original reports

# Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study

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abstract

**PURPOSE** To estimate the prevalence of frailty among childhood cancer survivors and to determine the direct and indirect effects of treatment exposures, lifestyle factors, and severe, disabling, and life-threatening chronic condition on frailty.

**METHODS** Childhood cancer survivors (≥ 5 years since diagnosis), treated between 1970 and 1999 when < 21 years old (n = 10,899; mean age, 37.6 ± 9.4 years; 48% male, 86% white) and siblings were included (n = 2,097; mean age, 42.9 ± 9.4 years). Frailty was defined as ≥ 3 of the following: low lean mass, exhaustion, low energy expenditure, walking limitations, and weakness. Generalized linear models were used to evaluate direct and indirect associations between frailty and treatment exposures, sociodemographic characteristics, lifestyle factors, and chronic condition.

**RESULTS** The overall prevalence of frailty among survivors was 3 times higher compared with siblings (6.4%; 95% CI, 4.1% to 8.7%; *v* 2.2%; 95% CI, 1.2% to 3.2%). Survivors of CNS tumors (9.5%; 95% CI, 5.2% to 13.8%) and bone tumors (8.1%; 95% CI, 5.1% to 11.1%) had the highest prevalence of frailty. Survivors exposed to cranial radiation, pelvic radiation ≥ 34 Gy, abdominal radiation > 40 Gy, cisplatin ≥ 600 mg/m$^2$, amputation, or lung surgery had increased risk for frailty. These associations were partially but not completely attenuated when sociodemographic characteristics, lifestyle factors, and chronic conditions were added to multivariable models. Cranial radiation (prevalence ratio [PR], 1.47; 95% CI, 1.20 to 1.76), pelvic radiation ≥ 34 Gy (PR, 1.46; 95% CI, 1.01 to 2.11), and lung surgery (PR, 1.75; 95% CI, 1.28 to 2.38) remained significant after sociodemographic, lifestyle, and chronic conditions were accounted for.

**CONCLUSION** Childhood cancer survivors reported a higher prevalence of frailty compared with siblings. Radiation and lung surgery exposures were associated with increased risk for frailty. Interventions to prevent, delay onset, or remediate chronic disease and/or promote healthy lifestyle are needed to decrease the prevalence of frailty and preserve function in this at-risk population.

**J Clin Oncol 38:232-247. © 2019 by American Society of Clinical Oncology**

## INTRODUCTION

Because of improvements in therapy, 5-year survival for children diagnosed with cancer has surpassed 85%.[1] Nevertheless, childhood cancer survivors continue to report problems with health status and experience chronic conditions at high frequencies, accumulating on average 4.7 (95% CI, 4.6 to 4.9) severe, disabling, or life-threatening chronic conditions by age 50 years,[2] compared with 2.3 (95% CI, 1.9 to 2.7) among peers.[2]

Consequently, current research and clinical care are focused on improving long-term health among survivors. To accomplish this goal, intermediate markers of health need to be identified. These markers may signal early disease and provide opportunities for intervention. Recent studies have described frailty, a loss of physiologic reserve typically seen in older adults, as a potential marker in adult survivors of childhood cancer.[3] In the general population, frailty increases with age and is predictive of chronic disease onset and mortality.[4]

Our previous single-institution study, using a clinically assessed population, provided important preliminary information about the prevalence of and risk factors for frailty phenotype.[3] However, replication of these findings in the Childhood Cancer Survivor Study (CCSS), a large multi-institutional cohort that has been followed for > 25 years, offers the opportunity to validate and further explore associations between treatment and frailty and test the hypothesis that chronic disease and/or health behaviors partially mediate the association between treatment and frailty in survivors. Thus, the aims of these analyses were to enumerate the prevalence of frailty in a large, geographically diverse population of survivors, compare

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 22, 2019 and published at ascopubs.org/journal/jco on December 4, 2019: DOI https://doi.org/10.1200/JCO.19.01226

rates among survivors to siblings, identify treatment-related risk factors for frailty, and examine direct and indirect effects of treatment exposures and health behaviors on frailty among survivors (Appendix Fig A1, online only).

## METHODS

### Study Population

The CCSS is a retrospective cohort of childhood cancer survivors and their siblings. Survivors were diagnosed when < 21 years of age, treated at one of 31 institutions in North America between January 1, 1970 and December 31, 1999, and survived ≥ 5 years after diagnosis, regardless of recurrence status. The cohort has been followed since 1995; current participants are a median 30 years from diagnosis. Diagnoses included leukemia, CNS tumor, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, Wilms tumor, soft tissue sarcoma, or bone tumor. At cohort entry, survivors identified a sibling nearest to them in age. A random sample of siblings were contacted to participate. Details of study methodology and data collection have been described.[5-7] Survivors and siblings provided informed consent, and institutional review boards at all sites approved the study. Participants completed a baseline survey that included sociodemographics, lifestyle factors, medical history, and chronic health conditions. A proxy (parent, spouse, or next of kin) completed the baseline survey for survivors who died ≥ 5 years after diagnosis or who were < 18 years old. Study documents are available at http://ccss.stjude.org.[8] To be eligible for these analyses, survivors and siblings were alive, ≥ 18 years old, and completed a follow-up questionnaire between 2014 and 2016 (follow-up 5). Data from all available questionnaires were used.

### Outcomes

The primary outcome was frailty, categorized using modified Fried frailty criteria[9]: (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[10]; (3) low energy expenditure: < 383 kcal/wk males and < 270 kcal/wk females from conversion of frequency and duration of low, moderate, and vigorous activities[11,12]; (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?"; and (5) weakness: "yes and the condition is still present" 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?" Participants endorsing at least 2 of 5 criteria were considered prefrail, and those endorsing ≥ 3 were considered frail.

### Other Variables

***Lifestyle factors.*** Smoking, alcohol use, sedentary behavior, and obesity characterized patterns of health behavior and were classified as never, former, or current engagement. Smokers reported smoking ≥ 100 cigarettes in their lifetime and smoking in the past month. Risky/heavy drinkers were males who reported ≥ 1 incident of ≥ 5 drinks in a single day, or an average of 14 drinks/wk, or females who reported ≥ 1 incident of ≥ 4 drinks in a single day or an average of 7 drinks/wk in the year before the questionnaire.[13] Persons who responded no to "During the past month, did you participate in any physical activities or exercise such as running, aerobic, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?" were classified as sedentary.[14,15] Obesity was defined as a BMI of ≥ 30 kg/m$^2$.[13,16]

***Chronic health conditions.*** Chronic conditions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, where 0 = none; 1 = mild or asymptomatic conditions; 2 = moderate conditions; 3 = severe, medically significant, or disabling conditions; and 4 = life-threatening conditions.[17] For these analyses, chronic conditions grade 3-4, overall and by individual organ system, were evaluated[18] as binary indicators and as continuous variables (time in years the condition was present).

***Treatment information.*** Treatment exposures within 5 years of cancer diagnosis were examined using continuous dose exposures and then, on the basis of preliminary analysis, categorized as: alkylating agents (yes/no), anthracyclines (yes/no), cisplatin (none, < 600 mg/m$^2$, ≥ 600 mg/m$^2$), carboplatin (none, < 2,500 mg/m$^2$, ≥ 2,500 mg/m$^2$), 6-mercaptopurine (yes/no), 6-thioguanine (yes/no), methotrexate (yes/no), vinca alkaloids (yes/no), cranial radiation (yes/no), chest radiation (yes/no), abdominal radiation (none, < 34 Gy, ≥ 34 Gy), pelvic radiation (none, < 20 Gy, 20-40 Gy, > 40 Gy), other region radiation (yes/no), amputation (yes/no), spleen removal (yes/no), and lung surgery (yes/no). Radiation dose was determined by summing prescribed doses to all overlapping fields within each respective region. Education status, employment, and annual household income data were captured from the most recent questionnaire.

### Statistical Analysis

Descriptive statistics characterized the study population. Two-sample *t* tests and $\chi^2$ tests compared participants with nonparticipants. Generalized linear models compared sex-stratified percentages of prefrailty, frailty, and frailty components by age group and included an error term for treating institution, and, when survivors were compared with siblings in age- and sex-adjusted models, an error term for family membership.

Generalized linear models,[19,20] including an error term for treating institution, examined the direct and indirect effects

**TABLE 1.** Demographic and Treatment Characteristics of Survivors of Childhood Cancer and Siblings

| Characteristic | Survivors of Childhood Cancer (N = 10,899) | Siblings (N = 2,097) | *P* |
|---|---|---|---|
| Age at baseline questionnaire, years | | | .50 |
| Mean (SD) | 24.3 (8.9) | 24.5 (8.4) | |
| Range | 5-56 | 5-50 | |
| Age at diagnosis, years | | | |
| 0-4 | 4,095 (40.2) | | |
| 5-9 | 2,430 (23.7) | | |
| 10-14 | 2,459 (20.6) | | |
| ≥ 15 | 1,915 (15.6) | | |
| Sex | | | < .001 |
| Female | 5,709 (52.3) | 1,214 (57.9) | |
| Male | 5,190 (47.7) | 883 (42.1) | |
| Race/ethnicity | | | < .001 |
| Non-Hispanic white | 9,401 (85.7) | 1,877 (89.5) | |
| Non-Hispanic black | 452 (4.3) | 27 (1.3) | |
| Hispanic | 661 (6.3) | 69 (3.3) | |
| Other* | 385 (3.7) | 124 (5.9) | |
| Age at assessment, years | | | |
| Mean (SD) | 37.6 (9.4) | 42.9 (9.4) | < .001 |
| 18-29 | 2,120 (24.7) | 161 (7.7) | < .001 |
| 30-39 | 4,206 (38.3) | 610 (29.1) | |
| 40-49 | 3,160 (25.6) | 725 (34.6) | |
| ≥ 50 | 1,413 (11.4) | 601 (28.6) | |
| Employment status | | | < .001 |
| Employed† | 8,191(75.0) | 1,870 (89.4) | |
| Unemployed, or looking for jobs | 1,810 (16.2) | 94 (4.5) | |
| Student or retired | 835 (8.8) | 129 (6.1) | |
| Not specified | 63 | 4 | |
| Education | | | < .001 |
| Less than high school | 408 (4.0) | 51 (2.4) | |
| High school graduate | 1,970 (18.1) | 293 (14.0) | |
| College graduate | 6,737 (62.6) | 1,283 (61.4) | |
| Post graduate | 1,677 (15.3) | 464 (22.2) | |
| Not specified | 107 | 6 | |
| Household income, USD | | | < .001 |
| < $40,000 | 3,156 (33.2) | 383 (19.7) | |
| ≥ $40,000 | 6,537 (66.8) | 1,558 (80.3) | |
| Not reported | 1,206 | 156 | |
| Smoking status | | | < .001 |
| Never | 7,484 (69.4) | 1,239 (59.1) | |
| Current | 1,904 (17.8) | 405 (19.3) | |
| Former | 1,473 (12.8) | 451 (21.6) | |
| Not reported | 38 | 2 | |

(continued on following page)

**TABLE 1.** Demographic and Treatment Characteristics of Survivors of Childhood Cancer and Siblings (continued)

| Characteristic | Survivors of Childhood Cancer (N = 10,899) | Siblings (N = 2,097) | *P* |
|---|---|---|---|
| Heavy drinking‡ | | | < .001 |
| Never | 8,747 (84.9) | 1,676 (80.7) | |
| Current | 367 (3.5) | 104 (5.0) | |
| Former | 1,170 (11.6) | 296 (14.3) | |
| Not reported | 615 | 21 | |
| Sedentary behavior§ | | | |
| Never | 7,214 (68.3) | 1,385 (66.0) | < .001 |
| Current | 2,135 (19.2) | 253 (12.1) | |
| Former | 1,550 (12.5) | 459 (21.9) | |
| Obesity (BMI ≥ 30 kg/m$^2$) | | | < .001 |
| Never | 7,840 (74.7) | 1,416 (67.5) | |
| Current | 2,572 (22.8) | 593 (28.5) | |
| Former | 301 (2.5) | 83 (3.9) | |
| Not reported | 186 | 5 | |
| Health insurance | | | < .001 |
| No | 979 (9.2) | 138 (6.6) | |
| Yes‖ | 9,860 (90.8) | 1,949 (93.4) | |
| Not reported | 60 | 10 | |
| Grade 3-4 chronic condition¶ | 3,409 (28.8) | 195 (9.3) | < .001 |
| Duration, years | | | |
| Mean (SD) | 17.1 (11.9) | 25.03 (15.2) | < .001 |
| Median | 16 | 26.5 | |
| Range | 0-57 | 0-57.0 | |
| Endocrine condition grade 3-4 | 802 (6.6) | 44 (2.1) | < .001 |
| Duration, years | | | |
| Mean (SD) | 19.8 (9.7) | 24.5 (9.4) | .01 |
| Median | 19.4 | 22.8 | |
| Range | 1.9-45.9 | 8.1-45.5 | |
| Respiratory condition grade 3-4 | 64 (0.5) | 3 (0.1) | .2 |
| Duration, years | | | |
| Mean (SD) | 20.6 (8.1) | 28.6 (11.2) | .10 |
| Median | 19.3 | 27.5 | |
| Range | 7.8-43.9 | 18.0-40.4 | |
| Cardiac condition grade 3-4 | 591 (5.1) | 28 (1.3) | < .001 |
| Duration, years | | | |
| Mean (SD) | 18.1 (9.1) | 17.1 (9.6) | .62 |
| Median | 16.9 | 11.1 | |
| Range | 2.8-43.9 | 7.3-37.1 | |
| Renal condition grade 3-4 | 85 (0.7) | 2 (0.1) | .01 |
| Duration, years | | | |
| Mean (SD) | 21.3 (9.1) | 21.1 (2.2) | .97 |
| Median | 20.9 | 21.1 | |
| Range | 6.8-42.8 | 19.5-22.6 | |

(continued on following page)

**TABLE 1.** Demographic and Treatment Characteristics of Survivors of Childhood Cancer and Siblings (continued)

| Characteristic | Survivors of Childhood Cancer (N = 10,899) | Siblings (N = 2,097) | *P* |
|---|---|---|---|
| SMN grade 3-4 | 500 (4.2) | 27 (1.3) | < .001 |
| Duration, years | | | |
| Mean (SD) | 15.3 (6.9) | 13.4 (7.9) | .64 |
| Median | 13.9 | 13.4 | |
| Range | 2.0-36.8 | 6.4-44.7 | |
| Neurologic condition grade 3-4 | 549 (4.7) | 25 (1.2) | < .001 |
| Duration, years | | | |
| Mean (SD) | 25.4 (8.7) | 24.7 (10.1) | .72 |
| Median | 25.9 | 23.3 | |
| Range | 3.8-45.7 | 7.3-42.2 | |
| Musculoskeletal condition grade 3-4 | 596 (5.0) | 10 (0.5) | < .001 |
| Duration, years | | | |
| Mean (SD) | 27.5 (10.7) | 17.2 (10.0) | .004 |
| Median | 29.3 | 13.8 | |
| Range | 4.7-46.8 | 7.8-34.4 | |
| All other grade 3-4 conditions | 1,354 (11.4) | 83 (4.0) | < .001 |
| Duration, years | | | |
| Mean (SD) | 22.9 (9.4) | 30.7 (14.0) | < .001 |
| Median | 22.7 | 28.9 | |
| Range | 4.1-46.5 | 7.1-66.5 | |

NOTE. Data presented as No. (%) unless otherwise noted. Sampling weights have been applied for all percentages.

Abbreviations: BMI, body mass index; SD, standard deviation; SMN, second malignant neoplasm; USD, United States dollars.

*Category other: Asian, not specified, or other.

†Employed: full time, part time, or caring for home/family.

‡Heavy drinking: ≥ 5 drinks per day or 14 drinks per week for men; ≥ 4 drinks per day or 7 drinks per week for women.

§Sedentary behavior: persons who responded no to the question: "During the past month, did you participate in any physical activities such as running, aerobic, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?"

‖Yes: includes participants with Canadian health insurance.

