Title: Attributable fraction of mortality in survivors of childhood cancer

Primary Working Group: Epidemiology and Biostatistics

Secondary Working Group: Genetics

Investigators:

Amy Berkman, MD*
Jenn French, PhD*
Kendrick Li, PhD
Kumar Srivastava, PhD
Eric Chow, MD, MPH
Cindy Im, PhD
Claire Snyder, MHS, PhD
I-Chan Huang, PhD
Matthew J Ehrhardt, MD, MS
Wendy Leisenring, PhD
Aron Onerup, MD, PhD
Melissa M Hudson, MD
Kirsten Ness, PhD
Yutaka Yasui, PhD
Greg Armstrong, MD
Stephanie Dixon, MD, MPH*
Yadav Sapkota, PhD*

Background:

Survivors of childhood cancer are a growing population, estimated to reach over half a million in the United States alone by 2040.[1] Despite reductions in short and long-term treatment toxicity and improvements in screening and medical care for late effects of treatment, survivors of childhood cancer remain at risk for late-mortality.[2] Specifically, the 40-year cumulative incidence of all-cause mortality among 5-year survivors in the Childhood Cancer Survivor Study (CCSS) is 23.3%, with 51.2% of deaths attributable to health-related causes and 34.0% attributable to cancer recurrence/progression.[3] As time from treatment increases, there is a decline in the proportion of deaths due to cancer recurrence/progression and an increase in proportion of deaths due to non-progression, non-external causes.[4]

Treatment factors, modifiable risk factors, and sociodemographic factors are all known to impact the risk of late mortality in survivors of childhood cancer. For example, chest radiation, cranial radiation, anthracyclines, and cyclophosphamide are each independently associated with health-related death.[3] An unhealthy lifestyle, including factors such as smoking, alcohol, physical activity, and weight, is associated with increased risk of death compared to healthy lifestyle (Standardized Mortality Ratio 6.2 vs. 3.5), and living in a census block with the highest level of area deprivation is associated with a nearly nine-fold increased risk of death compared to survivors living in areas of low deprivation.[3,5] While the aforementioned factors are known to be associated with risk of late mortality among survivors of childhood cancer, the proportion of deaths

due to specific risk factors remains unknown, as does the contribution of inherited genetic predisposition.

The role of genetic predisposition in risk of chronic health conditions among survivors of childhood cancer is a growing field, with evidence demonstrating links between genetic susceptibility and conditions such as diabetes, cardiomyopathy, coronary artery disease, pulmonary disease, obesity, and secondary malignancies among others.[6-12] A recent study found that genetic factors impact the risk of death after second malignancies in survivors of childhood cancer,[13] and there is ongoing work evaluating the association of actionable genetic variants with the risk of death in survivors.[14] Thus, we propose to estimate the attributable fraction (AF) of mortality among survivors due to treatment, genetic, modifiable lifestyle/cardiovascular, personal socioeconomic status (SES), and social determinants of health (SDOH) factors. An understanding of how each of these categories contributes to overall mortality among survivors is necessary to inform areas for targeted intervention to mitigate the risks.

Specific Aims

Aim 1: Estimate the attributable fraction (AF) of all-cause and cause-specific mortality in survivors of childhood cancer in the CCSS due to cancer treatment exposure, disease-specific genetic variants, modifiable lifestyle/cardiovascular risk factors, SES, and neighborhood social determinants of health (SDOH).

a. Genetic factors will include rare pathogenic/likely pathogenic (P/LP) variants in cancer susceptibility genes and disease-specific (e.g., cardiovascular disease, cancer) polygenic risk scores (PRSs) and the PRSs for mortality/longevity and CVD from the general population.

c. Because of the complex and often bidirectional relationship between certain lifestyle/cardiovascular risk factors, personal SES, and SDOH we will explore the change in AF when each of these components are added to the estimates to better understand their relationship to late mortality.

Aim 2: Assess whether the AFs for all-cause and cause-specific mortality differ among males and females, follow-up age periods (or treatment era), and race/ethnicity. Given the high correlation between attained age and treatment era, we will attempt stratified analyses based on either follow-up age periods or treatment era, if possible. Analyses based on race/ethnicity will be attempted only if sufficient sample sizes are available.

Aim 3: Compare the AF of all-cause and cause-specific mortality in CCSS participants (i.e., survivors) with those from the general population (e.g., NHANES and/or CCSS sibling controls). This comparison will focus on AFs due to modifiable cardiovascular/lifestyle factors, and personal SES that are available in NHANES and/or CCSS sibling questionnaire responses.

