### Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| Main source publication           | Leisenring et al. 2009 (32); Robison et al. 2009 (33) | Hudson et al. 2011 (34); Howell et al. 2021 (35) | Evans et al. 1991 (36); Lange et al. 2014 (37) | Teepen et al. 2017 (10) | Demoor-Goldschmidt et al. 2020 (38); Gbetchedji et al. 2020 (39) | Michel et al. 2008 (40); Kuehni et al. 2012 (41) | Van Leeuwen et al. 2000 (42); De Bruin et al. 2009 (43); Van Eggermond et al. 2017 (44) |

### Study Methodology

| Setting | Multi-institutional cohort study | Single-center study* | Multi-institutional cohort study | Multi-institutional cohort study | Nationwide population-based cohort study | Multi-institutional cohort study |
|---------|---------------------------------|----------------------|---------------------------------|---------------------------------|------------------------------------------|---------------------------------|
| Source for cohort identification | 31 children’s hospitals in the United States and Canada | Diagnosis of childhood malignancy treated at SJCRH | Clinical Trial databases of the NWTSG as basis for the Long Term Follow up Study | 7 pediatric oncology/hematology centers, including 2 hematopoietic stem cell transplant centers | 5-Pediatric Oncology-Department s of CLCC (Center for Struggle Against Cancer) in France | Swiss Childhood Cancer Registry |
| HL patients treated in 7 Dutch University Hospitals or Cancer Centers |
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|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| **Treatment exposure assessment** | - Data abstraction from medical records (ie, chemotherapy, radiation therapy, and surgery) - Region- and organ-based dosimetry from copies of all RT records for later dose reconstruction† | - Data abstraction from medical records | NWTSG Clinical Trial Database | - Medical record abstraction by trained data management staff - Digitization of RT paper-based records - Storage of X-ray reports | - Data abstraction from medical records (ie, chemotherapy, radiation therapy, and surgery) - Whole body and organ dosimetry from copies of RT records | Medical record abstraction | Medical record abstraction |
| **Follow-up methods** | Self-reported/next of kin reported health surveys or followed by a telephone call with validation of subsequent neoplasms. National Death Index | - Systematic clinical assessments supplemented by medical record validation of self- | - Bi-annual contact with family and health updates by treating center twice yearly | - Medical record abstraction - Central Bureau for Genealogy (vital status, decedents) - Centralized municipal resident | - National death certificate data - National Public and Private Hospitals | Medical record abstractions - Questionnaires surveys to patients or parents | - Medical records - Netherland s Cancer Registry - Vital status |

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| Participating collaborative groups | CCSS          | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|---------------|--------|-------|-------------|-------|-------|-----|
| SMN outcome assessment            | - Repeated questionnaire surveys; medical validation (including a pathology/oncology report review panel for subsequent malignancies, or the patient) | - Comprehensive clinical evaluation on the SJCRH campus | - At baseline (5 yr survival) abstraction of medical record for health outcomes | - Record linkage with national registries (cancer, pathology reports, hospital discharge diagnoses) | - Algorithms for identification of the SMN from the ICD codes and the drugs codes in the SNDS | - Causes of death and death records from the Swiss mortality statistics in the Swiss Federal Statistical Office | Up to 2004: - Medical records - By contacting general practitioners - By attending |
|                                   |               | reported health events | - Cancer Registry | registry database (tracing) and vital status | and National Health Insurance Database (SNDS) | - Hospital clinical files | - Linkage to cantonal cancer registries |
|                                   |               | - For decedents: Next-of-Kin contact |                        | | - Long term follow-up visits | - Self-completed questionnaires | - Linkage to national mortality statistics and birth statistics (Federal Statistical Office) |

for late mortality. Tracing protocol using multiple publicly available sources\(^1\), including e.g. Social Security Administration and National Death Index
**Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer**

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| **and/or parent response or death certificate and/or other institutional records were reviewed)** | | | | | | | |
| - Vital status and the cause of death were determined through the National Death Index (NDI) | | | | | | | |
| **Source for population cancer rates** | U.S. SEER Cancer Registries (National Cancer institute) | U.S. SEER Cancer Registries (National Cancer institute) | U.S. SEER Cancer Registries (National Cancer institute) | Netherlands Cancer Registry | FRANCIM (French Cancer Registry Network) | Swiss Childhood Cancer Registry and National Agency for Cancer Registration (www.nacr.ch) | Swiss Childhood Cancer Registry and National Agency for Cancer Registration (www.nacr.ch) |
| - Systematic clinical assessments except limited to risk-based screening for breast and colon cancer surveillance since 2015 | | | (physical examination forms) | - Self-administered questionnaire survey | - Specific item in self-questionnaires | - Self-administered questionnaire survey | physicians in other hospitals |
| - Clinical records or annual status reports | | | | | | | Up to 2010: linkage with the nationwide PALGA network and the Netherlands Cancer Registry |
| - Pathologic verification of subsequent malignant neoplasms | | | | | | | |
| - Causes of deaths | | | | | | | |
| - Contact with pathologists, and getting copy of pathological records for all neoplasms | | | | | | | |
| - Long term followup visits | | | | | | | |
| - Self-administered questionnaire survey | | | | | | | |

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Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| **Inclusion Criteria**            |      |        |       |             |       |       |     |
| Eligible survivors                | Alive 5 yrs after diagnosis<sup>4</sup> | Alive 5 yrs after diagnosis at time of cohort entry | Alive 5 yrs post-surgery | Alive 5 yrs after diagnosis | Alive 5 yrs after diagnosis | Alive 5 yrs after diagnosis | Alive 5 yrs after receiving treatment |
| Period of childhood cancer diagnosis | 1970-1999 | 1962-2012 | 1969-2002 | 1963-2001 | 1946-2000 | Since 1976 | 1965-1995 |
| Age at childhood cancer diagnosis (yrs) | <21 | <21 | <20 | <18 | <21 | <21 | <21 |<sup>5</sup> |

**Main Cohort Characteristics**

| Source Cohort fulfilling eligibility criteria (n) | - For survivors diagnosed between 1970-1986: 20,687 (both male and female) | 8,192 (both male and female) | 2,492 females | 6,165 (both male and female) | 7,670 (both male and female) | By 31 December 2010: 5,553 (both male and female) | 265 female pediatric HL survivors |
|-------------------------------------------------|-------------------------------------------------|-----------------|--------------|-----------------|-----------------|---------------------------------|-----------------------------|

<sup>4</sup> Alive 5 yrs after diagnosis

<sup>5</sup> <21 yrs
Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| **Base Cohort available for studies** | - For survivors diagnosed between 1970-1986: 14,361<br>- For survivors diagnosed between 1987-1999: 11,304 | Contacted for recruitment: 7,471 | 2,492 females | 6,015 (44% female) | 7,670 (both male and female) | Questionnaire survey 2007-11: 2,738/5,553 | 265 female pediatric HL survivors |
| **Participation rates (including loss to follow-up)** | - Follow-up 1, diagnosed 1970-86: 12,884 (participation 81%)<sup>11</sup> | Survivors have completed a campus visit (n=5,223)/Survivors contacted for recruitment (n=7,471) 69.9% | NA | NA | 1<sup>st</sup> self-questionnaire: 3,313/6,173 alive (53%)<sup>2</sup> | Questionnaire responded rate in adults and adolescents: 1,505/2,738 (for children aged 5-15 yr, mailing ongoing) | NA |
Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| - Follow-up 5, diagnosed 1970-1999: 18,041 (participation 63%) |      |        |       |             |       |       |     |
| - Follow-up 6, diagnosed 1970-1999: 17,301 (participation 76%) |      |        |       |             |       |       |     |

