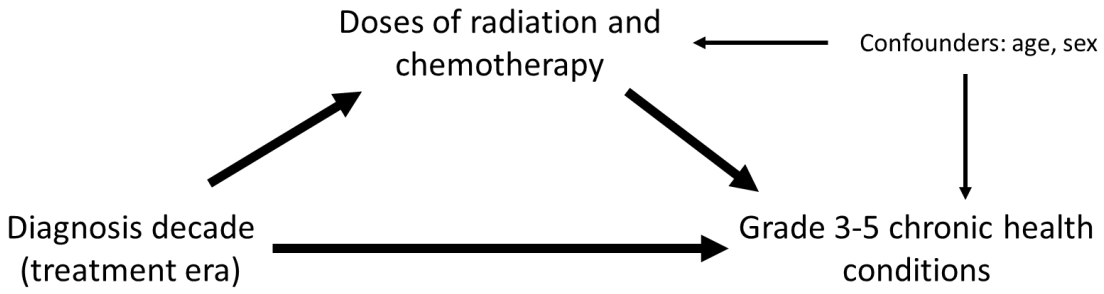
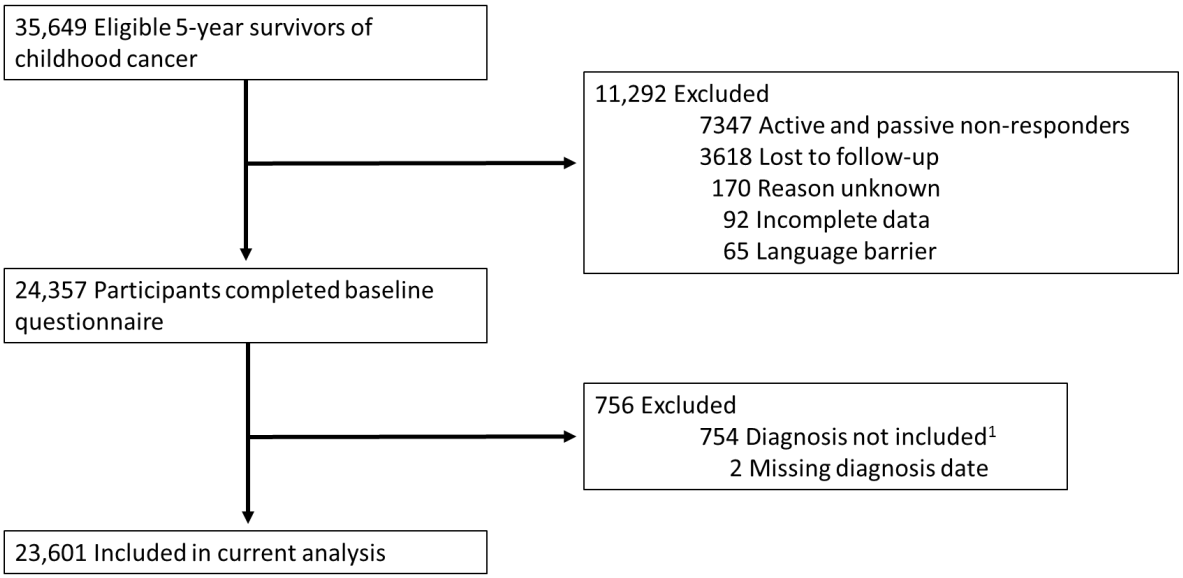
**Appendix Figure 1. Proposed causal diagram of the mediation analysis for the association of treatment era and subsequent neoplasm rates, mediated by doses of radiation and chemotherapy**

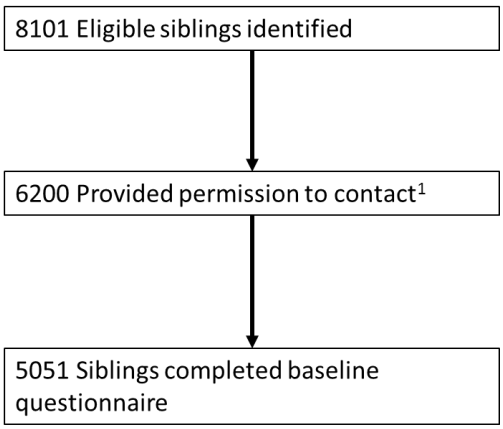


**Appendix Figure 2. Cohort composition diagram of eligible and participating childhood cancer survivors**




[1] All types of soft tissue sarcomas were included as eligible primary cancer diagnoses in survivors diagnosed from 1970-1986. When the Childhood Cancer Survivor Study was expanded to include survivors diagnosed from 1987-1999, only rhabdomyosarcoma was included among soft tissue sarcoma types as an eligible primary cancer diagnosis. Therefore, all survivors with a diagnosis of soft tissue sarcoma other than rhabdomyosarcoma were excluded from the current analysis.

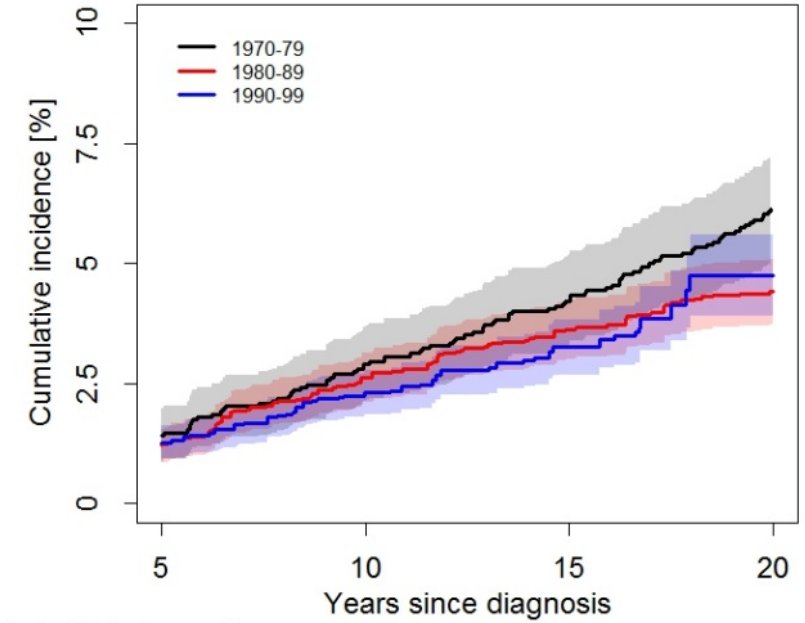
**Appendix Figure 3**. **Cohort composition diagram of eligible and participating siblings of childhood cancer survivors**




[1] Siblings were invited to participate for a randomly selected subgroup of participating survivors. If the participating survivor and then the sibling agreed to participate, the consent and baseline questionnaire were mailed.

**Appendix Figure 4. Diagnosis-specific cumulative incidence of two or more grade 3-5 chronic conditions by diagnosis decade.** Shaded area represents 95% confidence interval. The number of participants at risk (number censored) at each 5-year interval post-diagnosis is listed below the x-axis. The number censored does not include those who experienced a competing risk event (death from a cause other than a grade 5 chronic condition)

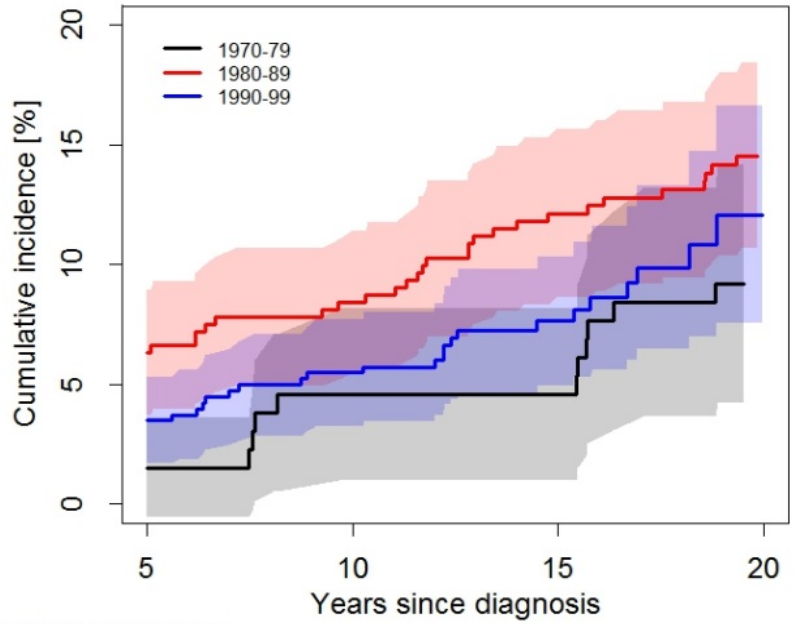
**Acute lymphoblastic leukemia**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 1824(0) | 1638 (0) | 1557 (2) | 1452 (84) |
| 1980-89 | 2892(0) | 2675(40) | 2377(281) | 1905(717) |
| 1990-99 | 1432(0) | 1322(39) | 805(534) | 149(1176) |

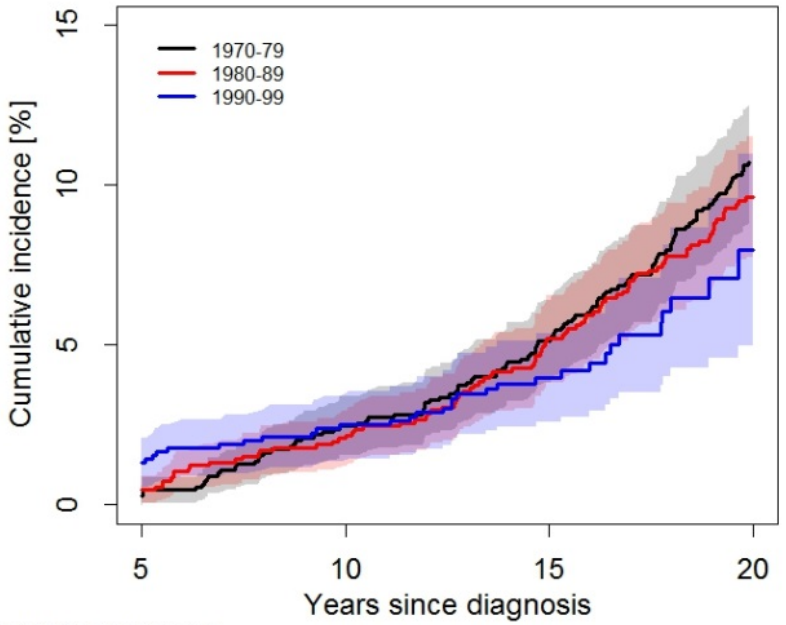
**Acute myeloid leukemia**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 131(0) | 118(0) | 111(1) | 99 (6) |
| 1980-89 | 333(0) | 288(2) | 260(18) | 214(52) |
| 1990-99 | 402(0) | 369(5) | 205(161) | 32(326) |

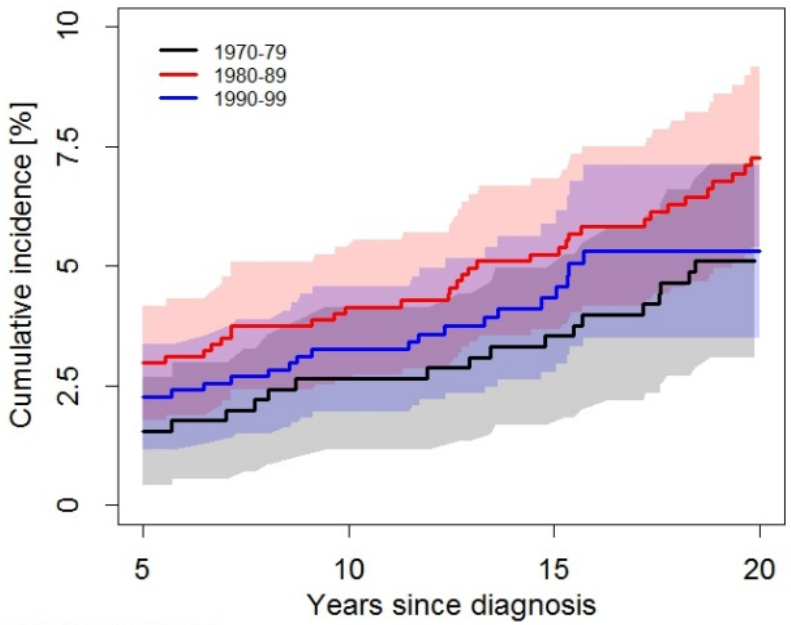
**Hodgkin lymphoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 1097(0) | 1019(0) | 954(0) | 816(46) |
| 1980-89 | 1057(0) | 994(10) | 864(88) | 694(200) |
| 1990-99 | 842(0) | 795(16) | 455(340) | 87(695) |