Analysis Framework

Population: Survivors and sibling controls enrolled in the CCSS Original Cohort (1970-1986) and Expansion Cohort (1986-1999) will be included in this analysis. Survivors with unknown treatment exposures will be excluded.

Outcome variables

Vital status, including cause of death and date of death

- Cause of death will be categorized as cancer recurrence/progression, cardiac, pulmonary, subsequent malignant neoplasm, other health-related, non-health related/non-recurrence.
- If numbers permit, will look at specific causes of death: subsequent cancer, heart disease, cerebrovascular disease, sepsis, influenza and pneumonia, kidney failure, diabetes, liver disease, chronic lower respiratory disease, complication of medical or surgical care.

Variables of interest

Sociodemographic variables

- Age at primary cancer diagnosis
- Attained age (age at event, death or last contact)
- Reported race/ethnicity
- Sex

Cancer diagnosis and treatment variables

- Primary cancer diagnosis
- Cancer treatment exposures within 5 years of primary diagnosis
    - Radiation
        - Cranial radiation dose
        - Chest radiation dose
        - TBI exposure
    - Chemotherapy
        - Alkylating agents: cyclophosphamide-equivalent dose[15]
        - Anthracyclines: doxorubicin-equivalent dose[16]
        - Epipodophyllotoxin dose
        - Platinating agent dose

Social determinants of health variables (at baseline)

- Neighborhood-level factors: Social Vulnerability Index (SVI)[17] and Minority Health Social Vulnerability Index (MHSVI).[18] Addresses will be geocoded and SVI and MHSVI will be derived as previously described in Choi et al.[19] Briefly, addresses are converted to Federal Information Processing System codes that correspond to U.S. census tracts and counties, with the year 2010 choses as the anticipated median year for CCSS participant address information. These codes are then linked to SVI and MHSVI. SVI and MHSVI are measured with percentile rank from 0 (lowest vulnerability) to 1 (highest vulnerability). SVI and MHSVI overall and domain specific scores will be tested, with the score that captures a higher proportion of death included in the final

analysis. Other neighborhood-level factors that will be explored via sensitivity analyses for potential inclusion are the area deprivation index (ADI)[5] and historical redlining.

- Individual-level SES factors
    - Educational attainment
    - Household income
    - Health insurance

Modifiable lifestyle and cardiovascular risk factor variables: chronic health conditions and lifestyle factors will be defined based on status at the time of Original or Expansion questionnaire at baseline.

- Hypertension: CTCAE grade 2+
- Diabetes: CTCAE grade 2+
- Dyslipidemia: CTCAE grade 2+
- BMI:
    - Underweight: < 18.5 kg/m^2
    - Normal weight: ≥18.5 and <24.9 kg/m2
    - Overweight: ≥24.9 and <30 kg/m2
    - Obese: ≥ 30 kg/m2
- Physical activity: Using published CCSS methodology by Scott et al. vigorous physical activity time will be calculated into metabolic hours per week (MET-h/week) and categorized as 0, 3-6, 9-12 and 15-21 MET-h/wk.[20] Adequate physical activity (Y/N) will be defined as survivors achieving at least 9 MET-h/wk.
- Smoking: Ever smoked >100 cigarettes in lifetime. Tertiles of smoking dose will also be considered.
- Heavy/Risky alcohol use:

    Heavy:

    - Men >6 drinks per day, at least once per month
    - Women >5 drinks per day, at least once per month

    Risky:

    - Men >4 drinks per day or 14 drinks per week
    - Women >3 drinks per day or 7 drinks per week

Genetic data

For CCSS survivors in the expansion cohort, we will use quality-controlled WGS data and for the CCSS original cohort, we will use quality-controlled WES or imputed genotype data. The WES or WGS data will be used for analysis of rare P/LP variants in 237 previously described cancer susceptibility genes[21]. We will use SnpEff[22] and dbNSFP[23] (version 4.1a) to identify predicted deleterious missense variants. dbNSFP uses about 40 *in silico* prediction tools for variant annotation. We will consider missense variants deleterious if >90% of annotations predict it is deleterious. ClinVar[24] will be used to identify P/LP variants, using variants without conflicting interpretations from clinical testing laboratories from 2015 onwards, regardless of the phenotype

reported in ClinVar, as phenotypes may be vague or broad. P/LPs will be examined as a carrier status, with 0 indicating a non-carrier and 1 indicating the presence of 1+ P/LPs. We will also use existing PRSs from the general population, to calculate a PRS for all CCSS survivors for cardiovascular disease, cancer, and mortality. PRS calculations will be completed using PRSice-2 and transformed to Z scores for inclusion in analysis.

