in adulthood is closely linked with the aging process,[11] it is possible that premature aging also plays a role in SN risk in survivors. Prior studies among childhood cancer survivors have found a 6.4% prevalence of frailty using the modified Fried criteria at a mean age of 24.3 years,[12] higher accumulation of comorbidities based on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) than age-standardized population values,[13] and higher mean deficit accumulation scores (DAI) than community controls. In the general population, data from the UK Biobank have demonstrated a 4% and 11% increased incidence of cancer among those with pre-frailty and frailty (defined by weight loss, fatigue, physical activity, walking speed, and grip strength components), respectively, compared to those with non-frail phenotypes.[14] In the same cohort recent evidence shows an increased risk for both early-onset and late-onset solid tumors in individuals with signs of accelerated aging based on serum biomarkers.[15]

Similar studies assessing the association of accelerated aging, using measures previously found to be elevated among survivors of childhood cancer, with SN risk are needed. If there is an association between accelerated aging (assessed with frailty, chronic condition burden, and deficit accumulation) and SN risk in survivors, interventions aimed at preventing and delaying onset of frailty, management of chronic conditions, and mitigating deficit burden in survivors may also be beneficial in reducing the risk of SNs. While there is some overlap in the three measures of accelerated aging, evaluating the association of each measure with SN risk will allow us to identify which one, if any, is better than another for risk assessment; additionally, if there are no differences between measures, this will allow for clinicians to interpret risk based on the measure that is most readily available.

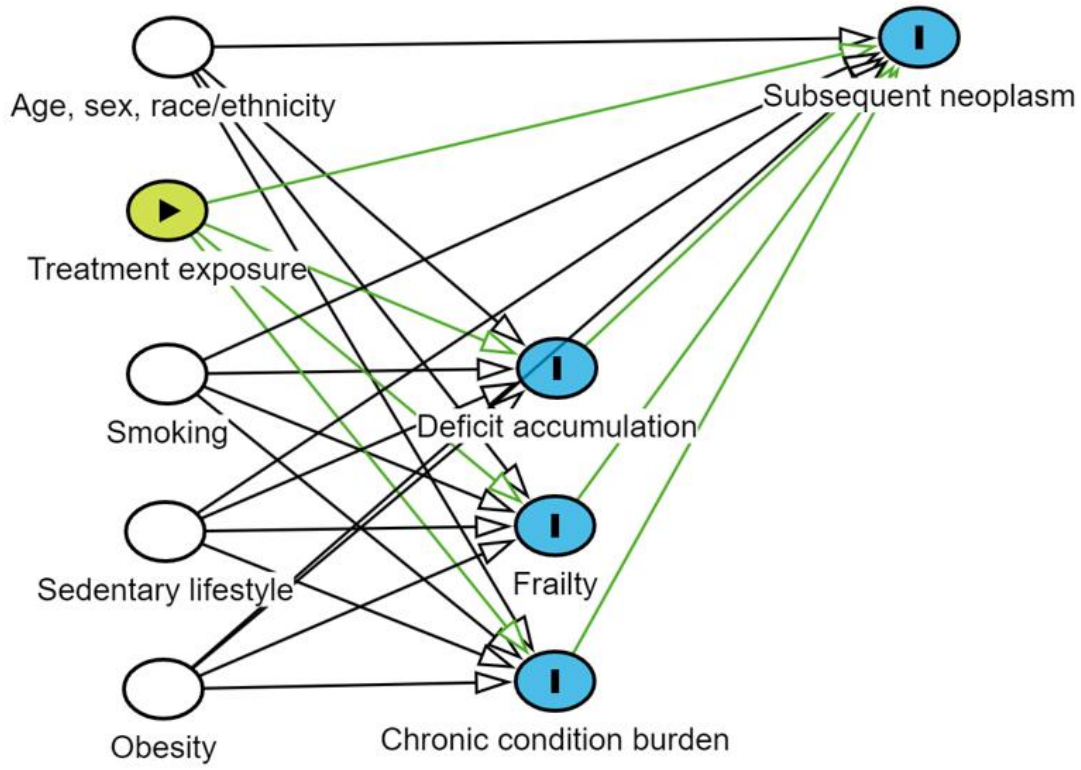


Figure 1. Directed Acyclic Graph (DAG) for the associations of Frailty, Chronic Disease Burden, and Deficit Accumulation with Subsequent Neoplasms (Primary Aim) and Assessment of these Factors to Mediate the Relationship Between Treatment Exposure and Subsequent Neoplasms (Exploratory Aim)

