

Childhood Cancer Survivor Study

Assessing the Contribution of Clinical, Lifestyle, and Genetic factors in Risk of Subsequent Neoplasms

Primary Working Group

Second Malignancy

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Background/Significance:

Childhood cancer survivors are at increased risk of treatment-related chronic health conditions (CHCs)¹. Among these, subsequent neoplasms (SNs) represent the leading cause of morbidity and mortality^{2,3} with an incidence that increases over time from diagnosis⁴⁻⁶. Many survivors also develop multiple SNs with increasing age⁷. After the age of 40 years, survivors were four times as likely as the general population to develop the first subsequent malignant neoplasm (SMN), with the highest risk observed for breast cancer, renal cancer, soft tissue sarcoma, and thyroid cancer⁸. Risk factors for developing SMN include exposure to radiation therapy, alkylating and platinum agents, and epipodophyllotoxins, family history of cancer, female sex, younger age at diagnosis, earlier treatment era, and diagnosis of Hodgkin lymphoma or soft tissue sarcoma⁴⁻⁶. Recently, germline pathogenic/likely pathogenic (P/LP)

mutations in cancer susceptibility genes and DNA repair genes have also been associated with increased risks of SNs⁹⁻¹². Furthermore, a polygenic risk score (PRS) derived from common genetic variants associated with breast cancer in the general population was associated with an increased risk of subsequent breast cancer and thyroid cancer in survivors^{13,14}.

Considering the high incidence of SNs and associated morbidity and mortality in survivors, it is important to identify those at risk to guide early screening and risk reduction strategies¹⁵. Such measures are largely based on relative risks (RRs) for factors associated with SNs in survivors. However, RRs alone may not provide sufficient information to quantify the disease burden or the number of survivors with SN related to different risk factors. For example, a risk factor with high RR to which only a small proportion of survivors is exposed may generate a lower disease burden than a weakly associated risk factor to which a large proportion of survivors is exposed¹⁶. Attributable fraction (AF) describes the contribution of a risk factor to the burden of SNs by combining the prevalence of the risk factor and its RR, thereby providing a more balanced measure of the likely impact of preventive interventions targeted at particular risk factors than RR alone.

At present, limited data exist regarding the contribution of different factors to the risk of CHCs in childhood cancer survivors. Using data from 1713 survivors from the St. Jude Lifetime Cohort (SJLIFE), fractions of CHCs attributed to therapeutic exposures were estimated but AFs for SNs were not estimated¹⁷. In a more recent SJLIFE study, about 21% and 16% of hypertensive survivors were attributed to PRS based on genetic loci associated with blood pressure in the general population and cancer therapies¹⁸. The PRS and cancer therapies jointly accounted for 40% of survivors with hypertension. To our knowledge, no study has estimated AF for SNs due to different risk factors in childhood cancer survivors.

To address this knowledge gap, we calculated AF for SNs due to treatment, genetic and lifestyle factors among 4,401 survivors of SJLIFE with whole-genome sequencing (WGS) data. We found significant AF for SNs due to treatment and genetic risk factors but the contribution by the lifestyle risk factors was negligible (Tables 2 and 3). Specifically, exposure to radiotherapy and PRSs accounted for the majority of the SNs (Table 4). With this request, we intend to re-calculate these AF in a combined sample of SJLIFE and CCSS survivors of childhood cancer, allowing increased power and precision using the largest population possible.

Please also note that this study focusing on AF of SNs will not overlap with Cindy Im's project on SNs, which has been discussed between Cindy Im (also a co-author in this study) and Yadav Sapkota (PI of this study) in presence of Yutaka Yasui. In fact, we are working together to assure consistency in methods between this study and Cindy's project. Greg Armstrong is aware of this agreement.

Objectives:

1. To calculate AF for SNs due to treatment, genetic and lifestyle risk factors among childhood cancer survivors
2. To assess if AF estimates differ by sex and age

Methods:

Study populations:

SJLIFE survivors with WGS/whole exome sequencing (WES) data

CCSS survivors with genome-wide association study (GWAS)/WES or WGS data

Outcomes of interest (first occurrence):

Any SNs (SMNs, non-melanoma skin cancer (NMSCs), meningioma)
Any SMNs
Non-melanoma skin cancers (NMSCs)
Breast SNs (both invasive and ductal carcinoma in situ)
Thyroid SNs
Meningioma SNs
Sarcoma SNs
Hematologic SNs such as tAML (if enough cases, n>25)