¶Grade 3-4 chronic condition: having at least one chronic condition grade 3-4.

of treatment exposures on frailty, treating lifestyle, and grade 3-4 of chronic conditions as mediators. Using the strategy described by Baron and Kenny,[21] 3 stages of regression models were constructed. The first stage regressed chronic conditions and lifestyle on treatment exposures (Appendix Tables A1 and A2, online only), the second regressed frailty on treatment exposures, and the third regressed frailty on treatment, chronic conditions, and lifestyle. We also investigated the effects of treatment era alone on frailty and then in a model that included treatment. Adding treatment to the model completely attenuated the effects of era; thus, we did not include era in our final model. Change in prevalence rate ratios, model $\chi^2$ statistics, and Akaike information criteria were examined to evaluate relative fit of each model.[22,23] In additional analyses, the frailty phenotype was evaluated as an ordinal outcome using multinomial logistic regression.

For all the analyses, survey weights were included to account for intentional undersampling of acute lymphoblastic leukemia survivors treated between 1987 and 1999. We used a false discovery rate < 10% to account for type I error related to multiple comparison.[24] SAS version 9.4 (Cary, NC) was used to conduct all statistical analyses (all 2-sided).

## RESULTS

### Participant Characteristics

Among 20,834 cohort members, 10,899 were ≥ 18 years old and completed the most recent follow-up questionnaire characterizing frailty. There were 6,355 nonresponders, 2,021 active refusals, 103 lost to follow-up, 373 with missing data, and 1,083 lost to follow-up at the time of the survey (Appendix Fig A2, online only). Compared with nonparticipants, participants were more likely to be older at diagnosis, female, non-Hispanic white, and treated for CNS tumors (Appendix Table A3, online only).

Among 2,146 siblings, 2,097 were ≥ 18 years old and completed the most recent follow-up questionnaire (Appendix

**TABLE 2.** Associations Between Treatment Exposures and Frailty Among Survivors

| Treatment Exposures | Survivors (N = 10,899) | Frailty (n = 681)* | | | Prefrailty (n = 1,953)† | | |
|---|---|---|---|---|---|---|---|
| | | Row (%)‡ | Adjusted PRR§ (95% CI) | *P* | Row (%)‡ | Adjusted PRR§ (95% CI) | *P* |
| Chest radiation | | | | | | | |
| Yes | 2,437 | 9.2 | 1.10 (0.96 to 1.26) | .18 | 23.1 | 1.10 (0.94 to 1.29) | .23 |
| No | 7,957 | 4.9 | Ref | | 15.3 | Ref | |
| Cranial radiation | | | | | | | |
| Yes | 2,885 | 8.6 | 2.07 (1.67 to 2.46) | < .001‖ | 22.7 | 1.62 (1.45 to 1.81) | < .001‖ |
| No | 7,509 | 4.8 | Ref | | 14. 8 | Ref | |
| Abdominal radiation dose, Gy¶ | | | | | | | |
| < 20 | 912 | 5.7 | 0.99 (0.64 to 1.56) | .99 | 17.8 | 0.90 (0.70 to 1.17) | .43 |
| 20-40 | 1,172 | 10.3 | 1.12 (0.82 to 1.75) | .34 | 25.5 | 1.04 (0.86 to 1.15) | .74 |
| > 40 | 184 | 15.2 | 1.71 (1.02 to 2.87) | .04‖ | 29.9 | 1.24 (0.87 to 1.76) | .23 |
| None | 8,126 | 5.1 | Ref | | 15.6 | Ref | |
| Pelvic radiation dose, Gy¶ | | | | | | | |
| < 34 | 1,243 | 7.1 | 0.81 (0.65 to 1.01) | .06 | 21.3 | 1.12 (0.88 to 1.41) | .35 |
| ≥ 34 | 641 | 14.5 | 1.52 (1.06 to 2.18) | .02‖ | 29.5 | 1.30 (1.03 to 1.63) | .03‖ |
| None | 8,510 | 5.1 | Ref | | 15.6 | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | | | | |
| < 600 | 661 | 8.5 | 0.96 (0.70 to 1.34) | .85 | 1.5 | 1.28 (1.07 to 1.54) | .007‖ |
| ≥ 600 | 144 | 11.8 | 1.81 (1.08 to 3.02) | .02‖ | 22.9 | 1.24 (0.85 to 1.76) | .27 |
| None | 9,374 | 5.5 | Ref | | 16.1 | Ref | |
| Carboplatin dose, mg/m$^2$ | | | | | | | |
| < 2,500 | 144 | 11.1 | 1.27 (0.71 to 2.24) | .42 | 20.8 | 0.87 (0.58 to 1.29) | .47 |
| ≥ 2,500 | 151 | 9.9 | 1.58 (0.91 to 2.71) | .10 | 29.1 | 1.56 (1.14 to 2.15) | .006‖ |
| None | 9,909 | 5.6 | Ref | | 16.6 | Ref | |
| Methotrexate | | | | | | | |
| Yes | 4,027 | 4.6 | 0.77 (0.60 to 0.99) | .03‖ | 14.8 | 0.93 (0.81 to 1.07) | .33 |
| No | 6,208 | 6.8 | Ref | | 18.6 | Ref | |
| Alkylating agents | | | | | | | |
| Yes | 5,450 | 6.2 | 1.11 (0.90 to 1.36) | .31 | 17.9 | 1.14 (1.02 to 1.29) | .02‖ |
| No | 4,895 | 5.4 | Ref | | 15.8 | Ref | |
| 6-mercaptopurine | | | | | | | |
| Yes | 2,362 | 4.0 | 1.58 (0.66 to 1.17) | .37 | 13.3 | 0.90 (0.76 to 1.05) | .17 |
| No | 7,873 | 6.5 | Ref | | 18.4 | Ref | |
| 6-thiogauine | | | | | | | |
| Yes | 982 | 4.6 | 1.05 (0.78 to 1.41) | .76 | 12.9 | 0.88 (0.75 to 1.06) | .18 |
| No | 9,253 | 5.9 | Ref | | 17.4 | Ref | |
| Vinca alkaloids | | | | | | | |
| Yes | 6,886 | 5.3 | 0.90 (0.73 to 1.11) | .34 | 15.7 | 0.90 (0.80 to 1.06) | .18 |
| No | 1,301 | 6.7 | Ref | | 19.6 | Ref | |
| Anthracycline | | | | | | | |
| Yes | 4,932 | 5.2 | 0.94 (0.76 to 1.16) | .57 | 15.5 | 0.92 (0.82 to 1.04) | .19 |
| No | 5,419 | 6.5 | Ref | | 18.4 | Ref | |

(continued on following page)

**TABLE 2.** Associations Between Treatment Exposures and Frailty Among Survivors (continued)

| Treatment Exposures | Survivors (N = 10,899) | Frailty (n = 681)* Row (%)‡ | Frailty (n = 681)* Adjusted PRR§ (95% CI) | Frailty (n = 681)* P | Prefrailty (n = 1,953)† Row (%)‡ | Prefrailty (n = 1,953)† Adjusted PRR§ (95% CI) | Prefrailty (n = 1,953)† P |
|---|---|---|---|---|---|---|---|
| Amputation | | | | | | | |
| Yes | 441 | 11.3 | 1.86 (1.30 to 2.67) | < .001‖ | 28.6 | 1.54 (1.11 to 1.39) | < .001‖ |
| No | 10,374 | 5.6 | Ref | | 16.5 | Ref | |
| Lung surgery | | | | | | | |
| Yes | 424 | 13.9 | 2.07 (1.53 to 2.80) | < .001‖ | 30.5 | 1.60 (1.31 to 1.94) | < .001‖ |
| No | 10,292 | 5.5 | Ref | | 16.3 | Ref | |
| Spleen removal | | | | | | | |
| Yes | 753 | 8.0 | 0.87 (0.62 to 1.24) | .49 | 22.8 | 1.14 (0.93 to 1.39) | .22 |
| No | 9,970 | 5.7 | Ref | | 16.6 | Ref | |

Abbreviations: PRR, prevalence rate ratio; Ref, reference.

*Frailty ≥ 3 components.

†Prefrailty ≥ 2 components.

‡Weighted row percentages are presented.

§The model was adjusted for sex, race, age at diagnosis, and age at assessment.

‖Indicates estimates with a false discovery rate < 10%.

¶Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

Fig A3, online only). Siblings were more likely than survivors to be female, non-Hispanic white, ≥ 50 years old at the last questionnaire, and employed, and had higher educational attainment and annual household incomes (Table 1). Siblings were also more likely than survivors to be current smokers, be heavy drinkers, report a sedentary lifestyle, and be classified as obese. Survivors reported a higher prevalence of any grade 3-4 chronic conditions than siblings.

### Prevalence

The prevalence of frailty was 6.4% (95% CI, 4.1% to 8.7%) among survivors, and 2.2% (95% CI, 1.2% to 3.2%) among siblings (Appendix Fig A4, online only). The prevalence of prefrailty and frailty were higher among females than males for both survivors and siblings in most age groups (Appendix Table A4, online only). Among survivors, walking limitations (85.0%; 95% CI, 82.2% to 87.7%), low energy expenditure (82.9%; 95% CI, 79.7% to 86.1%), and self-reported exhaustion (80.5%; 95% CI, 77.8% to 83.0%) were the three frailty components with the highest prevalence (Appendix Fig A5, online only). Appendix Figure A6 (online only) shows age-adjusted prevalence of prefrailty and frailty by diagnosis. Survivors with CNS tumors had the highest prevalence of frailty and prefrailty (9.5% and 26.1% respectively), followed by those with bone tumors (8.1% and 22.5%, respectively) and Hodgkin lymphoma (7.5% and 19.5%, respectively).

### Treatment Exposure and Frailty

Models adjusted for sex, race/ethnicity, age at diagnosis, and age at assessment showed that cranial radiation, pelvic radiation ≥ 34 Gy, abdominal radiation > 40 Gy, cisplatin ≥ 600 mg/m$^2$, amputation, or lung surgery increased risk for frailty. Exposure to cranial radiation, pelvic radiation ≥ 34 Gy, cisplatin < 600 mg/m$^2$, carboplatin ≥ 2,500 mg/m$^2$, alkylating agents, amputation, or lung surgery were associated with prefrailty (Table 2).

### Demographics, Lifestyle, and Frailty

Demographic and lifestyle variables associated with frailty and prefrailty included female sex, age at diagnosis, non-Hispanic black or Hispanic race/ethnicity, sedentary lifestyle, smoking, and obesity (Table 3).

### Chronic Conditions and Frailty

Table 4 and Appendix Table A5 (online only) show associations between prevalent grade 3-4 chronic conditions and duration of chronic conditions and frailty and prefrailty among survivors. Compared with those without organ system–specific chronic conditions, frailty prevalence was higher among those with respiratory, neurologic, musculoskeletal, cardiac, and endocrine conditions. Respiratory, second malignant neoplasm (SMN), cardiac, neurologic, and musculoskeletal grade 3-4 chronic conditions were associated with prefrailty. The prevalence of frailty and prefrailty was higher among survivors whose chronic conditions were of longer duration.

### Treatment Exposure, Chronic Conditions, Lifestyle, and Frailty

Table 5, Figures 1A and 1B, and Appendix Tables A6 and A7 (online only) show the mediating effects of chronic health conditions and lifestyle on the association of treatment exposures with frailty and prefrailty and the relative fit of each model. Adding grade 3-4 organ-specific chronic conditions to the model attenuated, but did not completely

**TABLE 3.** Associations Between Sociodemographic Characteristics, Lifestyle, and Frailty Among Survivors

| Factors | Survivors (N = 10,899) | Frailty (n = 681)* | | | Prefrailty (n = 1,953)† | | |
|---|---|---|---|---|---|---|---|
| | | Row (%)‡ | Adjusted PRR (95% CI) | *P* | Row (%)‡ | Adjusted PRR (95% CI) | *P* |
| Age at diagnosis, years | | | | | | | |
| 0-4 | 4,095 | 4.4 | 0.67 (0.52 to 0.86) | .002§ | 14.6 | 0.80 (0.70 to 0.94) | .005§ |
| 5-9 | 2,459 | 5.9 | 0.84 (0.66 to 1.07 | .68 | 16.8 | 0.86 (0.75 to 1.00) | .06§ |
| 10-14 | 2,430 | 7.3 | 0.94 (0.75 to 1.18) | .61 | 20.5 | 1.02 (0.88 to 1.17) | .77 |
| ≥ 15 | 1,915 | 7.6 | Ref | | 19.5 | Ref | |
| Sex | | | | | | | |
| Female | 5,709 | 6.8 | 1.30 (1.12 to 1.52) | < .001§ | 19.7 | 1.32 (1.21 to 1.44) | < .001§ |
| Male | 5,190 | 4.7 | Ref | | 14.2 | Ref | |
| Race/ethnicity | | | | | | | |
| Non-Hispanic black | 452 | 10.7 | 1.68 (1.27 to 2.22) | < .001§ | 26.4 | 1.43 (1.20 to 1.71) | < .001§ |
| Hispanic | 661 | 8.5 | 1.63 (1.26 to 2.12) | < .001§ | 20.4 | 1.27 (1.10 to 1.51) | .004§ |
| Others | 385 | 5.0 | 0.99 (0.65 to 1.53) | .99 | 17.3 | 1.10 (0.84 to 1.35) | .60 |
| Non-Hispanic white | 9,401 | 5.4 | Ref | | 16.4 | Ref | |
| Age at assessment, years | | | | | | | |
| 18-29 | 2,120 | 3.7 | Ref | | 12.8 | Ref | |
| 30-39 | 4,206 | 5.5 | 1.18 (0.92 to 1.50) | .19 | 16.7 | 1.10 (0.96 to 1.24) | .18 |
| 40-49 | 3,160 | 7.0 | 1.23 (0.93 to 1.21) | .12 | 19.4 | 1.10 (0.94 to 1.27) | .26 |
| ≥ 50 | 1,413 | 8.9 | 1.34 (0.90 to 1.85) | .08 | 22.3 | 1.11 (0.94 to 1.35) | .28 |
| Smoking status‖ | | | | | | | |
| Current | 1,904 | 7.9 | 1.29 (1.08 to 1.54) | .005§ | 22.2 | 1.31 (1.18 to 1.46) | < .001§ |
| Former | 1,473 | 5.8 | 0.96 (0.76 to 1.21) | .74 | 16.7 | 0.99 (0.87 to 1.14) | .92 |
| Never | 7,484 | 5.3 | Ref | | 15.7 | Ref | |
| Sedentary behavior¶ | | | | | | | |
| Current | 2,135 | 14.8 | 4.60 (3.88 to 5.46) | < .001§ | 34.8 | 2.84 (2.57 to 3.13) | < .001§ |
| Former | 1,550 | 8.0 | 2.43 (1.93 to 3.07) | < .001§ | 22.6 | 1.84 (1.61 to 2.10) | < .001§ |
| Never | 7,214 | 2.9 | Ref | | 11.1 | Ref | |
| Obesity (BMI ≥ 30 kg/m$^2$)# | | | | | | | |
| Current | 2,572 | 8.7 | 1.42 (1.21 to 1.67) | < .001§ | 24.2 | 1.41 (1.28 to 1.55) | < .001§ |
| Former | 301 | 9.6 | 1.32 (0.90 to 1.93) | .15 | 26.3 | 1.34 (1.06 to 1.70) | .01§ |
| Never | 7,840 | 4.8 | Ref | | 14.6 | Ref | |

Abbreviations: BMI, body mass index; PRR, prevalence rate ratio; Ref, reference.

*Frailty ≥ 3 components.

†Prefrailty ≥ 2 components.

‡Weighted row percentages.

§Indicates estimates with a false discovery rate < 10%.

‖Smoking status was defined as those who reported ≥ 100 cigarettes in their lifetime and smoking in the past month; 35 participants did not report their smoking status.

¶Sedentary behavior: persons who responded no to the question: "During the past month, did you participate in any physical activities such as running, aerobic, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?"

explain, associations between cranial radiation, pelvic radiation ≥ 34 Gy, lung surgery, and frailty. However, associations between cisplatin dose ≥ 600 mg/m$^2$, abdominal radiation dose > 40 Gy, amputation, and frailty became null when organ-specific grade 3-4 chronic conditions were added to the model. When lifestyle factors were included in the model with treatment and grade 3-4 organ-specific chronic health conditions, the association between cranial radiation and frailty was further attenuated but remained significant (Table 5).