Aims and Hypotheses:

Primary Aim. Evaluate the associations of frailty, increased chronic condition burden, and increased deficit accumulation with risk of SNs in adult survivors of childhood cancer (Figure 1).

- Evaluate the association of frailty (using modified Fried frailty criteria) with risk of SNs (overall and by specific SN type).
- Evaluate the association of accumulation of chronic disease (using the Cumulative Illness Rating Scale for Geriatrics, CIRS-G) with risk of SNs (overall and by specific SN type).
- Evaluate the association of phenotypic deficit accumulation (using the Deficit Accumulation Index, DAI) with risk of SNs (overall and by specific SN type).

Hypothesis: We hypothesize that survivors with frailty and those with higher total CIRS-G and DAI scores will have higher risks of SNs than those without frailty and those with lower CIRS-G and DAI scores.

Exploratory Aim. Evaluate the mediating effects of frailty, chronic disease burden, and deficit accumulation on associations between treatment exposures and SNs in adult survivors of childhood cancer (Figure 1).

Approach 1: Evaluate in SNs overall

- Frailty (using modified Fried frailty criteria) and high cumulative alkylating agent exposure (CED > 10,000 mg/m2) and risk of any SN
- Frailty (using modified Fried frailty criteria) and any radiation exposure and risk of any SN
- The above approaches will be repeated to test the mediating effects of chronic disease burden (using the CIRS-G), and deficit accumulation (using the DAI)

Approach 2: Evaluate in common SN types

- Frailty (using modified Fried frailty criteria) and chest radiation/anthracycline exposure and risk of subsequent breast cancer
- Frailty (using modified Fried frailty criteria) and head/neck/cranial radiation and risk of subsequent malignant thyroid cancer
- Frailty (using modified Fried criteria) and any radiation exposure and risk of subsequent malignant soft tissue and bone tumors (rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, Ewing/primitive neuroectodermal tumor, osteosarcoma, and malignant peripheral nerve sheath tumor)
- Frailty (using the modified Fried criteria) and any radiation exposure and risk of subsequent non-melanoma skin cancer
- Frailty (using the modified Fried criteria) and cranial radiation and risk of subsequent meningioma
- The above approaches will be repeated to test the mediating effects of chronic disease burden (using the CIRS-G), and deficit accumulation (using the DAI)

Hypothesis: We hypothesize that measures of accelerated aging (frailty, CIRS-G, DAI) will partially mediate the effect of various treatment exposures on risk of SNs.

Analysis Framework

Population: Survivors enrolled in the CCSS Original Cohort (1970-1986) and Expansion Cohort (1986-1999) will be included. Survivors with unknown treatment exposures will be excluded from this analysis. The specific study population for each analysis will depend on the mediating factor (frailty, chronic disease burden, and deficit accumulation) used in the given analysis.

Fried Frailty Index will include two subgroups of survivors: (1) Original cohort survivors who completed the FU2 questionnaire at age ≥18 years old, hadn't had a SN by 6 months after the completion of FU2, and completed at least one subsequent questionnaire (N = 7,028); (2) Expansion cohort survivors who completed the FU5 questionnaire at age ≥18 years old, hadn't had a SN by 6 months after the completion of FU5, and completed at least one subsequent questionnaire (N = 3,967).

Due to data availability, CIRS-G analysis will include original cohort survivors only who completed the FU5 questionnaire at age ≥18 years old, hadn't had a SN by 6 months after the completion of FU5, and completed at least one subsequent questionnaire (N = 3,819).

DAI analysis will include original and expansion cohort survivors who completed the FU5 questionnaire at age ≥18 years old, hadn't had a SN by 6 months after the completion of FU5, and completed at least one subsequent questionnaire (N = 7,786).