Funding sources

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- National Cancer Institute at the National Institutes of Health Cancer Center Support grant 5P30CA021765-33 and the St. Jude Lifetime Cohort Study Grant [U01 CA195547], and the American NIH grant 2 R01 CA054498
- Dutch Cancer Society KiKa Children Cancer Free ODAS Foundation European Union Dutch Childhood Oncology Group
- Fondation Pfizer for childhood and Adolescent Health. Ligue Nationale Contre le Cancer (LNCC), Institut de Recherche en Santé Publique (IRES).
- The SCCSS has been supported by the Swiss Cancer League and the Swiss Cancer Research foundation (KFS-02783-02-2011, KLS-3412-02-2014, KFS-4157-02-2017, KLS/KFS-4825-01-2019; KFS-4722-02-2019, KFS-5027-02-2020; KFS-5302-
- Dutch Cancer Society (NKI 2010-4720)
### Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|------|
| Lebanese Syrian Associated Charities. Registered at Clinicaltrials.gov (#NCT00760656) | | | | | | | |
| | | | | | | | |
| IRB and/or Ethics Committee approval | The St. Jude Children’s Research Hospital Institutional Review Board provides oversight and approval for all CCSS activities | The St. Jude Children’s Research Hospital Institutional Review Board provides oversight and approval for | Institutional Review Board for the Fred Hutchinson Cancer Research Center provides oversight and approval for all NWTSG activities | The study protocol of the DCCSS LATER was declared exempt from the review of medical intervention research by the institutional review boards of all | The FCCSS was approved by the French Data Protection Authority (CNIL) | The Swiss Childhood Cancer Registry and the Swiss Childhood Cancer Survivor Study have been approved by the | The Netherlands Cancer Institute’s Institutional Review Board approved |
| | | | | | | | |
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Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
|                                   | all SJLIFE activities | participating centers, in compliance with Dutch law and regulations for health research involving human beings | (Authorisation n°902287) and by the ethics committee of the INSERM. The FCCSSS also obtained a specific act in law from the French “Conseil d’Etat”, the highest court in France (Order of 2014–96 of 2014 February 3), that approved | cantonal ethics committee Bern (ethics approval KEK BE 166/2014); the data collection in Switzerland on second neoplasms within PanCareSurFup has been approved by the cantonal ethics committee Bern (ethics approval KEK BE 183/11) | participatio n in the current study |
### Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|-----------------------------------|------|--------|-------|-------------|-------|-------|-----|
| Study website                     | https://ccss.stjude.org/ | https://sjlife.stjude.org/ |       |             | the linkage with the SNDS (Système National des Données de Santé) data for all patients included in the FCCSS |       | www.fccss.fr |
| Yr = Year; SJCRH = St Jude Children’s Research Hospital, Memphis TN, USA; RT = Radiotherapy; NM = Not mentioned; NA = Not applicable |
| Includes patients referred to St. Jude for treatment and follow-up care, largely from the USA; eligible survivors were recruited at their last annual follow-up visit to the After Completion of Therapy (ACT) Clinic upon reaching age 18 years or at high school graduation, whichever comes and from the SJCRH Cancer Registry. |
| For details, see Stovall et al. 2006 (46) and Armstrong et al. 2009 (47). |
| Postal service address-correction requests, directory assistance, internet directories, reverse directories, contact of previous neighbors and/or relatives, voter registration records, post offices, Social Security Administration hand search, credit bureaus, property tax records, schools, social security death files, National Death Index. |
| Craniopharyngioma and meningioma were excluded. |
Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Participating collaborative groups | CCSS | SJLIFE | NWTSG | DCCSS LATER | FCCSS | SCCSS | DHL |
|------------------------------------|------|--------|-------|-------------|-------|-------|-----|

*The SJCRH generally restricts acceptance to children <25 years of diagnosis, but only survivors <21 years of diagnosis were included in our consortium.
*The DHL includes survivors who were <51 years at HL treatment. Only the information of the survivors who were diagnosed <21 years was provided to the consortium.
**Total/denominator as in column ‘base cohort’ unless otherwise specified.
††Participation among baseline participants still alive at initiation of Follow-up survey.
### Supplemental Table 2. Demographic, clinical, and childhood-cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study.

