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# Subsequent female breast cancer risk associated with anthracycline chemotherapy for childhood cancer

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**Supplementary Table 1 | Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status**

| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| **Primary childhood cancer[b]** | | | |
| Leukemia | 4,574 (25.5) | 81 (10.4) | 4,493 (26.2) |
| Non-Hodgkin lymphoma | 1,097 (6.1) | 37 (4.7) | 1,060 (6.2) |
| Hodgkin lymphoma | 2,101 (11.7) | 405 (51.8) | 1,696 (9.9) |
| Central nervous system tumor | 2,946 (16.5) | 14 (1.8) | 2,932 (17.1) |
| Neuroblastoma | 1,657 (9.3) | 15 (1.9) | 1,642 (9.6) |
| Retinoblastoma | 426 (2.4) | 2 (0.3) | 424 (2.5) |
| Renal tumor | 1,372 (7.7) | 45 (5.8) | 1,327 (7.8) |
| Bone tumor | 1,459 (8.1) | 106 (13.6) | 1,353 (7.9) |
| Soft tissue tumor | 1,405 (7.8) | 55 (7.0) | 1,350 (7.9) |
| Germ cell tumor | 440 (2.5) | 9 (1.2) | 431 (2.5) |
| Other malignant epithelial | 297 (1.7) | 11 (1.4) | 286 (1.7) |
| Other[c] | 129 (0.7) | 2 (0.2) | 127 (0.8) |
| **Cumulative doxorubicin dose, mg/m$^2$** | | | |
| 0 | 11,170 (62.4) | 431 (55.1) | 10,739 (62.7) |
| <100 | 912 (5.1) | 16 (2.0) | 896 (5.2) |
| 100-199 | 1,795 (10.0) | 69 (8.8) | 1,726 (10.1) |
| 200-299 | 1,026 (5.7) | 67 (8.6) | 959 (5.6) |
| 300-399 | 1,012 (5.7) | 64 (8.2) | 948 (5.5) |
| ≥400 | 779 (4.4) | 58 (7.4) | 721 (4.2) |
| Unknown[d] | 1,209 (6.8) | 77 (9.8) | 1,132 (6.6) |
| **Cumulative daunorubicin dose, mg/m$^2$** | | | |
| 0 | 14,630 (81.7) | 684 (87.5) | 13,946 (81.5) |
| <100 | 623 (3.5) | 7 (0.9) | 616 (3.6) |
| 100-199 | 953 (5.3) | 16 (2.0) | 937 (5.5) |
| ≥200 | 645 (3.6) | 17 (2.2) | 628 (3.7) |
| Unknown[e] | 1,052 (5.9) | 58 (7.4) | 994 (5.8) |
| **Epirubicin** | | | |
| No | 16,637 (92.9) | 717 (91.7) | 15,920 (93.0) |
| Yes | 325 (1.8) | 9 (1.2) | 316 (1.8) |
| Unknown | 941 (5.3) | 56 (7.2) | 885 (5.2) |
| **Idarubicin** | | | |
| No | 16,843 (94.1) | 725 (92.7) | 16,118 (94.1) |
| Yes | 107 (0.6) | 1 (0.1) | 106 (0.6) |
| Unknown | 953 (5.3) | 56 (7.2) | 897 (5.2) |
| **CED[f]** | | | |
| 0 | 7,951 (44.4) | 301 (38.5) | 7,650 (44.7) |
| <6000 | 3,069 (17.1) | 94 (12.0) | 2,975 (17.4) |
| 6000-17999 | 3,899 (21.8) | 192 (24.6) | 3,707 (21.7) |
| ≥18000 | 1,117 (6.2) | 47 (6.0) | 1,070 (6.2) |
| Unknown | 1,867 (10.4) | 148 (18.9) | 1,719 (10.0) |

**Supplementary Table 1 | Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status**

| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| **Epipodophyllotoxins** | | | |
| No | 13,434 (75.0) | 611 (78.1) | 12,823 (74.9) |
| Yes | 3,346 (18.7) | 78 (10.0) | 3,268 (19.1) |
| Unknown | 1,123 (6.3) | 93 (11.9) | 1,030 (6.0) |
| **Vinca Alkaloids** | | | |
| No | 6,194 (34.6) | 269 (34.4) | 5,925 (34.6) |
| Yes | 10,586 (59.1) | 420 (53.7) | 10,166 (59.4) |
| Unknown | 1,123 (6.3) | 93 (11.9) | 1,030 (6.0) |
| **Platinum Compounds** | | | |
| No | 14,219 (79.4) | 642 (82.1) | 13,577 (79.3) |
| Yes | 2,561 (14.3) | 47 (6.0) | 2,514 (14.7) |
| Unknown | 1,123 (6.3) | 93 (11.9) | 1,030 (6.0) |
| **Antimetabolites** | | | |
| No | 10,376 (58.0) | 504 (64.5) | 9,872 (57.7) |
| Yes | 6,404 (35.8) | 185 (23.7) | 6,219 (36.3) |
| Unknown | 1,123 (6.3) | 93 (11.9) | 1,030 (6.0) |
| **Chest radiotherapy fields and doses[g]** | | | |
| No chest radiotherapy | 13,004 (72.6) | 250 (32.0) | 12,754 (74.5) |
| High-dose mantle (≥36 Gy) median 40 Gy, IQR 39-44 Gy[h] | 698 (3.9) | 238 (30.4) | 460 (2.7) |
| Low-dose mantle (<36 Gy) median 26 Gy, IQR 21-30 Gy[h] | 524 (2.9) | 93 (11.9) | 431 (2.5) |
| Mediastinal median 26 Gy, IQR 21-36 Gy[h] | 469 (2.6) | 33 (4.2) | 436 (2.5) |
| TBI median 12 Gy, IQR 11-13 Gy[h] | 371 (2.1) | 22 (2.8) | 349 (2.0) |
| Whole lung median 16 Gy, IQR 12-23 Gy[h] | 184 (1.0) | 23 (2.9) | 161 (0.9) |
| Other median 28 Gy, IQR 21-36 Gy[h] | 1,316 (7.4) | 63 (8.1) | 1,253 (7.3) |
| Unknown | 1,337 (7.5) | 60 (7.7) | 1,277 (7.5) |
| **Pelvic radiotherapy dose[i]** | | | |
| No pelvic radiotherapy | 13,727 (76.7) | 505 (64.6) | 13,222 (77.2) |
| <10 Gy | 142 (0.8) | 6 (0.8) | 136 (0.8) |
| 10-19 Gy | 594 (3.3) | 24 (3.1) | 570 (3.3) |
| 20-29 Gy | 719 (4.0) | 38 (4.9) | 681 (4.0) |
| 30-39 Gy | 767 (4.3) | 82 (10.5) | 685 (4.0) |
| ≥40 Gy | 713 (4.0) | 72 (9.2) | 641 (3.7) |
| Unknown | 1,241 (6.9) | 55 (7.0) | 1,186 (6.9) |
| **Age at diagnosis of primary cancer, yrs** | | | |
| <5 | 7,376 (41.2) | 66 (8.4) | 7,310 (42.7) |
| 5-9 | 3,788 (21.2) | 65 (8.3) | 3,723 (21.7) |
| 10-14 | 3,930 (22.0) | 273 (34.9) | 3,657 (21.4) |
| 15-21 | 2,809 (15.7) | 378 (48.3) | 2,431 (14.2) |
| **Treatment subgroups[j]** | | | |
| Anthracycline[k] & Chest radiotherapy | 1,634 (9.1) | 163 (20.8) | 1,471 (8.6) |
| Anthracycline & No Chest radiotherapy | 5,714 (31.9) | 156 (19.9) | 5,558 (32.5) |

**Supplementary Table 1 | Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status**

| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| No Anthracycline & Chest radiotherapy | 1,962 (11.0) | 294 (37.6) | 1,668 (9.7) |
| No Anthracycline & No Chest radiotherapy | 7,096 (39.6) | 83 (10.6) | 7,013 (41.0) |
| Unknown | 1,497 (8.4) | 86 (11.0) | 1,411 (8.2) |
| **Period of primary cancer diagnosis** | | | |
| <1960 | 60 (0.3) | 9 (1.2) | 51 (0.3) |
| 1960-1969 | 384 (2.1) | 34 (4.3) | 350 (2.0) |
| 1970-1979 | 4,081 (22.8) | 343 (43.9) | 3,738 (21.8) |
| 1980-1989 | 6,121 (34.2) | 283 (36.2) | 5,838 (34.1) |
| 1990-1999 | 6,134 (34.3) | 107 (13.7) | 6,027 (35.2) |
| 2000-2012 | 1,123 (6.3) | 6 (0.8) | 1,117 (6.5) |
| **Time since five-year of primary cancer diagnosis, yrs** | | | |
| <10 | 2,448 (13.7) | 64 (8.2) | 2,384 (13.9) |
| 10-19 | 6,504 (36.3) | 310 (39.6) | 6,194 (36.2) |
| 20-29 | 5,332 (29.8) | 315 (40.3) | 5,017 (29.3) |
| ≥30 | 3,619 (20.2) | 93 (11.9) | 3,526 (20.6) |
| **Attained age, yrs** | | | |
| <20 | 1,870 (10.4) | 3 (0.4) | 1,867 (10.9) |
| 20-29 | 4,882 (27.3) | 76 (9.7) | 4,806 (28.1) |
| 30-39 | 5,847 (32.7) | 322 (41.2) | 5,525 (32.3) |
| ≥40 | 5,304 (29.6) | 381 (48.7) | 4,923 (28.8) |
| **Vital status** | | | |
| Alive at last contact | 15,278 (85.3) | 549 (70.2) | 14,729 (86.0) |
| Deceased at last contact | 2,625 (14.7) | 233 (29.8) | 2,392 (14.0) |

CED = Cyclophosphamide Equivalent Dose; Gy = Gray; IQR = Interquartile range; No. = number; TBI = Total Body Irradiation; yr = year

[a]Included both invasive and ductal carcinoma in situ breast cancer.