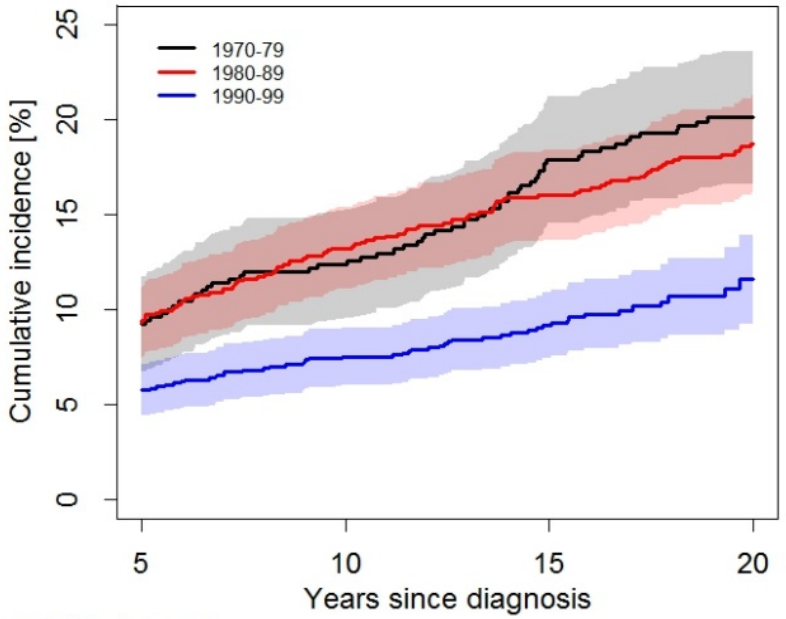
**Non-Hodgkin lymphoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 453(0) | 430(0) | 419(0) | 385(20) |
| 1980-89 | 774(0) | 712(15) | 637(76) | 520(175) |
| 1990-99 | 705(0) | 661(13) | 410(249) | 94(559) |

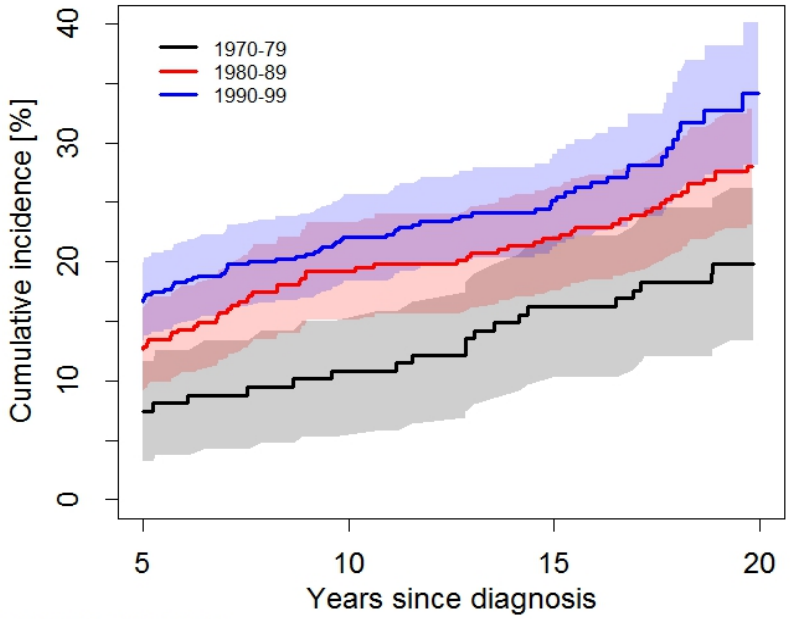
**Astrocytoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 508(0) | 425(0) | 388(1) | 347(16) |
| 1980-89 | 945(0) | 781(13) | 677(83) | 541(188) |
| 1990-99 | 1140(0) | 1011(14) | 620(371) | 146(827) |

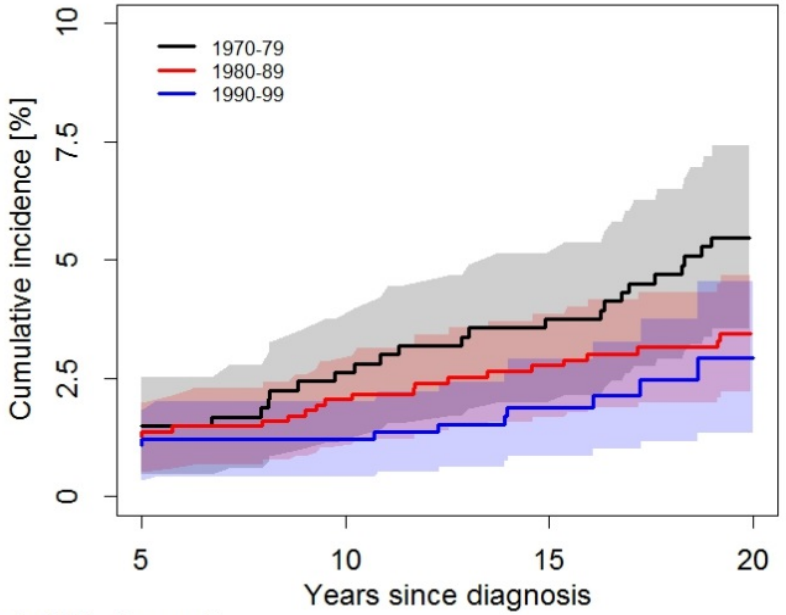
**Medulloblastoma/PNET**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 148(0) | 116(0) | 103(0) | 89(8) |
| 1980-89 | 349(0) | 257(4) | 223(23) | 177(49) |
| 1990-99 | 499(0) | 363(7) | 197(153) | 32(298) |

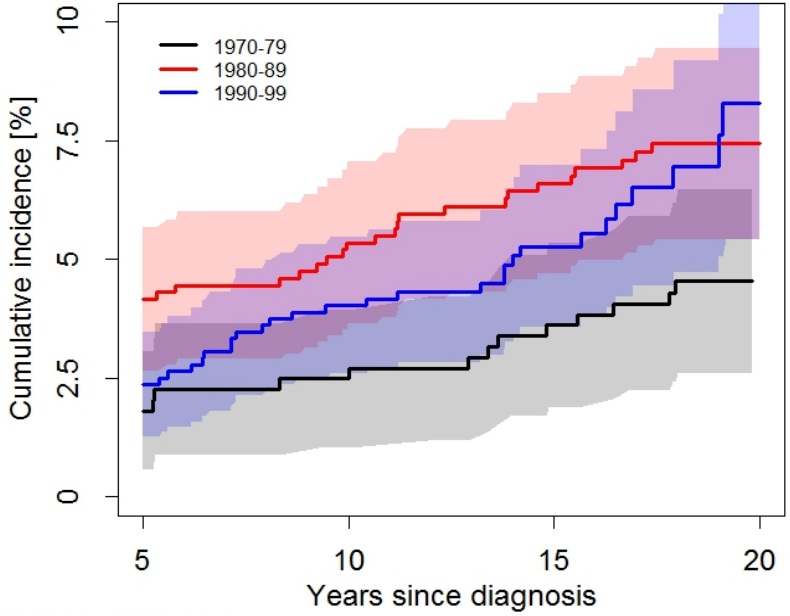
**Wilms tumor**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 534(0) | 515(0) | 502(0) | 459(29) |
| 1980-89 | 877(0) | 845(3) | 769(72) | 625(202) |
| 1990-99 | 737(0) | 709(11) | 465(249) | 106(600) |

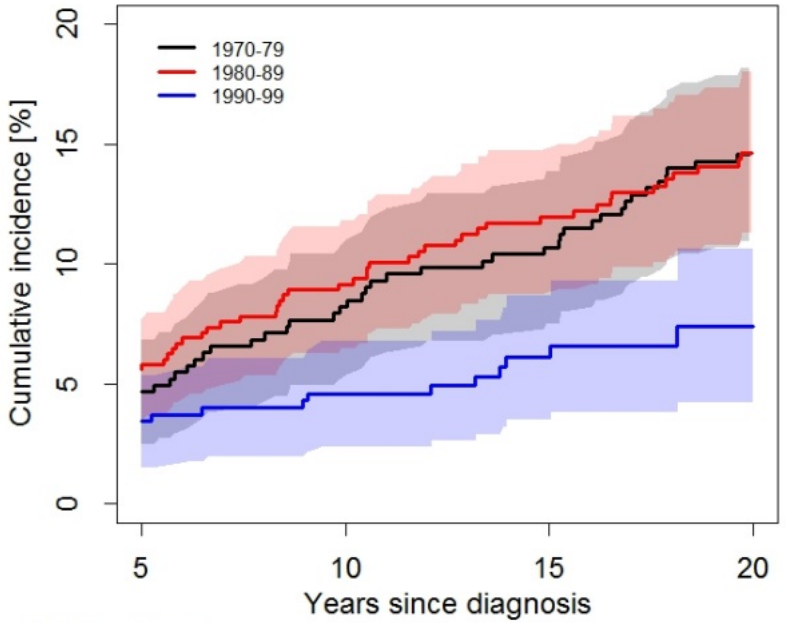
**Neuroblastoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 443(0) | 424(0) | 413(0) | 383(23) |
| 1980-89 | 674(0) | 613(9) | 561(51) | 466(138) |
| 1990-99 | 720(0) | 649(10) | 379(268) | 96(543) |

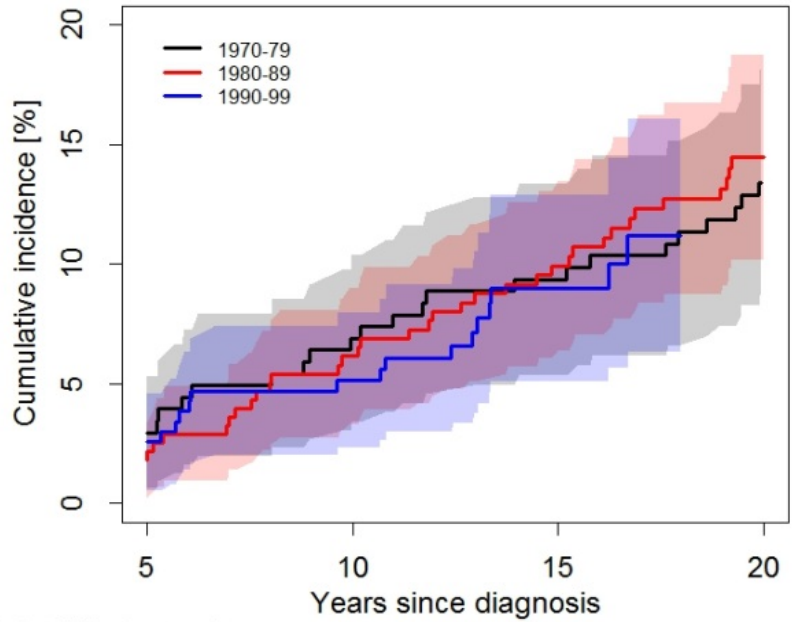
**Soft tissue sarcoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 365(0) | 326(0) | 313(0) | 282(12) |
| 1980-89 | 448(0) | 392(5) | 341(38) | 278(86) |
| 1990-99 | 349(0) | 322(4) | 195(122) | 46(267) |

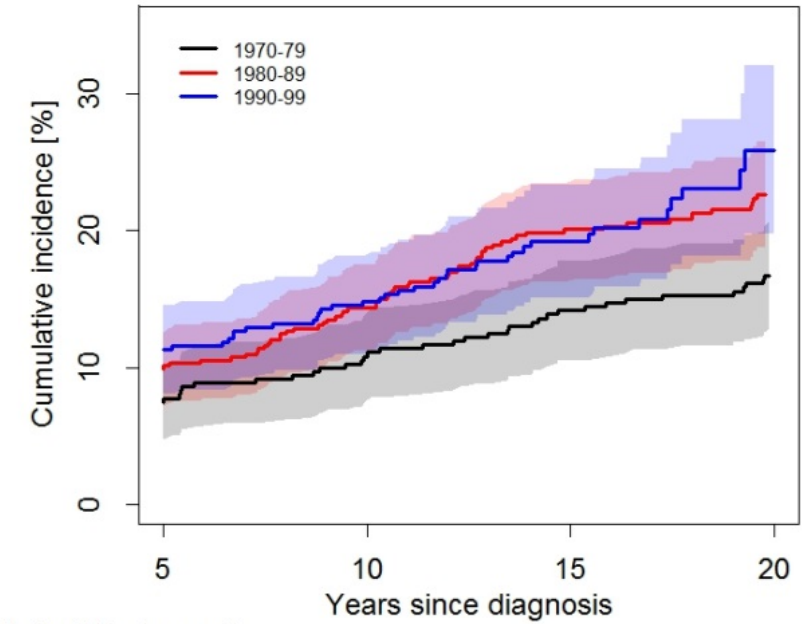
**Ewing sarcoma**




Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 203(0) | 165(0) | 151(0) | 136(6) |
| 1980-89 | 277(0) | 233(3) | 202(17) | 154(52) |
| 1990-99 | 234(0) | 206(5) | 100(99) | 18(179) |