| Participating study | CCSS (n=9671) | NWTS (n=3989) | IFCT (n=2236) | ILIPE (n=2237) | LATER (n=265) | DHL (n=79) | SCCSS (n=21892) | Non-SBC patients (n=21057) | SBC patients* (n=835) |
|---------------------|---------------|---------------|---------------|---------------|---------------|------------|---------------|--------------------------|---------------------|
| **Primary childhood cancer type** | | | | | | | | | |
| Leukemia | 2987 (30.9%) | - | - | 802 (35.9%) | 770 (34.4%) | - | 15 (19.0%) | 4574 (20.9%) | 4402 (21.3%) | 82 (0.8%) |
| Non-Hodgkin lymphoma | 586 (6.1%) | - | 235 (9.6%) | 115 (5.3%) | 157 (7.0%) | - | 4 (5.1%) | 1097 (5.0%) | 1060 (5.0%) | 37 (4.4%) |
| Hodgkin lymphoma | 1276 (13.2%) | - | 189 (5.3%) | 227 (10.2%) | 125 (5.6%) | 265 (100%) | 19 (24.1%) | 2101 (9.0%) | 1692 (8.0%) | 409 (40.0%) |
| CNS tumor | 1841 (19.0%) | - | 486 (14.6%) | 287 (12.8%) | 312 (13.9%) | - | 8 (10.1%) | 2946 (13.5%) | 2932 (13.9%) | 14 (1.7%) |
| Neuroblastoma | 901 (9.3%) | - | 505 (14.8%) | 101 (4.5%) | 145 (6.5%) | - | 5 (6.3%) | 1657 (7.6%) | 1642 (7.8%) | 15 (1.8%) |
| Retinoblastoma | - | - | 293 (4.6%) | 119 (15.3%) | 14 (0.6%) | - | - | 426 (1.1%) | 424 (2.0%) | 2 (0.0%) |
| Renal tumor | 389 (4.0%) | 3890 (100%) | 558 (16.3%) | 170 (7.6%) | 250 (11.2%) | - | 5 (6.3%) | 5361 (24.5%) | 5270 (25.0%) | 91 (10.9%) |
| Hepatic tumor | - | - | 32 (0.9%) | 10 (0.4%) | 19 (0.8%) | - | - | 61 (0.3%) | 60 (0.3%) | 1 (0.0%) |
| Bone tumor | 884 (9.1%) | - | 285 (8.0%) | 133 (5.9%) | 141 (6.3%) | - | 6 (7.6%) | 1489 (6.7%) | 1352 (6.4%) | 107 (12.8%) |
| Soft tissue tumor | 763 (7.9%) | - | 361 (10.0%) | 127 (5.7%) | 151 (6.8%) | - | 3 (3.8%) | 1405 (6.4%) | 1350 (6.4%) | 55 (6.0%) |
| Germ-cell tumor | 20 (0.2%) | - | 240 (7.3%) | 66 (3.0%) | 101 (4.5%) | - | 2 (2.5%) | 440 (2.0%) | 431 (2.0%) | 9 (1.1%) |
| Other malignant epithelial neoplasms | - | - | 187 (5.5%) | 49 (2.2%) | 52 (2.2%) | - | 11 (13.9%) | 297 (1.4%) | 288 (1.4%) | 11 (1.5%) |
| Other and unspecified | - | - | 7 (0.2%) | 28 (1.3%) | 2 (0.1%) | - | 1 (1.3%) | 38 (0.2%) | 37 (0.2%) | 1 (0.0%) |
| Unclassifed | 24 (0.2%) | - | 6 (0.2%) | - | - | - | - | 30 (0.1%) | 29 (0.1%) | 1 (0.0%) |
| **Age at primary childhood cancer diagnosis (yr)** | | | | | | | | | |
| Median [IQR] | 7.5 [3.1, 13.7] | 3.3 [1.8, 5.0] | 5.2 [1.7, 11.4] | 6.2 [2.7, 12.6] | 5.4 [2.7, 10.7] | 18.3 [16.6, 19.7] | 14.2 [6.0, 17.3] | 5.4 [2.5, 11.9] | 5.2 [2.4, 11.3] | 14.6 [11.6, 17.3] |
| **Age at primary childhood cancer diagnosis (yr) category** | | | | | | | | | |
| <5 | 3666 (37.9%) | 2900 (75.0%) | 1671 (48.0%) | 973 (43.5%) | 1049 (46.9%) | - | 17 (21.5%) | 10866 (47.4%) | 10828 (48.8%) | 84 (10.1%) |
| 5-9 | 2027 (21.0%) | 869 (21.8%) | 707 (20.7%) | 468 (20.9%) | 569 (25.0%) | 7 (2.6%) | 10 (12.5%) | 4657 (21.3%) | 4574 (21.7%) | 81 (9.9%) |
| 10-14 | 2204 (22.8%) | 115 (2.9%) | 744 (21.8%) | 472 (21.3%) | 471 (21.5%) | 21 (7.9%) | 18 (22.8%) | 4045 (18.5%) | 3759 (17.3%) | 286 (34.3%) |
| 15-21 | 1774 (18.3%) | 15 (0.4%) | 293 (8.0%) | 325 (14.4%) | 148 (6.6%) | 257 (99.4%) | 34 (43.0%) | 2824 (12.9%) | 2442 (11.6%) | 382 (45.7%) |
| **Period of childhood cancer diagnosis, range** | | | | | | | | | |
| Median [IQR] | 1985 [1979, 1992] | 1989 [1982, 1996] | 1986 [1978, 1994] | 1994 [1984, 2002] | 1989 [1981, 1996] | 1992 [1984, 1991] | 1990 [1984, 1999] | 1987 [1980, 1995] | 1987 [1980, 1995] | 1994 [1974, 1996] |
| Attained age at last follow-up (yr) | Median (IQR)       | Attained age at last follow-up (yr) | Median (IQR) |
|-----------------------------------|--------------------|-----------------------------------|--------------|
| <20                              | 838 (8.7%)         | <20                               | 1484 (37.2%) |
| 20-29                            | 2552 (26.4%)       | 20-29                             | 1128 (28.3%) |
| 30-39                            | 3314 (34.3%)       | 30-39                             | 921 (23.1%)  |
| ≥40                              | 2967 (30.7%)       | ≥40                               | 456 (11.4%)  |
| Subsequent invasive breast cancer diagnosed | 2967 (30.7%) | Subsequent invasive breast cancer diagnosed | 456 (11.4%) |
| No                                | 9315 (96.3%)       | No                                | 3955 (99.1%) |
| Yes                               | 356 (3.7%)         | Yes                               | 34 (0.9%)    |
| Subsequent in situ breast cancer diagnosed | 356 (3.7%) | Subsequent in situ breast cancer diagnosed | 34 (0.9%) |
| No                                | 9529 (98.5%)       | No                                | 3971 (98.5%) |
| Yes                               | 142 (1.5%)         | Yes                               | 48 (0.5%)    |
| Any subsequent breast cancer (invasive or in situ) | 142 (1.5%) | Any subsequent breast cancer (invasive or in situ) | 48 (0.5%) |
| No                                | 9214 (93.9%)       | No                                | 3843 (98.8%) |
| Yes                               | 457 (4.7%)         | Yes                               | 46 (1.2%)    |
| First subsequent breast cancer type |                    | First subsequent breast cancer type |              |
| Pelvis | Mediastinal | Chest radiation dose (Gy) | Radiotherapy exposure to the chest | Vital status at last point of contact |
|--------|-------------|---------------------------|----------------------------------|------------------------------------|
| Only in situ | 113 (24.7%) | 12 (21.3%) | 16 (12.5%) | 24 (30.8%) | 5 (12.5%) | 14 (21.5%) | - | 184 (22.0%) | - | 184 (22.0%) |
| Invasive and in situ diagnosed at the same moment | 8 (1.8%) | 4 (8.7%) | 2 (1.8%) | 2 (2.0%) | - | - | - | 16 (1.9%) | - | 16 (1.9%) |

| Radiotherapy exposure to the chest | No | Yes | Unknown | Chest radiation dose (Gy) | Median [IQR] | Chest radiation dose (Gy) category |
|----------------------------------|-----|------|---------|---------------------------|-------------|---------------------------------|
| No chest radiation | 6607 (68.3%) | 3415 (35.6%) | 2728 (79.9%) | 1706 (76.3%) | 1892 (84.9%) | 22 (8.3%) | 49 (62.0%) | 16419 (75.0%) | 16145 (76.7%) | 274 (32.8%) |
| <10 | 73 (0.8%) | 4 (0.1%) | 7 (0.2%) | 5 (0.2%) | 48 (2.1%) | - | - | 137 (6.0%) | 132 (6.6%) | 5 (0.6%) |
| 10-19 | 405 (4.2%) | 509 (12.8%) | 102 (5.0%) | 133 (3.5%) | 69 (3.5%) | 2 (0.4%) | 124 (5.6%) | 115 (5.5%) | 73 (6.7%) |
| 20-29 | 533 (5.5%) | 19 (0.5%) | 148 (4.3%) | 210 (4.9%) | 60 (2.7%) | 11 (4.2%) | 2 (2.5%) | 803 (4.5%) | 906 (4.3%) | 77 (2.2%) |
| 30-39 | 342 (3.6%) | 12 (0.3%) | 92 (2.7%) | 85 (3.8%) | 82 (3.7%) | 90 (3.4%) | 5 (6.3%) | 908 (4.1%) | 762 (3.6%) | 146 (17.5%) |
| ≥40 | 511 (5.3%) | 3 (0.1%) | 133 (3.9%) | 41 (1.8%) | 60 (3.0%) | 85 (3.2%) | 6 (7.6%) | 847 (3.9%) | 650 (1.1%) | 197 (23.6%) |
| Unknown | 1002 (10.4%) | 27 (0.7%) | 265 (6.0%) | 56 (2.5%) | 18 (0.8%) | 55 (20.8%) | 11 (13.9%) | 1374 (6.3%) | 1311 (6.2%) | 63 (7.5%) |