[b]Because of eligibility criteria of the cohort, the composition of primary cancer diagnosis groups in our pooled data may differ from the composition in underlying populations of childhood cancer survivors.

[c]Included the ICCC-3 classification groups "Hepatic Tumor" (0 case/61 survivors), "Other and Unspecified" (1 case/38 survivors), and "Unclassified" (1 case/30 survivors).

[d]The Unknown category under the variable "Doxorubicin dose" included both survivor groups with any doxorubicin (yes/no) unknown (56 cases/941 survivors) and with doxorubicin treatment but dose information unknown (21 cases/268 survivors).

[e]The Unknown category under the variable "Daunorubicin dose" included both survivor groups with any daunorubicin (yes/no) unknown (56 cases/953 survivors) and with daunorubicin treatment but dose information unknown (2 cases/99 survivors).

[f]Cyclophosphamide Equivalent Dose calculation: CED ($mg/m^2$) = 1.0 (cumulative cyclophosphamide dose ($mg/m^2$)) + 0.244 (cumulative ifosfamide dose ($mg/m^2$)) + 0.857 (cumulative procarbazine dose ($mg/m^2$)) + 14.286 (cumulative chlorambucil dose ($mg/m^2$)) + 15.0 (cumulative BCNU (carmustine) dose ($mg/m^2$)) + 16.0 (cumulative CCNU (lomustine) dose ($mg/m^2$)) + 40 (cumulative melphalan dose ($mg/m^2$)) + 50 (cumulative Thio-TEPA (thiotepa) dose ($mg/m^2$)) + 100 (cumulative nitrogen mustard dose ($mg/m^2$)) + 8.823 (cumulative busulfan dose ($mg/m^2$)).

[g]Included radiotherapy fields exposing (parts of) the chest. Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). Chest radiotherapy was categorized as the combination of chest radiation fields with the associated maximum chest radiotherapy dose below or above the median. The variable was classified as follows: high-dose mantle (median 40 Gy, IQR 39-44 Gy), low-dose mantle (median 26 Gy, IQR 21-30 Gy), mediastinal (median 26 Gy, IQR 21-36 Gy), TBI (median 12 Gy, IQR 11-13 Gy), whole lung (median 16 Gy, IQR 12-23 Gy), other (median 28 Gy, IQR 21-36 Gy), and unknown.

[h]Dose represents the maximum cumulative prescribed chest dose (including boost doses, if applicable) of survivors classified in this group. This could include doses to chest field other than this category.

[i]Included radiotherapy fields exposing (parts of) the pelvis (including TBI). Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). The Unknown category under the variable "Pelvic radiotherapy dose" included both survivor groups with any pelvic radiotherapy (yes/no) unknown (54 cases/1,212 survivors) and with pelvic radiotherapy treatment but dose information unknown (1 cases/29 survivors).
[j]Treatment subgroup variable set to unknown if either of the treatment categories was unknown.
[k]Anthracyclines included doxorubicin, daunorubicin, epirubicin, and idarubicin.

**Supplementary Table 2 | Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status (row percentage)**

| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. | No. (%) | No. (%) |
| **Primary childhood cancer[b]** | | | |
| Leukemia | 4,574 | 81 (1.8) | 4,493 (98.2) |
| Non-Hodgkin lymphoma | 1,097 | 37 (3.4) | 1,060 (96.6) |
| Hodgkin lymphoma | 2,101 | 405 (19.3) | 1,696 (80.7) |
| Central nervous system tumor | 2,946 | 14 (0.5) | 2,932 (99.5) |
| Neuroblastoma | 1,657 | 15 (0.9) | 1,642 (99.1) |
| Retinoblastoma | 426 | 2 (0.5) | 424 (99.5) |
| Renal tumor | 1,372 | 45 (3.3) | 1,327 (96.7) |
| Bone tumor | 1,459 | 106 (7.3) | 1,353 (92.7) |
| Soft tissue tumor | 1,405 | 55 (3.9) | 1,350 (96.1) |
| Germ cell tumor | 440 | 9 (2.0) | 431 (98.0) |
| Other malignant epithelial | 297 | 11 (3.7) | 286 (96.3) |
| Other[c] | 129 | 2 (1.6) | 127 (98.4) |
| **Cumulative doxorubicin dose, mg/m$^2$** | | | |
| 0 | 11,170 | 431 (3.9) | 10,739 (96.1) |
| <100 | 912 | 16 (1.8) | 896 (98.2) |
| 100-199 | 1,795 | 69 (3.8) | 1,726 (96.2) |
| 200-299 | 1,026 | 67 (6.5) | 959 (93.5) |
| 300-399 | 1,012 | 64 (6.3) | 948 (93.7) |
| ≥400 | 779 | 58 (7.4) | 721 (92.6) |
| Unknown[d] | 1,209 | 77 (6.4) | 1,132 (93.6) |
| **Cumulative daunorubicin dose, mg/m$^2$** | | | |
| 0 | 14,630 | 684 (4.7) | 13,946 (95.3) |
| <100 | 623 | 7 (1.1) | 616 (98.9) |
| 100-199 | 953 | 16 (1.7) | 937 (98.3) |
| ≥200 | 645 | 17 (2.6) | 628 (97.4) |
| Unknown[e] | 1,052 | 58 (5.5) | 994 (94.5) |
| **Epirubicin** | | | |
| No | 16,637 | 717 (4.3) | 15,920 (95.7) |
| Yes | 325 | 9 (2.8) | 316 (97.2) |
| Unknown | 941 | 56 (6.0) | 885 (94.0) |
| **Idarubicin** | | | |
| No | 16,843 | 725 (4.3) | 16,118 (95.7) |
| Yes | 107 | 1 (0.9) | 106 (99.1) |
| Unknown | 953 | 56 (5.9) | 897 (94.1) |
| **CED[f]** | | | |
| 0 | 7,951 | 301 (3.8) | 7,650 (96.2) |
| <6000 | 3,069 | 94 (3.1) | 2,975 (96.9) |
| 6000-17999 | 3,899 | 192 (4.9) | 3,707 (96.9) |
| ≥18000 | 1,117 | 47 (4.2) | 1,070 (95.8) |
| Unknown | 1,867 | 148 (7.9) | 1,719 (92.1) |

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| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. | No. (%) | No. (%) |
| **Epipodophyllotoxins** | | | |
| No | 13,434 | 611 (4.5) | 12,823 (95.5) |
| Yes | 3,346 | 78 (2.3) | 3,268 (97.7) |
| Unknown | 1,123 | 93 (8.3) | 1,030 (91.7) |
| **Vinca Alkaloids** | | | |
| No | 6,194 | 269 (4.3) | 5,925 (95.7) |
| Yes | 10,586 | 420 (4.0) | 10,166 (96.0) |
| Unknown | 1,123 | 93 (8.3) | 1,030 (91.7) |
| **Platinum Compounds** | | | |
| No | 14,219 | 642 (4.5) | 13,577 (95.5) |
| Yes | 2,561 | 47 (1.8) | 2,514 (98.2) |
| Unknown | 1,123 | 93 (8.3) | 1,030 (91.7) |
| **Antimetabolites** | | | |
| No | 10,376 | 504 (4.9) | 9,872 (95.1) |
| Yes | 6,404 | 185 (2.9) | 6,219 (97.1) |
| Unknown | 1,123 | 93 (8.3) | 1,030 (91.7) |
| **Chest radiotherapy fields and doses[g]** | | | |
| No chest radiotherapy | 13,004 | 250 (1.9) | 12,754 (98.1) |
| High-dose mantle (≥36 Gy) median 40 Gy, IQR 39-44 Gy[h] | 698 | 238 (34.1) | 460 (65.9) |
| Low-dose mantle (<36 Gy) median 26 Gy, IQR 21-30 Gy[h] | 524 | 93 (17.7) | 431 (82.3) |
| Mediastinal median 26 Gy, IQR 21-36 Gy[h] | 469 | 33 (7.0) | 436 (93.0) |
| TBI median 12 Gy, IQR 11-13 Gy[h] | 371 | 22 (5.9) | 349 (94.1) |
| Whole lung median 16 Gy, IQR 12-23 Gy[h] | 184 | 23 (12.5) | 161 (87.5) |
| Other median 28 Gy, IQR 21-36 Gy[h] | 1,316 | 63 (4.8) | 1,253 (95.2) |
| Unknown | 1,337 | 60 (4.5) | 1,277 (95.5) |
| **Pelvic radiotherapy dose[i]** | | | |
| No pelvic radiotherapy | 13,727 | 505 (3.7) | 13,222 (96.3) |
| <10 Gy | 142 | 6 (4.2) | 136 (95.8) |
| 10-19 Gy | 594 | 24 (4.0) | 570 (96.0) |
| 20-29 Gy | 719 | 38 (5.3) | 681 (94.7) |
| 30-39 Gy | 767 | 82 (10.7) | 685 (89.3) |
| ≥40 Gy | 713 | 72 (10.1) | 641 (89.9) |
| Unknown | 1,241 | 55 (4.4) | 1,186 (95.6) |
| **Age at diagnosis of primary cancer, yrs** | | | |
| <5 | 7,376 | 66 (0.9) | 7,310 (99.1) |
| 5-9 | 3,788 | 65 (1.7) | 3,723 (98.3) |
| 10-14 | 3,930 | 273 (6.9) | 3,657 (93.1) |
| 15-21 | 2,809 | 378 (13.5) | 2,431 (86.5) |
| **Treatment subgroups[j]** | | | |
| Anthracycline[k] & Chest radiotherapy | 1,634 | 163 (10.0) | 1,471 (90.0) |
| Anthracycline & No Chest radiotherapy | 5,714 | 156 (2.7) | 5,558 (97.3) |