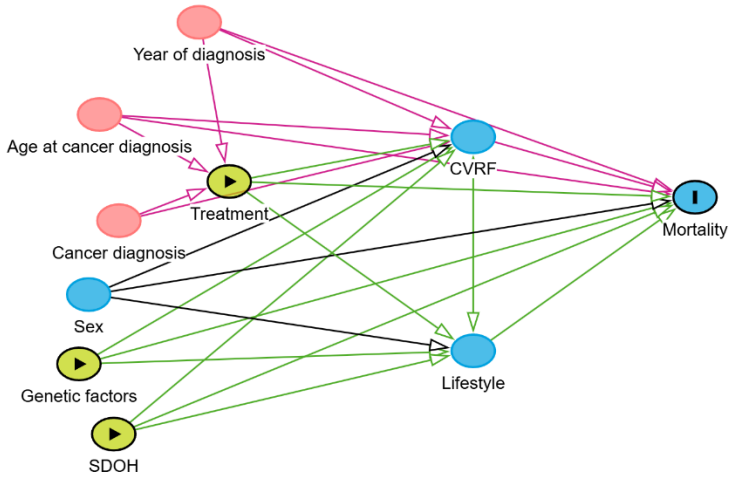
Genetic variables

- Polygenic risk scores from the general population, specifically for
    - Cardiovascular disease
        - Coronary artery disease: PGS003725[25]
        - Heart failure: PGS001790[26]
        - Atrial fibrillation: PGS005065[27]
        - Stroke: PGS000333[28]
    - Cancer (pan-cancer): PGS000356[29]
    - Mortality and longevity: PGS000318[30], PGS000319[30], and PGS000906[31]

Statistical Analysis

Descriptive statistics (frequency and percentage for categorical variables, and mean, standard deviation, median, and interquartile range for continuous variables) will be computed for the study participants' demographics, cancer diagnosis and treatment factors, genetic factors, baseline socioeconomic factors, baseline lifestyle factors, baseline cardiovascular factors, and mortality outcomes, stratified by cohorts and survivor/control status.

Aim 1: Estimate the attributable fraction (AF) of all-cause and cause-specific mortality in survivors of childhood cancer in the CCSS due to cancer treatment exposure, disease-specific genetic variants, modifiable lifestyle/cardiovascular risk factors, personal SES, and social determinants of health (SDOH).



To estimate the attribution function of different factors for overall and cause-specific mortality, we will use a similar analytic approach to Neupane 2025, Lancet Oncology.[7] Multivariable piecewise-exponential models, defined as generalized linear models with the logarithmic link function, the Poisson error distribution, and a piecewise-constant step function of age effects will be used to estimate the relative rates and attributable fractions of the exposures for overall and cause-specific mortality. Due to the possible correlation and mediation relationships between the exposures of interests, we will consider the following models, in order to understand the contribution to mortality of exposures in each separate domain:

Model 1 (clinical model): the exposure will include chemotherapy and radiation therapy variables;

Model 2 (clinical + genetics model): the exposure will include chemotherapy and radiation therapy variables, P/LP variants, and PRS;

Model 3 (clinical + SDOH and SES model): the exposure will include chemotherapy and radiation therapy variables, SVI, MHSVI, education attainment, insurance type, and household income;

Model 4 (clinical + lifestyle model): the exposure will include chemotherapy and radiation therapy variables, vigorous physical activity level, smoking, BMI, and drinking behavior;

Model 5 (clinical model + CVRF model): the exposure will include chemotherapy and cardiovascular risk factors, including hypertension, dyslipidemia, and diabetes;

Model 6 (combined model): the model will include all exposure variables considered, and thus inform the direct effects of the exposure variables of each domain to mortality.

We will treat Model 6 as the primary model, and the others as sensitivity analyses. In each model, preliminary variable selection will be performed using elastic net with 10-fold cross validation. AF's will be reported both by individual variables and by categories. All models will adjust for the survivors' sex, age, and age at primary cancer diagnosis. Relative rates and attributable fractions for all domains and individual variables will be reported.

Aim 2: Assess whether the AFs for all-cause and cause-specific mortality differ among males and females, follow-up age periods (or treatment era) and race/ethnicity. Given the high correlation between age and treatment era, we will attempt stratified analyses based on either follow-up age periods or treatment era, if possible. Analyses based on race/ethnicity will be attempted only if sufficient sample sizes are available.