Adding grade 3-4 organ-specific chronic conditions to the model attenuated associations between cranial radiation, carboplatin dose ≥ 2,500 mg/m$^2$, cisplatin dose < 600 mg/m$^2$,

**TABLE 4.** Associations Between Grade 3-4 Chronic Health Conditions and Frailty Among Survivors

| Grade 3-4 Chronic Conditions | Survivors (N = 10,899) | Frailty (n = 681)* | | | Prefrailty (n = 1,953)† | | |
|---|---|---|---|---|---|---|---|
| | | Row (%)‡ | Adjusted PRR (95% CI)§ | *P* | Row (%)‡ | Adjusted PRR (95% CI)§ | *P* |
| Any chronic conditionǁ | | | | | | | |
| Yes | 3,409 | 11.3 | 2.86 (2.45 to 3.3) | < .001¶ | 28.3 | 2.15 (1.97 to 2.34) | < .001¶ |
| No | 7,490 | 3.6 | Ref | | 12.5 | Ref | |
| Cardiac | | | | | | | |
| Yes | 591 | 17.4 | 1.90 (1. 52 to 2.35) | < .001¶ | 35.2 | 1.48 (1.31 to 1.68) | < .001¶ |
| No | 10,308 | 5.2 | Ref | | 16.1 | Ref | |
| SMN | | | | | | | |
| Yes | 500 | 12.0 | 1.26 (0.95 to 1.66) | .11 | 28.3 | 1.21 (1.02 to 1.41) | .03 |
| No | 10,399 | 5.6 | Ref | | 16.6 | Ref | |
| Neurologic | | | | | | | |
| Yes | 549 | 23.6 | 4.00 (3.27 to 4.89) | < .001¶ | 48.6 | 2.72 (2.41 to 3.06) | < .001¶ |
| No | 10,350 | 5.0 | Ref | | 15.5 | Ref | |
| Musculoskeletal | | | | | | | |
| Yes | 596 | 11.7 | 1.75 (1.36 to 2.25) | < .001¶ | 29.2 | 1.59 (1.39 to 1.82) | < .001¶ |
| No | 10,303 | 5.5 | Ref | | 16.4 | Ref | |
| Endocrine | | | | | | | |
| Yes | 802 | 12.1 | 1.61 (1.28 to 2.03) | < .001¶ | 27.5 | 1.31 (1.14 to 1.50) | < .001¶ |
| No | 10,097 | 5.4 | Ref | | 17.0 | Ref | |
| Respiratory | | | | | | | |
| Yes | 64 | 31.0 | 3.17 (2.03 to 4.94) | < .001¶ | 46.0 | 1.86 (1.43 to 2.43) | < .001¶ |
| No | 10,835 | 5.7 | Ref | | 16.9 | Ref | |
| Renal | | | | | | | |
| Yes | 85 | 10.5 | 1.35 (0.71 to 2.57) | .36 | 27.1 | 1.31 (0.90 to 1.90) | .16 |
| No | 10,814 | 5.8 | Ref | | 17.0 | Ref | |
| Other chronic conditions | | | | | | | |
| Yes | 1,354 | 10.8 | 1.57 (1.30 to 1.90) | < .001¶ | 28.7 | 1.56 (1.41 to 1.73) | < .001¶ |
| No | 9,545 | 5.2 | Ref | | 15.6 | Ref | |

Abbreviations: PRR, prevalence rate ratio; Ref, reference; SMN, second malignant neoplasm.
*Frailty ≥ 3 components.
†Prefrailty ≥ 2 components.
‡Weighted row percentages.
§The model was adjusted for sex, race, age at diagnosis, and age at assessment.
ǁAny chronic condition was conducted in separate model, and the PRR (95% CI) was reported in the table.
¶Indicates estimates with a false discovery rate < 10%.

lung surgery, and prefrailty. However, associations between pelvic radiation ≥ 34 Gy, alkylating agents, amputation, and prefrailty became null when organ-specific grade 3-4 chronic conditions were added to the model. When lifestyle factors were included in the model with treatment and grade 3-4 organ-specific chronic conditions, the association between cranial radiation and prefrailty was further attenuated but remained significant (Table 5). Results from multinomial logistic regressions were consistent with our dichotomous outcome findings (Appendix Tables A8-Tables A12, online only).

## DISCUSSION

Using a large longitudinal and geographically diverse cohort, this study further characterizes and provides new data about risk factors for frailty among childhood cancer survivors. Among nearly 11,000 5-year survivors, a mean age of 37.6 (± 9.4) years at assessment, the presence of frailty, a phenotype typically seen among older adults, was 3 times higher than among siblings. Our results identify a novel association between lung surgery and frailty, while validating previously reported associations between cranial or

**TABLE 5.** Associations Between Treatment Exposures, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Prefrailty or Frailty Among Survivors

| | Frailty (n = 681)[a] | | Prefrailty (n = 1,953)[b] | |
|---|---|---|---|---|
| **Factors** | **Adjusted PRR[c] (95% CI)** | ***P*** | **Adjusted PRR[d] (95% CI)** | ***P*** |
| Sex | | | | |
| Female | 1.41 (1.20 to 1.66) | < .001[e] | 1.38 (1.25 to 1.52) | < .001[e] |
| Male | | | | |
| Race/ethnicity | | | | |
| Non-Hispanic black | 1.76 (1.30 to 2.42) | < .001[e] | 1.46 (1.20 to 1.78) | < .001[e] |
| Hispanic | 1.80 (1.36 to 2.35) | < .001[e] | 1.25 (1.04 to 1.49) | .018[e] |
| Others | 0.96 (0.60 to 1.55) | .88 | 1.03 (0.80 to 1.38) | .83 |
| Non-Hispanic white | Ref | | | |
| Age at diagnosis, years | | | | |
| 0-4 | 0.60 (0.45 to 0.80) | < .001[e] | 0.79 (0.67 to 0.94) | .006[e] |
| 5-10 | 0.76 (0.58 to 0.99) | .04[e] | 0.87 (0.74 to 1.02) | .09 |
| 10-14 | 0.97 (0.76 to 1.23) | .80 | 0.99 (0.87 to 1.15) | .98 |
| ≥ 15 | Ref | | Ref | |
| Age at assessment, years | | | | |
| 18-29 | Ref | | Ref | |
| 30-39 | 1.02 (0.80 to 1.31) | .87 | 1.03 (0.90 to 1.17) | .74 |
| 40-49 | 1.06 (0.80 to 1.41) | .72 | 1.03 (0.87 to 1.28) | .77 |
| ≥ 50 | 1.12 (0.80 to 1.61) | .52 | 1.03 (0.83 to 1.28) | .80 |
| Cranial radiation | | | | |
| Yes | 1.47 (1.20 to 1.76) | < .001[e] | 1.25 (1.12 to 1.40) | < .001[e] |
| No | Ref | | Ref | |
| Abdominal radiation dose, Gy[f] | | | | |
| < 20 | 1.32 (0.90 to 2.01) | .19 | [g] | |
| 20-40 | 1.26 (0.90 to 1.77) | .20 | [g] | |
| > 40 | 1.46 (0.88 to 2.18) | .14 | [g] | |
| None | Ref | | [g] | |
| Pelvic radiation dose, Gy[f] | | | | |
| < 34 | 0.98 (0.67 to 1.45) | .95 | 1.06 (0.85 to 1.33) | .61 |
| ≥ 34 | 1.46 (1.01 to 2.11) | .04[e] | 1.20 (0.95 to 1.50) | .15 |
| None | Ref | | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 0.96 (0.70 to 1.32) | .78 | 1.22 (1.02 to 1.47) | .03[e] |
| ≥ 600 | 1.37 (0.82 to 2.28) | .22 | 0.97 (0.67 to 1.40) | .88 |
| None | Ref | | Ref | |
| Carboplatin dose, mg/m$^2$ | | | | |
| < 2,500 | [g] | | 0.82 (0.58 to 1.21) | .32 |
| ≥ 2,500 | [g] | | 1.35 (0.97 to 1.88) | .08 |
| None | Ref | | Ref | |
| Methotrexate | | | | |
| Yes | 0.83 (0.68 to 0.99) | .04[e] | 0.87 (0.78 to 0.97) | .01[e] |
| No | | | | |

(continued on following page)

**TABLE 5.** Associations Between Treatment Exposures, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Prefrailty or Frailty Among Survivors (continued)

| | Frailty (n = 681)[a] | | Prefrailty (n = 1,953)[b] | |
|---|---|---|---|---|
| **Factors** | **Adjusted PRR[c] (95% CI)** | ***P*** | **Adjusted PRR[d] (95% CI)** | ***P*** |
| Alkylating agents | | | | |
| Yes | [g] | | 1.12 (1.02 to 1.24) | .02[e] |
| No | [g] | | | |
| Amputation | | | | |
| Yes | 1.41 (0.90 to 2.21) | .13 | 1.17 (0.88 to 1.54) | .26 |
| No | Ref | | | |
| Lung surgery | | | | |
| Yes | 1.75 (1.28 to 2.38) | < .001[e] | 1.43 (1.17 to 1.74) | < .001[e] |
| No | Ref | | | |
| Cardiac | | | | |
| Yes | 1.56 (1.24 to 1.98) | < .001[e] | 1.28 (1.10 to 1.50) | .002[e] |
| No | Ref | | Ref | |
| Neurologic | | | | |
| Yes | 3.15 (2.51 to 3.95) | < .001[e] | 2.35 (2.03 to 2.72) | < .001[e] |
| No | Ref | | Ref | |
| Musculoskeletal | | | | |
| Yes | 1.28 (0.86 to 1.92) | .23 | 1.30 (1.01 to 1.64) | .04[e] |
| No | Ref | | | |
| Endocrine | | | | |
| Yes | 1.40 (1.10 to 1.78) | < .001[e] | 1.21 (1.03 to 1.42) | .02[e] |
| No | Ref | | Ref | |
| Respiratory | | | | |
| Yes | 2.62 (1.58 to 4.35) | < .001[e] | 1.50 (0.99 to 2.24) | .05[e] |
| No | Ref | | Ref | |
| SMN | | | | |
| Yes | [g] | | 1.05 (0.86 to 1.28) | .64 |
| No | [g] | | Ref | |
| Other chronic conditions | | | | |
| Yes | 1.33 (1.08 to 1.65) | .007[e] | 1.33 (1.17 to 1.51) | < .001[e] |
| No | Ref | | | |
| Smoking status[f] | | | | |
| Current | 1.50 (1.23 to 1.82) | < .001[e] | 1.44 (1.28 to 1.61) | < .001[e] |
| Former | 0.98 (0.76 to 1.30) | .92 | 1.06 (0.92 to 1.26) | .43 |
| Never | Ref | | | |
| Sedentary behavior | | | | |
| Current | 1.98 (1.54 to 2.54) | < .001[e] | 2.48 (2.24 to 2.75) | < .001[e] |
| Former | 1.47 (1.24 to 1.76) | < .001 | 1.63 (1.41 to 1.88) | < .001[e] |
| Never | Ref | | | |

(continued on following page)

**TABLE 5.** Associations Between Treatment Exposures, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Prefrailty or Frailty Among Survivors (continued)

| | Frailty (n = 681)[a] | | Prefrailty (n = 1,953)[b] | |
|---|---|---|---|---|
| **Factors** | **Adjusted PRR[c] (95% CI)** | ***P*** | **Adjusted PRR[d] (95% CI)** | ***P*** |
| Obesity (BMI ≥ 30 kg/m$^2$) | | | | |
| Current | 1.47 (1.23 to 1.76) | < .001[e] | 1.47 (1.33 to 1.63) | < .001[e] |
| Former | 1.24 (0.81 to 1.88) | .32 | 1.21 (0.94 to 1.57) | .15 |
| Never | Ref | | | |

Abbreviations: BMI, body mass index; PRR, prevalence rate ratio; Ref, reference; SMN, second malignant neoplasm.

[a]Frailty ≥ 3 components.

[b]Prefrailty ≥ 2 components.

[c]The model includes all treatment exposures, grade 3-4 chronic conditions, and lifestyle factors that were associated with frailty (significant in Tables 2-Tables 4).

[d]The model includes all treatment exposures, grade 3-4 chronic conditions, and lifestyle factors that were associated with prefrailty (significant in Tables 2-Tables 4).

[e]Indicates estimates with a false discovery rate < 10.

[f]Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

[g]Variable is not included in the current model.

abdominal/pelvic radiation and frailty.[3] Importantly, magnitudes of treatment exposure–frailty associations identified in preliminary models were attenuated when organ-specific grade 3-4 chronic conditions and lifestyle factors were added, indicating that burden of chronic disease in this population has a significant impact on physiologic well-being and function. Both the prevalence and duration of cardiac, neurologic, respiratory, musculoskeletal, and endocrine conditions and a history/presence of an SMN were associated with frailty. These data suggest that interventions to prevent, delay onset, or remediate chronic disease are needed to preserve function in survivors, given their early exposure to cancer treatments that appear to accelerate the aging process.

The prevalence of frailty among childhood cancer survivors in our study, where frailty was self-reported, was 7.7% for females and 4.9% for males, compared with rates (13.1% and 2.7%) reported in the St Jude Lifetime Cohort, where frailty was assessed clinically,[3] and in the general population (females, 9.6%; males, 5.2%) age ≥ 65 years.[25] The presence of frailty in young adult survivors of childhood cancer is concerning, as this aging phenotype is associated with early onset of chronic disease,[26-28] frequent hospital admissions, and early mortality.[3,9,29,30] Frailty interferes with usual daily activities and negatively affects quality of life.[31] Screening survivors for frailty and providing interventions to address excessive fatigue, low levels of activity, unexpected weight loss, weakness, or difficulty walking short distances may prevent or delay onset of undesirable health outcomes typically associated with aging.

Our findings expand on previous data by quantifying doses of abdominal (> 40 Gy) or pelvic (≥ 34 Gy) radiation that confer greatest risk for frailty. Our results also support previous studies that identified cranial radiation and abdominal or pelvic radiation as risk factors for frailty.[3] Radiation exposures to these sites are associated with endocrine dysfunction[32-34] and have known associations with reduced pituitary[3] and gonadal hormone production.[35-37] Because accounting for the presence of grade 3-4 chronic conditions explained some but not all the associations between radiation exposure and frailty, it is possible that frailty is an early sign of impending clinical disease. In fact, untreated abnormal growth hormone,[38] testosterone,[39,40] and estrogen[41] levels are associated with self-reported fatigue, limited muscular growth and repair, and insufficient energy for participation in regular physical activity, all of which are hallmarks of frailty.