| Chest radiation field | No chest radiation | Arilla | Mantle | Medialul | Others | Spine | Total body irradiation | Whole lung | Unknown | Radiotherapy exposure to the Pelvis |
|----------------------|--------------------|--------|---------|-----------|--------|-------|-----------------------|----------|---------|-------------------------------|
| 6607 (68.3%) | 3415 (35.6%) | 2728 (79.9%) | 1706 (76.3%) | 1892 (84.9%) | 22 (8.3%) | 49 (62.0%) | 16419 (75.0%) | 16145 (76.7%) | 274 (32.8%) |
| Axilla | 12 (0.1%) | - | 5 (0.3%) | 15 (0.7%) | 2 (0.5%) | - | 34 (2.0%) | 31 (1.5%) | 3 (0.4%) |
| Mantle | 723 (7.5%) | 46 (2.5%) | 191 (8.3%) | 39 (1.7%) | 102 (72.5%) | 11 (73.9%) | 124 (5.7%) | 914 (4.3%) | 331 (30.6%) |
| Medialul | 227 (2.3%) | 1 (0.1%) | 134 (3.9%) | 25 (1.8%) | 36 (1.6%) | 45 (17.0%) | 4 (5.1%) | 470 (21.4%) | 437 (21.4%) | 33 (4.0%) |
| Others | 177 (1.8%) | 19 (0.5%) | 117 (3.6%) | 35 (1.9%) | 40 (2.2%) | - | 1 (1.1%) | 396 (1.9%) | 344 (1.6%) | 52 (6.2%) |
| Spine | 596 (6.2%) | - | 98 (2.9%) | 131 (3.9%) | 100 (4.9%) | - | 3 (0.4%) | 839 (4.1%) | 927 (4.9%) | 12 (1.4%) |
| Total body irradiation | 223 (2.3%) | - | 10 (0.5%) | 67 (3.8%) | 60 (3.1%) | - | 2 (2.5%) | 371 (1.7%) | 348 (1.7%) | 21 (2.8%) |
| Whole lung | 79 (0.8%) | 527 (13.2%) | 37 (1.1%) | 44 (2.0%) | 22 (1.0%) | - | 2 (2.5%) | 711 (3.2%) | 663 (1.3%) | 48 (5.8%) |
| Unknown | 1025 (10.6%) | 27 (0.7%) | 265 (6.0%) | 36 (1.6%) | 6 (0.4%) | 3 (1.3%) | 130 (6.9%) | 123 (5.9%) | 59 (7.1%) |
| Doxorubicin dose (mg/m²) | 7191 (74.4%) | 1922 (48.2%) | 2287 (67.0%) | 1873 (63.8%) | 2129 (95.2%) | 179 (67.5%) | 68 (68.1%) | 15649 (71.5%) | 15133 (71.9%) | 516 (61.8%) |
|------------------------|---------------|---------------|---------------|---------------|---------------|-------------|-------------|----------------|----------------|-------------|
| Pelvic radiation dose (Gy) | Median [IQR] | 130.4, 358.3 | 215.7, 135.1, 396.2 | 177.4, 135.1, 296.2 | 191.0, 219.0, 280.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 219.9, 170.7, 371.8 |
| Doxorubicin | Median [IQR] | 224.7 [130.4, 358.3] | NA** | 215.7 [135.1, 396.2] | 177.4 [135.1, 296.2] | 191.0 [219.0, 280.0] | 200.0 [203.0, 240.0] | 201.0 [219.0, 230.0] | 200.0 [203.0, 240.0] | 219.9 [170.7, 371.8] |
| Doxorubicin dose (mg/m²) | Median [IQR] | 224.7 [130.4, 358.3] | NA** | 215.7 [135.1, 396.2] | 177.4 [135.1, 296.2] | 191.0 [219.0, 280.0] | 200.0 [203.0, 240.0] | 201.0 [219.0, 230.0] | 200.0 [203.0, 240.0] | 219.9 [170.7, 371.8] |
| Doxorubicin dose (mg/m²) | Unknown | 1315 (15.7%) | 923 (27.0%) | 337 (15.1%) | 105 (4.7%) | 81 (30.6%) | 3 (3.8%) | 2964 (15.5%) | 2740 (13.8%) | 234 (28.9%) |
| Pelvic radiation dose (Gy) | Median [IQR] | 130.4, 358.3 | 215.7, 135.1, 396.2 | 177.4, 135.1, 296.2 | 191.0, 219.0, 280.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 219.9, 170.7, 371.8 |
| Doxorubicin dose (mg/m²) | Unknown | 1315 (15.7%) | 923 (27.0%) | 337 (15.1%) | 105 (4.7%) | 81 (30.6%) | 3 (3.8%) | 2964 (15.5%) | 2740 (13.8%) | 234 (28.9%) |
| Pelvic radiation dose (Gy) | Median [IQR] | 130.4, 358.3 | 215.7, 135.1, 396.2 | 177.4, 135.1, 296.2 | 191.0, 219.0, 280.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 200.0, 203.0, 240.0 | 201.0, 219.0, 230.0 | 219.9, 170.7, 371.8 |
| Doxorubicin dose (mg/m²) | Unknown | 1315 (15.7%) | 923 (27.0%) | 337 (15.1%) | 105 (4.7%) | 81 (30.6%) | 3 (3.8%) | 2964 (15.5%) | 2740 (13.8%) | 234 (28.9%) |

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### Daunorubicin

| Daunorubicin dose (mg/m²) | Median (IQR) | No | <6000 | 6000-17999 | ≥18000 |
|---------------------------|--------------|----|-------|-------------|--------|
| No                        | 1210 (12.6%) | 375 (3.5%) | 6000 (26.8%) | 437 (19.5%) | 7 (0.9%) |
| Yes                       | 792 (8.2%)   | 14 (0.4%)  | 119 (3.5%)   | 18 (0.8%)   | 5 (0.2%)  |
| Unknown                   |              |           |              |             |          |

### Median [IQR]

| Daunorubicin dose (mg/m²) | Median [IQR] | No | <6000 | 6000-17999 | ≥18000 |
|---------------------------|--------------|----|-------|-------------|--------|
| No                        | 1210 (12.6%) | 375 (3.5%) | 6000 (26.8%) | 437 (19.5%) | 7 (0.9%) |
| Yes                       | 792 (8.2%)   | 14 (0.4%)  | 119 (3.5%)   | 18 (0.8%)   | 5 (0.2%)  |
| Unknown                   |              |           |              |             |          |

### Epipodophyllotoxins

| Epipodophyllotoxin dose (mg/m²) | Median [IQR] | No | <6000 | 6000-17999 | ≥18000 |
|--------------------------------|--------------|----|-------|-------------|--------|
| No                            | 1210 (12.6%) | 375 (3.5%) | 6000 (26.8%) | 437 (19.5%) | 7 (0.9%) |
| Yes                           | 792 (8.2%)   | 14 (0.4%)  | 119 (3.5%)   | 18 (0.8%)   | 5 (0.2%)  |
| Unknown                       |              |           |              |             |          |

### Alkalizing agents

| Alkalizing agents | Median [IQR] | No | <6000 | 6000-17999 | ≥18000 |
|-------------------|--------------|----|-------|-------------|--------|
| No                | 1210 (12.6%) | 375 (3.5%) | 6000 (26.8%) | 437 (19.5%) | 7 (0.9%) |
| Yes               | 792 (8.2%)   | 14 (0.4%)  | 119 (3.5%)   | 18 (0.8%)   | 5 (0.2%)  |
| Unknown           |              |           |              |             |          |

### CED™ dose (mg/m²)

| CED™ dose (mg/m²) | Median [IQR] | No | <6000 | 6000-17999 | ≥18000 |
|-------------------|--------------|----|-------|-------------|--------|
| No                | 1210 (12.6%) | 375 (3.5%) | 6000 (26.8%) | 437 (19.5%) | 7 (0.9%) |
| Yes               | 792 (8.2%)   | 14 (0.4%)  | 119 (3.5%)   | 18 (0.8%)   | 5 (0.2%)  |
| Unknown           |              |           |              |             |          |

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Among survivors with an in situ first subsequent breast cancer, 38 developed a second subsequent breast cancer (16 invasive, 17 DCIS, 5 LCIS), and 4 developed a third subsequent breast cancer (1 invasive, 2 DCIS, 1 LCIS).