Same analysis as in Aim 1. Hypothesis testing for difference in AFs will be obtained by nonparametric bootstrap.[32] For example, if we want to compare AFs of cancer treatments between male and female, we will use the following method:

1) Observations will be resampled for B=2,000 times with replacement;
2) In each resampled dataset b = 1, 2, …, B, calculate the AF of cancer treatments in male and in female separately, denoted as $AF_{Male,\ b}$ and $AF_{Female,\ b}$;

3) Obtain the $\alpha/2$-th and $(1-\frac{\alpha}{2})$-th percentiles of the ratios in AFs ($AF_{Male,\ b}$ / $AF_{Female,\ b}$);
4) Reject the null hypothesis if the $\alpha/2$-th percentile > 1 or the $(1-\frac{\alpha}{2})$-th percentile < 1.
5) Report the bootstrap 95% confidence interval of the AF ratio.

Aim 3: Compare the AF of all-cause and cause-specific mortality in survivors with those from the general population (e.g., NHANES and/or CCSS sibling controls). This comparison will focus on AFs due to modifiable cardiovascular/lifestyle factors and SDOH that are available in NHANES and/or CCSS sibling questionnaire responses.

NHANES and CCSS sibling controls will be used and analyzed separately. In NHANES data, individuals will be selected by matching year of birth, sex and race/ethnicity to the CCSS cancer survivors. In each of the two control cohorts, Models 3-6 will be repeated without the cancer treatment variables or genetics variables. Comparison of attribution functions will be performed using a similar nonparametric bootstrap approach in Aim 2, except that resampling will be performed stratified by cohorts.

References

1. Ehrhardt MJ, Krull KR, Bhakta N, et al. Improving quality and quantity of life for childhood cancer survivors globally in the twenty-first century. *Nat Rev Clin Oncol*. Oct 2023;20(10):678-696. doi:10.1038/s41571-023-00802-w
2. Armstrong GT, Yasui Y, Robison LL. Reduction in Late Mortality after Childhood Cancer. *N Engl J Med*. Jul 21 2016;375(3):290-2. doi:10.1056/NEJMc1604184
3. Dixon SB, Liu Q, Chow EJ, et al. Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet*. Apr 29 2023;401(10386):1447-1457. doi:10.1016/S0140-6736(22)02471-0
4. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. May 10 2009;27(14):2328-38. doi:10.1200/JCO.2008.21.1425
5. Ehrhardt MJ, Liu Q, Dixon SB, et al. Association of Modifiable Health Conditions and Social Determinants of Health With Late Mortality in Survivors of Childhood Cancer. *JAMA Netw Open*. Feb 1 2023;6(2):e2255395. doi:10.1001/jamanetworkopen.2022.55395
6. Im C, Neupane A, Baedke JL, et al. Trans-Ancestral Genetic Risk Factors for Treatment-Related Type 2 Diabetes Mellitus in Survivors of Childhood Cancer. *J Clin Oncol*. Jul 1 2024;42(19):2306-2316. doi:10.1200/JCO.23.02281
7. Neupane A, Liu Q, Taneja S, et al. Contributions of cancer treatment and genetic predisposition to risk of subsequent neoplasms in long-term survivors of childhood cancer: a report from the St Jude Lifetime Cohort and the Childhood Cancer Survivor Study. *Lancet Oncol*. Jun 2025;26(6):806-816. doi:10.1016/S1470-2045(25)00157-3