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| | Total (n = 17,903) | Subsequent breast cancer[a] (n = 782) | No subsequent breast cancer (n = 17,121) |
|---|---|---|---|
| | No. | No. (%) | No. (%) |
| No Anthracycline & Chest radiotherapy | 1,962 | 294 (15.0) | 1,668 (85.0) |
| No Anthracycline & No Chest radiotherapy | 7,096 | 83 (1.2) | 7,013 (98.8) |
| Unknown | 1,497 | 86 (5.7) | 1,411 (94.3) |
| **Period of primary cancer diagnosis** | | | |
| <1960 | 60 | 9 (15.0) | 51 (85.0) |
| 1960-1969 | 384 | 34 (8.9) | 350 (91.1) |
| 1970-1979 | 4,081 | 343 (8.4) | 3,738 (91.6) |
| 1980-1989 | 6,121 | 283 (4.6) | 5,838 (95.4) |
| 1990-1999 | 6,134 | 107 (1.7) | 6,027 (98.3) |
| 2000-2012 | 1,123 | 6 (0.5) | 1,117 (99.5) |
| **Time since five-year of primary cancer diagnosis, yrs** | | | |
| <10 | 2,448 | 64 (2.6) | 2,384 (97.4) |
| 10-19 | 6,504 | 310 (4.8) | 6,194 (95.2) |
| 20-29 | 5,332 | 315 (5.9) | 5,017 (94.1) |
| ≥30 | 3,619 | 93 (2.6) | 3,526 (97.4) |
| **Attained age, yrs** | | | |
| <20 | 1,870 | 3 (0.2) | 1,867 (99.8) |
| 20-29 | 4,882 | 76 (1.6) | 4,806 (98.4) |
| 30-39 | 5,847 | 322 (5.5) | 5,525 (94.5) |
| ≥40 | 5,304 | 381 (7.2) | 4,923 (92.8) |
| **Vital status** | | | |
| Alive at last contact | 15,278 | 549 (3.6) | 14,729 (96.4) |
| Deceased at last contact | 2,625 | 233 (8.9) | 2,392 (91.1) |

CED = Cyclophosphamide Equivalent Dose; Gy = Gray; IQR = Interquartile range; No. = number; TBI = Total Body Irradiation; yr = year

[a]Included both invasive and ductal carcinoma in situ breast cancer.

[b]Because of eligibility criteria of the cohort, the composition of primary cancer diagnosis groups in our pooled data may differ from the composition in underlying populations of childhood cancer survivors.

[c]Included the ICCC-3 classification groups "Hepatic Tumor" (0 case/61 survivors), "Other and Unspecified" (1 case/38 survivors), and "Unclassified" (1 case/30 survivors).

[d]The Unknown category under the variable "Doxorubicin dose" included both survivor groups with any doxorubicin (yes/no) unknown (56 cases/941 survivors) and with doxorubicin treatment but dose information unknown (21 cases/268 survivors).

[e]The Unknown category under the variable "Daunorubicin dose" included both survivor groups with any daunorubicin (yes/no) unknown (56 cases/953 survivors) and with daunorubicin treatment but dose information unknown (2 cases/99 survivors).

[f]Cyclophosphamide Equivalent Dose calculation: CED ($mg/m^2$) = 1.0 (cumulative cyclophosphamide dose ($mg/m^2$)) + 0.244 (cumulative ifosfamide dose ($mg/m^2$)) + 0.857 (cumulative procarbazine dose ($mg/m^2$)) + 14.286 (cumulative chlorambucil dose ($mg/m^2$)) + 15.0 (cumulative BCNU (carmustine) dose ($mg/m^2$)) + 16.0 (cumulative CCNU (lomustine) dose ($mg/m^2$)) + 40 (cumulative melphalan dose ($mg/m^2$)) + 50 (cumulative Thio-TEPA (thiotepa) dose ($mg/m^2$)) + 100 (cumulative nitrogen mustard dose ($mg/m^2$)) + 8.823 (cumulative busulfan dose ($mg/m^2$)).

[g]Included radiotherapy fields exposing (parts of) the chest. Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). Chest radiotherapy was categorized as the combination of chest radiation fields with the associated maximum chest radiotherapy dose below or above the median. The variable was classified as follows: high-dose mantle (median 40 Gy, IQR 39-44 Gy), low-dose mantle (median 26 Gy, IQR 21-30 Gy), mediastinal (median 26 Gy, IQR 21-36 Gy), TBI (median 12 Gy, IQR 11-13 Gy), whole lung (median 16 Gy, IQR 12-23 Gy), other (median 28 Gy, IQR 21-36 Gy), and unknown.

[h]Dose represents the maximum cumulative prescribed chest dose (including boost doses, if applicable) of survivors classified in this group. This could include doses to chest field other than this category.

[i]Included radiotherapy fields exposing (parts of) the pelvis (including TBI). Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). The Unknown category under the variable "Pelvic radiotherapy dose" included both survivor groups with any pelvic radiotherapy (yes/no) unknown (54 cases/1,212 survivors) and with pelvic radiotherapy treatment but dose information unknown (1 cases/29 survivors).
[j]Treatment subgroup variable set to unknown if either of the treatment categories was unknown.
[k]Anthracyclines included doxorubicin, daunorubicin, epirubicin, and idarubicin.

**Supplementary Table 3 | Demographic and treatment characteristics of female five-year childhood cancer survivors by cohort**