Phenotypes/covariates:

Clinical:

- Age at childhood cancer diagnosis
- Sex
- Age at last contact
- Max radiation dosages
 - Chest
 - Neck
 - Cranial
 - Pelvis
 - Abdomen
- Cumulative chemotherapy dosages
 - Alkylating agents (using cyclophosphamide equivalent dose)
 - Epipodophyllotoxins
 - Anthracyclines

Genetic:

- Monogenic (yes/no; carrier status)
 - P/LP mutations in Cancer susceptibility genes (Wang et al., JCO 2018)
 - P/LP mutations in DNA repair genes (Qin et al., JCO, 2020)
- Polygenic (tertiles)
 - PRS based on pleiotropic SNPs associated with multiple cancers in the general population (for SN and SMN)
 - Individual SN-specific PRSs based on the largest GWAS available in the general population (for NMSC, breast, thyroid, meningioma and sarcoma)

Lifestyle (first assessment after 18 years of age; for SN cases, most recent assessment assessed after 18 years of age but before SN diagnosis):

(Note: we will closely work with Kiri Ness to ensure accuracy and consistency of lifestyle factors between SJLIFE and CCSS)

- Smoking
 - Yes/no; current vs former/never
 - number of cigarette packs/year
- Physical activity
 - Yes/no; whether the survivor was engaged in activities to increase muscle strength, such as lifting weights or aerobics, once a week or more
 - Metabolic equivalent of task
- Body Mass Index (BMI)
 - Obesity (yes/no) variable will be created based on BMI ≥ 30 mg/m²
- Alcohol consumption
 - Yes/no; whether the survivor was a risky/heavy drinker
 - Number of drinks per week or similar to capture the dose

- Sun exposure/tanning (for analysis of NMSCs only)
 - Yes/no
 - Number of sun burns
- Hormone replacement therapy, HRT (for analysis of breast SNs only)
 - Yes/no
 - Exposure dose if available
- 6-mercaptopurine, 6MP (for analysis of meningioma SNs only)
 - Yes/no
 - Exposure dose if available

Analyses

We will use the same analytic approach as described earlier¹⁸⁻²⁰. Briefly, for each outcome of interest, a multivariable logistic regression model, modeling the probability of developing an SN of interest by age at last contact, including clinical, treatment, lifestyle, and genetic factors will be fit while adjusting for genetic ancestry, age at diagnosis, sex and age at last contact. In the multivariable models, we will consider the same clinical and treatment variables used in Qin et al.⁹, and add genetic, individual lifestyle factors listed above. We will consider lifestyle factors both as categorical and continuous (exposure dose) variables. Attributable fractions for SNs due to treatment, genetic, and lifestyle factors will be calculated. Analyses will be performed among all survivors, while adjusting for ancestry variables derived by ADMIXTURE or STRUCTURE. Stratified analyses by age and sex will be considered. While information on diet is not available in the CCSS, analyses in SJLIFE showed negligible contribution by diet on risk of SNs (which will be provided as Supplementary Information). Therefore, final analyses with both CCSS and SJLIFE will not include diet. Moreover, we will attempt exploratory analyses to assess contribution of additional lifestyle factors that may be individual SN specific (such as sun exposure/tanning for NMSCs; HRT for breast cancer SNs and 6MP for meningioma SNs) in addition to the above four lifestyle factors.

Statistical Results:

The main results of the SJLIFE analysis are provided in Tables 2, 3 and 4.

Specific Request to CCSS:

We would like to expand the study on attributable fractions in a combined population of survivors from SJLIFE and CCSS using a multivariable logistic regression model including the same clinical, lifestyle, and genetic factors as we have done in the SJLIFE population (see Tables below). We will expand the analysis to include survivors from the CCSS original cohort with both GWAS and WES, and survivors in the CCSS expansion cohort with WGS data. We will exclude CCSS survivors who are participants of the SJLIFE analyses.