71 patients developed both a subsequent invasive and in situ breast cancer.

Follow-up time was calculated from five years after a primary cancer diagnosis to the date of subsequent breast cancer diagnosis, death, or the date of the last follow-up observation, whichever occurred first.

Includes 172 DCIS and 12 LCIS.

Among survivors with both an invasive and in situ first subsequent breast cancer diagnosed at the same moment, 2 developed DCIS as a third subsequent breast cancer.

Chemotherapy dose information was not available in the NWTSG.

Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

Pelvic radiation information was not available in the NWTSG.

Includes patients with invasive and/or in situ breast cancer.

Follow-up time was calculated from five years after a primary cancer diagnosis to the date of subsequent breast cancer diagnosis, death, or the date of the last follow-up observation, whichever occurred first.

Includes 172 DCIS and 12 LCIS.

Among survivors with both an invasive and in situ first subsequent breast cancer diagnosed at the same moment, 2 developed DCIS as a third subsequent breast cancer.

Chemotherapy dose information was not available in the NWTSG.

Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

Pelvic radiation information was not available in the NWTSG.
## Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

| Study          | Title                                                                 | Study design | Number of female childhood/adolescent cancer survivors | Follow-up duration | Subsequent breast cancer | Subsequent breast cancer risk estimates | Findings                                                                 |
|---------------|----------------------------------------------------------------------|--------------|--------------------------------------------------------|--------------------|--------------------------|----------------------------------------|------------------------------------------------------------------------|
| CCSS (Kenney et al. 2004) (48) | Breast Cancer after Childhood Cancer: A Report from the Childhood Cancer Survivor Study | Cohort       | 6,068 female 5-yr survivors Diagnosed 1970-1986       | 95 survivors developed 111 cases of breast cancer | Radiotherapy exposure to the chest, yes/no & SIR (95% CI): 24.7 (19.3-31.0) | Breast cancer risk was increased in survivors who had radiotherapy exposure to the chest |

**Research question 1: Chest radiotherapy-related subsequent breast cancer risk**
| Study | Design | Subjects | Population | Subsequent Breast Cancer Cases | Radiation Dose Category, Gy & OR (95% CI) | Analysis Notes |
|-------|--------|----------|------------|-------------------------------|------------------------------------------|----------------|
| CCSS (Inskip et al. 2009) (25) | Case-control | 120 patients matched with 464 controls | Female 5-yr survivors Treated 1970-1986 | 120 breast cancer cases | Radiation dose category, Gy & OR (95% CI) 0 Gy: ref. >0-0.13 Gy: 1.4 (0.5-4.4) 0.14-1.29 Gy: 1.9 (0.7-5.4) 1.30-11.39 Gy: 1.9 (0.7-5.0) 11.40-29.99 Gy: 7.1 (2.9-17) 30.00-60.00 Gy: 10.8 (3.8-31) *P trend* < 0.001 | Analyses were adjusted for type of first cancer Excess OR per Gy: 0.36 for those who received ovarian doses <5 Gy; 0.06 for those A dose-response relation between reconstructed radiation dose to the breast and subsequent breast cancer risk, which was reduced among women with dose to the ovaries of >5 Gy |
| CCSS (Moskowitz et al. 2014) (27) | Breast Cancer after Chest Radiation Therapy for Childhood Cancer | Cohort | 1,230 female 5-yr survivors received chest irradiation within 5 years of their childhood cancer diagnosis Treated 1970-1986 | Median 25.9 (range 8.4-40.6) yr | 203 women had a confirmed breast cancer diagnosis | who received higher doses |
|----------------------------------|---------------------------------------------------------------|--------|-------------------------------------------------|-------------------------------|--------------------------------|-------------------|
| CCSS (Moskowitz) Breast Cancer following | Cohort | 363 female 5-yr | Median follow-up | 3 women were | Treated with spinal irradiation, yes/no | Delivered radiation dose/volume associated with subsequent breast cancer risk |

|  | Madeleina (median, 40 Gy; range, 5-54): 24.2 (20.7-28.3) | Mantle (median, 30 Gy; range, 3-54): 13.0 (8.4-20.2) | Mediastinal (median, 14 Gy; range, 2-20): 43.6 (27.1-70.1) | Whole lung (median, 12 Gy; range, 4-16): 19.3 (7.3-51.5) | Total body (median, 12 Gy; range, 4-16): 19.3 (7.3-51.5) | Abdominal (median, 20 Gy; range, 4-40): 10.8 (2.7-43.2) | Other one-sided anterior (median, 41 Gy; range, 10-61): 9.9 (3.2-30.6) | Median 25.9 (range 8.4-40.6) yr | 203 women had a confirmed breast cancer diagnosis | Delivered radiation dose/volume associated with subsequent breast cancer risk |
| Study | Title | Design | Participants | Follow-up | Diagnosed with Breast Cancer | SIR (95% CI) | Notes |
|-------|-------|--------|--------------|-----------|----------------------------|--------------|-------|
| et al. 2015) (49) | Spinal Irradiation for a Childhood Cancer: A Report from the Childhood Cancer Survivor Study | Cohort | Survivors of a pediatric central nervous system tumor or leukemia treated with spinal irradiation diagnosed 1970-1986 | 27 (range 10-38) yr | Diagnosed with breast cancer | SIR (95% CI): 2.4 (0.8-7.5) | May not be associated with an increased breast cancer risk |
| CCSS (Moskowitz et al. 2017) (50) | Radiation-associated Breast Cancer and Gonadal Hormone Exposure: A Report from the Childhood Cancer Survivor Study | Cohort | 1,108 female 5-yr survivors treated with chest radiotherapy, and survived to ages ≥20 years diagnosed 1970-1986 | Median follow-up 26 (range 5-38) yr | 195 women were diagnosed with breast cancer | Delivered chest radiation dose, dose in Gy & HR (95% CI) 1-19 Gy: ref. 20-29 Gy: 0.58 (0.31-1.11) 30-39 Gy: 0.68 (0.41-1.13) 40+ Gy: 0.80 (0.49-1.28) Univariable analysis Chest radiation ≤1 yr of menarche vs. >1 yr from menarche HR (95% CI): 1.80 (1.19-2.72) Analyses were adjusted for age at primary childhood | Chest radiotherapy increases breast cancer risk especially when administered near menarche |
| Study                          | Design                  | Cases/controls               | Cases/control Characteristics | Cases/control Analysis                                                                 | Cases/control Findings                                                                 |
|-------------------------------|-------------------------|-----------------------------|--------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| CCSS (Veiga et al. 2019) (12) | Case-control            | 271 cases matched with 1,044 controls | Range 5-40 yr since primary cancer diagnosis | Increasing radiation dose to the breast OR (95% CI) per 10 Gy, 3.9 (2.5-6.5)            | Increasing radiation dose associated with subsequent breast cancer risk; the combined effect of anthracycline and radiotherapy was stronger than the individual effects of these two treatments on subsequent breast cancer risk |
|                              | Female 5-yr survivors   | Diagnosed 1970-1986         |                                | Analyses were adjusted for first cancer diagnosis, chemotherapy (yes/no), calendar year of breast cancer diagnosis, and family history of breast/ovarian cancer |                                                                                        |
| SJLIFE (Ehrhardt et al. 2019) (28) | Cohort                 | 1,467 female 10-yr survivors | Median 22.7 yr since primary cancer diagnosis | 56 survivors developed 68 breast cancers                                               | Subsequent breast cancer risk was associated with 20 Gy or more of chest radiation    |
### Lifetime Cohort Study (SJLIFE)