| | CCSS (n = 9,671) | SJLIFE (n = 2,236) | DCCSS-LATER (n = 2,237) | FCCSS (n = 3,415) | DHL (n = 265) | SCCSS (n = 79) | Total (N = 17,903) |
|---|---|---|---|---|---|---|---|
| **Primary childhood cancer type** | | | | | | | |
| Leukemia | 2,987 (30.9%) | 802 (35.9%) | 770 (34.4%) | - | - | 15 (19.0%) | 4,574 (25.5%) |
| Non-Hodgkin lymphoma | 586 (6.1%) | 115 (5.1%) | 157 (7.0%) | 235 (6.9%) | - | 4 (5.1%) | 1,097 (6.1%) |
| Hodgkin lymphoma | 1,276 (13.2%) | 227 (10.2%) | 125 (5.6%) | 189 (5.5%) | 265 (100%) | 19 (24.1%) | 2,101 (11.7%) |
| Central nervous system tumor | 1,841 (19.0%) | 287 (12.8%) | 312 (13.9%) | 498 (14.6%) | - | 8 (10.1%) | 2,946 (16.5%) |
| Neuroblastoma | 901 (9.3%) | 101 (4.5%) | 145 (6.5%) | 505 (14.8%) | - | 5 (6.3%) | 1,657 (9.3%) |
| Retinoblastoma | - | 119 (5.3%) | 14 (0.6%) | 293 (8.6%) | - | - | 426 (2.4%) |
| Renal tumor | 389 (4.0%) | 170 (7.6%) | 250 (11.2%) | 558 (16.3%) | - | 5 (6.3%) | 1,372 (7.7%) |
| Bone tumor | 884 (9.1%) | 133 (5.9%) | 141 (6.3%) | 295 (8.6%) | - | 6 (7.6%) | 1,459 (8.1%) |
| Soft tissue tumor | 763 (7.9%) | 127 (5.7%) | 151 (6.8%) | 361 (10.6%) | - | 3 (3.8%) | 1,405 (7.8%) |
| Germ cell tumor | 20 (0.2%) | 68 (3.0%) | 101 (4.5%) | 249 (7.3%) | - | 2 (2.5%) | 440 (2.5%) |
| Other malignant epithelial | - | 49 (2.2%) | 50 (2.2%) | 187 (5.5%) | - | 11 (13.9%) | 297 (1.7%) |
| Other[a] | 24 (0.2%) | 38 (1.7%) | 21 (0.9%) | 45 (1.3%) | - | 1 (1.3%) | 129 (0.7%) |
| **Age at primary childhood cancer diagnosis (yr)** | | | | | | | |
| Median [IQR] | 7.5 [3.1, 13.7] | 6.2 [2.7, 12.6] | 5.4 [2.7, 10.7] | 5.2 [1.7, 11.4] | 18.3 [16.6, 19.7] | 14.2 [6.0, 17.3] | 6.7 [2.8, 13.0] |
| **Age at primary childhood cancer diagnosis (yr) category** | | | | | | | |
| <5 | 3,666 (37.9%) | 973 (43.5%) | 1,049 (46.9%) | 1,671 (48.9%) | - | 17 (21.5%) | 7,376 (41.2%) |
| 5-9 | 2,027 (21.0%) | 468 (20.9%) | 569 (25.4%) | 707 (20.7%) | 7 (2.6%) | 10 (12.7%) | 3,788 (21.2%) |
| 10-14 | 2,204 (22.8%) | 472 (21.1%) | 471 (21.1%) | 744 (21.8%) | 21 (7.9%) | 18 (22.8%) | 3,930 (22.0%) |
| 15-21 | 1,774 (18.3%) | 323 (14.4%) | 148 (6.6%) | 293 (8.6%) | 237 (89.4%) | 34 (43.0%) | 2,809 (15.7%) |
| **Period of childhood cancer diagnosis, range** | | | | | | | |
| Median [IQR] | 1985 [1979, 1992] | 1994 [1984, 2002] | 1989 [1981, 1996] | 1986 [1978, 1994] | 1982 [1974, 1991] | 1990 [1984, 1999] | 1986 [1979, 1994] |
| **Period of childhood cancer diagnosis category** | | | | | | | |
| <1960 | - | - | - | 60 (1.8%) | - | - | 60 (0.3%) |
| 1960-1969 | - | 42 (1.9%) | 49 (2.2%) | 264 (7.7%) | 29 (10.9%) | - | 384 (2.1%) |
| 1970-1979 | 2,639 (27.3%) | 274 (12.3%) | 386 (17.3%) | 693 (20.3%) | 81 (30.6%) | 8 (10.1%) | 4,081 (22.8%) |
| 1980-1989 | 3,737 (38.6%) | 535 (23.9%) | 711 (31.8%) | 1,035 (30.3%) | 76 (28.7%) | 27 (34.2%) | 6,121 (34.2%) |
| 1990-1999 | 3,295 (34.1%) | 633 (28.3%) | 871 (38.9%) | 1,233 (36.1%) | 76 (28.7%) | 26 (32.9%) | 6,134 (34.3%) |
| 2000-2012 | - | 752 (33.6%) | 220 (9.8%) | 130 (3.8%) | 3 (1.1%) | 18 (22.8%) | 1,123 (6.3%) |
| **Duration of follow-up since 5-yr survival and the end of follow-up[b] (yr)** | | | | | | | |
| Median [IQR] | 20.2 [14.7, 28.0] | 18.0 [10.3, 27.5] | 16.8 [10.8, 25.0] | 23.2 [16.3, 31.8] | 17.6 [12.3, 25.7] | 11.0 [6.7, 18.7] | 19.9 [14.1, 28.2] |
| **Duration of follow-up since 5-yr survival and the end of follow-up[b] (yr) category** | | | | | | | |
| <10 | 1,096 (11.3%) | 543 (24.3%) | 482 (21.5%) | 251 (7.4%) | 40 (15.1%) | 36 (45.6%) | 2,448 (13.7%) |
| 10-19 | 3,672 (38.0%) | 703 (31.4%) | 859 (38.4%) | 1,130 (33.1%) | 116 (43.8%) | 24 (30.4%) | 6,504 (36.3%) |
| 20-29 | 3,012 (31.1%) | 570 (25.5%) | 645 (28.8%) | 1,018 (29.8%) | 69 (26.0%) | 18 (22.8%) | 5,332 (29.8%) |
| ≥30 | 1,891 (19.6%) | 420 (18.8%) | 251 (11.2%) | 1,016 (29.8%) | 40 (15.1%) | 1 (1.3%) | 3,619 (20.2%) |
| **Attained age at last follow-up[b] (yr)** | | | | | | | |

**Supplementary Table 3 | Demographic and treatment characteristics of female five-year childhood cancer survivors by cohort**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Median [IQR] | 34.4 [26.7, 42.0] | 31.8 [23.7, 39.9] | 29.3 [22.1, 36.9] | 35.8 [27.3, 44.0] | 40.9 [35.5, 48.8] | 28.6 [24.3, 37.6] | 33.7 [25.9, 41.6] |
| **Attained age at last follow-up[b] age (yr) category** | | | | | | | |
| <20 | 838 (8.7%) | 380 (17.0%) | 395 (17.7%) | 242 (7.1%) | 1 (0.4%) | 14 (17.7%) | 1,870 (10.4%) |
| 20-29 | 2,552 (26.4%) | 614 (27.5%) | 798 (35.7%) | 862 (25.2%) | 26 (9.8%) | 30 (38.0%) | 4,882 (27.3%) |
| 30-39 | 3,314 (34.3%) | 688 (30.8%) | 666 (29.8%) | 1,068 (31.3%) | 93 (35.1%) | 18 (22.8%) | 5,847 (32.7%) |
| ≥40 | 2,967 (30.7%) | 554 (24.8%) | 378 (16.9%) | 1,243 (36.4%) | 145 (54.7%) | 17 (21.5%) | 5,304 (29.6%) |
| **SBC[c]** | | | | | | | |
| No | 9,219 (95.3%) | 2,159 (96.6%) | 2,196 (98.2%) | 3,288 (96.3%) | 200 (75.5%) | 59 (74.7%) | 17,121 (95.6%) |
| Yes | 452 (4.7%) | 77 (3.4%) | 41 (1.8%) | 127 (3.7%) | 65 (24.5%) | 20 (25.3%) | 782 (4.4%) |
| **First SBC type** | | | | | | | |
| Invasive | 344 (3.6%) | 54 (2.4%) | 36 (1.6%) | 111 (3.3%) | 51 (19.2%) | 20 (25.3%) | 616 (3.4%) |
| DCIS | 108 (1.1%) | 23 (1.0%) | 5 (0.2%) | 16 (0.5%) | 14 (5.3%) | - | 166 (0.9%) |
| **Vital status** | | | | | | | |
| Alive at last contact | 8,174 (84.5%) | 2,171 (97.1%) | 1,928 (86.2%) | 2,759 (80.8%) | 178 (67.2%) | 68 (86.1%) | 15,278 (85.3%) |
| Deceased at last contact | 1,497 (15.5%) | 65 (2.9%) | 309 (13.8%) | 656 (19.2%) | 87 (32.8%) | 11 (13.9%) | 2,625 (14.7%) |
| **Radiotherapy exposure to the chest** | | | | | | | |
| No | 6,607 (68.3%) | 1,706 (76.3%) | 1,892 (84.6%) | 2,728 (79.9%) | 22 (8.3%) | 49 (62.0%) | 13,004 (72.6%) |
| Yes | 2,098 (21.7%) | 506 (22.6%) | 341 (15.2%) | 482 (14.1%) | 243 (91.7%) | 23 (29.1%) | 3,693 (20.6%) |
| Unknown | 966 (10.0%) | 24 (1.1%) | 4 (0.2%) | 205 (6.0%) | - | 7 (8.9%) | 1,206 (6.7%) |
| **Chest radiation dose (Gy)** | | | | | | | |
| Median [IQR] | 30.0 [20.0, 39.0] | 25.3 [15.0, 33.0] | 25.0 [13.8, 35.2] | 27.5 [20.0, 40.0] | 38.0 [35.0, 40.0] | 36.0 [19.8, 40.0] | 28.0 [20.0, 39.0] |
| **Chest radiation dose (Gy) category** | | | | | | | |
| No chest radiation | 6,607 (68.3%) | 1,706 (76.3%) | 1,892 (84.6%) | 2,728 (79.9%) | 22 (8.3%) | 49 (62.0%) | 13,004 (72.6%) |
| <10 | 73 (0.8%) | 5 (0.2%) | 48 (2.1%) | 7 (0.2%) | - | - | 133 (0.7%) |
| 10-19 | 403 (4.2%) | 133 (5.9%) | 69 (3.1%) | 102 (3.0%) | 2 (0.8%) | 6 (7.6%) | 715 (4.0%) |
| 20-29 | 533 (5.5%) | 210 (9.4%) | 60 (2.7%) | 148 (4.3%) | 11 (4.2%) | 2 (2.5%) | 964 (5.4%) |
| 30-39 | 542 (5.6%) | 85 (3.8%) | 82 (3.7%) | 92 (2.7%) | 90 (34.0%) | 5 (6.3%) | 896 (5.0%) |
| ≥40 | 511 (5.3%) | 41 (1.8%) | 68 (3.0%) | 133 (3.9%) | 85 (32.1%) | 6 (7.6%) | 844 (4.7%) |
| Unknown | 1,002 (10.4%) | 56 (2.5%) | 18 (0.8%) | 205 (6.0%) | 55 (20.8%) | 11 (13.9%) | 1,347 (7.5%) |
| **Chest radiation field** | | | | | | | |
| No chest radiation | 6,607 (68.3%) | 1,706 (76.3%) | 1,892 (84.6%) | 2,728 (79.9%) | 22 (8.3%) | 49 (62.0%) | 13,004 (72.6%) |
| Axilla | 12 (0.1%) | 5 (0.2%) | 15 (0.7%) | - | 2 (0.8%) | - | 34 (0.2%) |
| Mantle | 723 (7.5%) | 191 (8.5%) | 39 (1.7%) | 86 (2.5%) | 192 (72.5%) | 11 (13.9%) | 1,242 (6.9%) |
| Mediastinal | 227 (2.3%) | 23 (1.0%) | 36 (1.6%) | 134 (3.9%) | 45 (17.0%) | 4 (5.1%) | 469 (2.6%) |
| Spine | 598 (6.2%) | 131 (5.9%) | 109 (4.9%) | 98 (2.9%) | - | 3 (3.8%) | 939 (5.2%) |
| Total body irradiation | 223 (2.3%) | 67 (3.0%) | 69 (3.1%) | 10 (0.3%) | - | 2 (2.5%) | 371 (2.1%) |
| Whole lung | 79 (0.8%) | 44 (2.0%) | 22 (1.0%) | 37 (1.1%) | - | 2 (2.5%) | 184 (1.0%) |
| Other | 177 (1.8%) | 33 (1.5%) | 49 (2.2%) | 117 (3.4%) | - | 1 (1.3%) | 377 (2.1%) |
| Unknown | 1,025 (10.6%) | 36 (1.6%) | 6 (0.3%) | 205 (6.0%) | 4 (1.5%) | 7 (8.9%) | 1,283 (7.2%) |
| **Radiotherapy exposure to the pelvis** | | | | | | | |
| No | 7,191 (74.4%) | 1,873 (83.8%) | 2,129 (95.2%) | 2,287 (67.0%) | 179 (67.5%) | 68 (86.1%) | 13,727 (76.7%) |
| Yes | 1,515 (15.7%) | 337 (15.1%) | 105 (4.7%) | 923 (27.0%) | 81 (30.6%) | 3 (3.8%) | 2,964 (16.6%) |
| Unknown | 965 (10.0%) | 26 (1.2%) | 3 (0.1%) | 205 (6.0%) | 5 (1.9%) | 8 (10.1%) | 1,212 (6.8%) |
| **Pelvic radiation dose (Gy)** | | | | | | | |