**Osteosarcoma**

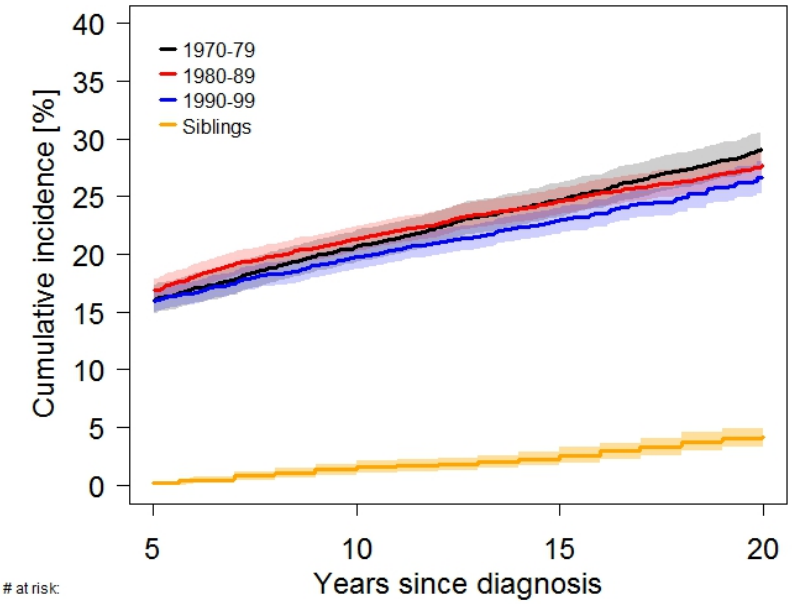



Number at risk (number censored)

| | | | | |
|---|---|---|---|---|
| 1970-79 | 360(0) | 314(0) | 295(0) | 265(17) |
| 1980-89 | 474(0) | 380(6) | 327(31) | 271(74) |
| 1990-99 | 371(0) | 294(2) | 162(117) | 32(237) |

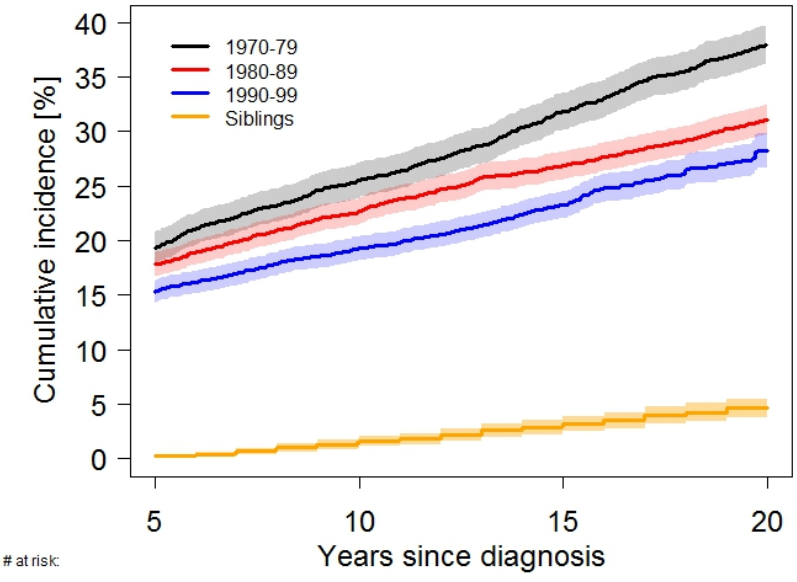
**Appendix Figure 5. Cumulative incidence of grade 3-5 chronic health conditions by diagnosis decade, stratified by sex. Panel A includes all male survivors and siblings. Panel B includes all female survivors and siblings. Panel C includes male survivors of Hodgkin lymphoma. Panel D includes female survivors of Hodgkin lymphoma.**

**A. Males**



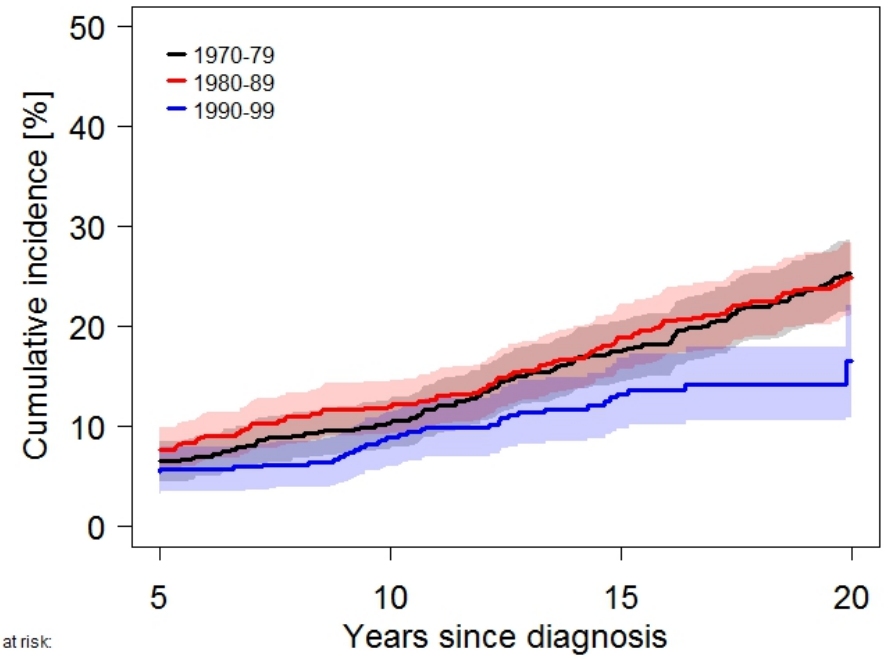

| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 3311 | 2488 | 2303 | 2027 |
| 1980-89 | 5070 | 3770 | 3239 | 2504 |
| 1990-99 | 4217 | 3141 | 1869 | 397 |
| Siblings | 2352 | 2288 | 2086 | 1658 |

**B. Females**



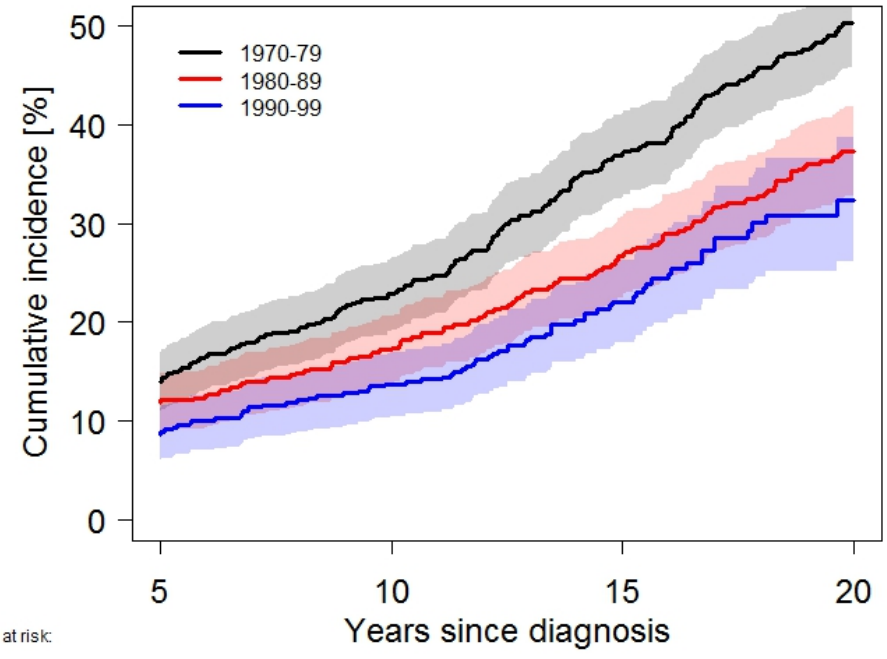

| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 2885 | 2059 | 1850 | 1584 |
| 1980-89 | 4302 | 3180 | 2772 | 2194 |
| 1990-99 | 3712 | 2800 | 1599 | 305 |
| Siblings | 2553 | 2485 | 2270 | 1834 |

**C. Male Hodgkin lymphoma survivors**




| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 584 | 500 | 448 | 369 |
| 1980-89 | 584 | 494 | 411 | 314 |
| 1990-99 | 404 | 361 | 208 | 34 |

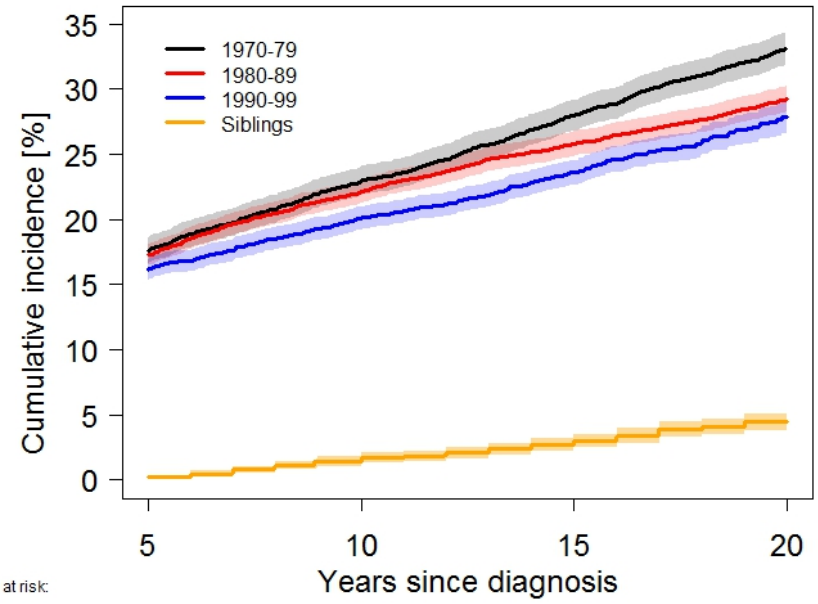
**D. Female Hodgkin lymphoma survivors**




| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 507 | 378 | 305 | 227 |
| 1980-89 | 471 | 383 | 317 | 237 |
| 1990-99 | 437 | 365 | 181 | 36 |

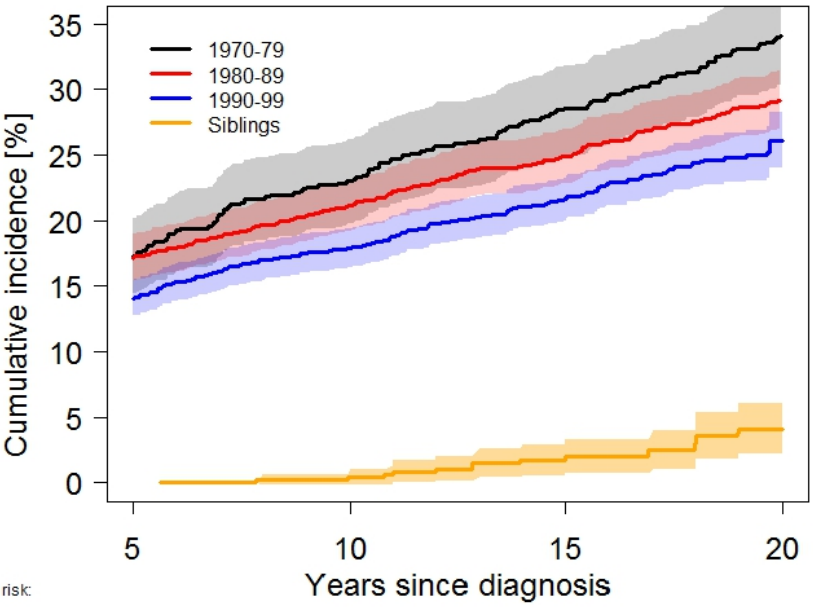
**Appendix Figure 6. Cumulative incidence of grade 3-5 chronic health conditions by diagnosis decade, stratified by race/ethnicity. Panel A includes non-Hispanic white survivors and siblings. Panel B includes survivors and siblings with self-reported race/ethnicity other than non-Hispanic white.**

**A. Non-Hispanic white**




| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 5509 | 4040 | 3691 | 3235 |
| 1980-89 | 7757 | 5755 | 5056 | 3994 |
| 1990-99 | 5998 | 4466 | 2555 | 510 |
| Siblings | 4246 | 4138 | 3795 | 3054 |

**B. Other race/ethnicity**




| # at risk: | | | | |
|---|---|---|---|---|
| 1970-79 | 665 | 490 | 447 | 365 |
| 1980-89 | 1573 | 1163 | 923 | 679 |
| 1990-99 | 1887 | 1438 | 893 | 185 |
| Siblings | 492 | 474 | 412 | 317 |