In each analysis, survivors missing measures of accelerated aging (Frailty, CIRS-G, or DAI) will be excluded as will survivors that experienced a first SN prior to the measurement of accelerated aging.

In the Exploratory Aim, analyses of secondary breast cancer will additionally be restricted to female survivors. In each analysis, the survivors missing the cancer treatment of interest will also be excluded.

Exposures:

a. **Frailty**: Frailty will be defined according to the modified Fried criteria[16] which takes into account the following components as previously delineated in Hayek et al.[12]: 1) low lean muscle mass: body mass index (BMI) of <18.5 kg/m^2 or unintentional weight loss of 10 pounds in the past year; 2) self-reported exhaustion: score of ≤ 40 on the Vitality subscale of the Medical Outcomes Survey Short Form-36; 3) low energy expenditure: <383 kcal/week in males and <270 kcal/week in females converted from frequency and duration of low, moderate, and vigorous physical activities; 4) walking limitations: "limited for more than 3 months" in response to "Over the last 2 years, how long has your health limited you in walking uphill or climbing a few flights of stairs?" or "Over the last 2 years, how long has your health limited you in walking one block?"; 5) weakness: "yes and the condition is still present" in response to "Have you ever been told by a doctor or other health care professional that you have, or have had, weakness or inability to move your arms?" Fried frailty index is available at FU2, FU5 and FU7 in the CCSS cohort. In the interest of having sufficient follow-up time for incident SNs to occur, we will use frailty measured at FU2 for the original cohort survivors and FU5 for the expansion cohort survivors.

   Prefrail: Meeting at least 2 of the 5 criteria
   Frail: Meeting ≥3 of the 5 criteria

b. **The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)**: The CIRS-G will be used to define the accumulation of comorbidities over time.[13,17] The CIRS-G encompasses disease burden across 14 systems: cardiac, vascular, hematopoietic, respiratory, eyes/ears/nose/throat/larynx, lower gastrointestinal, upper gastrointestinal, hepatic, renal, genitourinary, integument/musculoskeletal, neurological, endocrine/metabolic/breast, and psychiatric. Items are scored ranging from none to extremely severe on a 0-4 scale. Total score (TS) is a sum of the total number of conditions weighted by severity. Malignancies (leukemia, lymphoma, lung cancer, gastric cancer, bowel carcinoma, biliary tree carcinoma, renal carcinoma, any genitourinary carcinoma, prostate cancer, cervical cancer, any bone or muscle carcinoma, metastatic melanoma, and breast carcinoma) are included in the CIRS-G but will be omitted from the scoring in this analysis. Other scoring measures include: total organ system categories endorsed (TC), severity index (SI, TS divided by TC), number of organ system categories with scores in the 3-4 range (G3), and the number of organ system

categories with a score of 4 (G4). The main analysis will focus on the relationship between TS and SN. The relationship between other measures and SN will also be explored. CIRS-G is available for the original cohort at FU5 questionnaire.

c. **Deficit Accumulation Index (DAI):** The DAI includes 40 questionnaire items that characterize global burden of impairment in nine domains (task efficiency, emotional regulation, organization, memory, depression, somatization, anxiety, physical limitation, and limited instrumental activities of daily living) using 15 items from the CCSS Neurocognitive Questionnaire (CCSS-NCQ),[18] 14 from the 18-item Brief Symptom Inventory,[19] and 11-items from the physical performance and activity of daily living sections of the National Health and Nutrition Examination Survey[20]. Items are given a value of 1 if positively endorsed and 0 if not endorsed. Items are summed and divided by 40 to create a DAI that ranges from 0-1.The overall score can be categorized into low (<0.2), medium (0.2-<0.35), and high (≥0.35) deficit accumulation. Participants must have no more than 10% of the items missing to calculate the DAI. Those exceeding 10% missing will be excluded. The DAI is calculated at all CCSS questionnaire time points. DAI is available for the original and expansion cohorts at FU5 and FU7 questionnaires. We will focus on the DAI for both the original and expansion cohorts at FU5.