Excluding survivors with pathogenic/likely pathogenic mutations:
- Chest radiation, Gy & HR (95% CI)
  - None: ref.
  - >0-<10 Gy: 1.2 (0.3-5.0)
  - 10-<20 Gy: 8.0 (1.1-56.3)
  - ≥20 Gy: 10.0 (3.3-30.5)

Analyses were adjusted for age at diagnosis.

### NWTSG (Lange et al. 2014) (37)

**Breast Cancer in Female Wilms Tumor Survivors: A Report from the National Wilms Tumor Late Effects Study**

| Cohort | NM | 28 survivors developed 29 breast cancers | Cumulative risk (95% CI) of breast cancer at age 40: |
|--------|----|-----------------------------------------|--------------------------------------------------|
| 2,492 female 5-yr Wilms tumor survivors | | | No RT: 0.3% (0.0-2.3) |
| 1969-1995 | | | Chest RT: 14.8% (8.7-24.5) |
| | | | No chest dose: 2.3% (1.0-5.1) |
| | | | Chest dose 1-12 Gy: 14.4% (7.6-30.1) |
| | | | Chest dose >12 Gy: 14.2% (7.1-29.3) |
| Study                        | Cohort Description                                                                 | Cases/controls                                                                 | Risk Factors                                                                 |
|------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| **DCCSS LATER** (Teepen et al. 2017) (10) | Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy | Cohort: 2,731 female 5-yr survivors diagnosed 1963-2001                      | For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis | SIR (95% CI): No RT: 2.2, Chest RT: 27.6 (16.1-44.2), No chest dose: 4.6, Chest dose 1-12 Gy: 46.8, Chest dose >12 Gy: 18.9 |
| **DHL (van Leeuwen et al. 2003) (51)** | Roles of Radiation Dose, Chemotherapy, and Hormonal                                   | Case-control: 48 cases matched with 175 controls                               | For the breast cancer cases: Median 18.7 yr since                             | HR (95% CI): Chest radiotherapy (yes vs. no): 2.5 (1.3-4.9), Total body irradiation (yes vs. no): 10.6 (3.7-30.2), Analyses were adjusted for alkylating agents, anthracyclines, and type of radiation |
|                              |                                                                                    |                                                                                | Breast cancer risk increases with increasing reconstructed radiation dose up |                                                                            |
### Factors in Breast Cancer Following Hodgkin’s Disease

| DHL (Krul et al. 2017) (52) | Breast Cancer Risk After Radiation Therapy for Hodgkin Lymphoma: Influence of Gonadal Hormone Exposure |
|----------------------------|--------------------------------------------------------------------------------------------------|
| **Case-control** | **174 cases matched with 466 controls** |
| Female 5-yr HL survivors treated before age 41 | Treated 1965-2000 |
| **For the breast cancer cases:** Median 21.9 (IQR 16.9-26.8) yr since primary cancer diagnosis | **174 breast cancer cases** |
| Radiation dose to breast tumor location (median), dose in Gy & OR (95% CI) | Breast cancer risk in female HL survivors increases linearly with radiation dose; no indications that endogenous and exogenous gonadal hormones affect the radiation dose-response relationship |

#### Radiation Dose and Breast Cancer Risk

| Radiation Dose (Gy) | Median Dose | Range | OR (95% CI) |
|---------------------|-------------|-------|-------------|
| 0-2.9 (median 1.2)  | ref.        |       |             |
| 3.0-7.9 (median 4.9) | 1.33 (0.64-2.77) |       |             |
| 8.0-27.9 (median 17.5) | 2.21 (1.09-4.46) |       |             |
| 28.0-35.9 (median 33.9) | 2.38 (1.17-4.83) |       |             |
| 36.0-61.2 (median 39.4) | 4.70 (2.36-9.38) |       |             |

Analyses were adjusted for duration of breast cancer risk following RT is strongly reduced in women who have experienced CT-induced premature menopause.
| Study | Cohort | Subjects | Follow-up | Breast Cancers | Cumulative Incidence | Risk Factors |
|-------|--------|----------|-----------|----------------|---------------------|--------------|
| FCCSS (Guibout et al. 2005) (53) | Malignant Breast Tumors after Radiotherapy for a First Cancer during Childhood | 1,814 female 3-yr survivors* Treated 1946-1986 | Mean 16 yr since primary cancer diagnosis | 16 patients developed breast cancers | Cumulative incidence: After a 30-yr follow-up cumulative incidence (95% CI): 2.8% (1.0-4.5) After a 40-yr follow-up (95% CI): 10.7% (1.4-19.9) | Chest radiation dose, dose in Gy & RR (95% CI) Chest radiation yes vs. no: 1.3 (0.4-5.9) 0 Gy: ref. 0-<1 Gy: 1.3 (0.3-6.3) 1-<10 Gy: 1.5 (0.3-8.1) 10-<20 Gy: 3.7 (0.6-24.2) ≥20 Gy: 2.5 (0.1-22.1) \( P_{trend} = 0.06 \) Excess relative risk per Gy to the breasts (95% CI): 0.13 (<0.0-0.75) Analyses were adjusted for castration, chemotherapy, and | The high risk of breast cancer after HL may not only related to chemotherapy and a higher radiation dose to the breasts |
| Research question 2: Anthracycline-related subsequent breast cancer risk |
|---|
| CCSS (Henderson et al. 2016) (11) | Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study |
| Cohort | 3,768 female 5-yr childhood cancer survivors without a history of chest radiotherapy Diagnosed 1970-1986 |
| Median 25.5 (range 8.3-38.9) yr | 47 women developed breast cancer |
| Anthracycline, dose in mg/m$^2$ & SIR (95% CI) | Among childhood leukemia and sarcoma survivors |
| 0 mg/m$^2$: 2.0 (1.2-3.3) 1-249 mg/m$^2$: 4.0 (1.5-0.7) ≥250 mg/m$^2$: 8.3 (5.7-12.2) |

Anthracycline, dose in mg/m$^2$ & Relative SIR (95% CI)