**Supplementary Table 3 | Demographic and treatment characteristics of female five-year childhood cancer survivors by cohort**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Median [IQR] | 26.0 [15.0, 36.0] | 23.4 [16.8, 36.0] | 12.0 [7.5, 38.5] | 33.0 [22.0, 43.5] | NA[d] | 11.0 [10.5, 11.5] | 30.0 [19.0, 39.0] |
| **Pelvic radiation dose (Gy) category** | | | | | | | |
| No pelvic radiation | 7,191 (74.4%) | 1,873 (83.8%) | 2,129 (95.2%) | 2,287 (67.0%) | 179 (67.5%) | 68 (86.1%) | 13,727 (76.7%) |
| <10 | 66 (0.7%) | 4 (0.2%) | 47 (2.1%) | 25 (0.7%) | - | - | 142 (0.8%) |
| 10-19 | 369 (3.8%) | 89 (4.0%) | 20 (0.9%) | 114 (3.3%) | - | 2 (2.5%) | 594 (3.3%) |
| 20-29 | 365 (3.8%) | 120 (5.4%) | 2 (0.1%) | 232 (6.8%) | - | - | 719 (4.0%) |
| 30-39 | 398 (4.1%) | 66 (3.0%) | 6 (0.3%) | 216 (6.3%) | 81 (30.6%)[e] | - | 767 (4.3%) |
| ≥40 | 295 (3.1%) | 57 (2.5%) | 25 (1.1%) | 336 (9.8%) | - | - | 713 (4.0%) |
| Unknown | 987 (10.2%) | 27 (1.2%) | 8 (0.4%) | 205 (6.0%) | 5 (1.9%) | 9 (11.4%) | 1,241 (6.9%) |
| **Anthracyclines**[f] | | | | | | | |
| No | 4,889 (50.6%) | 955 (42.7%) | 1,250 (55.9%) | 2,095 (61.3%) | 155 (58.5%) | 36 (45.6%) | 9,380 (52.4%) |
| Yes | 3,990 (41.3%) | 1,263 (56.5%) | 982 (43.9%) | 1,201 (35.2%) | 98 (37.0%) | 36 (45.6%) | 7,570 (42.3%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 12 (4.5%) | 7 (8.9%) | 953 (5.3%) |
| **Doxorubicin** | | | | | | | |
| No | 5,729 (59.2%) | 1,377 (61.6%) | 1,541 (68.9%) | 2,300 (67.4%) | 181 (68.3%) | 42 (53.2%) | 11,170 (62.4%) |
| Yes | 3,150 (32.6%) | 841 (37.6%) | 691 (30.9%) | 996 (29.2%) | 84 (31.7%) | 30 (38.0%) | 5,792 (32.4%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | - | 7 (8.9%) | 941 (5.3%) |
| **Cumulative doxorubicin dose (mg/m²)** | | | | | | | |
| Median [IQR] | 224.7 [130.4, 358.3] | 177.4 [135.1, 256.2] | 150.0 [65.0, 300.0] | 235.7 [131.7, 346.8] | 210.0 [140.0, 280.0] | 200.0 [150.0, 300.0] | 203.3 [120.0, 340.0] |
| **Cumulative doxorubicin dose (mg/m²) category** | | | | | | | |
| 0 | 5,729 (59.2%) | 1,377 (61.6%) | 1,541 (68.9%) | 2,300 (67.4%) | 181 (68.3%) | 42 (53.2%) | 11,170 (62.4%) |
| <100 | 502 (5.2%) | 121 (5.4%) | 188 (8.4%) | 95 (2.8%) | 5 (1.9%) | 1 (1.3%) | 912 (5.1%) |
| 100-199 | 769 (8.0%) | 414 (18.5%) | 232 (10.4%) | 347 (10.2%) | 20 (7.5%) | 13 (16.5%) | 1,795 (10.0%) |
| 200-299 | 590 (6.1%) | 124 (5.5%) | 62 (2.8%) | 207 (6.1%) | 38 (14.3%) | 5 (6.3%) | 1,026 (5.7%) |
| 300-399 | 568 (5.9%) | 146 (6.5%) | 77 (3.4%) | 203 (5.9%) | 11 (4.2%) | 7 (8.9%) | 1,012 (5.7%) |
| ≥400 | 474 (4.9%) | 35 (1.6%) | 124 (5.5%) | 137 (4.0%) | 6 (2.3%) | 3 (3.8%) | 779 (4.4%) |
| Unknown | 1,039 (10.7%) | 19 (0.8%) | 13 (0.6%) | 126 (3.7%) | 4 (1.5%) | 8 (10.1%) | 1,209 (6.8%) |
| **Daunorubicin** | | | | | | | |
| No | 7,660 (79.2%) | 1,618 (72.4%) | 1,795 (80.2%) | 3,239 (94.8%) | 253 (95.5%) | 65 (82.3%) | 14,630 (81.7%) |
| Yes | 1,219 (12.6%) | 600 (26.8%) | 437 (19.5%) | 57 (1.7%) | - | 7 (8.9%) | 2,320 (13.0%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 12 (4.5%) | 7 (8.9%) | 953 (5.3%) |
| **Cumulative daunorubicin (mg/m²)** | | | | | | | |
| Median [IQR] | 151.0 [100.0, 319.4] | 87.5 [50.0, 106.7] | 120.0 [120.0, 175.0] | 255.7 [140.8, 419.7] | - | 150.0 [120.0, 247.5] | 120.0 [98.1, 234.1] |
| **Cumulative daunorubicin dose (mg/m²) category** | | | | | | | |
| 0 | 7,660 (79.2%) | 1,618 (72.4%) | 1,795 (80.2%) | 3,239 (94.8%) | 253 (95.5%) | 65 (82.3%) | 14,630 (81.7%) |
| <100 | 263 (2.7%) | 339 (15.2%) | 16 (0.7%) | 5 (0.1%) | - | - | 623 (3.5%) |
| 100-199 | 373 (3.9%) | 198 (8.9%) | 361 (16.1%) | 17 (0.5%) | - | 4 (5.1%) | 953 (5.3%) |
| ≥200 | 494 (5.1%) | 62 (2.8%) | 51 (2.3%) | 35 (1.0%) | - | 3 (3.8%) | 645 (3.6%) |
| Unknown | 881 (9.1%) | 19 (0.8%) | 14 (0.6%) | 119 (3.5%) | 12 (4.5%) | 7 (8.9%) | 1,052 (5.9%) |
| **Epirubicin** | | | | | | | |
| No | 8,877 (91.8%) | 2,217 (99.2%) | 2,104 (94.1%) | 3,116 (91.2%) | 251 (94.7%) | 72 (91.1%) | 16,637 (92.9%) |
| Yes | 2 (0.0%) | 1 (0.0%) | 128 (5.7%) | 180 (5.3%) | 14 (5.3%) | - | 325 (1.8%) |