**Appendix Table 1. List of grade 3-4 chronic conditions included in the CCSS categorization matrix, stratified by organ system. Grade 5 conditions are deaths, so no further definition is provided.**

| Chronic Condition | Grade 3 Definition | Grade 4 Definition |
|---|---|---|
| **Cardiovascular** | | |
| Coronary artery disease | Myocardial infarction, angina, or coronary heart disease not requiring cardiac catheterization but on anti-anginal medication | Myocardial infarction requiring cardiac catheterization, angioplasty, or coronary artery bypass graft |
| Heart failure | Congestive heart failure, requiring medication | Heart transplant |
| Arrhythmia | Arrhythmia, requiring pacemaker | Ventricular fibrillation/flutter |
| Valvular heart disease | Not applicable | Heart valve replacement |
| Stroke | Occlusion of cerebral arteries | Stroke/cerebrovascular accident |
| Pericardial disease | Pericardial disease requiring surgical intervention | Not applicable |
| Other cardiac conditions | Thromboangiitis obliterans (Buerger disease)<br>Hypotension, unspecified<br>Other chronic pulmonary heart disease | Not applicable |
| Thromboembolic disease | Blood clot in head, lung, arm, leg, or pelvis, not otherwise specified | Pulmonary embolism and infarction<br>Embolism and thrombosis of unspecified artery |
| Other vascular conditions | Aorta-subclavian-carotid bypass<br>Other (peripheral) vascular shunt or bypass<br>Other repair of aneurysm<br>Repair of arteriovenous fistula | Other excision of vessels, aorta, abdominal (aorta) |
| Hypertension | Hypertensive chronic kidney disease<br>Hypertensive heart disease | Not applicable |
| **Endocrine** | | |
| Thyroid nodules | Thyroid nodules, requiring surgery | Not applicable |
| Diabetes | Diabetes, requiring insulin | Not applicable |
| Gonadal dysfunction | Postablative ovarian failure or testicular hypofunction<br>Premature menopause, onset <40 years of age<br>Female infertility<br>Azoospermia | Not applicable |
| Other hormone conditions | Panhypopituitarism<br>Diabetes insipidus<br>Corticoadrenal hormone insufficiency<br>Glucocorticoid deficiency | Not applicable |
| **Gastrointestinal** | | |
| Hepatitis | Cirrhosis | Liver transplant |
| Intestinal obstruction | Surgery for intestinal obstruction | Not applicable |
| **Hearing** | | |
| Loss of hearing | Hearing loss, requiring a hearing aid<br>Deafness in one ear not completely corrected by hearing aid | Deafness in both ears not completely corrected by hearing aid |
| **Musculoskeletal** | | |
| Amputation | Total ostectomy, femur<br>Disarticulation of elbow<br>Amputation through humerus, upper arm amputation<br>Disarticulation of shoulder<br>Interthoracoscapular amputation, forequarter amputation<br>Disarticulation of knee<br>Amputation above knee, amputation of leg through femur, amputation of thigh<br>Disarticulation of hip<br>Abdominopelvic amputation, hemipelvectomy, hindquarter amputation<br>Lower leg or ankle reattachment, reattachment of leg not otherwise specified<br>Traumatic amputation of arm and hand, unilateral, at or above elbow<br>Upper limb amputation<br>Lower limb amputation | Not applicable |
| Joint replacement | Major joint replacement | Not applicable |

| | | |
|---|---|---|
| **Neurologic** | | |
| Balance | Problems with balance or ability to manipulate objects, severe | Problems with balance or ability to manipulate objects, disabling |
| Paralysis | Disorders of accessory ($11^{th}$) nerve | Hemiplegia; quadriplegia |
| Other neurologic conditions | Intracranial ventricular shunt or anastomosis<br>Ventricular shunt to abdominal cavity and organs<br>Irrigation and exploration of ventricular shunt<br>Replacement of ventricular shunt<br>Multiple sclerosis<br>Difficulty in walking | Coma |
| **Pulmonary** | | |
| Emphysema | Emphysema, requiring medication | Not applicable |
| Pulmonary fibrosis | Requiring oxygen therapy | Not applicable |
| Other respiratory conditions | Primary pulmonary hypertension | Chronic respiratory failure<br>Respiratory arrest<br>Respirator dependency status |
| **Renal** | | |
| Renal failure | Not applicable | Dialysis or kidney transplant |
| Urinary incontinence | Neurogenic bladder | Not applicable |
| Other renal conditions | Nephrotic syndrome with unspecified pathologic lesion in kidney | Rupture of bladder, nontraumatic |
| **Secondary neoplasms** | | |
| | Thyroid carcinoma<br>Benign meningiomas requiring resection<br>Lobular cancer in situ of the breast | Invasive malignancies<br>Ductal carcinoma in situ of the breast |
| **Vision and eye** | | |
| Cataract | Cataracts, requiring surgery | Not applicable |
| Blindness | Legally blind in only one eye | Legally blind in both eyes or loss of an eye |

**Appendix Table 2. Descriptive characteristics of CCSS participants with and without data collected on treatment exposures.**

| | | Missing Treatment Information[1] N=1909 | | Treatment Information N=21692 | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| Sex | Female | 760 | 39.8 | 10187 | 47.0 |
| | Male | 1149 | 60.2 | 11505 | 53.0 |
| Race/ethnicity | Non-Hispanic White | 1386 | 72.6 | 17960 | 82.8 |
| | Non-Hispanic Black | 269 | 14.1 | 1231 | 5.7 |
| | Hispanic | 160 | 8.4 | 1624 | 7.5 |
| | Other | 94 | 4.9 | 877 | 4.0 |
| Age at diagnosis | 0-9 | 1230 | 64.4 | 13581 | 62.6 |
| | 10-20 | 679 | 35.6 | 8111 | 37.4 |
| Time since diagnosis | 5-9 years | 123 | 6.4 | 1162 | 5.4 |
| | 10-19 years | 668 | 35.0 | 8748 | 40.3 |
| | 20-29 years | 831 | 43.5 | 9033 | 41.6 |
| | 30+ years | 287 | 15.0 | 2749 | 12.7 |
| Diagnosis | Acute lymphoblastic leukemia | 535 | 28.0 | 5613 | 25.9 |
| | Acute myeloid leukemia | 44 | 2.3 | 822 | 3.8 |
| | Astrocytomas | 171 | 9.0 | 2423 | 11.2 |
| | Ewing sarcoma | 52 | 2.7 | 662 | 3.1 |
| | Hodgkin lymphoma | 267 | 14.0 | 2729 | 12.6 |
| | Wilms tumor | 195 | 10.2 | 1953 | 9.0 |
| | Medulloblastoma, PNET | 58 | 3.0 | 939 | 4.3 |
| | Neuroblastoma | 142 | 7.4 | 1696 | 7.8 |
| | Non-Hodgkin lymphoma | 178 | 9.3 | 1754 | 8.1 |
| | Osteosarcoma | 106 | 5.6 | 1099 | 5.1 |
| | Soft tissue sarcoma | 89 | 4.7 | 1073 | 4.9 |
| | Other diagnoses | 72 | 3.8 | 929 | 4.2 |
| Highest level of education | ≤High school graduate | 813 | 42.6 | 7332 | 33.8 |
| | >High school graduate | 1047 | 54.8 | 14157 | 65.3 |
| | Unknown | 49 | 2.6 | 203 | 0.9 |
| Household income | <$60,000 | 1078 | 56.5 | 11377 | 52.5 |
| | $60,000+ | 516 | 27.0 | 8227 | 37.9 |
| | Unknown | 315 | 16.5 | 2088 | 9.6 |
| CTCAE chronic health conditions | Any grade 3-5 condition | 672 | 35.2 | 7633 | 35.2 |
| | 2 or more grade 3-5 conditions | 224 | 11.7 | 2725 | 12.6 |

[1] Participants did not provide consent for release of medical records

**Appendix Table 3. Proportion of baseline participants at each 5-year follow-up interval who were eligible to provide outcome data within that interval but were missing data due to non-response to follow-up questionnaires.**

| | | Missing Data Due to Non-Response Beyond This Point of Follow-Up | | |
|---|---|---|---|---|
| | | 10 years post-diagnosis | 15 years post-diagnosis | 20 years post-diagnosis |
| | | % | % | % |
| Year of diagnosis | 1970-1979[1] | 0.0 | 0.1 | 5.0 |
| | 1980-1989 | 1.4 | 9.0 | 21.6 |
| | 1990-1999[2] | 0.0 | 0.0 | 0.0 |
| Sex | Female | 0.5 | 3.6 | 12.5 |
| | Male | 0.6 | 4.7 | 15.5 |
| Race/Ethnicity | Non-Hispanic white | 0.5 | 3.6 | 12.7 |
| | Non-Hispanic black | 0.7 | 7.0 | 24.4 |
| | Hispanic | 0.7 | 5.7 | 19.3 |
| | Other | 0.6 | 9.8 | 23.3 |
| Age at Primary Diagnosis(yrs) | 0-4 | 0.5 | 4.5 | 16.0 |
| | 5-9 | 0.8 | 5.0 | 15.0 |
| | 10-14 | 0.7 | 3.6 | 12.5 |
| | 15-20 | 0.4 | 3.0 | 9.7 |
| Primary Diagnosis | Acute lymphoblastic leukemia | 0.8 | 5.3 | 17.1 |
| | Acute myeloid leukemia | 0.2 | 2.8 | 10.7 |
| | Bone tumors | 0.7 | 3.6 | 12.4 |
| | CNS tumors | 0.5 | 3.6 | 12.7 |
| | Hodgkin lymphoma | 0.4 | 3.5 | 10.9 |
| | Wilms tumor | 0.1 | 3.8 | 15.0 |
| | Neuroblastoma | 0.5 | 3.6 | 14.0 |
| | Non-Hodgkin lymphoma | 0.9 | 5.2 | 14.9 |
| | Soft tissue sarcoma | 0.4 | 4.1 | 11.7 |
| Age at baseline | 0-19 | 1.3 | 9.8 | 28.3 |
| | 20-29 | 0.4 | 2.8 | 10.8 |
| | 30-39 | 0.0 | 0.9 | 4.5 |
| | 40+ | 0.0 | 0.0 | 0.0 |
| Health Status at baseline | Excellent | 0.7 | 5.3 | 18.1 |
| | Fair | 0.5 | 4.0 | 11.9 |
| | Good | 0.4 | 4.1 | 12.6 |
| | Poor | 1.2 | 3.6 | 11.9 |
| | Very good | 0.6 | 3.9 | 13.4 |
| Education at baseline | <18 years of age | 4.7 | 16.5 | 35.3 |
| | ≤ High school | 1.2 | 9.2 | 26.9 |
| | Post-high school/some college | 0.4 | 2.8 | 10.5 |
| | College graduate | 0.1 | 1.3 | 5.3 |

[1] The baseline questionnaire was administered to survivors diagnosed from 1970-1986 starting in 1992.

99% of survivors diagnosed from 1970-79 were at least 15 years post-diagnosis at the time of the baseline questionnaire, and 100% were at least 10 years post-diagnosis.

[2] Survivors diagnosed from 1987-1999 were administered the baseline questionnaire starting in 2008, and all data for this group was obtained from the baseline questionnaire.