The discovery of an association between platinum exposure and frailty in initial analytic models is unique but was completely explained by grade 3-4 chronic conditions and lifestyle factors. Platinum agents have well-known toxicity profiles[42] that likely cause early onset of irreversible chronic conditions, leaving exposed survivors with permanent organ system dysfunction, increasing their vulnerability to functional loss. For example, nephrotoxicity,[43,44] hearing loss,[45,46] vestibular dysfunction,[47] and peripheral neuropathy[48,49] are all common effects of platinum exposure and are associated with loss of physical function, sarcopenia, and frailty in other patient populations.[50-52] Interestingly, sarcoma survivors exposed to either cisplatin or carboplatin, even when renal function is normal, demonstrate lower levels of serum magnesium,[53,54] a finding suggestive of malnutrition and associated with low lean muscle mass and fatigue.[55,56]

Both lung surgery and amputation were associated with frailty in our study. Structural damage to the lungs or loss of an extremity early in life are acutely associated with respiratory function and with mobility.[57-60] Previous data from the CCSS and other survivor cohorts indicate that adequate pulmonary function and musculoskeletal integrity are

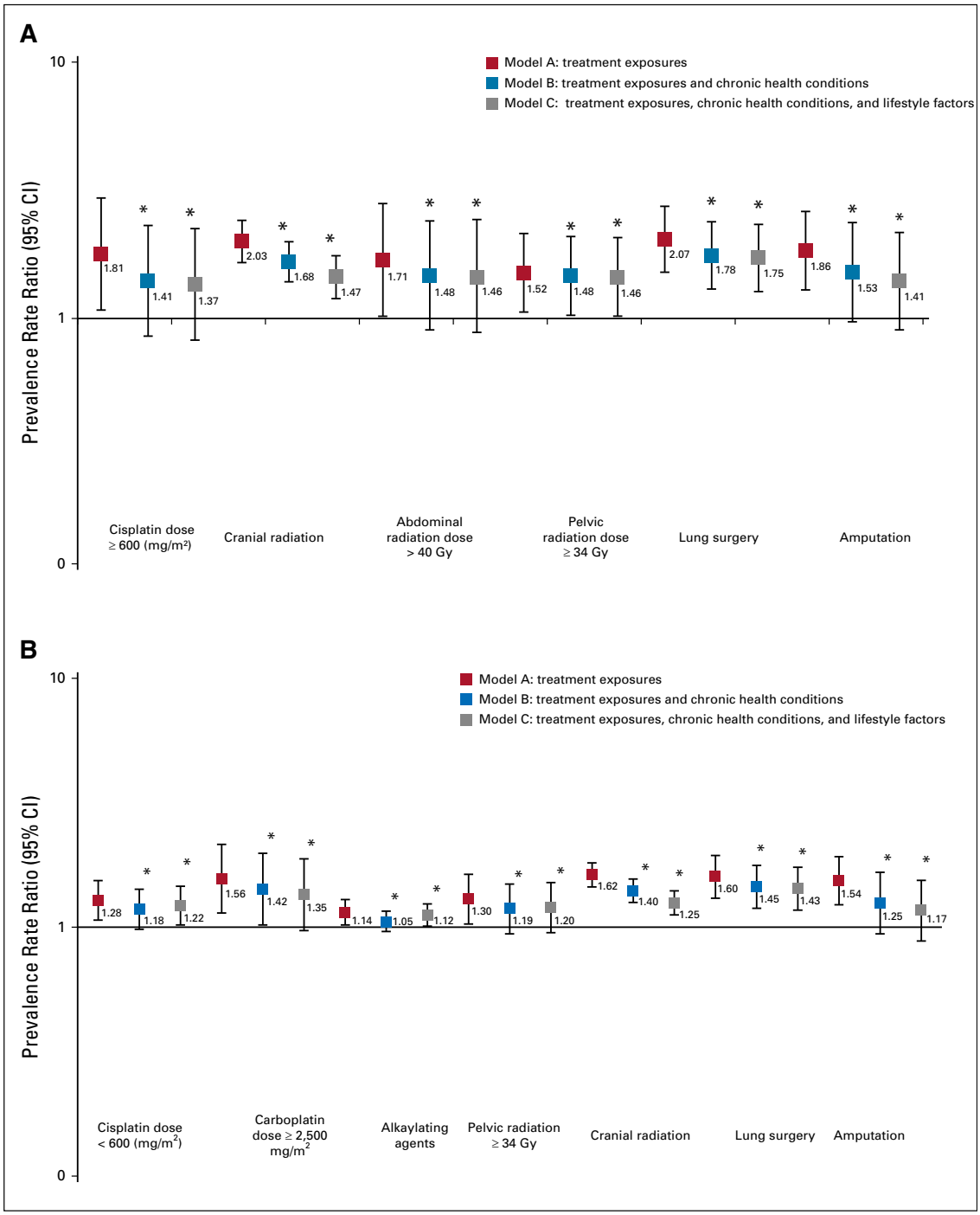


**FIG 1.** (A) Associations between treatment exposures and frailty (model A), adjusted for grade 3-4 chronic health conditions (model B), and lifestyle (model C). Models adjusted for sex, race/ethnicity, age at diagnosis, and age at assessment. Model A includes treatment exposures. Model B includes treatment exposures (significant in model A) and cardiac, neurologic, respiratory, musculoskeletal, endocrine, and all other chronic conditions. Model C includes treatment exposures, chronic conditions from model B, and smoking, obesity, and sedentary behavior. Appendix Table A6 (online only) includes data on model fit. (B) Associations between treatment exposures and prefrailty (Model A), adjusted for grade 3-4 chronic health conditions (Model B), and lifestyle (Model C). Models adjusted for sex, race/ethnicity, age at diagnosis, and age at assessment. Model A includes treatment exposures. Model B includes treatment exposures (significant in model A) and cardiac, neurologic, respiratory, musculoskeletal, endocrine, and all other chronic conditions. Model C includes treatment exposures, chronic conditions from model B, and smoking, obesity, and sedentary behavior. Appendix Table A7 (online only) includes data on model fit. (*) The difference between the model and model A (with treatment exposures only) was significant; $P$ value $< .05$.

necessary for daily activity and mobility.[60-65] Over time, associated physical inactivity likely compounds initial impairments,[62] contributing to development and progression of frailty with age.[66] In studies of older adults, both respiratory and mobility impairments are associated with frailty.[9,16,67]

As in other adult populations,[68-71] sedentary lifestyle was associated with prefrailty and frailty in childhood cancer survivors. In addition, smoking and obesity were associated with frailty. However, adding lifestyle factors to evaluation of the association between treatment and frailty when chronic conditions were accounted for did not appreciably change estimates of the association between treatment and frailty. The influence of chronic conditions on development of frailty is substantial, even in the context of modifiable health behaviors, which likely contributed to the development of chronic disease. Lifestyle modification can prevent onset of many chronic diseases.[72-74] Well-designed interventions that target physical activity, smoking cessation, and weight control, specifically designed for survivors whose therapy exposures are unalterable and increase vulnerability to disease, are needed. Siblings may also benefit from interventions that promote a healthy lifestyle, particularly as they are more likely than survivors to adopt unhealthy behaviors.

Although our study uniquely characterizes and provides new data about risk factors for frailty among a large childhood cancer survivor cohort, there are potential limitations. First, not all eligible survivors participated; our prevalence estimates may be inflated or deflated if frail health is associated with participation. Second, data are self-reported, subject to reporting and recall bias, even though our results align with estimates from the St Jude Lifetime Cohort, where frailty ascertainment is based on clinical measures.[3] Third, survival bias is possible; the frailest survivors likely did not live long enough to participate. However, a sensitivity analysis, classifying participants who died after baseline survey completion and before follow-up 5 as frail did not change our conclusions (Appendix Tables A13-Tables A16, online only). Fourth, therapies for many childhood cancers have evolved over time; our results may not be directly generalizable to more recently treated populations. However, traditional chemotherapeutics and radiotherapy continue to be the backbone of cancer treatment of most childhood malignancies.[75,76] Finally, as the prevalence of frailty among siblings was low, we were unable to evaluate risk factors for this outcome among siblings.

In conclusion, childhood cancer survivors reported a higher prevalence of frailty compared with siblings, suggesting that specific cancer therapies place survivors at early risk for development of an aging phenotype. Those associations are mediated partially by chronic disease, physical activity, smoking, and obesity. Our results suggest that interventions designed to delay onset or remediate chronic disease and/or that promote healthy lifestyle choices are needed to prevent development of frailty in childhood cancer survivors, where early onset of chronic conditions shortens life expectancy.


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## SUPPORT

Support was provided to St Jude Children's Research Hospital by the National Cancer Institute Cancer Center Support (CORE) Grant No. CA55727 (G.T.A., principal investigator) and Grant No. CA21765 (C. Roberts, principal investigator), and the American Lebanese Syrian Associated Charities.



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01226.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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**Consulting or Advisory Role:** Oncology Research Information Exchange Network, Princess Máxima Center, SurvivorLink

**Kevin R. Krull**
**Patents, Royalties, Other Intellectual Property:** Royalties from Wolters Kluwer

No other potential conflicts of interest were reported.

## APPENDIX

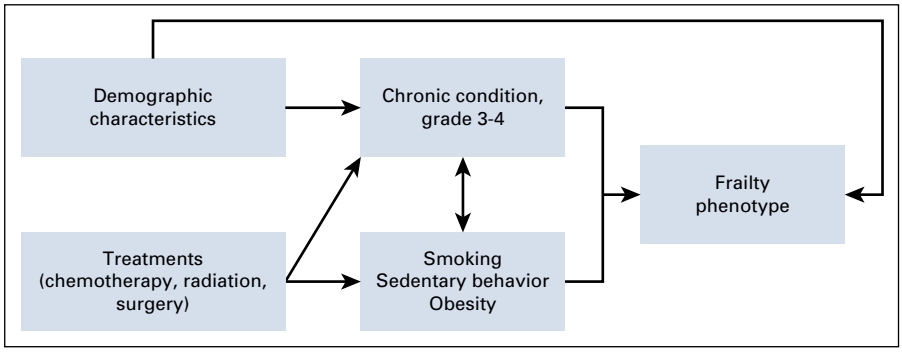


**FIG A1.** Hypothesized model.

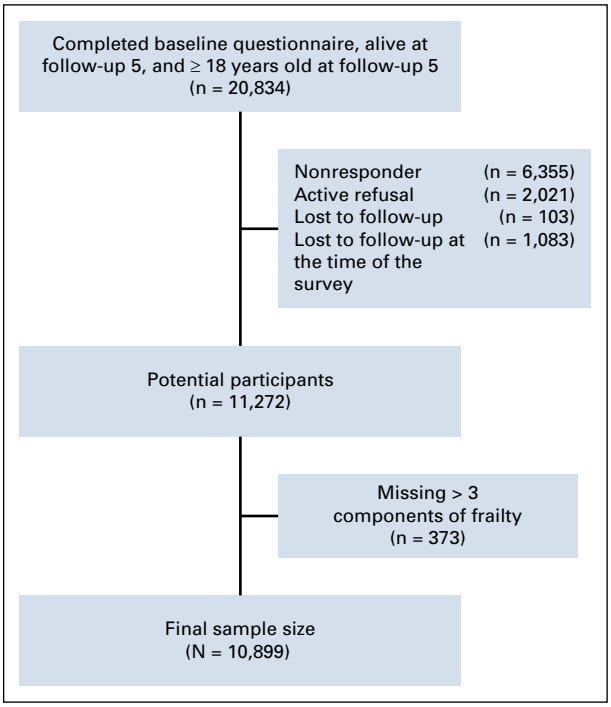


**FIG A2.** Selection of study participants from Childhood Cancer Survivors Study: survivors.

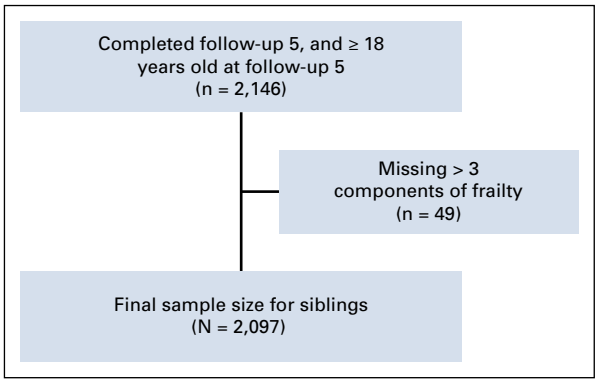


**FIG A3.** Selection of study participants from Childhood Cancer Survivors Study: siblings.

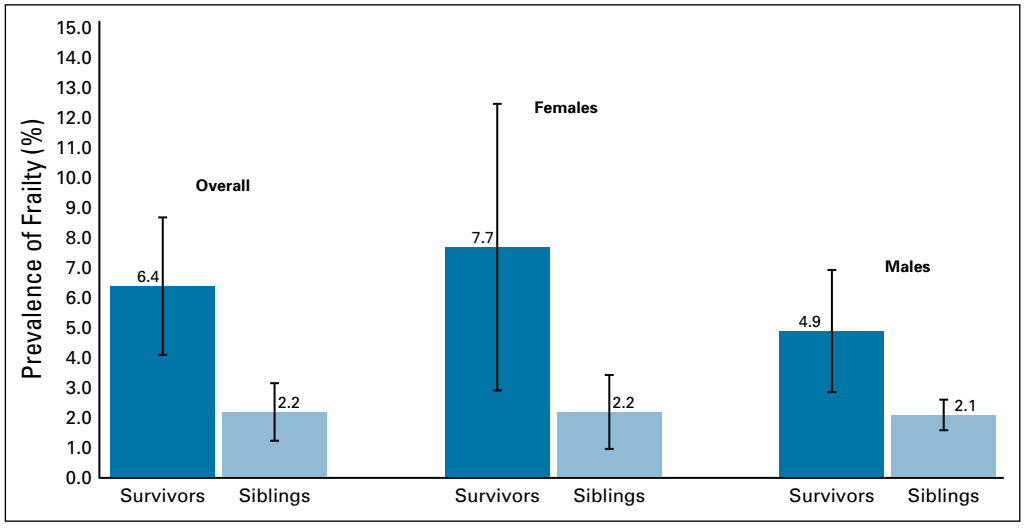


**FIG A4.** Age-adjusted prevalence of frailty by sex. Weighted percentages and 95% CIs are presented. Frailty ≥ 3 components.

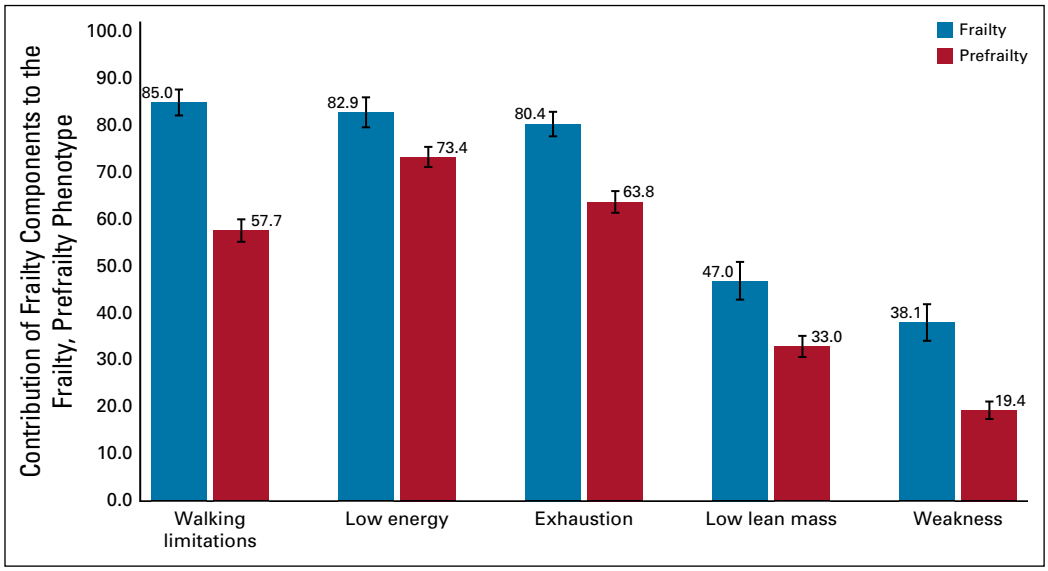


**FIG A5.** Contribution of frailty components to the frailty and prefrailty phenotypes. Weighted percentages and 95% CIs are presented. Frailty ≥ 3 components; prefrailty ≥ 2 components.

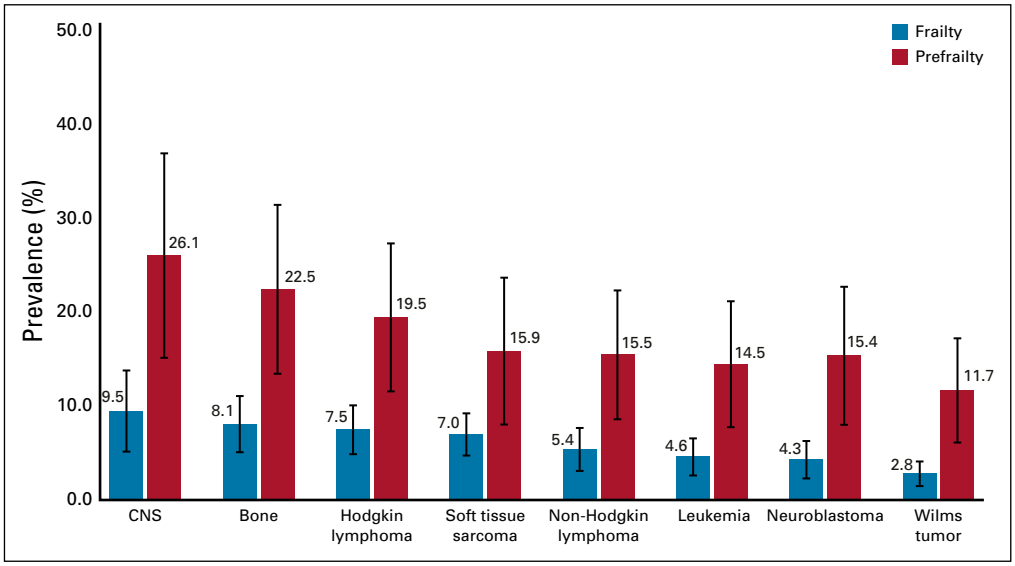


**FIG A6.** Age-adjusted prevalence of frailty and prefrailty among childhood cancer survivors by primary diagnosis. Weighted percentages and 95% CIs are presented. Frailty ≥ 3 components; prefrailty ≥ 2 components.