**Supplementary Table 3 | Demographic and treatment characteristics of female five-year childhood cancer survivors by cohort**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | - | 7 (8.9%) | 941 (5.3%) |
| **Idarubicin** | | | | | | | |
| No | 8,814 (91.1%) | 2,198 (98.3%) | 2,212 (98.9%) | 3,296 (96.5%) | 253 (95.5%) | 70 (88.6%) | 16,843 (94.1%) |
| Yes | 65 (0.7%) | 20 (0.9%) | 20 (0.9%) | - | - | 2 (2.5%) | 107 (0.6%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 12 (4.5%) | 7 (8.9%) | 953 (5.3%) |
| **Alkylating agents** | | | | | | | |
| No | 4,003 (41.4%) | 947 (42.4%) | 1,152 (51.5%) | 1,597 (46.8%) | 100 (37.7%) | 33 (41.8%) | 7,832 (43.7%) |
| Yes | 4,876 (50.4%) | 1,271 (56.8%) | 1,080 (48.3%) | 1,699 (49.8%) | 153 (57.7%) | 39 (49.4%) | 9,118 (50.9%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 12 (4.5%) | 7 (8.9%) | 953 (5.3%) |
| **CED[g] dose ($mg/m^2$)** | | | | | | | |
| 0 | 4,093 (42.3%) | 956 (42.8%) | 1,160 (51.9%) | 1,608 (47.1%) | 100 (37.7%) | 34 (43.0%) | 7,951 (44.4%) |
| <6000 | 1,687 (17.4%) | 489 (21.9%) | 265 (11.8%) | 606 (17.7%) | - | 22 (27.8%) | 3,069 (17.1%) |
| 6000-17999 | 1,876 (19.4%) | 631 (28.2%) | 563 (25.2%) | 819 (24.0%) | - | 10 (12.7%) | 3,899 (21.8%) |
| ≥18000 | 561 (5.8%) | 139 (6.2%) | 192 (8.6%) | 222 (6.5%) | - | 3 (3.8%) | 1,117 (6.2%) |
| Unknown | 1,454 (15.0%) | 21 (0.9%) | 57 (2.5%) | 160 (4.7%) | 165 (62.3%) | 10 (12.7%) | 1,867 (10.4%) |
| **Epipodophyllotoxins** | | | | | | | |
| No | 7,567 (78.2%) | 1,402 (62.7%) | 1,796 (80.3%) | 2,531 (74.1%) | 83 (31.3%) | 55 (69.6%) | 13,434 (75.0%) |
| Yes | 1,312 (13.6%) | 816 (36.5%) | 436 (19.5%) | 765 (22.4%) | - | 17 (21.5%) | 3,346 (18.7%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 182 (68.7%) | 7 (8.9%) | 1,123 (6.3%) |
| **Vinca alkaloids** | | | | | | | |
| No | 3,351 (34.7%) | 706 (31.6%) | 653 (29.2%) | 1,367 (40.0%) | 83 (31.3%) | 34 (43.0%) | 6,194 (34.6%) |
| Yes | 5,528 (57.2%) | 1,512 (67.6%) | 1,579 (70.6%) | 1,929 (56.5%) | - | 38 (48.1%) | 10,586 (59.1%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 182 (68.7%) | 7 (8.9%) | 1,123 (6.3%) |
| **Platinum compounds** | | | | | | | |
| No | 7,817 (80.8%) | 1,870 (83.6%) | 1,911 (85.4%) | 2,473 (72.4%) | 83 (31.3%) | 65 (82.3%) | 14,219 (79.4%) |
| Yes | 1,062 (11.0%) | 348 (15.6%) | 321 (14.3%) | 823 (24.1%) | - | 7 (8.9%) | 2,561 (14.3%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 182 (68.7%) | 7 (8.9%) | 1,123 (6.3%) |
| **Antimetabolites** | | | | | | | |
| No | 5,012 (51.8%) | 1,151 (51.5%) | 1,261 (56.4%) | 2,816 (82.5%) | 83 (31.3%) | 53 (67.1%) | 10,376 (58.0%) |
| Yes | 3,867 (40.0%) | 1,067 (47.7%) | 971 (43.4%) | 480 (14.1%) | - | 19 (24.1%) | 6,404 (35.8%) |
| Unknown | 792 (8.2%) | 18 (0.8%) | 5 (0.2%) | 119 (3.5%) | 182 (68.7%) | 7 (8.9%) | 1,123 (6.3%) |

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; DCCSS-LATER = Dutch Childhood Cancer Survivor Study LATER; DCIS = Ductal carcinoma in situ; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; Gy = Gray; IQR = Interquartile range; NA = Not applicable; SBC = Subsequent breast cancer; SCCSS = Swiss Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; yr = year

[a]Included the ICCC-3 classification groups "Hepatic Tumor", "Other and Unspecified", and "Unclassified".

[b]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.

[c]Included both invasive and DCIS breast cancer.

[d]Precise pelvic radiation dose information was not available in the DHL.

[e]Dose of pelvic radiation information was not available for the DHL. We assume the survivors in the DHL who had pelvic radiotherapy received 30 Gy radiotherapy exposure to the pelvis since Hodgkin lymphoma patients usually receive 30 Gy pelvic radiation.

[f]Anthracyclines included doxorubicin, daunorubicin, epirubicin, and idarubicin.

[g]Cyclophosphamide Equivalent Dose calculation: CED ($mg/m^2$) = 1.0 (cumulative cyclophosphamide dose ($mg/m^2$)) + 0.244 (cumulative ifosfamide dose ($mg/m^2$)) + 0.857 (cumulative procarbazine dose ($mg/m^2$)) + 14.286 (cumulative chlorambucil dose ($mg/m^2$)) + 15.0 (cumulative BCNU (carmustine) dose ($mg/m^2$)) + 16.0 (cumulative CCNU (lomustine) dose ($mg/m^2$)) + 40 (cumulative melphalan dose ($mg/m^2$)) + 50 (cumulative Thio-TEPA (thiotepa) dose ($mg/m^2$)) + 100 (cumulative nitrogen mustard dose ($mg/m^2$)) + 8.823 (cumulative busulfan dose ($mg/m^2$)).

**Supplementary Table 4 | Sensitivity analyses for risk of subsequent breast cancer by excluding each cohort on a one-by-one basis**