d. Treatment Exposures Associated with SN risk (Exploratory Aim 1):

- **Chest radiation and subsequent breast cancer:** Risk groups 10-19 Gy and ≥20 Gy[21]
- **Neck radiation and subsequent thyroid cancer:** Risk groups >0-10 Gy, >10-30 Gy[22,23]
- **Anthracyclines and subsequent female breast cancer:** Risk group >200 mg/m^2 doxorubicin equivalents[10]
- **Alkylating agents and any SN:** Risk group >10,000 mg/m^2 cyclophosphamide equivalents[9]
- **Radiation and subsequent malignant soft tissue and bone tumors:** Risk groups 0-<10 Gy, ≥10 Gy[24]
- **Radiation and subsequent non-melanoma skin cancers:** Risk group any radiotherapy[25]
- **Cranial radiation and subsequent meningioma:** Risk groups 4-24 Gy and >24 Gy[26]

Outcomes

Subsequent Neoplasms: SN data will be identified from the most recently frozen dataset. SNs will be considered overall and by individual type using the standard CCSS definition provided below (Figure 2). For this analysis we will include non-melanoma skin cancers and meningiomas but will exclude all other benign lesions as they are not routinely validated. SNs will only be included if they occur after the assessment of frailty, chronic disease burden, and deficit accumulation as “incident” SNs. As some items used to define measures of accelerated aging (i.e. weight loss, functional decline) could be secondary to a SN, we will restrict SNs to those diagnosed ≥6 months from the time of frailty, CIRS-G, and DAI determination.

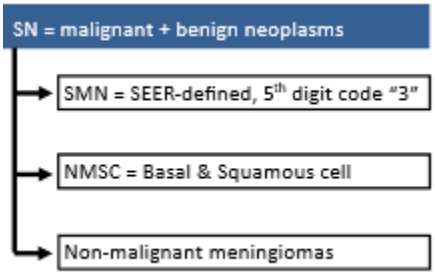


Figure 2. Childhood Cancer Survivor Study Definition of Subsequent Neoplasms

Covariates

Sociodemographic: Sex, race and ethnicity (baseline), attained age, insurance status, household income, marital status (at measurement of accelerated aging)

Cancer and treatment history: Age at diagnosis, 5-year treatment eras, radiation exposure (all site and doses, dose will be included as continuous variables), anthracycline exposure, cyclophosphamide exposure

Modifiable (at measurement of accelerated aging): Smoking status, obesity (at any questionnaire time point), sedentary behavior (at measurement of accelerated aging)

Statistical Analysis:

Summary statistics of the demographic variables, cancer treatments, socioeconomic variables (at time of measurement of frailty, chronic disease burden, and deficit accumulation), and clinical outcomes, will be provided for the survivors included in the analysis, stratified by SN status (no SN, SN). Separate summary tables will be provided for the eligible study population of three different measures of accelerated aging (frailty, chronic disease burden, and deficit accumulation).

Primary Aim:

To evaluate the association between frailty/CIRS-G/DAI and risk of at least one incident SN, we will conduct two analyses. (a) Cox proportional hazards model for time to first SN, adjusting for sociodemographic, cancer treatment, and modifiable variables (listed above); (b) Robust Poisson regression model for number of new SNs during the time between, with log time between measurement of frailty and last visit as offset, adjusting for sociodemographic, cancer treatment, and modifiable variables (listed above). In Appendix B, we presented a brief calculation of statistical power for Approach (a) in an unadjusted analysis. For all three analyses, the statistical power exceeds 80% with a hazard ratio < 0.5 or > 2. The above analysis will be replicated for SMN, NMSC and meningiomas as sub-groups of the larger definition of SN.

Exploratory Aim:

We will use the change-in-coefficient approach[27] to investigate mediation by frailty, chronic disease burden, and deficit accumulation between each pair of exposure/outcome factors of interest, using Poisson regression models as in the Primary Aim, using time between measurement of frailty, chronic disease burden, and deficit accumulation and most recent visit as an offset, and adjusting for sociodemographic and modifiable variables. We will report both direct and indirect effects. Using time to the first SN as the outcome, we will calculate the direct and indirect effects in Aalen's additive hazard regression models.