- Among childhood leukemia and sarcoma survivors
- Anthracycline, dose in mg/m$^2$ & SIR (95% CI)
  - 0 mg/m$^2$: 1.8 (0.9-3.6)
  - 1-249 mg/m$^2$: 5.0 (1.8-13.1)
  - ≥250 mg/m$^2$: 9.5 (6.4-14.0)

High-dose anthracycline chemotherapy increases the risk of subsequent breast cancer

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| Study | Cohort Description | Number of Survivors | Range since Primary Cancer Diagnosis | Number of Breast Cancer Cases | Anthracyclines Category, mg/m² & RR (95% CI) in Survivors Treated with Only Chemotherapy: per 100 mg/m² | Dose-response Relationship between Anthracyclines and the Risk of Subsequent Breast Cancer |
|-------|-------------------|---------------------|-------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| CCSS  | (Turcotte et al. 2019) (54) | 10,440 female 5-yr survivors Diagnosed 1970-1999 | Range 5-46.7 yr since primary cancer diagnosis | 51 breast cancer cases | Anthracyclines category, mg/m² & RR (95% CI) in survivors treated with only chemotherapy: per 100 mg/m²: 1.3 (1.2-1.6) None: ref. 0-100 mg/m²: 0.9 (0.1-9.1) 101-300 mg/m²: 1.8 (0.6-6.0) | Dose-response relationship between anthracyclines and the risk of subsequent breast cancer |

In childhood cancer survivors:
- 0 mg/m²: ref.
- 1-249 mg/m²: 2.6 (0.8-8.7)
- ≥250 mg/m²: 3.8 (1.7-8.3)

P trend = 0.004

Among childhood leukemia and sarcoma survivors:
- 0 mg/m²: ref.
- 1-249 mg/m²: 4.3 (1.1-16.6)
- ≥250 mg/m²: 5.1 (1.9-13.7)

P trend = 0.005
| Study                                      | Design         | Cases                                      | Controls                                   | Findings                                                                 |
|-------------------------------------------|----------------|--------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------|
| CCSS (Veiga et al. 2019) (12)             | Case-control   | 271 cases matched with 1,044 controls      |                                            | 301-600 mg/m²: 3.7 (1.3-10.8) >600 mg/m²: 8.1 (1.2-56.0) P trend = 0.10    |
|                                           | Female 5-yr survivors | Diagnosed 1970-1986                          |                                            | Analyses were adjusted for attained age, age at primary cancer diagnosis, 5-yr treatment era, history of splenectomy, cumulative dose levels of chemotherapy classes (alkylating agents, epipodophyllotoxins, and platinum-based agents) |
|                                           | Range 5-40 yr since primary cancer diagnosis | 271 breast cancer cases                      |                                            | 301-600 mg/m²: 3.7 (1.3-10.8) >600 mg/m²: 8.1 (1.2-56.0) P trend = 0.10    |
|                                           |                |                                            |                                            | Analyses were adjusted for attained age, age at primary cancer diagnosis, 5-yr treatment era, history of splenectomy, cumulative dose levels of chemotherapy classes (alkylating agents, epipodophyllotoxins, and platinum-based agents) |

Anthracyclines dose OR (95% CI) per 100 mg/m² in survivors with LFS-associated cancers: 1.31 (1.1-1.5)

Anthracycline dose associated with subsequent breast cancer risk; the combined effect of breast radiation and anthracycline was stronger than the
| Childhood Cancer Survivor Study | Anthracyclines dose OR (95% CI) per 100 mg/m² in survivors with non LFS-associated cancers: 1.16 (1.0-1.4) | Anthracycline, dose in mg/m² & OR (95% CI) None: ref. 1-223 mg/m²: 2.3 (1.3-4.2) 224-343 mg/m²: 2.4 (1.3-4.6) 344-455 mg/m²: 1.5 (0.7-3.2) >455 mg/m²: 3.8 (1.8-8.2) P trend < 0.01 | individual effects of these two treatments on subsequent breast cancer risk |
|--------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------|
|                                | Analyses were adjusted for type of first cancer, breast radiation dose, calendar year of follow-up, family history of breast/ovarian cancer, |

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| SJLIFE (Ehrhardt et al. 2019) (28) | Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE) | Cohort | 1,467 female 10-yr survivors | Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis | 56 survivors developed 68 breast cancers | and treatment with alkylating agents |
|----------------------------------|---------------------------------------------------------------------------------------------------------------|-------|-----------------------------|-----------------------------------------------------------------|---------------------------------------------|--------------------------------------|
|                                  | Anthracycline exposure, mg/m$^2$ & HR (95% CI):                                                                  |       |                             | Higher doses of anthracyclines are associated with increased risk of breast cancer independent of mutations in known cancer predisposition genes |
| None: ref.                       | 1-249 mg/m$^2$: 2.6 (1.1-6.2)                                                                                 |       |                             |                                                                |
| ≥250 mg/m$^2$: 13.4 (5.5-32.5)   | Excluding pathogenic/likely pathogenic mutations:                                                              |       |                             |                                                                |
| Anthracycline exposure, mg/m$^2$ & HR (95% CI):                                                                  |       |                             |                                                                |
| None: ref.                       | 1-249 mg/m$^2$: 2.5 (1.0-6.1)                                                                                 |       |                             |                                                                |
| ≥250 mg/m$^2$: 15.1 (6.1-37.6)   | Excluding Survivors with ≥10 Gy of chest radiation and pathogenic/likely pathogenic mutations:                |       |                             |                                                                |
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| Study | Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy | Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Cohort (Teepen et al. 2017) (10) | Anthracycline exposure, mg/m² & HR (95% CI): None: ref. 1-249 mg/m²: 2.1 (0.2-27.0) ≥250 mg/m²: 16.9 (2.2-126.6) |
|---|---|---|---|
| DCCSS LATER | 2,731 female 5-yr survivors | For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis | 45 breast cancer cases |
| Doxorubicin dose, mg/m² & HR (95% CI): None: ref. ≤270 mg/m²: 1.1 (0.4-2.9) 271-443 mg/m²: 2.6 (1.1-6.5) >443 mg/m²: 5.8 (2.7-12.5) P trend < 0.001 |
| Doxorubicin was associated with a dose-dependent increased risk of female breast cancer, especially for survivors who had LFS-associated childhood cancer types (leukemia, CNS, and non-Ewing sarcoma) |
| Doxorubicin dose, mg/m² & HR (95% CI) | \( \leq 270 \text{ mg/m²} \): 0.6 (0.1-3.2) | 271-443 mg/m²: 9.1 (2.5-32.8) | >443 mg/m²: 14.8 (5.1-43.2) |
|--------------------------------------|---------------------------------|----------------------------|----------------------------|
| \( P \text{ trend} < 0.001 \)        | \( P \text{ trend} = 0.94 \)    |                            |                            |

Non-LFS-associated CCSs:

Analyses were adjusted for chest radiation, TBI, and chemotherapy groups.
## Research question 3: Attained age-related subsequent breast cancer risk

| CCSS (Kenney et al. 2004) (48) | Breast Cancer after Childhood Cancer: A Report from the Childhood Cancer Survivor Study | Cohort | 6,068 female 5-yr survivors diagnosed 1970-1986 | For subsequent breast cancer cases: median 19 (range 6-29) yr since primary cancer diagnosis; For non-subsequent breast cancer cases: median 18 (range 5-31) yr since primary cancer diagnosis | 95 survivors developed 111 cases of breast cancer | Subsequent breast cancer, cumulative incidence: At age 40 yr exposed to chest radiation in HL survivors: 12.9% (9.3-16.5) | Increased subsequent breast cancer risk in survivors at age 40 yr |
| --- | --- | --- | --- | --- | --- | --- | --- |
| CCSS (Turcotte et al. 2004) | Risk of Subsequent Neoplasms | Cohort | 1,510 female 5-yr survivors completed at least one study | NM | 103 breast cancer cases | In patients age 40 yr or older, subsequent breast cancer risk: SIR | Childhood cancer survivors remain at |
| SJLIFE (Ehrhardt et al. 2019) (28) | During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort | questionnaire after age 40 yr | (95% CI): 5.5 (4.5-6.7); EAR 1.04 | increased risk for treatment related subsequent breast cancer even after age 40 yr |
| SJLIFE | Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE) | Cohort | 1,467 female 10-yr survivors | 56 survivors developed 68 breast cancers | Subsequent breast cancer, cumulative incidence: By age 35 yr unexposed to chest radiation: 1% By age 50 yr unexposed to chest radiation: 15% By age 35 yr ≥10 Gy chest radiation: 8% By age 50 yr ≥10 Gy chest radiation: 41% By age 35 yr unexposed to anthracyclines: 2% By age 50 yr unexposed to anthracyclines: 15% By age 35 yr ≥250 mg/m² anthracyclines: 7% |
| SJLIFE | Cohort | Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis | Attained age associated with increased subsequent breast cancer risk |
| DCCSS LATER (Teepen et al. 2017) (10) | Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy | Cohort 2,731 female 5-yr survivors Diagnosed 1963-2001 | For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis | 45 breast cancer cases | Attained age, yr & SIR (95% CI) and EAR <10 yr at childhood cancer diagnosis <20 yr: 10.5 (8.0-13.4); EAR: 13.5 20-29 yr: 4.6 (3.4-6.2); EAR: 14.6 30-39 yr: 4.3 (3.1-5.9); EAR: 32.1 ≥40 yr: 4.3 (2.3-7.2); EAR: 73.1 10-17 yr at childhood cancer diagnosis <30 yr: 5.8 (4.1-8.1); EAR: 16.9 30-39 yr: 5.6 (4.0-7.6); EAR: 43.4 40-49 yr: 3.2 (1.9-4.9); EAR: 51.4 ≥50 yr: 2.0 (0.8-4.2); EAR: 65.4 | Chest radiotherapy and total body irradiation were risk factors for female breast cancer |

By age 50 yr ≥250 mg/m² anthracyclines: 46%
| Study (Authors) | Cohort Description | Cohort Size | Risk Group | Risk Estimates |
|----------------|-------------------|-------------|------------|----------------|
| DHL (van Leeuwen et al. 2000) (42) | Long-Term Risk of Second Malignancy in Survivors of Hodgkin’s Disease Treated During Adolescence or Young Adulthood | 544 female 1-yr survivors treated for HL before the age of 40 yr | For the whole cohort (both males and females): Median 14.1 yr | 27 breast cancer cases | Breast cancer risk, RR (95% CI) and EAR: 5.2 (3.4-7.6); EAR per 10 000 female patient-years: 29.4 |
| DHL (Schaapveld et al. 2015) (19) | Second Cancer Risk Up to 40 Years after Treatment for Hodgkin’s Lymphoma | 1,698 female 5-yr HL survivors | Range 5.0-47.2 yr | 183 survivors with breast cancer | Attained age, yr & SIR (95% CI) and EAR: 15-24 at HL <30 yr: 19.8 (5.4-50.6); E: 12.3 30-39 yr: 12.9 (8.8-18.3); E: 55.3 40-49 yr: 9.4 (6.6-12.9); E: 138 50-59 yr: 8.6 (5.1-13.4); E: 215 ≥60 yr: 7.4 (1.5-21.7); E: 218 |

The increased risk of solid tumors in patients who were young (<20 yr of age) at the first treatment seems to decrease as these patients grow older.

Increased risk in survivors previously treated with (high dose) chest radiation with an attained age ≥60 yr.
| Age Group | SIR (95% CI) | EAR (95% CI) |
|-----------|-------------|-------------|
| 25-34 at HL | 3.7 (1.4-8.1) | 15.2 (4.0-6.3) |
| 35-50 at HL | 1.4 (0.4-3.5) | 6.4 (1.8-3.0) |
| 35-50 at HL | 1.8 (0.9-3.0) | 20.1 (6.0-3.4) |
| 50-59 yr | 5.2 (3.6-7.3) | 69.3 (2.4-6.3) |
| 50-59 yr | 4.0 (2.4-6.3) | 82.5 (0.7-6.9) |
| 60-69 yr | 2.7 (0.7-6.9) | 57.5 (1.7-3.4) |
| 70-79 yr | 2.9 (0.6-8.5) | 67.8 (2.9-0.6) |
| SIR: $P_{trend} = 0.06$; EAR: $P_{trend} < 0.001$ |

Other papers on subsequent breast cancer
| Moskowitz et al. (2019) (8) | Mortality After Breast Cancer Among Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study | Case-control | 274 cases matched with 1,095 controls with de novo breast cancer  
Female 5-yr survivors  
Diagnosed 1970-1986 | For cases: Median 38 (range 20-58) yr | 274 breast cancer cases | HR (95% CI)  
Death after breast cancer (survivors vs. controls): 2.2 (1.7-3.0); after adjusting for breast cancer treatment with RT: 2.2 (1.7-3.1); after adjusting for breast cancer treatment with CT: 2.3 (1.8-3.2); both: 2.4 (1.7-3.2) | Mortality is significantly elevated among childhood cancer survivors |
|--------------------------|------------------------------------------------------------------------------------------------|-------------|---------------------------------|-----------------------------|-----------------------------|-------------------------------------------------|------------------------------------------------|
| Moskowitz et al. (2021) (55) | Development and Validation of a Breast Cancer Risk Prediction Model for Childhood Cancer Survivors Treated With Chest Radiation: A Report From the Childhood Cancer Survivor Study and the Dutch | Cohort | Model development cohort: was based on 1,120 female 5-yr survivors treated with chest radiation (diagnosed 1970-1986);  
Model validation cohort: 1,027 female 5-yr survivors treated with chest radiation (diagnosed 1963-2001) | Among women alive at last contact:  
Model development cohort: Median 32.3 (range 9.7-45.7) yr;  
Model validation cohort: median 18.6 (range 6.3-46.0) yr | Model development cohort: 242  
Model validation cohort: 105 | Ten-year risk estimates: 2-23% for 30-year-old women; 5-34% for 40-year-old women | The model included current age, chest radiation field, whether chest radiation was delivered within 1 year of menarche, anthracycline exposure, age at menopause, and history of a first-degree relative with breast cancer |
| Hodgkin Late Effects and LATER Cohorts |
|---------------------------------------|

*Included both French and UK data

Yr = year; SIR = Standardized incidence ratio; CI = Confidence interval; OR = Odds ratio; HR = Hazard ratio; HL = Hodgkin lymphoma; IQR = Interquartile range; RR = Relative risk; LFS = Li-Fraumeni syndrome; TBI = Total body irradiation; CNS = Central nervous system; NM = Not mentioned; EAR = Excess absolute risk; RT = Radiotherapy; CT = Chemotherapy; CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort
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