| | Without CCSS[a] | | | | Without SJLIFE[b] | | | | Without DCCSS-LATER[c] | | | | Without FCCSS[d] | | | | Without DHL[e] | | | | Without SCCSS[f] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** |
| **Cumulative doxorubicin dose, mg/m²** | | | | | | | | | | | | | | | | | | | | | | | | |
| 0 | 179 (54.2%) | 5,441 (66.1%) | 1.0 | Ref. | 395 (56.0%) | 9,793 (62.5%) | 1.0 | Ref. | 409 (55.2%) | 9,629 (61.5%) | 1.0 | Ref. | 370 (56.5%) | 8,870 (61.2%) | 1.0 | Ref. | 379 (52.9%) | 10,989 (62.3%) | 1.0 | Ref. | 423 (55.5%) | 11,128 (62.4%) | 1.0 | Ref. |
| <100 | 6 (1.8%) | 410 (5.0%) | 1.18 | 0.47-2.97 | 15 (2.1%) | 791 (5.0%) | 2.10 | 1.01-4.35 | 14 (1.9%) | 724 (4.6%) | 1.90 | 0.90-3.99 | 13 (2.0%) | 817 (5.6%) | 1.77 | 0.80-3.93 | 16 (2.2%) | 907 (5.1%) | 1.75 | 0.88-3.49 | 16 (2.1%) | 911 (5.1%) | 1.74 | 0.88-3.47 |
| 100-199 | 42 (12.7%) | 1,026 (12.5%) | 2.34 | 1.49-3.67 | 54 (7.7%) | 1,381 (8.8%) | 1.72 | 1.20-2.47 | 66 (8.9%) | 1,563 (10.0%) | 1.84 | 1.34-2.54 | 52 (7.9%) | 1,448 (10.0%) | 1.63 | 1.15-2.30 | 66 (9.2%) | 1,775 (10.1%) | 1.75 | 1.28-2.39 | 65 (8.5%) | 1,782 (10.0%) | 1.66 | 1.21-2.26 |
| 200-299 | 27 (8.2%) | 436 (5.3%) | 2.35 | 1.39-3.99 | 61 (8.7%) | 902 (5.8%) | 2.74 | 1.99-3.78 | 66 (8.9%) | 964 (6.2%) | 2.59 | 1.90-3.53 | 55 (8.4%) | 819 (5.7%) | 2.41 | 1.73-3.36 | 60 (8.4%) | 988 (5.6%) | 2.46 | 1.81-3.34 | 66 (8.7%) | 1,021 (5.7%) | 2.42 | 1.78-3.28 |
| 300-399 | 28 (8.5%) | 444 (5.4%) | 3.03 | 1.80-5.11 | 52 (7.4%) | 866 (5.5%) | 2.02 | 1.40-2.92 | 60 (8.1%) | 935 (6.0%) | 2.33 | 1.66-3.26 | 55 (8.4%) | 809 (5.6%) | 2.42 | 1.71-3.43 | 62 (8.6%) | 1,001 (5.7%) | 2.31 | 1.67-3.19 | 63 (8.3%) | 1,005 (5.6%) | 2.30 | 1.67-3.19 |
| ≥400 | 23 (7.0%) | 305 (3.7%) | 4.09 | 2.35-7.14 | 51 (7.2%) | 744 (4.7%) | 2.42 | 1.68-3.48 | 49 (6.6%) | 655 (4.2%) | 2.72 | 1.91-3.88 | 53 (8.1%) | 642 (4.4%) | 2.84 | 1.99-4.06 | 57 (7.9%) | 773 (4.4%) | 2.74 | 1.96-3.82 | 57 (7.5%) | 776 (4.4%) | 2.78 | 1.99-3.87 |
| Unknown | 25 (7.6%) | 170 (2.1%) | - | - | 77 (10.9%) | 1,190 (7.6%) | - | - | 77 (10.4%) | 1,196 (7.6%) | - | - | 57 (8.7%) | 1,083 (7.5%) | - | - | 77 (10.7%) | 1,205 (6.8%) | - | - | 72 (9.4%) | 1,201 (6.7%) | - | - |
| **Cumulative daunorubicin dose, mg/m²** | | | | | | | | | | | | | | | | | | | | | | | | |
| 0 | 284 (86.1%) | 6,970 (84.7%) | 1.0 | Ref. | 619 (87.8%) | 13,012 (83.1%) | 1.0 | Ref. | 648 (87.4%) | 12,835 (81.9%) | 1.0 | Ref. | 581 (88.7%) | 11,391 (78.6%) | 1.0 | Ref. | 619 (86.3%) | 14,377 (81.5%) | 1.0 | Ref. | 669 (87.8%) | 14,565 (81.7%) | 1.0 | Ref. |
| <100 | 5 (1.5%) | 360 (4.4%) | 1.42 | 0.56-3.61 | 2 (0.3%) | 284 (1.8%) | 0.48 | 0.12-1.93 | 7 (0.9%) | 607 (3.9%) | 1.00 | 0.47-2.16 | 7 (1.1%) | 618 (4.3%) | 1.01 | 0.47-2.18 | 7 (1.0%) | 623 (3.5%) | 0.98 | 0.46-2.09 | 7 (0.9%) | 623 (3.5%) | 0.97 | 0.45-2.07 |
| 100-199 | 11 (3.3%) | 580 (7.0%) | 1.60 | 0.81-3.19 | 11 (1.6%) | 755 (4.8%) | 0.72 | 0.34-1.55 | 11 (1.5%) | 592 (3.8%) | 0.81 | 0.41-1.61 | 15 (2.3%) | 936 (6.5%) | 1.06 | 0.59-1.92 | 16 (2.2%) | 953 (5.4%) | 0.98 | 0.55-1.75 | 16 (2.1%) | 949 (5.3%) | 0.98 | 0.55-1.75 |
| ≥200 | 6 (1.8%) | 151 (1.8%) | 2.99 | 1.14-7.85 | 15 (2.1%) | 583 (3.7%) | 1.07 | 0.58-1.98 | 17 (2.3%) | 594 (3.8%) | 1.29 | 0.72-2.32 | 14 (2.1%) | 610 (4.2%) | 0.99 | 0.52-1.89 | 17 (2.4%) | 645 (3.7%) | 1.21 | 0.68-2.15 | 16 (2.1%) | 642 (3.6%) | 1.21 | 0.68-2.14 |
| Unknown | 24 (7.3%) | 171 (2.1%) | - | - | 58 (8.2%) | 1,033 (6.6%) | - | - | 58 (7.8%) | 1,038 (6.6%) | - | - | 38 (5.8%) | 933 (6.4%) | - | - | 58 (8.1%) | 1,040 (5.9%) | - | - | 54 (7.1%) | 1,045 (5.9%) | - | - |
| **Epirubicin** | | | | | | | | | | | | | | | | | | | | | | | | |
| No | 297 (90.0%) | 7,760 (94.3%) | 1.0 | Ref. | 640 (90.8%) | 14,420 (92.0%) | 1.0 | Ref. | 677 (91.4%) | 14,533 (92.8%) | 1.0 | Ref. | 616 (94.0%) | 13,521 (93.3%) | 1.0 | Ref. | 654 (91.2%) | 16,386 (92.9%) | 1.0 | Ref. | 701 (92.0%) | 16,565 (92.9%) | 1.0 | Ref. |
| Yes | 9 (2.7%) | 323 (3.9%) | 3.64 | 1.72-7.72 | 9 (1.3%) | 324 (2.1%) | 3.35 | 1.63-6.89 | 8 (1.1%) | 197 (1.3%) | 4.13 | 1.97-8.66 | 3 (0.5%) | 145 (1.0%) | 3.99 | 1.31-12.11 | 7 (1.0%) | 311 (1.8%) | 2.61 | 1.11-6.13 | 9 (1.2%) | 325 (1.8%) | 3.36 | 1.65-6.86 |
| Unknown | 24 (7.3%) | 149 (1.8%) | - | - | 56 (7.9%) | 923 (5.9%) | - | - | 56 (7.6%) | 936 (6.0%) | - | - | 36 (5.5%) | 822 (5.7%) | - | - | 56 (7.8%) | 941 (5.3%) | - | - | 52 (6.8%) | 934 (5.2%) | - | - |
| **Chest radiotherapy field and dose** | | | | | | | | | | | | | | | | | | | | | | | | |
| No chest radiotherapy | 96 (29.1%) | 639,7 (77.7%) | 1.0 | Ref. | 229 (32.5%) | 11,298 (72.1%) | 1.0 | Ref. | 226 (30.5%) | 11,112 (70.9%) | 1.0 | Ref. | 205 (31.3%) | 10,276 (70.9%) | 1.0 | Ref. | 250 (34.9%) | 12,982 (73.6%) | 1.0 | Ref. | 244 (32.0%) | 12,955 (72.7%) | 1.0 | Ref. |
| High-dose mantle (≥36 Gy) | 89 (27.0%) | 237 (2.9%) | 11.20 | 7.10-17.67 | 223 (31.6%) | 652 (4.2%) | 8.55 | 6.55-11.16 | 233 (31.4%) | 669 (4.3%) | 9.33 | 7.20-12.11 | 222 (33.9%) | 651 (4.5%) | 8.67 | 6.69-11.24 | 192 (26.8%) | 591 (3.4%) | 9.03 | 7.01-11.64 | 231 (30.3%) | 690 (3.9%) | 8.37 | 6.56-10.69 |
| Low-dose mantle(<36 Gy) | 43 (13.0%) | 252 (3.1%) | 5.83 | 3.63-9.37 | 69 (9.8%) | 377 (2.4%) | 4.29 | 3.02-6.11 | 90 (12.1%) | 506 (3.2%) | 4.70 | 3.43-6.44 | 89 (13.6%) | 485 (3.3%) | 4.66 | 3.40-6.38 | 81 (11.3%) | 477 (2.7%) | 4.85 | 3.54-6.65 | 93 (12.2%) | 523 (2.9%) | 4.61 | 3.40-6.25 |
| Mediastinal | 18 (5.5%) | 242 (2.9%) | 1.40 | 0.59-3.28 | 31 (4.4%) | 446 (2.8%) | 1.59 | 0.98-2.60 | 33 (4.5%) | 433 (2.8%) | 1.83 | 1.13-2.97 | 23 (3.5%) | 335 (2.3%) | 1.45 | 0.83-2.55 | 27 (3.8%) | 424 (2.4%) | 1.64 | 1.00-2.69 | 33 (4.3%) | 465 (2.6%) | 1.73 | 1.09-2.75 |
| TBI | 11 (3.3%) | 148 (1.8%) | 9.42 | 4.44-19.99 | 16 (2.3%) | 304 (1.9%) | 5.47 | 2.92-10.25 | 19 (2.6%) | 302 (1.9%) | 7.31 | 4.08-13.10 | 21 (3.2%) | 361 (2.5%) | 7.55 | 4.30-13.26 | 22 (3.1%) | 371 (2.1%) | 7.38 | 4.30-12.69 | 21 (2.8%) | 369 (2.1%) | 6.93 | 4.04-11.86 |
| Whole lung | 14 (4.2%) | 105 (1.3%) | 8.33 | 4.24-16.38 | 20 (2.8%) | 140 (0.9%) | 7.29 | 4.36-12.19 | 19 (2.6%) | 162 (1.0%) | 6.83 | 4.02-11.60 | 18 (2.7%) | 147 (1.0%) | 8.42 | 4.86-14.59 | 23 (3.2%) | 184 (1.0%) | 7.74 | 4.77-12.56 | 21 (2.8%) | 182 (1.0%) | 7.04 | 4.32-11.46 |
| Other | 39 (11.8%) | 541 (6.6%) | 4.58 | 2.97-7.07 | 59 (8.4%) | 1,152 (7.4%) | 2.54 | 1.79-3.60 | 62 (8.4%) | 1,158 (7.4%) | 2.95 | 2.09-4.16 | 30 (4.6%) | 1,101 (7.6%) | 1.42 | 0.88-2.29 | 63 (8.8%) | 1,316 (7.5%) | 2.67 | 1.91-3.73 | 62 (8.1%) | 1,312 (7.4%) | 2.51 | 1.80-3.51 |
| Unknown | 20 (6.1%) | 310 (3.8%) | - | - | 58 (8.2%) | 1,298 (8.3%) | - | - | 59 (8.0%) | 1,324 (8.5%) | - | - | 47 (7.2%) | 1,132 (7.8%) | - | - | 59 (8.2%) | 1,293 (7.3%) | - | - | 57 (7.5%) | 1,328 (7.5%) | - | - |
| **Pelvic radiotherapy ≥5 Gy** | | | | | | | | | | | | | | | | | | | | | | | | |
| No | 192 (58.2%) | 6,551 (79.6%) | 1.0 | Ref. | 452 (64.1%) | 1,1876 (75.8%) | 1.0 | Ref. | 469 (63.3%) | 11,620 (74.2%) | 1.0 | Ref. | 462 (70.5%) | 11,453 (79.1%) | 1.0 | Ref. | 462 (64.4%) | 13,572 (76.9%) | 1.0 | Ref. | 488 (64.0%) | 13,683 (76.8%) | 1.0 | Ref. |
| Yes | 120 (36.4%) | 1,427 (17.3%) | 1.36 | 1.00-1.86 | 201 (28.5%) | 2,577 (16.4%) | 1.03 | 0.83-1.28 | 217 (29.3%) | 2,813 (18.0%) | 0.94 | 0.76-1.15 | 151 (23.1%) | 1,999 (13.8%) | 0.83 | 0.65-1.06 | 200 (27.9%) | 2,830 (16.0%) | 0.90 | 0.73-1.11 | 221 (29.0%) | 2,909 (16.3%) | 0.97 | 0.79-1.19 |
| Unknown | 18 (5.5%) | 254 (3.1%) | - | - | 52 (7.4%) | 1,214 (7.7%) | - | - | 55 (7.4%) | 1,233 (7.9%) | - | - | 42 (6.4%) | 1,036 (7.2%) | - | - | 55 (7.7%) | 1,236 (7.0%) | - | - | 53 (7.0%) | 1,232 (6.9%) | - | - |