**Appendix Table 4. Treatment exposures by diagnosis decade within specific primary cancer diagnosis groups**

| | | 1970-1979 | | 1980-1989 | | 1990-1999 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| **Acute lymphoblastic leukemia** | | | | | | | |
| Participants with treatment information | | 1602 | | 2608 | | 1403 | |
| Cranial RT max dose (Gy) | None | 247 | 16·1 | 1113 | 43·9 | 992 | 72·4 |
| | >0 - <20 | 337 | 22·0 | 1038 | 41·0 | 298 | 21·8 |
| | ≥20 | 950 | 61·9 | 382 | 15·1 | 80 | 5·8 |
| | Unknown | 68 | | 75 | | 33 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 1027 | 68·1 | 1150 | 46·2 | 171 | 12·6 |
| | 1-<150 | 124 | 8·2 | 514 | 20·6 | 680 | 50·1 |
| | 150-<300 | 138 | 9·2 | 680 | 16·5 | 393 | 29·0 |
| | 300-<450 | 130 | 8·6 | 298 | 12·0 | 105 | 7·7 |
| | 450-<600 | 74 | 4·9 | 91 | 3·7 | 4 | 0·3 |
| | ≥600 | 16 | 1·1 | 27 | 1·1 | 4 | 0·3 |
| | Unknown | 93 | | 118 | | 46 | |
| Epipodophyllotoxin ($mg/m^2$) | None | 1513 | 95·8 | 2057 | 81·3 | 837 | 61·2 |
| | 1-<1000 | 41 | 2·6 | 75 | 3·0 | 88 | 6·4 |
| | 1000-<4000 | 16 | 1·0 | 137 | 5·4 | 214 | 15·7 |
| | ≥4000 | 9 | 0·6 | 262 | 10·4 | 228 | 16·7 |
| | Unknown | 23 | | 77 | | 36 | |
| Methotrexate | No | 1073 | 68·6 | 1403 | 55·1 | 471 | 34·0 |
| | Yes | 491 | 31·4 | 1144 | 44·9 | 914 | 66·0 |
| | Unknown | 38 | | 61 | | 18 | |
| Steroids | None | 26 | 1·6 | 67 | 2·6 | 93 | 3·3 |
| | Prednisone only | 1454 | 91·3 | 2057 | 79·3 | 572 | 40·9 |
| | Dexamethasone only | 24 | 1·5 | 15 | 0·6 | 96 | 6·9 |
| | Both | 88 | 5·5 | 454 | 17·5 | 636 | 45·5 |
| | Unknown | 10 | | 15 | | 6 | |
| **Hodgkin lymphoma** | | | | | | | |
| Participants with treatment information | | 955 | | 943 | | 831 | |
| Any RT max dose (Gy) | None | 53 | 5·8 | 114 | 12·6 | 175 | 22·6 |
| | >0-<20 | 6 | 0·7 | 28 | 3·1 | 35 | 4·5 |
| | 20-<30 | 81 | 8·8 | 246 | 27·2 | 402 | 51·8 |
| | 30-<40 | 340 | 37·0 | 237 | 26·2 | 99 | 12·8 |
| | 40-<50 | 397 | 43·2 | 256 | 28·3 | 54 | 7·0 |
| | ≥50 | 43 | 4·7 | 24 | 2·7 | 11 | 1·4 |
| | Unknown | 35 | | 38 | | 55 | |
| Alkylating agent, cyclophosphamide equivalent dose ($mg/m^2$) | None | 358 | 47·0 | 329 | 40·3 | 226 | 29·1 |
| | 1-<4000 | 24 | 3·2 | 31 | 3·8 | 59 | 7·6 |
| | 4000-<8000 | 67 | 8·8 | 139 | 17·0 | 365 | 47·0 |
| | 8000-<12000 | 126 | 16·5 | 166 | 20·3 | 78 | 10·0 |
| | 12000-<16000 | 106 | 13·9 | 113 | 13·8 | 23 | 3·0 |
| | 16000-<20000 | 35 | 4·6 | 19 | 2·3 | 11 | 1·4 |
| | ≥20000 | 46 | 6·0 | 20 | 2·5 | 15 | 1·9 |
| | Unknown | 193 | | 126 | | 54 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 827 | 88·9 | 512 | 56·6 | 95 | 11·9 |
| | 1-<150 | 12 | 1·3 | 118 | 13·0 | 198 | 24·8 |
| | 150-<300 | 44 | 4·7 | 194 | 21·4 | 434 | 54·5 |
| | ≥300 | 47 | 5·1 | 81 | 9·0 | 70 | 8·8 |
| | Unknown | 25 | | 38 | | 34 | |
| Platinum ($mg/m^2$) | None | 944 | 99·8 | 929 | 99·2 | 779 | 95·0 |
| | 1-<400 | 2 | 0·2 | 7 | 0·8 | 23 | 2·8 |
| | ≥400 | 0 | 0·0 | 1 | 0·1 | 18 | 2·2 |
| | Unknown | 9 | | 6 | | 11 | |
| Bleomycin | No | 865 | 91·3 | 533 | 56·9 | 291 | 35·6 |
| | Yes | 82 | 8·7 | 403 | 43·1 | 526 | 64·4 |
| | Unknown | 8 | | 7 | | 14 | |
| Splenectomy | No | 233 | 24·5 | 381 | 41·1 | 672 | 90·3 |
| | Yes | 720 | 75·6 | 547 | 58·9 | 72 | 9·7 |
| | Unknown | 2 | | 15 | | 87 | |
| **Astrocytoma** | | | | | | | |
| Participants with treatment information | | 450 | | 869 | | 1104 | |
| Cranial RT max dose (Gy) | None | 150 | 35·5 | 394 | 48·1 | 759 | 71·8 |
| | >0-<50 | 147 | 34·8 | 147 | 17·9 | 67 | 6·3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 50-<60 | 98 | 23·2 | 229 | 27·9 | 192 | 18·2 |
| | ≥60 | 28 | 6·6 | 50 | 6·1 | 39 | 3·7 |
| | Unknown | 27 | | 49 | | 47 | |
| Alkylating agents | No | 397 | 88·2 | 724 | 83·3 | 945 | 85·6 |
| | Yes | 49 | 10·9 | 136 | 15·7 | 145 | 13·1 |
| | Unknown | 4 | | 9 | | 14 | |
| Platinum agents | No | 444 | 99·3 | 785 | 91·0 | 889 | 81·4 |
| | Yes | 3 | 0·7 | 78 | 9·0 | 203 | 18·6 |
| | Unknown | 3 | | 6 | | 12 | |
| **Wilms tumor** | | | | | | | |
| Participants with treatment information | | 454 | | 783 | | 716 | |
| Abdomen/pelvis RT max dose (Gy) | None | 102 | 23·1 | 377 | 49·7 | 358 | 52·1 |
| | >0-<20 | 44 | 10·0 | 173 | 22·8 | 293 | 42·7 |
| | 20-<30 | 149 | 33·7 | 177 | 23·3 | 23 | 3·4 |
| | 30-<40 | 120 | 27·2 | 23 | 3·0 | 10 | 1·5 |
| | ≥40 | 27 | 6·1 | 9 | 1·2 | 3 | 0·4 |
| | Unknown | 12 | | 24 | | 29 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 328 | 74·7 | 393 | 51·7 | 337 | 47·7 |
| | 1-<150 | 8 | 1·8 | 44 | 5·8 | 187 | 26·5 |
| | 150-<300 | 66 | 15·0 | 215 | 28·3 | 146 | 20·7 |
| | ≥300 | 37 | 8·4 | 108 | 14·2 | 37 | 5·2 |
| | Unknown | 15 | | 23 | | 9 | |
| Platinum agents | No | 453 | 99·8 | 768 | 98·3 | 664 | 92·7 |
| | Yes | 1 | 0·2 | 13 | 1·7 | 52 | 7·3 |
| | Unknown | 0 | | 2 | | 0 | |
| Vincristine | No | 63 | 14·2 | 32 | 4·2 | 22 | 3·1 |
| | Yes | 380 | 85·8 | 734 | 95·8 | 692 | 96·9 |
| | Unknown | 11 | | 17 | | 2 | |
| Splenectomy | No | 436 | 96·0 | 779 | 99·5 | 716 | 100·0 |
| | Yes | 18 | 4·0 | 4 | 0·5 | 0 | 0·0 |
| **Non-Hodgkin lymphoma** | | | | | | | |
| Participants with treatment information | | 380 | | 692 | | 682 | |
| Any RT max dose (Gy) | None | 72 | 19·8 | 350 | 52·1 | 573 | 86·0 |
| | >0-<20 | 24 | 6·6 | 95 | 14·1 | 48 | 7·2 |
| | 20-<30 | 104 | 28·7 | 146 | 21·7 | 11 | 1·7 |
| | 30-<40 | 108 | 29·8 | 50 | 7·4 | 18 | 2·7 |
| | 40-<50 | 42 | 11·6 | 23 | 3·4 | 15 | 2·3 |
| | ≥50 | 13 | 3·6 | 8 | 1·2 | 1 | 0·2 |
| | Unknown | 17 | | 20 | | 16 | |
| Alkylating agent, cyclophosphamide equivalent dose ($mg/m^2$) | None | 63 | 19·7 | 40 | 6·3 | 56 | 8·6 |
| | 1-<4000 | 50 | 15·6 | 143 | 22·5 | 158 | 24·2 |
| | 4000-<8000 | 38 | 11·9 | 177 | 27·8 | 268 | 41·0 |
| | 8000-<12000 | 66 | 20·6 | 133 | 20·9 | 125 | 19·1 |
| | 12000-<16000 | 45 | 14·1 | 67 | 10·5 | 17 | 2·6 |
| | 16000-<20000 | 23 | 7·2 | 51 | 8·0 | 15 | 2·3 |
| | ≥20000 | 35 | 10·9 | 25 | 3·9 | 14 | 2·1 |
| | Unknown | 60 | | 56 | | 29 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 206 | 59·0 | 192 | 29·5 | 76 | 11·6 |
| | 1-<100 | 8 | 2·3 | 15 | 2·3 | 75 | 11·4 |
| | 100-<250 | 32 | 9·2 | 178 | 27·3 | 365 | 55·5 |
| | 250-<400 | 60 | 17·2 | 193 | 29·6 | 127 | 19·3 |
| | ≥400 | 43 | 12·3 | 74 | 11·4 | 15 | 2·3 |
| | Unknown | 31 | | 40 | | 24 | |
| Platinum ($mg/m^2$) | None | 379 | 100·0 | 676 | 98·3 | 609 | 90·1 |
| | 1-<400 | 0 | 0·0 | 9 | 1·3 | 35 | 5·2 |
| | ≥400 | 0 | 0·0 | 3 | 0·4 | 32 | 4·7 |
| | Unknown | 1 | | 4 | | 6 | |
| Bleomycin | No | 355 | 93·9 | 654 | 94·7 | 672 | 98·8 |
| | Yes | 23 | 6·1 | 37 | 5·4 | 8 | 1·2 |
| | Unknown | 2 | | 1 | | 2 | |
| Methotrexate | No | 272 | 72·5 | 334 | 49·0 | 180 | 26·5 |
| | Yes | 103 | 27·5 | 348 | 51·0 | 499 | 73·5 |
| | Unknown | 5 | | 10 | | 3 | |
| Splenectomy | No | 353 | 93·1 | 677 | 98·0 | 682 | 100·0 |
| | Yes | 26 | 6·9 | 14 | 2·0 | 0 | 0·0 |
| | Unknown | 1 | | 1 | | 0 | |
| **Ewing sarcoma** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Participants with treatment information | | 179 | | 255 | | 228 | |
| Any RT max dose (Gy) | None | 21 | 12·3 | 77 | 31·4 | 104 | 48·2 |
| | >0-<40 | 13 | 7·6 | 33 | 13·5 | 22 | 10·2 |
| | 40-<50 | 21 | 12·3 | 34 | 13·9 | 29 | 13·4 |
| | ≥50 | 116 | 67·8 | 101 | 41·2 | 61 | 28·2 |
| | Unknown | 8 | | 10 | | 12 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 45 | 28·1 | 11 | 4·7 | 1 | 0·5 |
| | 1-<100 | 2 | 1·3 | 3 | 1·3 | 5 | 2·3 |
| | 100-<250 | 11 | 6·9 | 18 | 7·7 | 26 | 12·0 |
| | 250-<400 | 52 | 32·5 | 121 | 51·7 | 145 | 67·1 |
| | ≥400 | 50 | 31·3 | 81 | 34·6 | 39 | 18·1 |
| | Unknown | 19 | | 21 | | 12 | |
| Amputation surgery | None | 109 | 60·9 | 154 | 60·4 | 152 | 66·7 |
| | Limb-sparing | 50 | 27·9 | 67 | 26·3 | 55 | 24·1 |
| | Amputation | 20 | 11·2 | 34 | 13·3 | 21 | 9·2 |
| **Neuroblastoma** | | | | | | | |
| Participants with treatment information | | 388 | | 610 | | 698 | |
| Any RT max dose (Gy) | None | 145 | 38·2 | 405 | 68·9 | 501 | 74·0 |
| | >0-<20 | 88 | 23·2 | 86 | 14·6 | 58 | 8·6 |
| | 20-<30 | 80 | 21·1 | 52 | 8·8 | 86 | 12·7 |
| | 30-<40 | 50 | 13·2 | 25 | 4·3 | 24 | 3·6 |
| | ≥40 | 17 | 4·5 | 20 | 3·4 | 8 | 1·2 |
| | Unknown | 8 | | 22 | | 21 | |
| Alkylating agent, cyclophosphamide equivalent dose ($mg/m^2$) | None | 149 | 44·5 | 259 | 45·3 | 262 | 41·3 |
| | 1-<4000 | 23 | 6·9 | 50 | 8·7 | 92 | 14·5 |
| | 4000-<8000 | 37 | 11·0 | 120 | 21·0 | 143 | 22·5 |
| | 8000-<12000 | 27 | 8·1 | 60 | 10·5 | 32 | 5·0 |
| | 12000-<16000 | 30 | 9·0 | 34 | 5·9 | 46 | 7·2 |
| | 16000-<20000 | 24 | 7·2 | 19 | 3·3 | 25 | 3·9 |
| | ≥20000 | 45 | 13·4 | 30 | 5·2 | 35 | 5·5 |
| | Unknown | 53 | | 38 | | 63 | |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | 321 | 85·2 | 362 | 61·4 | 302 | 45·2 |
| | 1-<150 | 9 | 2·4 | 82 | 13·9 | 201 | 30·1 |
| | 150-<300 | 14 | 3·7 | 115 | 19·5 | 143 | 21·4 |
| | ≥300 | 33 | 8·8 | 31 | 5·3 | 22 | 3·3 |
| | Unknown | 11 | | 20 | | 30 | |
| Platinum ($mg/m^2$) | None | 370 | 97·1 | 436 | 74·3 | 328 | 49·9 |
| | 1-<400 | 7 | 1·8 | 62 | 10·6 | 75 | 11·4 |
| | ≥400 | 4 | 1·1 | 89 | 15·2 | 254 | 38·7 |
| | Unknown | 7 | | 23 | | 41 | |
| Epipodophyllotoxin ($mg/m^2$) | None | 370 | 96·9 | 456 | 77·2 | 330 | 50·5 |
| | 1-<1000 | 5 | 1·3 | 67 | 11·3 | 76 | 11·6 |
| | ≥1000 | 7 | 1·8 | 68 | 11·5 | 247 | 37·8 |
| | Unknown | 6 | | 19 | | 45 | |
| **Medulloblastoma/PNET** | | | | | | | |
| Participants with treatment information | | 135 | | 322 | | 482 | |
| Cranial RT max dose (Gy) | None | 3 | 2·3 | 12 | 4·0 | 39 | 8·5 |
| | >0-<50 | 54 | 42·2 | 71 | 23·5 | 34 | 7·4 |
| | ≥50 | 71 | 55·5 | 219 | 72·5 | 386 | 84·1 |
| | Unknown | 7 | | 20 | | 23 | |
| Alkylating agent, cyclophosphamide equivalent dose ($mg/m^2$) | None | 77 | 64·7 | 132 | 45·8 | 68 | 15·2 |
| | 1-<4000 | 4 | 3·4 | 26 | 9·0 | 23 | 5·1 |
| | 4000-<8000 | 8 | 6·7 | 17 | 5·9 | 64 | 14·3 |
| | 8000-<12000 | 12 | 10·1 | 45 | 15·6 | 146 | 32·6 |
| | 12000-<16000 | 11 | 9·2 | 47 | 16·3 | 61 | 13·6 |
| | 16000-<20000 | 5 | 4·2 | 9 | 3·1 | 46 | 10·3 |
| | ≥20000 | 2 | 1·7 | 12 | 4·2 | 40 | 8·9 |
| | Unknown | 16 | | 34 | | 34 | |
| Platinum ($mg/m^2$) | None | 132 | 99·3 | 187 | 60·5 | 83 | 18·3 |
| | 1-<400 | 0 | 0·0 | 59 | 19·1 | 153 | 33·7 |
| | ≥400 | 1 | 0·8 | 63 | 20·4 | 218 | 48·0 |
| | Unknown | 2 | | 13 | | 28 | |
| Vincristine | No | 76 | 63·3 | 127 | 41·8 | 73 | 15·3 |
| | Yes | 44 | 36·7 | 177 | 58·2 | 404 | 84·7 |
| | Unknown | 15 | | 18 | | 5 | |
| **Acute myeloid leukemia** | | | | | | | |
| Participants with treatment information | | 114 | | 314 | | 394 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Any RT max dose (Gy) | None | 62 | 56·4 | 179 | 61·5 | 293 | 75·3 |
| | >0-<20 | 18 | 16·4 | 85 | 29·2 | 84 | 21·6 |
| | ≥20 | 30 | 27·3 | 27 | 9·3 | 12 | 3·1 |
| | Unknown | 4 | | 23 | | 5 | |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | 38 | 39·6 | 111 | 38·3 | 190 | 50·9 |
| | 1-<4000 | 14 | 14·6 | 85 | 29·3 | 90 | 24·1 |
| | 4000-<8000 | 24 | 25·0 | 59 | 20·3 | 29 | 7·8 |
| | 8000-<12000 | 7 | 7·3 | 17 | 5·9 | 39 | 10·5 |
| | ≥12000 | 13 | 13·5 | 18 | 6·2 | 25 | 6·7 |
| | Unknown | 18 | | 24 | | 21 | |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | 29 | 28·2 | 16 | 5·5 | 14 | 3·6 |
| | 1-<300 | 23 | 22·3 | 150 | 51·4 | 265 | 68·8 |
| | 300-<450 | 22 | 21·4 | 95 | 32·5 | 95 | 24·7 |
| | ≥450 | 29 | 28·2 | 31 | 10·6 | 11 | 2·9 |
| | Unknown | 11 | | 22 | | 9 | |
| Epipodophyllotoxin (mg/m$^2$) | None | 105 | 92·1 | 118 | 39·5 | 60 | 15·8 |
| | 1-<1000 | 0 | 0·0 | 77 | 25·8 | 129 | 34·0 |
| | 1000-<4000 | 3 | 2·6 | 66 | 22·1 | 176 | 46·4 |
| | ≥4000 | 6 | 5·3 | 38 | 12·7 | 14 | 3·7 |
| | Unknown | 0 | | 15 | | 15 | |
| Dexamethasone | No | 108 | 98·2 | 196 | 63·8 | 194 | 49·5 |
| | Yes | 2 | 1·8 | 111 | 36·2 | 198 | 50·5 |
| | Unknown | 4 | | 7 | | 2 | |
| **Soft tissue sarcoma** | | | | | | | |
| Participants with treatment information | | 323 | | 412 | | 338 | |
| Any RT max dose (Gy) | None | 59 | 19·4 | 96 | 24·3 | 96 | 30·0 |
| | >0-<40 | 32 | 10·5 | 38 | 9·6 | 24 | 7·5 |
| | 40-<50 | 80 | 26·3 | 146 | 37·0 | 77 | 24·1 |
| | ≥50 | 133 | 43·8 | 115 | 29·1 | 123 | 38·4 |
| | Unknown | 19 | | 17 | | 18 | |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | 37 | 13·8 | 74 | 19·5 | 57 | 17·8 |
| | 1-<8000 | 42 | 15·7 | 47 | 12·4 | 21 | 6·5 |
| | 8000-<12000 | 36 | 13·4 | 64 | 16·9 | 29 | 9·0 |
| | 12000-<16000 | 30 | 11·2 | 70 | 18·5 | 21 | 6·5 |
| | 16000-<20000 | 39 | 14·6 | 69 | 18·2 | 20 | 6·2 |
| | ≥20000 | 84 | 31·3 | 55 | 14·5 | 173 | 53·9 |
| | Unknown | 55 | | 33 | | 17 | |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | 193 | 62·3 | 173 | 43·5 | 230 | 69·3 |
| | 1-<300 | 55 | 17·7 | 62 | 15·6 | 57 | 17·2 |
| | 300-<450 | 34 | 11·0 | 126 | 31·7 | 33 | 9·9 |
| | ≥450 | 28 | 9·0 | 37 | 9·3 | 12 | 3·6 |
| | Unknown | 13 | | 14 | | 6 | |
| **Osteosarcoma** | | | | | | | |
| Participants with treatment information | | 314 | | 425 | | 360 | |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | 163 | 56·2 | 126 | 32·2 | 104 | 30·3 |
| | 1-<4000 | 22 | 7·6 | 71 | 18·2 | 42 | 12·2 |
| | 4000-<8000 | 82 | 28·3 | 160 | 40·9 | 39 | 11·4 |
| | 8000-<12000 | 15 | 5·2 | 20 | 5·1 | 82 | 23·9 |
| | 12000-<16000 | 5 | 1·7 | 2 | 0·5 | 49 | 14·3 |
| | ≥16000 | 3 | 1·0 | 12 | 3·1 | 27 | 7·9 |
| | Unknown | 24 | | 34 | | 17 | |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | 56 | 20·1 | 51 | 13·1 | 20 | 5·8 |
| | 1-<300 | 53 | 19·0 | 100 | 25·7 | 66 | 19·1 |
| | 300-<450 | 90 | 32·3 | 165 | 42·4 | 197 | 56·9 |
| | ≥450 | 80 | 28·7 | 73 | 18·8 | 63 | 18·2 |
| | Unknown | 35 | | 36 | | 14 | |
| Platinum (mg/m$^2$) | None | 273 | 88·6 | 138 | 34·9 | 52 | 15·0 |
| | 1-<400 | 13 | 4·2 | 67 | 17·0 | 100 | 28·8 |
| | ≥400 | 22 | 7·1 | 190 | 48·1 | 195 | 56·2 |
| | Unknown | 6 | | 30 | | 13 | |
| Methotrexate, IV (mg/m$^2$) | None | 94 | 32·9 | 91 | 22·9 | 57 | 16·5 |
| | 1-<12000 | 45 | 15·7 | 59 | 14·8 | 61 | 17·6 |
| | ≥12000 | 147 | 51·4 | 248 | 62·3 | 228 | 65·9 |
| | Unknown | 28 | | 27 | | 14 | |