Appendix A: Event counts for the Primary Aim:

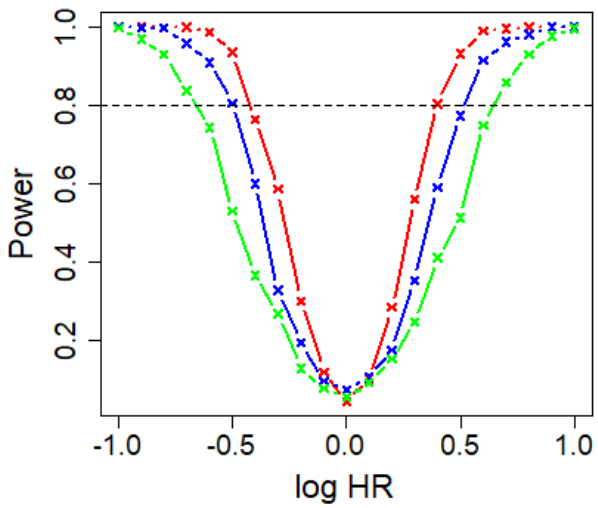
We roughly investigated the eligible study sample for each analysis. The final sample sizes and case numbers will be smaller due to missing data. See Appendix Table 1.

Appendix Table 1: Population size and counts of new SN for each measure of accelerated aging

	Eligible study sample size	New SN	New SMN	New NMSC	New non-malignant meningiomas
Fried Frailty Index	**10,995**	**1,311**	**560**	**614**	**216**
DAI	**7,786**	**445**	**200**	**178**	**57**
CIRS-G	**3,819**	**175**	**115**	**118**	**34**

Appendix B: Power calculation for unadjusted time-to-event analysis in the Primary Aim

We roughly estimated statistical power for investigating the association between frailty measures and new SN using Cox proportional hazards regression models in the primary aim. For each measure, we use the actual eligible study sample size and follow-up time as shown in Appendix Table 1. We simulate time to first new SN using an exponential hazard regression model, letting risk during the follow-up be approximately 5% (close to the observed risk of new SN in Appendix Table 1). For simplicity, we simulate the frailty exposure from a Uniform(-0.5,0.5) distribution, and vary the hazards ratio between the exposure and the SN. Power is calculated by averaging over 500 Monte Carlo experiments.



Appendix Figure 1: Power of three analyses in unadjusted Cox proportional hazards regression models. Red: Fried Frailty Index; Blue: DAI; Green: CIRS-G.

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Table 1. Participant Characteristics

Characteristic	All Survivors, n (%)	Survivors with a SN, n (%)	Survivors without a SN, n (%)	p-value
Age at primary cancer diagnosis, years				
Mean (SD)				
0-4				
5-9				
10-14				
≥15				
Sex				
Female				
Male				
Race and ethnicity				
Hispanic				
Non-Hispanic Black				
Non-Hispanic White				
Other				
Unknown				
Household income				
< $40,000				
≥ $40,000				
Unknown				
Insurance Status				
Private insurance				
Public insurance				
Uninsured				
Unknown				
Primary cancer diagnosis				
ALL				
AML				
Other leukemia				
Astrocytoma				
Medulloblastoma				
Other CNS tumor				
HL				
NHL				
Kidney tumors				
Neuroblastoma				
Soft tissue sarcoma				
Ewing sarcoma				
Osteosarcoma				
Other bone tumors				
Other cancer type				
Treatment				
Anthracyclines				

Mean dose±SD, mg/m^2				
Alkylating agents				
Mean dose±SD, mg/m^2				
Chest radiation				
Mean dose±SD, Gy				
Cranial/neck radiation				
Mean dose±SD, Gy				
Any radiation				
Mean dose±SD, Gy				
Treatment era				
1970-1974				
1975-1979				
1980-1984				
1985-1989				
1990-1994				
1995-1999				
Follow-up time, years (mean±SD)				
Smoking status				
Current				
Former				
Never				
Unknown				
Body mass index class				
Underweight (BMI <18.5 kg/m^2)				
Normal (BMI 18.5-24.9 kg/m^2)				
Overweight (BMI 25.0-29.9 kg/m^2)				
Obese (BMI ≥30 kg/m^2)				