**TABLE A1.** Associations Between Treatment Exposures and Grade 3-4 Chronic Health Conditions

| Treatment Exposures | Any Chronic Condition | Cardiac Conditions | SMN Conditions | Neurological Conditions | Musculoskeletal Conditions | Endocrine Conditions | Renal Conditions | Respiratory Conditions | All Other Chronic Conditions |
|---|---|---|---|---|---|---|---|---|---|
| Chest radiation | | | | | | | | | |
| Yes | 1.05 (0.94 to 1.12) | 1.43*† (1.10 to 1.87) | 1.81*† (1.37 to 2.40) | 1.20 (0.85 to 1.68) | 0.53*† (0.36 to 0.80) | 1.76*† (1.42 to 2.19) | 0.46 (0.22 to 0.94) | 1.65 (0.57 to 4.78) | 0.68*† (0.55 to 0.84) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Cranial radiation | | | | | | | | | |
| Yes | 1.82*† (1.66 to 1.97) | 2.20*† (1.78 to 2.71) | 2.10*† (1.64 to 2.67) | 2.20*† (1.80 to 1.68) | 0.70*† (0.50 to 0.97) | 1.40*† (1.14 to 1.71) | 1.08 (0.62 to 1.90) | 0.66 (0.17 to 2.50) | 2.90*† (2.54 to 3.31) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Abdominal radiation, maximum dose, Gy | | | | | | | | | |
| < 20 | 0.91 (0.75 to 1.10) | 0.80 (0.51 to 1.25) | 1.04 (0.74 to 1.38) | 0.57 (0.32 to 1.02) | 0.42*† (0.17 to 0.99) | 0.90 (0.62 to 1.27) | 2.94* (1.14 to 7.57) | 0.20 (0.01 to 2.47) | 1.10 (0.78 to 1.45) |
| 20-40 | 1.07 (0.91 to 1.23) | 0.98 (0.67 to 1.44) | 0.90 (0.62 to 1.33) | 1.23 (0.76 to 1.99) | 0.22*† (0.09 to 0.53) | 1.25 (0.93 to 1.66) | 1.24 (0.41 to 3.73) | 0.71 (0.12 to 4.10) | 1.25 (0.94 to 1.66) |
| > 40 | 1.25 (0.99 to 1.62) | 1.29 (0.75 to 2.24) | 1.12 (0.64 to 1.98) | 1.85 (0.97 to 3.51) | 0.25 (0.06 to 1.05) | 1.20 (0.75 to 1.93) | 2.10 (0.43 to 10.07) | 4.09 (0.44 to 35.31) | 1.55*† (1.03 to 2.35) |
| None | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Pelvic radiation, maximum dose, Gy | | | | | | | | | |
| < 34 | 1.18*† (1.00 to 1.41) | 0.94 (0.63 to 1.39) | 1.17 (0.78 to 1.75) | 0.82 (0.50 to 1.33) | 3.38*† (1.61 to 7.13) | 1.63*† (1.22 to 2.17) | 0.99 (0.39 to 2.55) | 1.69 (0.30 to 10.2) | 1.24 (0.95 to 1.63) |
| ≥ 34 | 1.17 (0.98 to 1.39) | 1.19 (0.81 to 1.75) | 1.17 (0.76 to 1.74) | 1.19 (0.73 to 1.92) | 2.18*† (1.33 to 3.5) | 1.13 (0.83 to 1.55) | 1.19 (0.40 to 3.53) | NA | 1.22 (0.92 to 62) |
| None | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Cisplatin dose, mg/m$^2$ | | | | | | | | | |
| < 600 | 1.48*† (1.30 to 1.68) | 1.50*† (1.08 to 2.06) | 1.10 (0.71 to 1.72) | 1.26 (0.90 to 1.76) | 1.29*† (1.00 to 1.67) | 0.94 (0.66 to 1.35) | 1.18 (0.53 to 2.65) | NA | 1.64*† (1.34 to 1.99) |
| ≥ 600 | 1.57*† (1.25 to 1.98) | 2.54*† (1.58 to 4.10) | 0.80 (0.30 to 2.17) | 1.92‡ (1.15 to 3.20) | 1.32 (0.87 to 1.99) | 1.02 (0.53 to 2.00) | 1.32 (0.32 to 5.55) | NA | 1.80*† (1.27 to 2.53) |
| None | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Carboplatin dose, mg/m$^2$ | | | | | | | | | |
| < 2,500 | 1.10 (0.83 to 1.44) | 1.26 (0.68 to 2.34) | 1.10 (0.43 to 2.69) | 1.16 (0.70 to 2.03) | 0.96 (0.42 to 2.18) | 0.95 (0.44 to 2.04) | 0.73* (0.09 to 5.48) | NA | 1.03 (0.73 to 1.48) |
| ≥ 2,500 | 1.83*† (1.45 to 2.30) | 1.32 (0.67 to 2.60) | 0.57 (0.14 to 2.35) | 1.21 (0.69 to 2.14) | 1.35 (0.75 to 2.42) | 0.93 (0.38 to 2.26 ) | NA | NA | 2.10*† (1.57 to 2.78) |
| None | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Methotrexate | | | | | | | | | |
| Yes | 0.91*† (0.82 to 1.00) | 0.87* (0.61 to 1.00) | 0.95 (0.72 to 1.25) | 0.83 (0.62 to 1.10) | 1.39*† (1.11 to 1.74) | 0.80 (0.63 to 0.99) | 1.27 (0.74 to 2.23) | 0.44 (0.13 to 1.59) | 0.63*† (0.52 to 0.75) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Alkylating agents | | | | | | | | | |
| Yes | 1.19*† (1.08 to 1.29) | 1.10 (0.88 to 1.36) | 1.17 (0.92 to 1.48) | 1.28*† (1.01 to 1.62) | 1.15 (0.92 to 1.42) | 1.50*† (1.24 to 1.83) | 1.55 (0.88 to 2.71) | 1.30 (0.46 to 3.60) | 1.19*† (1.03 to 1.38) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| 6-mercaptopurine | | | | | | | | | |
| Yes | 0.60*† (0.52 to 0.66) | 0.63*† (0.47 to 0.85) | 0.72 (0.52 to 1.00) | 0.66 (0.47 to 0.92) | 0.53*† (0.36 to 0.77) | 0.77 (0.60 to 1.00) | 0.36* (0.17 to 0.74) | 0.80 (0.14 to 4.30) | 0.53*† (0.43 to 0.66) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| 6-thiogauine | | | | | | | | | |
| Yes | 0.92 (0.80 to 1.05) | 1.27 (0.94 to 1.73) | 0.72 (0.47 to 1.09) | 1.47 (1.06 to 2.04) | 0.82 (0.54 to 1.24) | 1.00 (0.74 to 1.34) | 0.78 (0.38 to 1.62) | 0.80 (0.16 to 3.54) | 0.96 (0.76 to 1.21) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Vinca alkaloids | | | | | | | | | |
| Yes | 0.86*† (0.89 to 0.97) | 0.87 (0.71 to 1.10) | 1.06 (0.82 to 1.36) | 0.65*† (0.52 to 0.81) | 0.65*† (0.53 to 0.80) | 0.77 (0.63 to 0.94) | 1.27 (0.72 to 2.29) | 0.60 (0.20 to 1.74) | 1.02 (0.88 to 1.17) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |

(continued on following page)

**TABLE A1.** Associations Between Treatment Exposures and Grade 3-4 Chronic Health Conditions (continued)

| Treatment Exposures | Any Chronic Condition | Cardiac Conditions | SMN Conditions | Neurological Conditions | Musculoskeletal Conditions | Endocrine Conditions | Renal Conditions | Respiratory Conditions | All Other Chronic Conditions |
|---|---|---|---|---|---|---|---|---|---|
| Anthracycline | | | | | | | | | |
| Yes | 1.03 (0.94 to 1.12) | 1.39*† (1.11 to 1.73) | 0.95 (0.75 to 1.21) | 0.55*† (0.44 to 0.71) | 1.66*† (1.26 to 2.20) | 1.17 (0.96 to 1.42) | 1.37 (0.80 to 2.37) | 3.60* (1.11 to 11.50) | 0.76*† (0.66 to 0.88) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Amputation | | | | | | | | | |
| Yes | 2.61*† (2.3 to 3.04) | 1.56*† (1.06 to 2.29) | 1.22 (0.80 to 1.96) | 0.45 (0.18 to 1.12) | 9.60*† (7.53 to 12.18) | 0.70 (0.43 to 1.14) | 0.58 (0.16 to 2.06) | NA | 1.13 (0.80 to 1.60) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Lung surgery | | | | | | | | | |
| Yes | 1.25*† (1.07 to 1.44) | 1.84*† (1.35 to 2.51) | 1.60*† (1.11 to 2.30) | 1.16 (0.68 to 1.98) | 1.20 (0.95 to 1.52) | 1.46*† (1.08 to 1.97) | 0.50 (0.12 to 2.04) | 5.87*† (2.10 to 46.46) | 1.56*† (1.18 to 2.06) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Spleen removal | | | | | | | | | |
| Yes | 1.41*† (1.22 to 1.63) | 1.84*† (1.35 to 2.51) | 2.01*† (1.48 to 2.72) | 0.44*† (0.24 to 0.83) | 0.45*† (0.22 to 0.94) | 1.99*† (1.57 to 2.51) | 0.50 (0.12 to 2.04) | 1.80 (0.46 to 6.92) | 1.30 (0.99 to 1.71) |
| No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |

NOTE. Nine separate regression models were used to estimate PRR (95% CI). All models were adjusted for sex, age at diagnosis, age at assessment, and race.

Abbreviations: NA, number of participants is not available for the specific category; PRR, prevalence rate ratio; Ref, reference.

*$P$ value $< .05$; the effect of the treatment on the outcome was statistically significant.

†Indicates estimates with a false discovery rate $< 10$.

**TABLE A2.** Associations Between Treatment Exposures and Lifestyle Factors

| Treatment Exposures | Smoking (current *v* never) | Smoking (past *v* never) | Obesity (current *v* never) | Obesity (past *v* never) | Sedentary (current *v* never) | Sedentary (current *v* never) |
|---|---|---|---|---|---|---|
| Chest radiation | | | | | | |
| Yes | 0.80* (0.67 to 0.97) | 0.90 (0.74 to 1.08) | 0.95 (0.80 to 1.12) | 0.80 (0.53 to 1.21) | 1.08 (0.90 to 1.30) | 1.05 (0.86 to 1.29) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Cranial radiation | | | | | | |
| Yes | 0.83*† (0.73 to 0.94) | 0.60*† (0.50 to 0.70) | 1.86*† (1.66 to 2.08) | 1.55*† (1.12 to 2.13) | 1.42*† (1.26 to 1.60) | 1.33*† (1.13 to 1.55) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Abdominal radiation, maximum dose, Gy | | | | | | |
| < 20 | 1.20 (0.90 to 1.60) | 0.96 (0.70 to 1.32) | 0.78 (0.59 to 1.03) | 1.60 (0.87 to 2.94) | 0.72*† (0.54 to 0.97) | 0.87 (0.63 to 1.21) |
| 20-40 | 0.98 (0.75 to 1.30) | 1.06 (0.87 to 1.29) | 0.82 (0.64 to 1.06) | 1.33 (0.78 to 2.27) | 1.05 (0.80 to 1.37) | 1.11 (0.84 to 1.47) |
| > 40 | 0.80 (0.42 to 1.20) | 0.89 (0.54 to 1.43) | 0.62 (0.37 to 1.03) | 3.11*† (1.40 to 6.91) | 1.08 (0.69 to 1.67) | 1.10 (0.70 to 1.82) |
| None | Ref | Ref | Ref | Ref | Ref | Ref |
| Pelvic radiation, maximum dose, Gy | | | | | | |
| < 34 | 1.07 (0.82 to 1.41) | 1.13 (0.85 to 1.52) | 0.75* (0.58 to 1.00) | 0.90 (0.52 to 1.54) | 1.23 (0.94 to 1.62) | 0.91 (0.67 to 1.22) |
| ≥ 34 | 1.03 (0.76 to 1.40) | 0.90 (0.65 to 1.21) | 0.70* (0.52 to 0.92) | 0.47* (0.24 to 0.93) | 1.34*† (1.04 to 1.80) | 0.93 (0.76 to 1.14) |
| None | Ref | Ref | Ref | Ref | Ref | Ref |
| Cisplatin dose, mg/m$^2$ | | | | | | |
| < 600 | 0.87 (0.67 to 1.11) | 0.96 (0.72 to 1.28) | 0.78 (0.61 to 1.00) | 0.74 (0.30 to 1.87) | 1.14 (0.91 to 1.42) | 1.13 (0.80 to 1.61) |
| ≥ 600 | 1.02 (0.65 to 1.60) | 0.53 (0.27 to 1.04) | 0.73 (0.30 to 1.87) | NA | 1.85*† (1.25 to 2.73) | 1.38 (0.77 to 2.50) |
| None | Ref | Ref | Ref | Ref | Ref | Ref |
| Carboplatin dose, mg/m$^2$ | | | | | | |
| < 2,500 | 1.04 (0.64 to 1.68) | 0.54 (0.23 to 1.25) | 1.37 (0.85 to 2.20) | NA | 1.45 (0.97 to 2.17) | NA |
| ≥ 2,500 | 1.10 (0.70 to 1.73) | 0.87 (0.46 to 1.66) | 1.37 (0.90 to 2.10) | NA | 1.32 (0.88 to 1.97) | 0.26 (0.04 to 1.93) |
| None | Ref | Ref | Ref | Ref | Ref | Ref |
| Methotrexate | | | | | | |
| Yes | 0.92 (0.78 to 1.08) | 0.91 (0.76 to 1.08) | 1.06 (0.92 to 1.22) | 1.45* (1.00 to 1.46) | 1.10 (0.95 to 1.30) | 0.97 (0.80 to 1.17) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Alkylating agents | | | | | | |
| Yes | 0.88 (0.78 to 1.00) | 1.00 (0.87 to 1.16) | 0.93 (0.834 to 1.04) | 0.93 (0.67 to 1.29) | 0.92 (0.81 to 1.03) | 1.08 (0.93 to 1.27) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| 6-mercaptopurine | | | | | | |
| Yes | 1.30*† (1.09 to 1.53) | 1.18 (0.97 to 1.43) | 1.08 (0.92 to 1.26) | 0.73 (0.48 to 1.13) | 1.08 (0.99 to 1.17) | 1.03 (0.93 to 1.15) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |

(continued on following page)

**TABLE A2.** Associations Between Treatment Exposures and Lifestyle Factors (continued)

| Treatment Exposures | Smoking (current *v* never) | Smoking (past *v* never) | Obesity (current *v* never) | Obesity (past *v* never) | Sedentary (current *v* never) | Sedentary (current *v* never) |
|---|---|---|---|---|---|---|
| 6-thiogauine | | | | | | |
| Yes | 0.82*† (0.69 to 0.98) | 0.86 (0.69 to 1.06) | 0.77*† (0.65 to 0.92) | 0.98 (0.56 to 1.69) | 0.85 (0.72 to 1.03) | 0.93 (0.71 to 1.20) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Vinca alkaloids | | | | | | |
| Yes | 0.84 (0.73 to 0.96) | 0.93 (0.80 to 1.04) | 0.90 (0.80 to 1.01) | 0.92 (0.65 to 1.30) | 0.88 (0.77 to 1.01) | 1.05 (0.88 to 1.24) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Anthracycline | | | | | | |
| Yes | 1.23*† (1.08 to 1.39) | 1.03 (0.90 to 1.20) | 0.97 (0.60 to 1.70) | 0.66*† (0.46 to 0.92) | 0.91 (0.80 to 1.03) | 0.77*† (0.66 to 0.90) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Amputation | | | | | | |
| Yes | 1.22 (0.92 to 1.62) | 1.08 (0.92 to 1.62) | 0.92 (0.70 to 1.20) | 0.90 (0.44 to 1.78) | 1.62*† (1.23 to 2.13) | 1.83*† (1.35 to 2.48) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Lung surgery | | | | | | |
| Yes | 1.03 (0.78 to 1.37) | 1.08 (0.81 to 1.45) | 0.77 (0.60 to 1.01) | 0.85 (0.42 to 1.70) | 1.16 (0.90 to 1.51) | 1.13 (0.82 to 1.54) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |
| Spleen removal | | | | | | |
| Yes | 0.82 (0.63 to 1.07) | 1.05 (0.83 to 1.33) | 0.90 (0.72 to 1.14) | 1.44 (0.90 to 2.31) | 0.66*† (0.52 to 0.86) | 1.06 (0.83 to 1.35) |
| No | Ref | Ref | Ref | Ref | Ref | Ref |

NOTE. Data presented as odds ratio (95% CI). Three different multinomial regression models were carried out to estimate the odds ratio (95% CI) and all the models were adjusted for sex, age at diagnosis, age at assessment, and race.