RT: radiation therapy; Gy: Gray; PNET: primitive neuroectodermal tumor; IV: intravenous administration
Percentages are among those with known values

**Appendix Table 5. Cumulative incidence of grade 3-5 chronic health conditions among siblings, with siblings stratified based on the diagnosis decade of their related survivor**

| | Time Period Post-Diagnosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 years | | 10 years | | 15 years | | 20 years | |
| Era | # at risk | Cumulative incidence (95% C.I.) | # at risk | Cumulative incidence (95% C.I.) | # at risk | Cumulative incidence (95% C.I.) | # at risk | Cumulative incidence (95% C.I.) |
| 1970-79 | 1757 | 0.1 (0.0- 0.3) | 1720 | 2.2 ( 1.5- 2.9) | 1679 | 3.6 ( 2.8- 4.5) | 1582 | 5.5 ( 4.5- 6.6) |
| 1980-89 | 2366 | 0.3 ( 0.1- 0.5) | 2298 | 1.1 ( 0.7- 1.5) | 2094 | 2.0 ( 1.4- 2.6) | 1606 | 3.5 ( 2.7- 4.3) |
| 1990-99[1] | 782 | 0.0 ( 0.0- 0.0) | 754 | 1.2 ( 0.4- 2.0) | 582 | 2.9 ( 1.7- 4.2) | 302 | 6.0 ( 4.0- 8.0) |

[1] When the CCSS cohort was expanded to include survivors diagnosed from 1987-1999, due to cost restraints, a smaller group of siblings was recruited compared to the original cohort (survivors diagnosed 1970-1986). This accounts for the smaller numbers of siblings at risk in the 1990-99 group.

**Appendix Table 6. Cumulative incidence of grade 3-5 chronic health conditions by cancer diagnosis at 15 years after primary cancer diagnosis among 5-year survivors**

| Cancer Diagnosis | Cumulative Incidence at 15 Years Post-Diagnosis (95% CI) | | | P-Values | | |
|---|---|---|---|---|---|---|
| | 1970-1979 | 1980-1989 | 1990-1999 | 1980s vs. 1970s | 1990s vs. 1970s | 1990s vs. 1980s |
| Acute lymphoblastic leukemia | 15·7 (14·1-17·4) | 14·5 (13·3-15·6) | 14·6 (13·5-15·8) | 0·22 | 0·28 | 0·84 |
| Acute myeloid leukemia | 19·1 (12·4-25·8) | 26·9 (22·0-31·7) | 25·7 (21·3-30·2) | 0·065 | 0·11 | 0·74 |
| Astrocytoma | 47·3 (42·9-51·7) | 41·0 (37·9-44·2) | 30·5 (27·8-33·2) | 0·022 | <0·0001 | <0·0001 |
| Medulloblastoma/PNET | 42·9 (34·9-50·9) | 50·4 (45·1-55·7) | 58·9 (54·4-63·3) | 0·12 | 0·00060 | 0·016 |
| Hodgkin lymphoma | 26·4 (23·8-29·1) | 22·1 (19·6-24·7) | 17·7 (15·0-20·5) | 0·021 | <0·0001 | 0·021 |
| Non-Hodgkin lymphoma | 23·8 (19·9-27·7) | 23·1 (20·1-26·1) | 16·9 (14·0-19·7) | 0·79 | 0·0053 | 0·0031 |
| Wilms tumor | 17·6 (14·3-20·8) | 15·5 (13·1-18·0) | 11·9 (9·5-14·3) | 0·32 | 0·034 | 0·0055 |
| Neuroblastoma | 18·0 (14·5-21·6) | 22·7 (19·5-25·9) | 25·0 (21·8-28·2) | 0·056 | 0·0045 | 0·32 |
| Soft tissue sarcoma | 36·5 (31·5-41·4) | 36·9 (32·4-41·4) | 28·3 (23·5-33·1) | 0·90 | 0·021 | 0·011 |
| Ewing sarcoma | 30·6 (24·3-37·0) | 35·6 (29·9-41·3) | 29·0 (23·0-35·0) | 0·25 | 0·71 | 0·12 |
| Osteosarcoma | 87·5 (84·1-91·0) | 75·7 (71·8-79·6) | 65·6 (60·6-70·6) | <0·0001 | <0·0001 | 0·0017 |