Inclusion Criteria

- Long-term (≥ 5 years) survivors from the CCSS Original with GWAS/WES and Expansion Cohort with WGS

Exclusion Criteria

- Survivors who are also SJLIFE participants with WGS
- Participants with missing phenotype/covariate data

- History of allogeneic stem cell transplantation

Analyses will require the use of the following CCSS data:

- GWAS and WES data for the Original cohort and WGS data for the Expansion cohort
- CCSS genetic ancestry variables derived by ADMIXTURE/STRUCTURE
- Age at primary cancer diagnosis (years)
- Age at first SN diagnosis (years)
- Sex
- Age at last contact (years)
- SN diagnosis (the first SN after five years of childhood cancer)
- Age at SN diagnosis
- Max radiation doses to
 - Chest
 - Neck
 - Brain
 - Pelvis
 - Abdomen
- Cumulative chemotherapy doses (within 5 years of primary cancer diagnosis)
 - Alkylating Agents
 - Anthracyclines
 - Epipodophyllotoxins
- *Lifestyle (first assessment after 18 years of age; for SN cases, most recent assessment assessed after 18 years of age but before SN diagnosis):*
(Note: we will closely work with Kiri Ness to ensure accuracy and consistency of lifestyle factors between SJLIFE and CCSS)
 - Smoking
 - Yes/no; current vs former/never
 - Number of cigarette packs/year
 - Physical activity
 - Yes/no; whether the survivor was engaged in activities to increase muscle strength, such as lifting weights or aerobics, once a week or more
 - Metabolic equivalent of task
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 - Sun exposure/tanning (for analysis of NMSCs only)
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 - Hormone replacement therapy, HRT (for analysis of breast SNs only)
 - Yes/no
 - Exposure dose if available
 - 6-mercaptopurine, 6MP (for analysis of meningioma SNs only)
 - Yes/no
 - Exposure dose if available