Abbreviations: NA, number of participants is not available for the specific category; Ref, reference.

*$P$-value $< 0.05$; the effect of the treatment on the outcome was statistically significant.

†Indicates estimates with a false discovery rate $< 10$.

**TABLE A3.** Characteristics of Participants and Nonparticipants

| Characteristics | Participants (N = 10,899) | Nonparticipants (n = 9,935) | *P* |
|---|---|---|---|
| Mean age at diagnosis, years (SD) | 8.05 (6.0) | 7.00 (5.7) | < .001 |
| Sex | | | < .001 |
| Female | 5,709 (52.3) | 4,142 (41.5) | |
| Male | 5,190 (47.7) | 5,793 (58.5) | |
| Race/ethnicity | | | < .001 |
| Non-Hispanic white | 9,401 (85.7) | 7,544 (74.6) | |
| Non-Hispanic black | 452 (4.3) | 828 (8.4) | |
| Hispanic | 661 (6.3) | 915 (10.2) | |
| Other* | 385 (3.7) | 648 (7.0) | |
| Site at primary diagnosis | | | < .001 |
| Leukemia | 3,276 (38.7) | 3,202 (42.0) | |
| Hodgkin lymphoma | 1,338 (10.8) | 938 (8.1) | |
| Non-Hodgkin lymphoma | 904 (7.3) | 881 (7.6) | |
| CNS | 1,905 (15.3) | 1,626 (14.0) | |
| Neuroblastoma | 790 (6.4) | 880 (7.6) | |
| Wilms tumor | 1,018 (8.2) | 997 (8.6) | |
| Soft tissue sarcoma | 740 (6.0) | 696 (6.0) | |
| Bone tumor | 928 (7.5) | 715 (6.20 | |

NOTE. Data shown as No. (%) unless otherwise noted. Unweighted frequencies and weighted % are presented.
Abbreviation: SD, standard deviation.
*Other: includes Asian and not-specified race.

**TABLE A4.** Frailty Phenotype Among Cancer Survivors and Siblings by Sex and Age Group (N = 12,996)

| | Females Age (years; n = 6,923) | | | | | | Males Age (years; n = 6,073) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phenotype** | **18-29** | **30-39** | **40-49** | **≥ 50** | ***P* for Trend*** | **Overall** | **18-29** | **30-39** | **40-49** | **≥ 50** | ***P* for Trend*** | |
| Cancer survivors | | | | | | | | | | | | |
| No. of participants | 5,709 | 1,128 | 2,224 | 1,590 | 767 | | 5,190 | 992 | 1,982 | 1,570 | 646 | |
| Low lean mass | 10.1 (9.2 to 10.9) | 10.4 (8.4 to 12.4) | 9.7 (8.3 to 11.0) | 9.4 (8.0 to 10.8) | 12.0 (9.7 to 14.3) | .92 | 9.6 (8.7 to 10.5) | 9.7 (7.5 to 11.9) | 9.4 (7.9 to 10.9) | 8.8 (7.4 to 10.2) | 11.8 (9.3 to 14.3) | .61 |
| Low energy expenditure | 26.4 (25.2 to 27.7) | 22.3 (19.5 to 25.1) | 24.5 (22.5 to 26.5) | 31.7 (29.4 to 33.9) | 30.6 (27.4 to 33.9) | < .001 | 25.2 (23.9 to 26.5) | 24.5 (21.3 to 27.7) | 24.1 (22.0 to 26.2) | 26.9 (24.7 to 29.1) | 26.8 (23.4 to 30.2) | .24 |
| Exhaustion | 21.5 (20.3 to 22.7) | 19.3 (16.5 to 22.7) | 21.3 (19.4 to 23.2) | 23.2 (21.1 to 25.3) | 23.1 (20.2 to 26.1) | .009 | 13.5 (12.4 to 14.5) | 10.3 (8.0 to 12.5) | 15.1 (13.3 to 16.8) | 13.8 (12.1 to 15.5) | 14.0 (11.3 to 16.7) | .10 |
| Weakness | 4.5 (4.0 to 5.0) | 2.6 (1.8 to 3.4) | 5.0 (4.0 to 6.0) | 5.5 (4.4 to 6.6) | 4.6 (3.1 to 6.1) | .20 | 3.7 (3.2 to 4.3) | 3.2 (2.0 to 4.4) | 3.4 (2.5 to 4.3) | 4.0 (3.1 to 5.0) | 5.2 (3.4 to 6.9) | .16 |
| Slow walking | 14.9 (14.0 to 15.9) | 8.7 (6.9 to 10.4) | 13.4 (11.9 to 15.0) | 19.3 (17.3 to 21.2) | 24.0 (21.0 to 27.0) | < .001 | 10.3 (9.5 to 11.2) | 7.4 (5.5 to 9.3) | 9.2 (7.9 to 10.6) | 11.8 (10.2 to 13.4) | 17.2 (14.3 to 20.1) | < .001 |
| Prefrail† | 19.7 (18.6 to 20.8) | 13.6 (11.4 to 15.8) | 19.2 (17.4 to 21.0) | 23.7 (21.6 to 25.8) | 26.0 (22.8 to 29.0) | < .001 | 14.2 (13.2 to 15.2) | 11.9 (9.6 to 14.2) | 13.9 (12.4 to 15.6) | 15.1 (13.3 to 16.9) | 18.0 (15.0 to 20.9) | .006 |
| Frail‡ | 6.9 (6.2 to 7.5) | 3.9 (2.8 to 5.0) | 6.0 (4.9 to 7.1) | 9.3 (7.9 to 10.8) | 10.6 (8.4 to 12.7) | < .001 | 4.7 (4.1 to 5.4) | 3.5 (2.2 to 4.8) | 4.9 (3.9 to 5.9) | 4.7 (3.7 to 5.7) | 7.0 (5.0 to 8.9) | .003 |
| Sibling comparison group | | | | | | | | | | | | |
| No. of participants | 1,214 | 94 | 348 | 429 | 343 | | 883 | 67 | 262 | 296 | 258 | |
| Low lean muscle mass | 4.9 (3.7 to 6.1) | 6.4 (1.4 to 11.1) | 4.6 (2.6 to 7.0) | 4.7 (2.7 to 6.7) | 4.9 (2.6 to 7.1) | .81 | 4.7 (3.3 to 6.1) | 7.5 (1.2 to 13.8) | 3.7 (1.5 to 5.9) | 4.0 (1.7 to 6.2) | 5.8 (2.9 to 8.7) | .79 |
| Low energy expenditure | 19.9 (17.5 to 21.9) | 11.6 (5.1 to 18.0) | 16.0 (12.1 to 19.7) | 22.1 (18.2 to 26.0) | 22.7 (18.2 to 27.0) | .003 | 21.0 (18.4 to 23.8) | 16.4 (7.5 to 25.3) | 17.2 (12.7 to 21.9) | 20.7 (16.1 to 25.3) | 26.5 (21.2 to 31.9) | .006 |
| Exhaustion | 14.0 (11.9 to 15.8) | 9.6 (3.6 to 15.5) | 15.5 (11.6 to 19.2) | 13.6 (10.2 to 16.6) | 14.0 (10.5 to 17.8) | .79 | 8.9 (7.0 to 10.8) | 11.9 (4.2 to 19.7) | 9.9 (6.3 to 13.5) | 9.1 (5.8 to 12.3) | 7.0 (3.8 to 10.1) | .14 |
| Weakness | 1.4 (0.7 to 2.0) | 1.1 (0 to 3.1) | 1.4 (0.2 to 2.6) | 0.5 (0 to 1.1) | 2.6 (0.9 to 4.3) | .21 | 1.5 (0.7 to 2.6) | 0.0 | 0.4 (0 to 1.1) | 1.7 (0.2 to 3.1) | 2.7 (0.7 to 4.7) | .016 |
| Slow walking | 7.7 (6.1 to 9.1) | 5.3 (0.8 to 9.7) | 4.2 (2.1 to 6.4) | 7.7 (5.1 to 10.2) | 11.6 (8.2 to 14.9) | < .001 | 3.7 (2.5 to 4.9) | 3.0 (0 to 7.1) | 1.2 (0 to 2.4) | 3.4 (1.3 to 5.4) | 6.9 (3.8 to 10.0) | .002 |
| Prefrail† | 10.0 (8.3 to 11.7) | 6.4 (1.4 to 11.3) | 8.1 (5.2 to 10.9) | 9.6 (6.7 to 12.3) | 13.4 (9.8 to 17.0) | .009 | 6.9 (5.2 to 8.6) | 8.9 (2.1 to 15.8) | 3.8 (1.5 to 6.1) | 7.8 (4.7 to 10.8) | 8.5 (5.1 to 11.9) | .17 |
| Frail‡ | 2.1 (1.3 to 2.9) | 1.1 (0 to 3.1) | 1.7 (0.4 to 3.1) | 1.9 (0.6 to 3.1) | 2.9 (1.1 to 4.7) | .19 | 1.8 (0.9 to 2.7) | 0.0 | 0.4 (0 to 1.1) | 1.4 (0.04 to 2.7) | 4.3 (1.8 to 6.7) | .007 |

NOTE. Prevalence of frailty by age group, and weighted (%). Data are presented as % (95% CI).

**P* for trend was estimated by Cochrane-Armitage trend.

†Prefrail: having ≥ 2 components of frailty.

‡Frail: having ≥ 3 components of frailty.

**TABLE A5.** Associations Between Length of Grade 3-4 Chronic Health Conditions and Frailty Among Survivors

| | Frailty (n = 681)* | | Prefrailty (n = 1,953)† | |
|---|---|---|---|---|
| **5-Year Duration of Organ-Specific Chronic Condition** | **Adjusted PRR‡ (95% CI)** | ***P*** | **Adjusted PRR‡ (95% CI)** | ***P*** |
| Cardiac | 1.02 (1.01 to 1.03) | < .001 | 1.01 (1.01 to 1.21) | < .001 |
| Neurologic | 1.05 (1.05 to 1.04) | < .001 | 1.04 (1.03 to 1.04) | < .001 |
| Musculoskeletal | 1.02 (1.01 to 1.03) | < .001 | 1.01 (1.08 to 1.02) | < .001 |
| Endocrine | 1.02 (1.04 to 1.14) | .02 | 1.01 (1.00 to 1.02) | .001 |
| Respiratory | 1.26 (1.14 to 1.38) | .002 | 1.03 (1.01 to 1.04) | .001 |
| Renal | 1.01 (0.98 to 1.04) | .50 | 1.00 (0.98 to 1.02) | .60 |
| Others chronic condition | 1.05 (1.03 to 1.07) | < .001 | 1.02 (1.01 to 1.02) | < .001 |

NOTE. The PRR is presented for 5-year increase in duration.
Abbreviation: PRR, prevalence rate ratio.
*Frailty ≥ 3 components.
†Prefrailty ≥ 2 components.
‡The models were adjusted for sex, race, age at diagnosis and age at assessment.

**TABLE A6.** Assessment of Goodness of Fit for the Associations Between Treatment, Grade 3-4 Chronic Health Conditions, Lifestyle Factors, and Frailty

| **Models** | **Degrees of Freedom*** | $\chi^2$ | **Log-Likelihood** | **AIC** | **BIC** | **−2 Log-Likelihood†** | ***P*‡** |
|---|---|---|---|---|---|---|---|
| Null model§ | 30 | 10427.0951 | −2291.6260 | 4645.2520 | 4868.1652 | — | |
| Model with chronic health conditions‖ | 27 | 10019.0127 | −2222.2335 | 4500.4670 | 4702.1175 | 138.785 | < .01 |
| Model with lifestyle factors¶ | 33 | 8779.9661 | −2035.4406 | 4138.8811 | 4383.0566 | 512.3708 | < .01 |

NOTE. The analysis was adjusted for sex, race/ethnicity, age at diagnosis, and age at assessments.
Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criterion.
*Degrees of freedom are based on number of parameters.
†−2 log-likelood: the difference between the log-likelihood of the null model and the model with chronic conditions, and the model with treatment exposures and lifestyle.
‡*P* value for the −2 log-likelihood. *P* value is for the difference between the distribution of the two models.
§Null model: includes treatment exposures associated with frailty.
‖Model with chronic health conditions: includes treatment exposures and grade 3-4 cardiac, neurologic, respiratory, musculoskeletal, endocrine, renal, and all other conditions.
¶Model with lifestyle factors: includes treatment exposures, cardiac, neurologic, respiratory, musculoskeletal, endocrine, renal, all other chronic conditions, sedentary behavior, obesity, and smoking.

**TABLE A7.** Assessment of Goodness of Fit for the Associations Between Treatment, Grade 3-4 Chronic Health Conditions, and Lifestyle Factors and Prefrailty

| Models | Degrees of Freedom* | $\chi^2$ | Log-Likelihood | AIC | BIC | −2 Log-Likelihood† | *P*‡ |
|---|---|---|---|---|---|---|---|
| Null model§ | 30 | 9383.6931 | −5027.0552 | 10116.11 | 10339.023 | — | — |
| Model with chronic health conditions‖ | 31 | 9059.229 | −4818.14 | 9700.295 | 9930.0153 | 417.8304 | < .01 |
| Model with lifestyle factors¶ | 37 | 8711.82 | −4617.21 | 9310.4174 | 9583.2098 | 819.6904 | < .01 |

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criterion.

*Degrees of freedom are based on number of parameters.

†−2 log-likelood: the difference between the log-likelihood of the null model and the model with chronic conditions, and the model with treatment exposures and lifestyle.

‡*P* value for the −2 log-likelihood. *P* value is for the difference between the distribution of the two models.

§Null model: includes treatment exposures associated with frailty.

‖Model with chronic health conditions: includes treatment exposures and grade 3-4 cardiac, neurologic, respiratory, musculoskeletal, endocrine, renal, and all other conditions.

¶Model with lifestyle factors: includes treatment exposures, cardiac, neurologic, respiratory, musculoskeletal, endocrine, renal, all other chronic conditions, sedentary behavior, obesity, and smoking.