**Appendix Table 7. Cumulative incidence of grade 3-5 chronic health conditions by cancer diagnosis at 15 years after primary cancer diagnosis among 5-year survivors.**

| Cancer Diagnosis | Cumulative Incidence (%) at 15 Years Post-Diagnosis (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | 1970-1974 | 1975-1979 | 1980-1984 | 1985-1989 | 1990-1994 | 1995-1999 |
| Acute lymphoblastic leukemia | 14·6 (12·0-17·3) | 16·4 (14·3-18·6) | 15·1 (13·4-16·8) | 13·9 (12·3-15·5) | 12·3 (10·8-13·7) | 16·9 (15·2-18·6) |
| Acute myeloid leukemia | 12·1 (1·0-23·3) | 21·9 (13·7-30·1) | 28·4 (21·0-35·9) | 25·7 (19·4-32·0) | 23·5 (17·3-29·6) | 27·5 (21·1-33·8) |
| Astrocytoma | 46·1 (39·2-52·9) | 48·3 (42·7-54·0) | 39·2 (34·6-43·8) | 42·7 (38·3-47·0) | 30·9 (27·0-34·7) | 30·4 (26·4-34·5) |
| Medulloblastoma/PNET | 38·6 (24·2-53·0) | 44·7 (35·2-54·3) | 47·0 (39·2-54·9) | 53·2 (46·1-60·3) | 55·1 (48·6-61·6) | 63·1 (56·6-69·5) |
| Hodgkin lymphoma | 24·7 (20·9-28·4) | 28·0 (24·4-31·7) | 23·8 (20·4-27·3) | 20·0 (16·3-23·7) | 18·3 (14·5-22·2) | 17·5 (13·4-21·7) |
| Non-Hodgkin lymphoma | 28·0 (20·1-35·8) | 22·2 (17·7-26·7) | 21·1 (17·2-25·1) | 25·4 (20·9-30·0) | 13·7 (10·0-17·4) | 20·1 (15·6-24·6) |
| Wilms tumor | 18·3 (12·9-23·7) | 17·3 (13·2-21·3) | 14·7 (11·6-17·8) | 16·7 (12·9-20·5) | 10·0 (7·0-13·0) | 14·4 (10·4-18·3) |
| Neuroblastoma | 19·9 (14·0-25·9) | 17·0 (12·6-21·5) | 20·0 (15·8-24·2) | 25·8 (20·9-30·6) | 22·6 (18·0-27·2) | 27·2 (22·6-31·9) |
| Soft tissue sarcoma | 40·6 (32·8-48·3) | 33·6 (27·3-40·0) | 35·8 (29·4-42·1) | 38·1 (31·7-44·5) | 28·5 (21·8-35·3) | 28·1 (21·2-35·0) |
| Ewing sarcoma | 25·4 (14·1-36·7) | 32·9 (25·3-40·5) | 39·0 (31·1-47·0) | 31·9 (23·8-40·1) | 31·5 (22·0-41·0) | 28·2 (19·8-36·6) |
| Osteosarcoma | 88·8 (82·8-94·8) | 87·0 (82·8-91·2) | 78·9 (73·9-83·8) | 71·6 (65·4-77·8) | 64·0 (56·6-71·3) | 68·4 (60·9-75·8) |

**Appendix Table 8. Cumulative incidence of two or more grade 3-5 chronic health conditions by cancer diagnosis at 15 years after primary cancer diagnosis among 5-year survivors**

| Cancer Diagnosis | Cumulative Incidence at 15 Years Post-Diagnosis (95% CI) | | | P-Values | | |
|---|---|---|---|---|---|---|
| | 1970-1979 | 1980-1989 | 1990-1999 | 1980s vs. 1970s | 1990s vs. 1970s | 1990s vs. 1980s |
| Acute lymphoblastic leukemia | 4·3 (3·4-5·2) | 3·6 (3·0-4·2) | 3·2 (2·7-3·8) | 0·23 | 0·060 | 0·39 |
| Acute myeloid leukemia | 5·0 (1·2-8·7) | 12·1 (8·6-15·6) | 7·7 (5·0-10·4) | 0·0064 | 0·25 | 0·051 |
| Astrocytoma | 17·2 (13·9-20·5) | 16·0 (13·7-18·4) | 9·2 (7·4-10·9) | 0·57 | <0·0001 | <0·0001 |
| Medulloblastoma/PNET | 16·2 (10·3-22·2) | 22·1 (17·7-26·5) | 25·0 (21·1-28·9) | 0·12 | 0·015 | 0·34 |
| Hodgkin lymphoma | 5·1 (3·8-6·4) | 5·0 (3·7-6·3) | 4·0 (2·6-5·4) | 0·89 | 0·25 | 0·31 |
| Non-Hodgkin lymphoma | 3·5 (1·8-5·1) | 5·3 (3·7-6·9) | 4·5 (2·9-6·1) | 0·11 | 0·39 | 0·46 |
| Wilms tumor | 3·7 (2·1-5·3) | 2·8 (1·7-3·9) | 1·9 (0·9-2·9) | 0·35 | 0·062 | 0·25 |
| Neuroblastoma | 3·5 (1·8-5·2) | 6·6 (4·7-8·5) | 5·3 (3·6-7·0) | 0·016 | 0·15 | 0·30 |
| Soft tissue sarcoma | 10·8 (7·7-14·0) | 11·9 (8·9-14·9) | 6·3 (3·6-9·0) | 0·64 | 0·031 | 0·0063 |
| Ewing sarcoma | 9·5 (5·5-13·6) | 10·0 (6·4-13·6) | 9·0 (5·1-12·9) | 0·86 | 0·85 | 0·70 |
| Osteosarcoma | 14·1 (10·5-17·7) | 19·9 (16·3-23·6) | 19·2 (15·1-23·3) | 0·024 | 0·066 | 0·79 |

**Appendix Table 9. Results of multivariable regression models with and without treatment variables, by diagnosis group.** The specific treatment variables included for each diagnosis-specific model are listed in Appendix Tables 12 and 13 (pp. 29-32)

| Diagnosis | Prevalent Conditions at 5 Years Post-Diagnosis | | Incident Conditions 5-15 Years Post-Diagnosis | |
|---|---|---|---|---|
| | Model Unadjusted for Treatment | Model Adjusted for Treatment | Model Unadjusted for Treatment | Model Adjusted for Treatment |
| | PR (95% CI) | PR (95% CI) | HR (95% CI) | HR (95% CI) |
| Acute lymphoblastic leukemia | 1·05 (0·93-1·17) | 1·14 (0·95-1·36) | 0·85 (0·77-0·95) | 0·93 (0·79-1·10) |
| Acute myeloid leukemia | 1·14 (0·92-1·41) | 1·09 (0·81-1·48) | 0·87 (0·64-1·18) | 0·72 (0·43-1·20) |
| Hodgkin lymphoma | 0·87 (0·76-1·00) | 1·11 (0·88-1·40) | 0·75 (0·65-0·85) | 0·91 (0·73-1·12) |
| Non-Hodgkin lymphoma | 0·85 (0·75-0·97) | 0·75 (0·60-0·94) | 0·79 (0·63-0·99) | 0·96 (0·66-1·39) |
| Astrocytoma | 0·84 (0·78-0·89) | 0·88 (0·81-0·95) | 0·77 (0·64-0·92) | 0·89 (0·72-1·11) |
| Medulloblastoma/PNET | 1·20 (1·08-1·32) | 1·13 (0·98-1·31) | 1·14 (0·89-1·47) | 1·30 (0·91-1·84) |
| Wilms tumor | 1·18 (1·00-1·40) | 1·38 (1·09-1·74) | 0·57 (0·46-0·70) | 0·62 (0·44-0·86) |
| Neuroblastoma | 1·30 (1·16-1·44) | 0·93 (0·79-1·09) | 1·01 (0·80-1·26) | 0·83 (0·57-1·21) |
| Ewing sarcoma | 1·17 (0·99-1·39) | 1·09 (0·88-1·35) | 0·69 (0·52-0·91) | 0·82 (0·56-1·21) |
| Osteosarcoma | 0·87 (0·84-0·90) | 0·85 (0·80-0·91) | 0·96 (0·69-1·34) | 0·83 (0·54-1·29) |
| Soft tissue sarcoma | 0·89 (0·79-1·00) | 0·95 (0·84-1·08) | 0·96 (0·76-1·23) | 0·98 (0·73-1·32) |

Note: all models were adjusted for sex and attained age (cubic spline)

**Appendix Table 10. Statistical evaluation of treatment variables as a mediator of the association between diagnosis decade and rates of grade 3-5 chronic conditions**

| Diagnosis | p-value |
|---|---|
| Hodgkin lymphoma | 0·024 |
| Non-Hodgkin lymphoma | 0·088 |
| Wilms tumor | 0·27 |
| Acute lymphoblastic leukemia | 0·21 |
| Astrocytoma | 0·0085 |

The difference in regression coefficients for diagnosis decade from models with and without relevant treatment variables (potential mediator) included was evaluated based on 1000 bootstrap samples, with a null hypothesis of no difference or positive change. P-value is based on the proportion of samples with a negative change between coefficients (with – without), indicating significant attenuation.

**Appendix Table 11. Prevalence ratio or hazard ratio per decade of grade 3-5 chronic health conditions by organ system at 15 years after primary cancer diagnosis among 5-year survivors.** Prevalence ratio models examined conditions prevalent at study entry among 5-year survivors. Hazard ratios examined conditions that occurred 5-15 years post-diagnosis.

| Chronic Conditions by Organ System | Per Decade Prevalence Ratio (95% CI) | Per Decade Hazard Ratio (95% CI) |
|---|---|---|
| **Endocrine** | 0·82 (0·72-0·93) | 0·61 (0·55-0·68) |
| Thyroid nodules requiring surgery | 0·63 (0·49-0·81) | 0·70 (0·59-0·83) |
| Gonadal dysfunction | 0·74 (0·62-0·89) | 0·38 (0·32-0·45) |
| Diabetes mellitus requiring insulin | 1·59 (1·09-2·34) | 1·53 (1·16-2·01) |
| **2nd Malignant Neoplasms** | 1·20 (0·85-1·68) | 0·82 (0·73-0·92) |
| **Cardiovascular** | 1·05 (0·95-1·16) | 0·93 (0·85-1·03) |
| Congestive heart failure | 0·72 (0·54-0·96) | 1·03 (0·84-1·25) |
| Myocardial infarction | 0·88 (0·56-1·39) | 0·85 (0·64-1·12) |
| Stroke | 1·15 (0·99-1·34) | 0·95 (0·80-1·12) |
| Thromboembolic disease | 0·99 (0·84-1·17) | 0·89 (0·76-1·04) |
| **Neurological** | 0·97 (0·90-1·05) | 0·79 (0·68-0·92) |
| Memory problems | 1·18 (1·06-1·32) | 1·14 (0·87-1·49) |
| Balance problems | 1·28 (1·08-1·52) | 1·34 (0·91-1·99) |
| Paralysis | 0·43 (0·38-0·49) | 0·42 (0·33-0·54) |
| **Hearing Loss** | 1·37 (1·25-1·50) | 1·19 (1·04-1·36) |
| **Visual impairment** | 0·91 (0·84-0·99) | 1·10 (0·95-1·27) |
| Cataracts requiring surgery | 1·24 (0·98-1·57) | 1·21 (0·98-1·49) |
| Blindness | 0·86 (0·79-0·94) | 1·00 (0·84-1·19) |
| **Gastrointestinal** | 0·84 (0·72-0·97) | 0·72 (0·60-0·88) |
| Intestinal obstruction | 0·76 (0·65-0·87) | 0·66 (0·53-0·83) |
| Hepatitis | 1·51 (0·95-2·39) | 0·80 (0·54-1·17) |
| **Musculoskeletal** | 0·69 (0·64-0·75) | 1·13 (0·95-1·35) |
| Amputation | 0·47 (0·43-0·52) | 0·80 (0·60-1·06) |
| Major joint replacement | 1·67 (1·44-1·95) | 1·47 (1·18-1·82) |
| **Respiratory** | 1·42 (1·01-2·00) | 0·89 (0·68-1·17) |
| Pulmonary fibrosis | 2·28 (1·50-3·46) | 1·30 (0·87-1·96) |
| **Renal** | 1·42 (1·13-1·79) | 1·01 (0·78-1·31) |
| Dialysis | 1·48 (1·16-1·88) | 0·98 (0·76-1·28) |