Table 1 | Characteristic of childhood cancer survivors included in this study

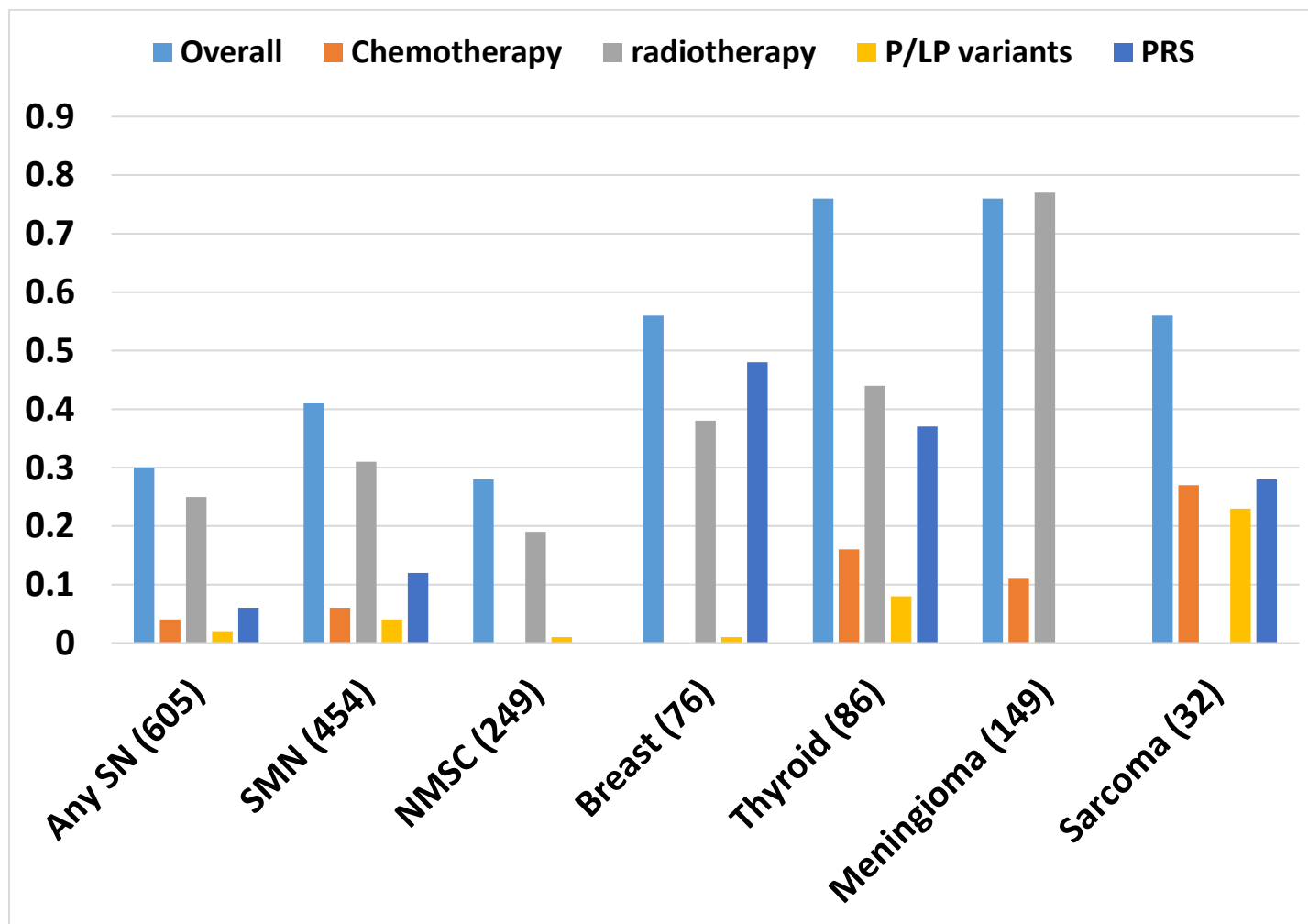


Figure 1 | Attributable fractions of subsequent neoplasms among childhood cancer survivors due to treatment and genetic risk factors

Table 2 | Attributable fractions of subsequent neoplasms among 4,401 childhood cancer survivors in the St. Jude Lifetime Cohort (SJLIFE) due to treatment, genetic and lifestyle risk factors based on the SJLIFE data

SN Types (# SN)	Treatment						Genetics						Lifestyle					
	Without Diet					With Diet	Without Diet					With Diet	Without Diet					With Diet
	Overall	Males	Females	<35 years	>=35 years	Overall	Overall	Males	Females	<35 years	>=35 years	Overall	Overall	Males	Females	<35 years	>=35 years	Overall
Any SN (605)	0.28	0.30	0.26	0.36	0.26	0.28	0.08	0.09	0.08	0.12	0.07	0.08	NS	NS	NS	NS	NS	NS
SMN (454)	0.35	0.38	0.32	0.38	0.34	0.35	0.15	0.17	0.14	0.19	0.14	0.15	NS	NS	NS	NS	NS	0.10
NMSC (249)	0.19	0.19	0.18	0.27	0.18	0.19	0.22	0.22	0.22	0.37	0.21	0.22	NS	NS	NS	NS	NS	NS
Breast (76)	0.37	0.40	0.35	0.33	0.37	0.38	0.50	0.58	0.44	0.62	0.49	0.49	NS	NS	NS	NS	NS	NS
Thyroid (86)	0.55	0.61	0.51	0.64	0.52	0.55	0.42	0.44	0.40	0.44	0.41	0.42	NS	NS	NS	NS	NS	0.09
Meningioma (149)	0.81	0.86	0.77	0.89	0.79	0.81	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Sarcoma (32)	0.27	0.29	0.25	0.27	0.27	0.27	0.46	0.45	0.46	0.44	0.47	0.46	NS	NS	NS	NS	NS	NS

NS, non-significant contribution as a risk factor

Table 3 | Attributable fractions of subsequent neoplasms among 4,401 SJLIFE survivors due to the combined effect of treatment, genetics, and lifestyle factors

SN Types (# SN)	Treatment+Genetics+lifestyle (Without diet)	Treatment+Genetics+lifestyle (With diet)
Any SN (605)	0.30	0.30
SMN (454)	0.41	0.49
NMSC (249)	0.28	0.22
Breast (76)	0.56	0.67
Thyroid (86)	0.76	0.78
Meningioma (149)	0.76	0.77
Sarcoma (32)	0.56	0.55

Table 4 | Attributable fractions of subsequent neoplasms among 4,401 SJLIFE survivors due to chemotherapy, radiation therapy, pathogenic/likely pathogenic variants and polygenic risk scores. Models were fit using treatment, genetic and lifestyle variables without diet

SN types (# SN)	Chemotherapy	Radiotherapy	Pathogenic/Likely Pathogenic variants	Polygenic Risk Score
Any SN (605)	0.04	0.25	0.02	0.06
SMN (454)	0.06	0.31	0.04	0.12
NMSC (249)	NS	0.19	0.01	NS
Breast (76)	NS	0.38	0.01	0.48
Thyroid (86)	0.16	0.44	0.08	0.37
Meningioma (149)	0.11	0.77	NS	NS
Sarcoma (32)	0.27	NS	0.23	0.28

NS, non-significant contribution as a risk factor

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