Table 2. Frailty, comorbidity burden, and deficit accumulation index among survivors of childhood cancer with and without SNs

Characteristic	All survivors	Survivors with a SN	Survivors without a SN	P-value
Frailty, n (%)				
Not frail				
Pre-frail				
Frail				
Comorbidity burden, CIRS-G score				
Total score				
TC[a]				
Severity index				
G3[b]				
G4[c]				
Deficit Accumulation Index, score				
Overall score				
Low (<0.2)				
Medium (0.2-<0.35)				
High (≥0.35)				

[a]TC: Total organ system categories endorsed; [b]G3: Number of organ system categories with scores in the 3-4 range; [c]G4: Number of organ system categories with a score of 4

Table 3. Association of frailty, comorbidity burden, and deficit accumulation index with SNs in survivors of childhood cancer

	Frailty (RR, 95% CI)				**Comorbidity burden (RR, 95% CI)**			**Deficit accumulation index (RR, 95% CI)**			
Subsequent Neoplasm	**Not frail**	**Pre-frail**	**Frail**	**p-value**				**Low**	**Med**	**High**	**p-value**
Any SN											
Any Malignant SN (SMN)											
Breast cancer											
Lung cancer											
Thyroid cancer											
Glioma											
Malignant gastrointestinal tumors											
Leukemia											
Melanoma											
Bone cancer											
Soft tissue sarcoma											
Lymphoma											
Kidney cancer											
Head and neck cancer											
Female genital cancers											
Selected Subsequent Neoplasms (SNs)											
Non-Malignant Meningioma											
Non-Melanoma Skin Cancer											

Table 4a. Mediating analysis of treatment factors on the associations between accelerated aging (frailty, chronic condition burden, deficit accumulation) and overall SN risk

Exposure	Outcome	Mediator	Direct effect		Indirect effect	
			β	95% CI	β	95% CI
Cumulative alkylating agent (CED[1]>10,000 mg/m^2)	Any SN	Frailty				
		DAI				
		CIRS-G				
Any Radiation	Any SN	Frailty				
		DAI				
		CIRS-G				

[1]CED: cyclophosphamide equivalent dose

Table 4b. Mediating analysis of treatment factors on the associations between accelerated aging (frailty, chronic condition burden, deficit accumulation) and SN risk by specific SN type

Exposure	Outcome	Mediator	Direct effect		Indirect effect	
			β	95% CI	β	95% CI
Chest RT (10-19 Gy)	Breast cancer	Frailty				
		DAI				
		CIRS-G				
Chest RT (≥ 20 Gy)	Breast cancer	Frailty				
		DAI				
		CIRS-G				
Anthracyclines (>200 mg/m^2 doxorubicin equivalent dose)	Breast cancer	Frailty				
		DAI				
		CIRS-G				
Neck RT (0-10 Gy)	Thyroid cancer	Frailty				
		DAI				
		CIRS-G				
Neck RT (> 10 Gy)	Thyroid cancer	Frailty				
		DAI				
		CIRS-G				
Any RT (Yes/No)	Soft tissue and bone tumors	Frailty				
		DAI				
		CIRS-G				
Any RT	NMSC	Frailty				
		DAI				
		CIRS-G				

Cranial RT (Yes/No)	Meningioma	Frailty				
		DAI				
		CIRS-G				

Possible figures:

1) Cumulative incidence on the y-axis, time since diagnosis on the x-axis, plot lines for frailty (lines for not frail, pre-frail, frail) and CIRS-G (if we come up with categories) and DAI (lines for low, med, high)
2) If there are any particularly striking mediation effects presented in table 4 could also visualize those as figures for each SN of interest – potentially cats-eye plots with relative risk on the y-axis and plots for risk factor alone (i.e. frailty), tx alone (i.e. cranial radiation) and risk factor+tx