**Appendix Table 12. Hazard ratios for association between diagnosis decade and grade 3-5 chronic health conditions among 5-year survivors of childhood cancer and the impact of adding specific treatment exposures to multivariable Cox regression models.**

| | | Model without treatment variables | Model with treatment variables |
|---|---|---|---|
| | | HR (95% CI) | HR (95% CI |
| **Acute lymphoblastic leukemia** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·85 (0·77-0·95)** | **0·93 (0·79-1·10)** |
| Cranial RT max dose (Gy) | None | | 1·00 (reference) |
| | >0 - <20 | | 2·19 (1·74-2·74) |
| | ≥20 | | 2·96 (2·29-3·83) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 1·02 (0·77-1·36) |
| | 150-<300 | | 1·00 (0·74-1·36) |
| | 300-<450 | | 1·20 (0·86-1·69) |
| | 450-<600 | | 1·31 (0·77-2·23) |
| | ≥600 | | 2·00 (0·92-4·34) |
| Epipodophyllotoxin (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<1000 | | 2·25 (1·56-3·24) |
| | 1000-<4000 | | 1·42 (1·04-1·95) |
| | ≥4000 | | 1·68 (1·24-2·26) |
| Methotrexate | No | | 1·00 (reference) |
| | Yes | | 1·18 (0·95-1·46) |
| Steroids | None | | 1·00 (reference) |
| | Prednisone only | | 0·38 (0·27-0·54) |
| | Dexamethasone only | | 0·50 (0·28-0·91) |
| | Both | | 0·56 (0·39-0·80) |
| **Hodgkin lymphoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·75 (0·65-0·85)** | **0·91 (0·73-1·12)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 0·87 (0·20-3·84) |
| | 20-<30 | | 2·71 (1·52-4·84) |
| | 30-<40 | | 3·27 (1·78-6·00) |
| | 40-<50 | | 3·33 (1·76-6·30) |
| | ≥50 | | 3·60 (1·49-8·69) |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<4000 | | 0·86 (0·41-1·79) |
| | 4000-<8000 | | 1·33 (0·91-1·94) |
| | 8000-<12000 | | 1·24 (0·87-1·78) |
| | 12000-<16000 | | 1·26 (0·83-1·91) |
| | 16000-<20000 | | 1·48 (0·71-3·08) |
| | ≥20000 | | 2·88 (1·64-5·07) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 0·85 (0·45-1·61) |
| | 150-<300 | | 1·12 (0·67-1·88) |
| | ≥300 | | 1·06 (0·55-2·03) |
| Platinum (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<400 | | 2·12 (0·83-5·43) |
| | ≥400 | | 1·13 (0·34-3·75) |
| Bleomycin | No | | 1·00 (reference) |
| | Yes | | 1·22 (0·81-1·84) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | 1·20 (0·89-1·62) |
| **Astrocytoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·77 (0·64-0·92)** | **0·89 (0·72-1·11)** |
| Cranial RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<50 | | 1·91 (1·08-3·37) |
| | 50-<60 | | 2·75 (1·91-3·95) |
| | ≥60 | | 3·71 (2·08-6·64) |
| Alkylating agents | No | | 1·00 (reference) |
| | Yes | | 1·82 (1·21-2·75) |
| Platinum | No | | 1·00 (reference) |
| | Yes | | 1·65 (1·01-2·70) |
| **Wilms tumor** | | | |

| | | | |
|---|---|---|---|
| **Diagnosis decade** | **Per 10 years** | **0·57 (0·46-0·70)** | **0·62 (0·44-0·86)** |
| Abdomen/pelvis RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 1·28 (0·68-2·41) |
| | 20-<30 | | 1·99 (1·11-3·54) |
| | 30-<40 | | 2·24 (1·13-4·42) |
| | ≥40 | | 2·23 (0·72-6·95) |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 1·48 (0·70-3·14) |
| | 150-<300 | | 0·94 (0·55-1·60) |
| | ≥300 | | 1·90 (1·11-3·27) |
| Platinum | No | | 1·00 (reference) |
| | Yes | | 3·31 (1·50-7·31) |
| Vincristine | No | | 1·00 (reference) |
| | Yes | | 1·22 (0·55-2·67) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | 1·96 (0·71-5·39) |
| **<u>Non-Hodgkin lymphoma</u>** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·79 (0·63-0·99)** | **0·96 (0·66-1·39)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 1·02 (0·47-2·22) |
| | 20-<30 | | 1·41 (0·76-2·63) |
| | 30-<40 | | 2·51 (1·36-4·63) |
| | 40-<50 | | 2·56 (1·13-5·82) |
| | ≥50 | | 1·04 (0·14-8·01) |
| Alkylating agent, cyclophosphamide equivalent dose ($mg/m^2$) | None | | 1·00 (reference) |
| | 1-<4000 | | 1·25 (0·53-2·93) |
| | 4000-<8000 | | 1·36 (0·63-2·97) |
| | 8000-<12000 | | 1·22 (0·54-2·76) |
| | 12000-<16000 | | 0·82 (0·28-2·38) |
| | 16000-<20000 | | 1·49 (0·52-4·25) |
| | ≥20000 | | 1·37 (0·49-3·85) |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | | 1·00 (reference) |
| | 1-<100 | | 2·88 (1·18-7·05) |
| | 100-<250 | | 1·33 (0·68-2·61) |
| | 250-<400 | | 2·15 (1·14-4·08) |
| | ≥400 | | 2·41 (1·15-5·05) |
| Platinum ($mg/m^2$) | None | | 1·00 (reference) |
| | 1-<400 | | 0·36 (0·05-2·74) |
| | ≥400 | | 2·83 (1·05-7·59) |
| Bleomycin | No | | 1·00 (reference) |
| | Yes | | 0·36 (0·09-1·54) |
| Methotrexate | No | | 1·00 (reference) |
| | Yes | | 0·68 (0·43-1·07) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | 2·17 (0·80-5·89) |
| **<u>Ewing sarcoma</u>** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·69 (0·52-0·91)** | **0·82 (0·56-1·21)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<40 | | 4·24 (1·56-11·5) |
| | 40-<50 | | 3·10 (1·18-8·16) |
| | ≥50 | | 3·12 (1·35-7·25) |
| Anthracycline, doxorubicin equivalent dose ($mg/m^2$) | None | | 1·00 (reference) |
| | 1-<100 | | 3·34 (0·36-31·3) |
| | 100-<250 | | 1·28 (0·32-5·03) |
| | 250-<400 | | 1·88 (0·67-5·23) |
| | ≥400 | | 2·37 (0·86-6·55) |
| Amputation surgery | None | | 1·00 (reference) |
| | Limb-sparing | | 1·79 (0·52-6·09) |
| | Amputation | | 1·17 (0·65-2·09) |

RT: radiation therapy; Gy: Gray;

Note: All models include sex and attained age (cubic splines)

**Appendix Table 13. Prevalence ratios for association between diagnosis decade and grade 3-5 chronic health conditions in the first 5 years post-diagnosis among 5-year survivors of childhood cancer and the impact of adding specific treatment exposures to multivariable regression models.**

| | | Model without treatment variables | Model with treatment variables |
|---|---|---|---|
| | | PR (95% CI) | PR (95% CI |
| **Hodgkin lymphoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·87 (0·76-1·00)** | **1·11 (0·88-1·40)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 1·29 (0·49-3·37) |
| | 20-<30 | | 1·18 (0·72-1·95) |
| | 30-<40 | | 1·75 (1·00-3·07) |
| | 40-<50 | | 2·83 (1·57-5·10) |
| | ≥50 | | 3·72 (1·67-8·32) |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<4000 | | 2·24 (1·34-3·74) |
| | 4000-<8000 | | 1·12 (0·72-1·76) |
| | 8000-<12000 | | 1·12 (0·74-1·70) |
| | 12000-<16000 | | 1·19 (0·79-1·79) |
| | 16000-<20000 | | 1·67 (0·91-3·09) |
| | ≥20000 | | 1·92 (1·11-3·32) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 0·52 (0·26-1·02) |
| | 150-<300 | | 0·58 (0·33-1·00) |
| | ≥300 | | 0·55 (0·26-1·18) |
| Platinum (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<400 | | 0·41 (0·05-3·32) |
| | ≥400 | | 0·99 (0·33-3·00) |
| Bleomycin | No | | 1·00 (reference) |
| | Yes | | 2·28 (1·44-3·60) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | 1·31 (0·95-1·79) |
| **Wilms tumor** | | | |
| **Diagnosis decade** | **Per 10 years** | **1·18 (1·00-1·40)** | **1·38 (1·09-1·74)** |
| Abdomen/pelvis RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 1·61 (1·06-2·46) |
| | 20-<30 | | 3·14 (1·92-5·12) |
| | 30-<40 | | 3·02 (1·56-5·84) |
| | ≥40 | | 14·8 (6·83-31·9) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 1·52 (0·91-2·55) |
| | 150-<300 | | 1·32 (0·87-1·99) |
| | ≥300 | | 1·84 (1·08-3·12) |
| Platinum | No | | 1·00 (reference) |
| | Yes | | 1·99 (1·17-3·37) |
| Vincristine | No | | 1·00 (reference) |
| | Yes | | 0·85 (0·51-1·43) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | - |
| **Non-Hodgkin lymphoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·85 (0·75-0·97)** | **0·75 (0·60-0·94)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 0·90 (0·58-1·39) |
| | 20-<30 | | 0·91 (0·65-1·29) |
| | 30-<40 | | 1·42 (0·89-2·28) |
| | 40-<50 | | 2·64 (1·42-4·92) |
| | ≥50 | | 4·75 (2·02-11·2) |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<4000 | | 1·42 (0·88-2·29) |
| | 4000-<8000 | | 1·04 (0·63-1·72) |
| | 8000-<12000 | | 0·97 (0·58-1·62) |
| | 12000-<16000 | | 0·85 (0·48-1·51) |
| | 16000-<20000 | | 0·89 (0·47-1·68) |
| | ≥20000 | | 0·67 (0·29-1·54) |
| | None | | 1·00 (reference) |

| | | | |
|---|---|---|---|
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | 1-<100 | | 1·16 (0·69-1·94) |
| | 100-<250 | | 1·08 (0·77-1·52) |
| | 250-<400 | | 1·15 (0·80-1·65) |
| | ≥400 | | 0·65 (0·34-1·24) |
| Platinum (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<400 | | 1·44 (0·72-2·88) |
| | ≥400 | | 0·90 (0·37-2·17) |
| Bleomycin | No | | 1·00 (reference) |
| | Yes | | 1·78 (0·95-3·33) |
| Methotrexate | No | | 1·00 (reference) |
| | Yes | | 1·52 (1·15-2·01) |
| Splenectomy | No | | 1·00 (reference) |
| | Yes | | 1·27 (0·41-4·00) |
| **Neuroblastoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **1·30 (1·16-1·44)** | **0·93 (0·79-1·09)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<20 | | 0·86 (0·67-1·11) |
| | 20-<30 | | 1·71 (1·30-2·24) |
| | 30-<40 | | 2·40 (1·49-3·86) |
| | ≥40 | | 4·13 (2·05-8·30) |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<4000 | | 0·55 (0·37-0·81) |
| | 4000-<8000 | | 0·74 (0·52-1·05) |
| | 8000-<12000 | | 0·74 (0·47-1·14) |
| | 12000-<16000 | | 1·04 (0·68-1·57) |
| | 16000-<20000 | | 0·96 (0·57-1·61) |
| | ≥20000 | | 0·84 (0·55-1·27) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<150 | | 1·50 (1·07-2·11) |
| | 150-<300 | | 1·58 (1·15-2·16) |
| | ≥300 | | 1·72 (1·13-2·63) |
| Platinum (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<400 | | 1·35 (0·73-2·50) |
| | ≥400 | | 1·50 (0·90-2·51) |
| Epipodophyllotoxin (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<1000 | | 1·38 (0·75-2·54) |
| | 1000-<4000 | | 1·53 (0·92-2·55) |
| | ≥4000 | | 2·59 (1·38-4·86) |
| **Soft tissue sarcoma** | | | |
| **Diagnosis decade** | **Per 10 years** | **0·89 (0·79-1·00)** | **0·95 (0·84-1·08)** |
| Any RT max dose (Gy) | None | | 1·00 (reference) |
| | >0-<40 | | 1·95 (1·15-3·31) |
| | 40-<50 | | 2·56 (1·69-3·87) |
| | ≥50 | | 3·83 (2·55-5·77) |
| Anthracycline, doxorubicin equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<300 | | 1·31 (1·01-1·70) |
| | 300-<450 | | 1·28 (0·98-1·66) |
| | ≥450 | | 1·17 (0·76-1·82) |
| Alkylating agent, cyclophosphamide equivalent dose (mg/m$^2$) | None | | 1·00 (reference) |
| | 1-<8000 | | 0·93 (0·62-1·40) |
| | 8000-<12000 | | 0·79 (0·55-1·15) |
| | 12000-<16000 | | 0·78 (0·53-1·15) |
| | 16000-<20000 | | 0·78 (0·54-1·14) |
| | ≥20000 | | 0·73 (0·51-1·03) |

RT: radiation therapy; Gy: Gray;

Note: All models include sex and attained age (cubic spline)