8. Sapkota Y, Qiu W, Dixon SB, et al. Genetic risk score enhances the risk prediction of severe obesity in adult survivors of childhood cancer. *Nat Med*. Aug 2022;28(8):1590-1598. doi:10.1038/s41591-022-01902-3
9. Petrykey K, Chen Y, Neupane A, et al. Predicting the 10-year risk of cardiomyopathy in long-term survivors of childhood cancer. *Ann Oncol*. Jun 4 2025;doi:10.1016/j.annonc.2025.05.539
10. Im C, Yuan Y, Austin ED, et al. Leveraging Therapy-Specific Polygenic Risk Scores to Predict Restrictive Lung Defects in Childhood Cancer Survivors. *Cancer Res*. Aug 16 2022;82(16):2940-2950. doi:10.1158/0008-5472.CAN-22-0418
11. Sapkota Y, Qin N, Ehrhardt MJ, et al. Genetic Variants Associated with Therapy-Related Cardiomyopathy among Childhood Cancer Survivors of African Ancestry. *Cancer Res*. May 1 2021;81(9):2556-2565. doi:10.1158/0008-5472.CAN-20-2675
12. Sapkota Y, Liu Q, Li N, et al. Contribution of Genome-Wide Polygenic Score to Risk of Coronary Artery Disease in Childhood Cancer Survivors. *JACC CardioOncol*. Jun 2022;4(2):258-267. doi:10.1016/j.jaccao.2022.04.003
13. Chen C, Qin N, Wang M, et al. Cancer germline predisposing variants and late mortality from subsequent malignant neoplasms among long-term childhood cancer survivors: a report from the St Jude Lifetime Cohort and the Childhood Cancer Survivor Study. *Lancet Oncol*. Oct 2023;24(10):1147-1156. doi:10.1016/S1470-2045(23)00403-5
14. Im C, Neupane A, Hasan H, et al. Actionable genetic variants and their associations with late effects risks and mortality among long-term survivors of childhood cancer. https://ccss.stjude.org/content/dam/en_US/shared/ccss/documents/concept-prop/concept-proposal%2024-05_2024-05-31T17_02_30.pdf
15. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. Jan 2014;61(1):53-67. doi:10.1002/pbc.24679
16. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 6.0. Children's Oncology Group. Accessed 11/7/2025, www.survivorshipguidelines.org
17. Flanagan BE, Hallisey EJ, Adams E, Lavery A. Measuring Community Vulnerability to Natural and Anthropogenic Hazards: The Centers for Disease Control and Prevention's Social Vulnerability Index. *J Environ Health*. Jun 2018;80(10):34-36.
18. MINORITY HEALTH SOCIAL VULNERABILITY INDEX OVERVIEW
19. Choi J, Horan MR, Brinkman TM, et al. Neighborhood vulnerability and associations with poor health-related quality of life among adult survivors of childhood cancer. *JNCI Cancer Spectr*. Nov 1 2024;8(6)doi:10.1093/jncics/pkae088
20. Scott JM, Li N, Liu Q, et al. Association of Exercise With Mortality in Adult Survivors of Childhood Cancer. *JAMA Oncol*. Oct 1 2018;4(10):1352-1358. doi:10.1001/jamaoncol.2018.2254
21. Kim J, Gianferante M, Karyadi DM, et al. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in the Childhood Cancer Survivor Study. *JNCI Cancer Spectr*. Apr 2021;5(2)doi:10.1093/jncics/pkab007
22. Cingolani P, Platts A, Wang le L, et al. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila

melanogaster strain w1118; iso-2; iso-3. *Fly (Austin)*. Apr-Jun 2012;6(2):80-92. doi:10.4161/fly.19695
23. Liu X, Li C, Mou C, Dong Y, Tu Y. dbNSFP v4: a comprehensive database of transcript-specific functional predictions and annotations for human nonsynonymous and splice-site SNVs. *Genome Med*. Dec 2 2020;12(1):103. doi:10.1186/s13073-020-00803-9
24. Landrum MJ, Chitipiralla S, Brown GR, et al. ClinVar: improvements to accessing data. *Nucleic Acids Res*. Jan 8 2020;48(D1):D835-D844. doi:10.1093/nar/gkz972
25. Patel AP, Wang M, Ruan Y, et al. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. *Nat Med*. Jul 2023;29(7):1793-1803. doi:10.1038/s41591-023-02429-x
26. Wang Y, Namba S, Lopera E, et al. Global Biobank analyses provide lessons for developing polygenic risk scores across diverse cohorts. *Cell Genom*. Jan 11 2023;3(1):100241. doi:10.1016/j.xgen.2022.100241
27. Gunn S, Wang X, Posner DC, et al. Comparison of methods for building polygenic scores for diverse populations. *HGG Adv*. Jan 9 2025;6(1):100355. doi:10.1016/j.xhgg.2024.100355
28. Mishra A, Malik R, Hachiya T, et al. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. Nov 2022;611(7934):115-123. doi:10.1038/s41586-022-05165-3
29. Fritsche LG, Patil S, Beesley LJ, et al. Cancer PRSweb: An Online Repository with Polygenic Risk Scores for Major Cancer Traits and Their Evaluation in Two Independent Biobanks. *Am J Hum Genet*. Nov 5 2020;107(5):815-836. doi:10.1016/j.ajhg.2020.08.025
30. Meisner A, Kundu P, Zhang YD, et al. Combined Utility of 25 Disease and Risk Factor Polygenic Risk Scores for Stratifying Risk of All-Cause Mortality. *Am J Hum Genet*. Sep 3 2020;107(3):418-431. doi:10.1016/j.ajhg.2020.07.002
31. Tesi N, van der Lee SJ, Hulsman M, et al. Polygenic Risk Score of Longevity Predicts Longer Survival Across an Age Continuum. *J Gerontol A Biol Sci Med Sci*. Apr 30 2021;76(5):750-759. doi:10.1093/gerona/glaa289
32. Efron, Bradley, Tibshirani R. *An introduction to the bootstrap*. Chapman and Hall/CRC; 1994.