**TABLE A8.** Multinomial Logistic Regression for the Association Between Treatment Exposures and Frailty Among Survivors

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Treatment Exposures** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Chest radiation | | | | |
| Yes | 1.07 (0.87 to 1.34) | .60 | 1.22 (0.91 to 1.68) | .24 |
| No | Ref | | Ref | |
| Cranial radiation | | | | |
| Yes | 1.60 (1.35 to 1.85) | < .001§ | 2.40 (1.94 to 2.96) | < .001§ |
| No | Ref | | Ref | |
| Abdominal radiation dose, Gyll | | | | |
| < 20 | 0.92 (0.64 to 1.32) | .55 | 1.02 (0.62 to 1.66) | .94 |
| 20-40 | 1.01 (0.73 to 1.39) | .88 | 1.30 (0.80 to 1.84) | .26 |
| > 40 | 1.18 (0.70 to 2.02) | .80 | 1.86 (1.04 to 3.33) | .04 |
| None | Ref | | Ref | |
| Pelvic radiation dose, Gyll | | | | |
| < 34 | 1.18 (0.86 to 1.64) | .16 | 0.96 (0.63 to 1.48) | .86 |
| ≥ 34 | 1.12 (0.80 to 1.60) | .36 | 1.77 (1.18 to 2.64) | .006§ |
| None | Ref | | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 1.68 (1.30 to 2.16) | < .001§ | 1.02 (0.70 to 1.45) | .92 |
| ≥ 600 | 1.05 (0.60 to 1.84) | .85 | 2.01 (1.14 to 3.52) | .02 |
| None | Ref | | Ref | |
| Carboplatin dose, mg/m$^2$ | | | | |
| < 2,500 | 0.66 (0.36 to 1.24) | .20 | 1.35 (0.72 to 2.53) | .35 |
| ≥ 2,500 | 1.60 (0.98 to 3.45) | .06 | 1.86 (0.99 to 3.45) | .06 |
| None | Ref | | Ref | |
| Methotrexate | | | | |
| Yes | 0.96 (0.80 to 1.16) | .63 | 0.75 (0.60 to 0.98) | .04§ |
| No | Ref | | Ref | |
| Alkylating agents | | | | |
| Yes | 1.20 (1.02 to 1.40) | .03§ | 1.16 (0.92 to 1.45) | .20 |
| No | Ref | | Ref | |
| 6-mercaptopurine | | | | |
| Yes | 0.93 (0.75 to 1.15) | .56 | 0.82 (0.61 to 1.12) | .31 |
| No | Ref | | Ref | |
| 6-thiogauine | | | | |
| Yes | 0.87 (0.68 to 1.10) | .25 | 1.04 (0.80 to 1.44) | .80 |
| No | Ref | | Ref | |
| Vinca alkaloids | | | | |
| Yes | 0.91 (0.77 to 1.07) | .26 | 0.85 (0.68 to 1.07) | .19 |
| No | Ref | | Ref | |
| Anthracycline | | | | |
| Yes | 0.80 (0.70 to 0.94) | .03§ | 0.90 (0.71 to 1.12) | .65 |
| No | Ref | | Ref | |

(continued on following page)

**TABLE A8.** Multinomial Logistic Regression for the Association Between Treatment Exposures and Frailty Among Survivors (continued)

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Treatment Exposures** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Amputation | | | | |
| Yes | 1.58 (1.14 to 2.20) | .006§ | 2.00 (1.32 to 3.00) | .001§ |
| No | Ref | | Ref | |
| Lung surgery | | | | |
| Yes | 1.61 (1.20 to 2.18) | .002§ | 2.40 (1.70 to 3.42) | < .001§ |
| No | Ref | | Ref | |
| Spleen removal | | | | |
| Yes | 1.36 (1.02 to 1.80) | .03§ | 0.95 (0.65 to 1.40) | .80 |
| No | Ref | | Ref | |

Abbreviations: OR, odds ratio; Ref, reference.

*Prefrailty = 2 components.

†Frailty ≥ 3 components.

‡The model was adjusted for sex, race, age at diagnosis, and age at assessment.

‖Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

§Indicates estimates with a false discovery rate < 10.

**TABLE A9.** Multinomial Logistic Regression for the Association Between Sociodemographic Characteristics, Lifestyle, and Frailty Among Survivors

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Treatment Exposures** | **Adjusted OR (95% CI)** | ***P*** | **Adjusted OR (95% CI)** | ***P*** |
| Sex | | | | |
| Female | 1.43 (1.27 to 1.61) | < .001§ | 1.44 (1.22 to 1.68) | < .001§ |
| Male | Ref | | Ref | |
| Race/ethnicity | | | | |
| Non-Hispanic black | 1.52 (1.17 to 1.97) | .002§ | 2.03 (1.47 to 2.78) | < .001§ |
| Hispanic | 1.20 (0.94 to 1.52) | .13 | 1.80 (1.35 to 2.40) | < .001§ |
| Others | 1.17 (0.87 to 1.58) | .31 | 1.02 (0.65 to 1.60) | .93 |
| Non-Hispanic white | Ref | | Ref | |
| Age at diagnosis, years | | | | |
| 0-4 | 0.83 (0.70 to 1.01) | .07 | 0.63 (0.47 to 0.81) | < .001§ |
| 5-10 | 0.80 (0.61 to 1.03) | .09 | 1.08 (0.90 to 1.30) | .08 |
| 10-14 | 0.84 (0.70 to 1.03) | .44 | 0.80 (0.61 to 1.03) | .66 |
| ≥ 15 | Ref | | Ref | |
| Age at assessment, years | | | | |
| 18-29 | Ref | | Ref | |
| 30-39 | 1.07 (0.91 to 1.27) | .41 | 1.20 (0.93 to 1.54) | .16 |
| 40-49 | 1.05 (0.86 to 1.27) | .63 | 1.26 (0.95 to 1.67) | .10 |
| ≥ 50 | 1.04 (0.80 to 1.34) | .80 | 1.38 (0.97 to 1.96) | .07 |
| Smoking status‖ | | | | |
| Current | 1.43 (1.24 to 1.65) | < .001§ | 1.42 (1.12 to 1.73) | < .001§ |
| Former | 1.01 (0.85 to 1.21) | .90 | 0.96 (0.75 to 1.22) | .74 |
| Never | Ref | | Ref | |
| Sedentary behavior¶ | | | | |
| Current | 3.06 (2.68 to 3.50) | < .001§ | 6.33 (5.3 to 7.57) | < .001§ |
| Former | 1.83 (1.53 to 2.18) | < .001§ | 2.73 (2.14 to 3.50) | < .001§ |
| Never | Ref | | Ref | |
| Obesity (BMI ≥ 30 kg) | | | | |
| Current | 1.58 (1.39 to 1.80) | < .001§ | 1.62 (1.36 to 1.93) | < .001§ |
| Former | 1.52 (1.10 to 2.10) | .01§ | 1.50 (0.98 to 2.28) | .06 |
| Never | Ref | | Ref | |

Abbreviations: BMI, body mass index; OR, odds ratio; Ref, reference.

*Prefrailty = 2 components.

†Frailty ≥ 3 components.

§Indicates estimates with a false discovery rate < 10.

‖Smoking status was defined as those who reported ≥ 100 cigarettes in their lifetime and smoking in the past month; 35 participants did not report their smoking status.

¶Sedentary behavior: persons who responded no to the question: "During the past month, did you participate in any physical activities such as running, aerobic, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?"

**TABLE A10.** Multinomial Logistic Regression for the Association Between Grade 3-4 Chronic Health Conditions and Frailty Among Survivors

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Grade 3-4 Chronic Health Conditions** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Any chronic condition§ | | | | |
| Yes | 2.23 (2.04 to 2.60) | < .001‖ | 3.75 (3.21 to 4.40) | < .001‖ |
| No | Ref | | Ref | |
| Cardiac | | | | |
| Yes | 1.54 (1.23 to 1.93) | < .001‖ | 2.46 (1.92 to 3.15) | < .001‖ |
| No | Ref | | Ref | |
| SMN | | | | |
| Yes | 1.26 (0.97 to 1.64) | .08 | 1.36 (1.00 to 1.88) | .04‖ |
| No | Ref | | Ref | |
| Neurologic | | | | |
| Yes | 3.57 (2.88 to 4.44) | < .001 | 7.12 (5.61 to 9.05) | < .001 |
| No | Ref | | Ref | |
| Musculoskeletal | | | | |
| Yes | 1.78 (1.42 to 2.24) | < .001‖ | 2.11 (1.60 to 2.80) | < .001‖ |
| No | Ref | | Ref | |
| Endocrine | | | | |
| Yes | 1.26 (1.01 to 1.56) | .03‖ | 1.80 (1.40 to 2.31) | < .001‖ |
| No | Ref | | Ref | |
| Respiratory | | | | |
| Yes | 1.49 (0.70 to 3.05) | .30 | 4.83 (2.67 to 3.71) | < .001‖ |
| No | Ref | | Ref | |
| Renal | | | | |
| Yes | 1.41 (0.80 to 2.50) | .22 | 1.48 (0.72 to 3.04) | .25 |
| No | Ref | | Ref | |
| Other chronic conditions | | | | |
| Yes | 1.83 (1.57 to 2.15) | < .001‖ | 1.90 (1.53 to 2.31) | .001‖ |
| No | Ref | | Ref | |

Abbreviations: OR, odds ratio; Ref, reference; SMN, second malignant neoplasm.

*Prefrailty = 2 components.

†Frailty ≥ 3 components.

‡The model was adjusted for sex, race, age at diagnosis, age at assessment.

§Any chronic condition was conducted in separate model, and the prevalence rate ratio (95% CI) was reported in the table.

‖Indicates estimates with a false discovery rate < 10.

**TABLE A11.** Multinomial Logistic Regression for the Association Between Treatment Exposure, Grade 3-4 Chronic Conditions, and Frailty

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Cranial radiation | | | | |
| Yes | 1.43 (1.23 to 1.67) | < .001§ | 1.90 (1.54 to 2.34) | |
| No | Ref | | Ref | |
| Abdominal radiation dose, Gyll | | | | |
| < 20 | 0.93 (0.66 to 1.32) | .68 | 1.20 (0.75 to 1.90) | .45 |
| 20-40 | 0.92 (0.67 to 1.27) | .56 | 1.20 (0.81 to 1.77) | .36 |
| > 40 | 0.94 (0.54 to 1.62) | .82 | 1.54 (0.85 to 2.80) | .14 |
| None | Ref | | Ref | |
| Pelvic radiation dose, Gyll | | | | |
| < 34 | 1.32 (0.95 to 1.83) | .09 | 0.99 (0.64 to 1.53) | .96 |
| ≥ 34 | 1.17 (0.82 to 1.65) | .38 | 1.76 (1.17 to 2.65) | .007§ |
| None | Ref | | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 1.53 (1.20 to 1.96) | < .001§ | 0.96 (0.67 to 1.37) | .80 |
| ≥ 600 | 0.90 (0.50 to 1.68) | .62 | 1.48 (0.82 to 2.61) | .19 |
| None | Ref | | Ref | |
| Methotrexate | | | | |
| Yes | 0.96 (0.83 to 1.12) | .60 | 0.77 (0.62 to 0.96) | .02§ |
| No | Ref | | Ref | |
| Alkylating agents | | | | |
| Yes | 1.10 (0.95 to 1.27) | .20 | 1.05 (0.86 to 1.29) | .61 |
| No | Ref | | Ref | |
| Anthracycline | | | | |
| Yes | 0.85 (0.73 to 0.99) | .05 | 0.99 (0.80 to 1.24) | .91 |
| No | Ref | | Ref | |
| Amputation | | | | |
| Yes | 1.20 (0.80 to 1.80) | .40 | 1.54 (0.91 to 2.60) | .10 |
| No | Ref | | Ref | |
| Lung surgery | | | | |
| Yes | 1.60 (1.17 to 2.15) | .003§ | 2.17 (1.51 to 3.11) | < .001§ |
| No | Ref | | Ref | |
| Spleen removal | | | | |
| Yes | 1.44 (1.10 to 1.91) | .01§ | 0.94 (0.64 to 1.38) | .74 |
| No | Ref | | Ref | |

Abbreviations: OR, odds ratio; Ref, reference.

*Prefrailty = 2 components.

†Frailty ≥ 3 components.

‡The model includes treatments that were significant in first model (Table A8). The model was adjusted for sex, race, age at diagnosis, age at assessment, and grade 3-4 chronic health condition.

§Indicates estimates with a false discovery rate < 10.

‖Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

**TABLE A12.** Multinomial Logistic Regression for the Association Between Treatment Exposure, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Frailty

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Sex | | | | |
| Female | 1.47 (1.30 to 1.68) | < .001§ | 1.50 (1.24 to 1.81) | < .001§ |
| Male | Ref | | Ref | |
| Race/ethnicity | | | | |
| Non-Hispanic black | 1.72 (1.30 to 2.30) | < .001§ | 2.20 (1.51 to 3.21) | < .001§ |
| Hispanic | 1.10 (0.83 to 1.43) | .54 | 1.99 (1.44 to 2.76) | < .001§ |
| Others | 1.08 (0.77 to 1.53) | .65 | 0.98 (0.60 to 1.66) | .94 |
| Non-Hispanic white | Ref | | Ref | |
| Age at diagnosis, years | | | | |
| 0-4 | 0.87 (0.70 to 1.10) | .25 | 0.70 (0.50 to 0.94) | .01§ |
| 5-10 | 1.02 (0.82 to 1.26) | .88 | 0.94 (0.71 to 1.24) | .65 |
| 10-14 | 0.83 (0.65 to 1.05) | .11 | 0.55 (0.40 to 0.76) | < .001§ |
| ≥ 15 | Ref | | Ref | |
| Age at assessment, years | | | | |
| 18-29 | Ref | | Ref | |
| 30-39 | 1.01 (0.84 to 1.22) | .87 | 1.01 (0.76 to 1.34) | .95 |
| 40-49 | 0.95 (0.76 to 1.20) | .70 | 0.99 (0.72 to 1.40) | .99 |
| ≥ 50 | 0.83 (0.61 to 1.13) | .24 | 1.01 (0.66 to 1.55) | .95 |
| Cranial radiation | | | | |
| Yes | 1.28 (1.10 to 1.50) | .002§ | 1.72 (1.38 to 2.15) | < .001§ |
| No | Ref | | Ref | |
| Abdominal radiation dose, Gy‖ | | | | |
| < 20 | 1.04 (0.73 to 1.48) | .89 | 1.39 (0.90 to 2.23) | .17 |
| 20-40 | 0.96 (0.71 to 1.31) | .81 | 1.26 (0.84 to 1.89) | .26 |
| > 40 | 1.06 (0.61 to 1.86) | .83 | 1.63 (0.88 to 3.04) | .12 |
| None | Ref | | Ref | |
| Pelvic radiation dose, Gy‖ | | | | |
| < 34 | 1.32 (0.95 to 1.83) | .16 | 0.99 (0.64 to 1.53) | .92 |
| ≥ 34 | 1.17 (0.82 to 1.65) | .45 | 1.76 (1.17 to 2.65) | .007§ |
| None | Ref | | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 1.56 (1.20 to 2.02) | < .001§ | 0.98 (0.67 to 1.44) | .93 |
| ≥ 600 | 0.81 (0.50 to 1.45) | .48 | 1.36 (0.74 to 2.51) | .32 |
| None | Ref | | Ref | |
| Methotrexate | | | | |
| Yes | 0.92 (0.80 to 1.07) | .28 | 0.74 (0.60 to 0.92) | .007§ |
| No | Ref | | Ref | |
| Alkylating agents | | | | |
| Yes | 1.17 (1.01 to 1.36) | .03§ | 1.14 (0.92 to 1.40) | .23 |
| No | Ref | | Ref | |

(continued on following page)

**TABLE A12.** Multinomial Logistic Regression for the Association Between Treatment Exposure, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Frailty (continued)