Table 1. Participant Characteristics

Characteristic	Survivors, n (%)	CCSS Sibling controls, n (%)
Sex		
Male		
Female		
Race and ethnicity		
Hispanic		
Non-Hispanic Black		
Non-Hispanic White		
Other		
Unknown		
Educational attainment		
<High school		
Completed high school		
Some college		
College graduate		
Household income		
Less than $19,000		
$20,000-39,000		
$40,000-60,000		
≥$60,000		
Insurance status		
Insured/Canadian citizen		
Uninsured		
Social vulnerability index, median (IQR)		
Lowest tertile		
Middle tertile		
Highest tertile		
Age at primary cancer diagnosis, median (IQR)		N/A
0-4 years		
5-9 years		
>10 years		
Age at last follow-up, median (IQR)		
Decade of diagnosis		N/A
1970-79		
1980-89		
1990-99		
Primary cancer diagnosis		N/A
ALL		
AML		
Other leukemia		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
CNS tumor		
Bone tumor		
Soft tissue sarcoma		
Kidney tumors		
Neuroblastoma		
Radiation exposure		N/A
Any radiation		

TBI		
Yes		
No		
Cranial radiation		
Any exposure		
Median dose (Gy), (IQR)		
Chest radiation		
Any exposure		
Median dose (Gy), (IQR)		
Anthracycline exposure (mg/m^2)		N/A
Any exposure		
Median dose (doxorubicin equivalent), (IQR)		
Alkylating agents (mg/m^2)		N/A
Any exposure		
Median dose (cyclophosphamide equivalent), (IQR)		
Epipodophyllotoxins (mg/m^2)		N/A
Any exposure		
Median dose (IQR)		
Platinating agents (mg/m^2)		N/A
Any exposure		
Median dose (IQR)		
Body mass index (kg/m^2), median (IQR)		
Underweight		
Healthy		
Overweight		
Obese		
Physical activity (MET-hr/week), median (IQR)		
Active		
Inactive		
Smoking		
Never		
Former		
Current		
Alcohol Use		
Heavy/risky drinking		
Chronic conditions		
Hypertension, CTCAE grade 2+		
Diabetes, CTCAE grade 2+		
Dyslipidemia, CTCAE grade 2+		

Figure: Consider figures similar to Neupane et al. figures 2-4 (PMID: 40449499). Attributable fraction percent on y-axis with mortality (all-cause and cause specific) on x-axis and bars representing proportion attributable to:

- Treatment
- Treatment plus genetics
- Treatment plus SDOH and SES
- Treatment plus lifestyle (PA, alcohol, smoking, BMI)

- Treatment plus cardiovascular risk factors (hypertension, dyslipidemia, diabetes)
- Combined model with all variables considered

Table 2. Proportions of overall and cause-specific mortality attributable to treatment, genetics, SDOH and SES, lifestyle factors, and cardiovascular risk factors by sex, follow-up age period, and race/ethnicity

	All-Cause Mortality	Mortality due to Recurrence/ Progression	Pulmonary Mortality	SMN Mortality	Cardiovascular Mortality	Other Health – related Mortality	Non- Health related, Non-recurrence Mortality
AF (%, 95% CI) in Females							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							
CVRF							
AF (%, 95% CI) in Males							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							
CVRF							
AF (%, 95% CI) by follow-up age period							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							
CVRF							
AF (%, 95% CI) in Hispanic Survivors							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							

CVRF							
AF (%, 95% CI) in non-Hispanic Black Survivors							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							
CVRF							
AF (%, 95% CI) in non-Hispanic White Survivors							
Treatment							
Genetics							
SDOH and SES							
Lifestyle							
CVRF							

Figure. Mirror figures above with 2 bars (survivors, controls) for each attributable fraction (SDOH and SES, lifestyle, CVRF).