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Anthracycline | | | | |
| Yes | 0.87 (0.73 to 1.02) | .09 | 1.06 (0.84 to 1.34) | .64 |
| No | Ref | | Ref | |
| Amputation | | | | |
| Yes | 1.18 (0.77 to 1.81) | .43 | 1.54 (0.91 to 2.60) | .11 |
| No | Ref | | Ref | |
| Lung surgery | | | | |
| Yes | 1.64 (1.20 to 2.24) | .002§ | 2.25 (1.54 to 3.29) | < .001§ |
| No | Ref | | Ref | |
| Spleen removal | | | | |
| Yes | 1.57 (1.18 to 2.10) | .002§ | 1.10 (0.73 to 1.62) | .68 |
| No | Ref | | Ref | |
| Cardiac | | | | |
| Yes | 1.37 (1.06 to 1.78) | .01§ | 2.00 (1.50 to 2.68) | < .001§ |
| No | Ref | | Ref | |
| Neurologic | | | | |
| Yes | 3.44 (2.70 to 4.40) | < .001§ | 6.17 (4.65 to 8.20) | < .001§ |
| No | Ref | | Ref | |
| Musculoskeletal | | | | |
| Yes | 1.48 (1.03 to 2.13) | .03§ | 1.35 (0.83 to 2.19) | .22 |
| No | Ref | | | |
| Endocrine | | | | |
| Yes | 1.20 (0.93 to 1.53) | .16 | 1.63 (1.21 to 2.11) | .001§ |
| No | Ref | | Ref | |
| Respiratory | | | | |
| Yes | 0.99 (0.41 to 2.38) | .97 | 3.41 (1.64 to 7.10) | .001§ |
| No | Ref | | Ref | |
| SMN | | | | |
| Yes | 0.99 (0.73 to 1.36) | .99 | 1.10 (0.73 to 1.56) | .74 |
| No | Ref | | Ref | |
| Other chronic conditions | | | | |
| Yes | 1.47 (1.22 to 1.78) | < .001§ | 1.56 (1.21 to 1.99) | < .001§ |
| No | Ref | | Ref | |
| Smoking status‖ | | | | |
| Current | 1.60 (1.40 to 1.87) | < .001§ | 1.74 (1.39 to 2.18) | < .001§ |
| Former | 1.10 (0.90 to 1.33) | .40 | 1.10 (0.80 to 1.41) | .67 |
| Never | Ref | | Ref | |
| Sedentary behavior¶ | | | | |
| Current | 3.0 (2.60 to 3.47) | < .001§ | 5.19 (4.23 to 6.35) | < .001§ |
| Former | 1.74 (1.43 to 2.13) | < .001§ | 2.35 (1.80 to 3.11) | < .001§ |
| Never | Ref | | Ref | |

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**TABLE A12.** Multinomial Logistic Regression for the Association Between Treatment Exposure, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Frailty (continued)

| | Prefrail* *v* Nonfrail Prefrail (n = 1,272) | | Frail† *v* Nonfrail Frail (n = 681) | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR‡ (95% CI)** | ***P*** | **Adjusted OR‡ (95% CI)** | ***P*** |
| Obesity (BMI ≥ 30 kg/m$^2$)# | | | | |
| Current | 1.73 (1.50 to 1.99) | < .001§ | 1.74 (1.43 to 2.13) | < .001§ |
| Former | 1.30 (0.90 to 1.92) | .18 | 1.40 (0.85 to 2.29) | .18 |
| Never | Ref | | Ref | |

Abbreviations: BMI, body mass index; OR, odds ratio; Ref, reference; SMN, second malignant neoplasm.

*Prefrailty = 2 components.

†Frailty ≥ 3 components.

‡The model includes treatments that were significant in first model (Table A8). The model was adjusted for sex, race, age at diagnosis, age at assessment, and grade 3-4 chronic health condition.

§Indicates estimates with a false discovery rate < 10.

‖Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

**TABLE A13.** Associations Between Treatment Exposures and Frailty Among Childhood Cancer Participants (survivors and deceased participants)[1]

| | | Frailty (n = 4,050)* | | |
|---|---|---|---|---|
| **Treatment Exposures** | **Participants (n = 14,268)** | **Row (%)†** | **Adjusted PRR‡ (95% CI)** | ***P*** |
| Chest radiation | | | | |
| Yes | 3,664 | 39.5 | 1.20 (0.91 to 1.58) | .19 |
| No | 9,716 | 20.7 | Ref | |
| Cranial radiation | | | | |
| Yes | 4,034 | 33.6 | 2.06 (1.70 to 2.51) | < .001§ |
| No | 9,346 | 22.0 | Ref | |
| Abdominal radiation dose, Gyll | | | | |
| < 20 | 1,195 | 28.6 | 0.98 (0.62 to 1.56) | .96 |
| 20-41 | 1,827 | 42.5 | 1.15 (0.77 to 1.71) | .47 |
| ≥ 41 | 362 | 56.9 | 1.60 (0.94 to 2.73) | .08 |
| None | 9,996 | 21.4 | Ref | |
| Pelvic radiation dose, Gyll | | | | |
| < 34 | 1,716 | 32.8 | 0.93 (0.62 to 1.34) | .81 |
| ≥ 34 | 1,141 | 52.0 | 1.84 (1.10 to 3.10) | .02§ |
| None | 10,523 | 21.8 | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 911 | 33.6 | 0.96 (0.68 to 1.04) | .09 |
| ≥ 600 | 212 | 40.1 | 1.52 (1.08 to 2.15) | .02§ |
| None | 11,789 | 23.9 | Ref | |
| Carboplatin dose, mg/m$^2$ | | | | |
| < 2,500 | 198 | 36.6 | 1.27 (0.71 to 2.24) | .42 |
| ≥ 2,500 | 202 | 31.3 | 1.48 (0.84 to 2.60) | .17 |
| None | 12,639 | 24.6 | Ref | |
| Methotrexate | | | | |
| Yes | 4,921 | 19.4 | 0.77 (0.60 to 1.00) | .05 |
| No | 8,169 | 29.3 | Ref | |
| Alkylating agents | | | | |
| Yes | 7,288 | 28.3 | 1.11 (0.90 to 1.38) | .30 |
| No | 6,010 | 21.6 | Ref | |
| 6-mercaptopurine | | | | |
| Yes | 2,670 | 13.8 | 0.85 (0.64 to 1.15) | .29 |
| No | 10,420 | 29.2 | Ref | |
| 6-thiogauine | | | | |
| Yes | 1,128 | 14.8 | 1.04 (0.76 to 1.41) | .82 |
| No | 11,962 | 26.1 | Ref | |
| Vinca alkaloids | | | | |
| Yes | 8,319 | 20.1 | 0.88 (0.71 to 1.10) | .26 |
| No | 4,771 | 34.8 | Ref | |
| Anthracycline | | | | |
| Yes | 6,232 | 22.9 | 0.96 (0.77 to 1.20) | .74 |
| No | 7,082 | 27.9 | Ref | |

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**TABLE A13.** Associations Between Treatment Exposures and Frailty Among Childhood Cancer Participants (survivors and deceased participants)[1] (continued)

| | | Frailty (n = 4,050)* | | |
|---|---|---|---|---|
| **Treatment Exposures** | **Participants (n = 14,268)** | **Row (%)†** | **Adjusted PRR‡ (95% CI)** | ***P*** |
| Amputation | | | | |
| Yes | 583 | 33.0 | 1.74 (1.18 to 2.53) | .004§ |
| No | 12,936 | 22.1 | Ref | |
| Lung surgery | | | | |
| Yes | 184 | 34.7 | 2.08 (1.52 to 2.85) | < .001§ |
| No | 3,137 | 22.2 | Ref | |
| Spleen removal | | | | |
| Yes | 753 | 8.0 | 0.93 (0.65 to 1.34) | .70 |
| No | 12,747 | 23.4 | Ref | |

NOTE. The analysis includes survivors and deceased participants; deceased participants were considered as frail.

Abbreviations: PRR, prevalence rate ratio; Ref, reference.

*Frailty ≥ 3 components.

†Weighted row percentages are presented.

‡The model was adjusted for sex, race, age at diagnosis, and age at assessment.

§Indicates estimates with a false discovery rate < 10%.

‖Radiation dose: maximum tumor dose was determined by summing the prescribed dose to all overlapping fields within each respective region.

**TABLE A14.** Associations Between Sociodemographic Characteristics, Lifestyle, and Frailty Among Childhood Cancer Participants (survivors and deceased participants)

| | | Frailty (n = 4,050)* | | |
|---|---|---|---|---|
| **Factors** | **Participants (n = 14,268)** | **Row (%)†** | **Adjusted PRR (95% CI)** | ***P*** |
| Sex | | | | |
| Female | 7,109 | 24.0 | 1.02 (0.97 to 1.15) | .19 |
| Male | 7,159 | 29.0 | Ref | |
| Race/ethnicity | | | | |
| Non-Hispanic black | 682 | 38.2 | 1.11 (0.96 to 1.27) | .16 |
| Hispanic | 869 | 28.4 | 1.11 (0.96 to 1.29) | .14 |
| Others | 495 | 3.1 | 0.90 (0.74 to 1.08) | .25 |
| Non-Hispanic white | 12,219 | 25.9 | Ref | |
| Age at diagnosis, years | | | | |
| 0-4 | 3,549 | 20.1 | 0.80 (0.73 to 0.87) | < .001‡ |
| 5-9 | 3,546 | 24.1 | 0.96 (0.88 to 1.03) | .26 |
| 10-14 | 3,088 | 30.1 | 1.10 (1.02 to 1.170) | .02‡ |
| ≥ 15 | 4,079 | 35.2 | Ref | |
| Age at assessment, years | | | | |
| < 30 | 4,053 | 42.5 | Ref | |
| 30-39 | 4,912 | 17.8 | 1.07 (0.99 to 1.14 | .06 |
| 40-49 | 3,674 | 20.0 | 0.90 (0.84 to 0.96) | .004‡ |
| ≥ 50 | 1,629 | 21.0 | 0.82 (0.74 to 0.90) | < .001‡ |
| Smoking status‖ | | | | |
| Current | 1,904 | 7.9 | 0.92 (0.77 to 1.09) | .33 |
| Former | 2,153 | 34.1 | 1.07 (0.99 to 1.18) | .07 |
| Never | 9,356 | 22.0 | Ref | |
| Sedentary behavior¶ | | | | |
| Current | 2,135 | 14.8 | 1.54 (1.40 to 1.68) | < .001‡ |
| Former | 3,016 | 52.7 | 2.02 (1.85 to 2.21) | < .001‡ |
| Never | 7,214 | 2.9 | Ref | |
| Obesity (BMI ≥ 30 kg/m$^2$) | | | | |
| Current | 2,572 | 8.7 | 0.6 (0.66 to 0.72) | < .001‡ |
| Former | 2,752 | 90.1 | 2.89 (2.26 to 3.11) | < .001‡ |
| Never | 8,286 | 10.6 | Ref | |

NOTE. The analysis includes survivors and deceased participants; deceased participants were considered as frail.

Abbreviations: BMI, body mass index; PRR, prevalence rate ratio; Ref, reference.

*Frailty ≥ 3 components.

†Weighted row percentages.

‡Indicates estimates with a false discovery rate < 10%.

‖Smoking status was defined as those who reported ≥ 100 cigarettes in their lifetime and smoking in the past month. The mean (standard deviation) for number of cigarettes per day was calculated among those who reported current or former smoker.

¶Sedentary behavior: persons who responded no to the question: "During the past month, did you participate in any physical activities such as running, aerobic, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?"

**TABLE A15.** Associations Between Grade 3-4 Chronic Health Conditions and Frailty Among Childhood Cancer Participants (survivors and deceased participants)

| | | Frailty (n = 4,050)* | | |
|---|---|---|---|---|
| **Grade 3-4 Chronic Health Conditions** | **Participants (n = 14,268)** | **Row (%)†** | **Adjusted PRR‡ (95% CI)** | ***P*** |
| Any chronic condition§ | 4,983 | 39.2 | | |
| Yes | 9,285 | 20.4 | 1.70 (1.57 to 1.83) | < .001‖ |
| No | | | Ref | |
| Cardiac | 1,018 | 51.6 | | |
| Yes | 13,250 | 24.8 | 1.37 (1.23 to 1.53) | < .001‖ |
| No | | | Ref | |
| SMN | 671 | 34.8 | | |
| Yes | 13,597 | 26.2 | 1.14 (0.99 to 1.31) | .06 |
| No | | | Ref | |
| Neurologic | 878 | 51.5 | | |
| Yes | 13,390 | 25.0 | 2.02 (1.81 to 2.22) | < .001‖ |
| No | | | Ref | |
| Musculoskeletal | 838 | 36.6 | | |
| Yes | 13,430 | 26.0 | 1.32 (1.16 to 1.50) | < .001‖ |
| No | | | Ref | |
| Endocrine | 1,098 | 35.8 | | |
| Yes | 13,170 | 25.9 | 1.27 (1.13 to 1.43) | < .001‖ |
| No | | | Ref | |
| Respiratory | 166 | 74.5 | | |
| Yes | 14,102 | 26.0 | 1.79 (1.43 to 2.23) | < .001 |
| No | | | Ref | |
| Renal | 189 | 59.8 | | |
| Yes | 14,079 | 23.3 | 1.18 (0.85 to 1.62) | .32 |
| No | | | Ref | |
| Other chronic conditions | 1,986 | 38.9 | | |
| Yes | 12,282 | 24.7 | 1.28 (1.16 to 1.40) | < .001‖ |
| No | | | Ref | |

NOTE. The analysis includes survivors and deceased participants, deceased participants were considered as frail.
Abbreviations: PRR, prevalence rate ratio; Ref, reference; SMN, second malignant neoplasm.
*Frailty ≥ 3 components.
†Weighted row percentages.
‡The model was adjusted for sex, race, age at diagnosis, and age at assessment.
§Any chronic condition was conducted in separate model, and the PRR (95% CI) was reported in the table.
‖Indicates estimates with a false discovery rate < 10%.

**TABLE A16.** Associations Between Treatment Exposures, Grade 3-4 Chronic Conditions, Lifestyle Factors, and Frailty Among Childhood Cancer Participants (survivors and deceased participants)

| | Frailty* (n = 4,050) | | | |
|---|---|---|---|---|
| **Factors** | **Adjusted PRR† (95% CI)** | ***P*** | **Adjusted PRR‡ (95% CI)** | ***P*** |
| Cranial radiation | | | | |
| Yes | 1.31 (1.20 to 1.44) | < .001§ | 1.22 (1.10 to 1.35) | < .001§ |
| No | Ref | | Ref | |
| Abdominal radiation dose, Gyll | | | | |
| < 20 | 1.003 (0.75 to 1.35) | .98 | 1.06 (0.80 to 1.43) | .67 |
| 20-41 | 0.99 (0.80 to 1.23) | .97 | 0.98 (0.80 to 1.21) | .87 |
| ≥ 41 | 1.15 (0.80 to 1.65) | .43 | 1.12 (0.80 to 1.21) | .51 |
| None | Ref | | Ref | |
| Pelvic radiation dose, Gy | | | | |
| < 34 | 0.85 (0.68 to 1.07) | .16 | 088 (0.86 to 1.09) | .28 |
| ≥ 34 | 1.35 (1.10 to 1.66) | .006§ | 1.33 (1.07 to 1.65) | .008§ |
| None | Ref | | Ref | |
| Cisplatin dose, mg/m$^2$ | | | | |
| < 600 | 0.81 (0.62 to 1.05) | .11 | 0.86 (0.66 to 1.13) | .30 |
| ≥ 600 | 1.34 (0.95 to 1.90) | .09 | 1.28 (0.91 to 1.45) | .15 |
| None | Ref | | Ref | |
| Methotrexate | | | | |
| Yes | 0.90 (0.81 to 0.98) | .02§ | 0.90 (0.80 to 1.02) | .03§ |
| No | Ref | | Ref | |
| Amputation | | | | |
| Yes | 1.51 (0.93 to 2.44) | .09 | 1.35 (0.84 to 2.17) | .21 |
| No | Ref | | Ref | |
| Lung surgery | | | | |
| Yes | 1.75 (1.27 to 2.43) | < .001§ | 1.73 (1.24 to 2.39) | .001§ |
| No | Ref | | Ref | |

NOTE. The dead survivors were considered as frail.

Abbreviations: PRR, prevalence rate ratio; Ref, reference.

*Frailty ≥ 3 components.

†The model was adjusted for sex, race, age at diagnosis, age at assessment, and grade 3-4 chronic conditions.

‡The model was adjusted for sex, race, age at diagnosis, age at assessment, grade 3-4 chronic conditions, and smoking, obesity, and sedentary behavior.

§Indicates estimates with a false discovery rate < 10%.