**Supplementary Table 4 | Sensitivity analyses for risk of subsequent breast cancer by excluding each cohort on a one-by-one basis**

| | Without CCSS[a] | | | | Without SJLIFE[b] | | | | Without DCCSS-LATER[c] | | | | Without FCCSS[d] | | | | Without DHL[e] | | | | Without SCCSS[f] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** | **No. SBC** | **Total** | **HR** | **95%CI** |
| **Age at primary childhood cancer diagnosis, yr** | | | | | | | | | | | | | | | | | | | | | | | | |
| <5 | 46 (13.9%) | 3,710 (45.1%) | 1.0 | Ref. | 59 (8.4%) | 6,403 (40.9%) | 1.0 | Ref. | 58 (7.8%) | 6,327 (40.4%) | 1.0 | Ref. | 36 (5.5%) | 5,705 (39.4%) | 1.0 | Ref. | 66 (9.2%) | 7,376 (41.8%) | 1.0 | Ref. | 65 (8.5%) | 7,359 (41.3%) | 1.0 | Ref. |
| 5-9 | 33 (10.0%) | 1,761 (21.4%) | 0.90 | 0.54-1.52 | 59 (8.4%) | 3,320 (21.2%) | 1.14 | 0.75-1.74 | 58 (7.8%) | 3,219 (20.5%) | 1.25 | 0.81-1.92 | 46 (7.0%) | 3,081 (21.3%) | 1.20 | 0.72-2.02 | 65 (9.1%) | 3,781 (21.4%) | 1.13 | 0.76-1.69 | 64 (8.4%) | 3,778 (21.2%) | 1.13 | 0.76-1.69 |
| 10-14 | 117 (35.5%) | 1,726 (21.0%) | 1.87 | 1.23-2.83 | 240 (34.0%) | 3,458 (22.1%) | 1.92 | 1.37-2.69 | 257 (34.7%) | 3,459 (22.1%) | 2.25 | 1.60-3.17 | 220 (33.6%) | 3,186 (22.0%) | 2.22 | 1.46-3.36 | 265 (37.0%) | 3,909 (22.2%) | 2.01 | 1.46-2.76 | 266 (34.9%) | 3,912 (21.9%) | 2.03 | 1.47-2.79 |
| 15-21 | 134 (40.6%) | 1,035 (12.6%) | 1.51 | 0.93-2.45 | 347 (49.2%) | 2,486 (15.9%) | 1.81 | 1.27-2.58 | 368 (49.7%) | 2,661 (17.0%) | 1.97 | 1.38-2.81 | 353 (53.9%) | 2,516 (17.4%) | 1.89 | 1.24-2.88 | 321 (44.8%) | 2,572 (14.6%) | 1.86 | 1.33-2.59 | 367 (48.2%) | 2,775 (15.6%) | 1.91 | 1.37-2.66 |
| **CED[g], mg/m²** | | | | | | | | | | | | | | | | | | | | | | | | |
| None | 120 (36.4%) | 3,858 (46.9%) | 1.0 | Ref. | 279 (39.6%) | 6,995 (44.6%) | 1.0 | Ref. | 285 (38.5%) | 6,791 (43.3%) | 1.0 | Ref. | 259 (39.5%) | 6,343 (43.8%) | 1.0 | Ref. | 266 (37.1%) | 7,851 (44.5%) | 1.0 | Ref. | 296 (38.8%) | 7,917 (44.4%) | 1.0 | Ref. |
| <6000 | 48 (14.5%) | 1,382 (16.8%) | 1.03 | 0.68-1.57 | 76 (10.8%) | 2,580 (16.5%) | 0.87 | 0.65-1.17 | 91 (12.3%) | 2,804 (17.9%) | 0.86 | 0.66-1.13 | 71 (10.8%) | 2,463 (17.0%) | 0.84 | 0.62-1.14 | 94 (13.1%) | 3,069 (17.4%) | 0.87 | 0.67-1.14 | 90 (11.8%) | 3,047 (17.1%) | 0.85 | 0.65-1.11 |
| 6000-17999 | 80 (24.2%) | 2,023 (24.6%) | 0.85 | 0.57-1.26 | 159 (22.6%) | 3,268 (20.9%) | 1.10 | 0.87-1.39 | 180 (24.3%) | 3,336 (21.3%) | 1.00 | 0.80-1.26 | 160 (24.4%) | 3,080 (21.3%) | 1.06 | 0.84-1.34 | 192 (26.8%) | 3,899 (22.1%) | 1.03 | 0.82-1.28 | 189 (24.8%) | 3,889 (21.8%) | 1.01 | 0.81-1.26 |
| ≥18000 | 23 (7.0%) | 556 (6.8%) | 0.78 | 0.43-1.42 | 43 (6.1%) | 978 (6.2%) | 1.47 | 0.99-2.18 | 38 (5.1%) | 925 (5.9%) | 1.18 | 0.79-1.75 | 38 (5.8%) | 895 (6.2%) | 1.26 | 0.84-1.89 | 47 (6.6%) | 1,117 (6.3%) | 1.21 | 0.84-1.76 | 46 (6.0%) | 1,114 (6.3%) | 1.16 | 0.80-1.68 |
| Unknown | 59 (17.9%) | 413 (5.0%) | - | - | 148 (21.0%) | 1,846 (11.8%) | - | - | 147 (19.8%) | 1,810 (11.6%) | - | - | 127 (19.4%) | 1,707 (11.8%) | - | - | 118 (16.5%) | 1,702 (9.6%) | - | - | 141 (18.5%) | 1,857 (10.4%) | - | - |

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; DCCSS-LATER = Dutch Childhood Cancer Survivor Study LATER; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; Gy = Gray; HR = Hazard ratio; NA = Not applicable; No. = number; SBC = Subsequent breast cancer; SCCSS = Swiss Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; TBI = Total Body Irradiation; yr = year

[a]In total, 9,671 survivors with 452 SBC cases were excluded.

[b]In total, 2,236 survivors with 77 SBC cases were excluded.

[c]In total, 2,237 survivors with 41 SBC cases were excluded.

[d]In total, 3,415 survivors with 127 SBC cases were excluded.

[e]In total, 265 survivors with 65 SBC cases were excluded.

[f]In total, 79 survivors with 20 SBC cases were excluded.

[g]Cyclophosphamide Equivalent Dose calculation: CED (mg/m$^2$) = 1.0 (cumulative cyclophosphamide dose (mg/m$^2$)) + 0.244 (cumulative ifosfamide dose (mg/m$^2$)) + 0.857 (cumulative procarbazine dose (mg/m$^2$)) + 14.286 (cumulative chlorambucil dose (mg/m$^2$)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m$^2$)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m$^2$)) + 40 (cumulative melphalan dose (mg/m$^2$)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m$^2$)) + 100 (cumulative nitrogen mustard dose (mg/m$^2$)) + 8.823 (cumulative busulfan dose (mg/m$^2$)).

**Supplementary Table 5 | Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors in each cohort[a]**

| | CCSS[b] | | SJLIFE[b] | | DCCSS-LATER[c] | | FCCSS[d] | | DHL[e] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** |
| **Cumulative doxorubicin dose, mg/m²** | | | | | | | | | | |
| 0 | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. |
| <100 | 2.58 | 0.99-6.74 | 0.99 | 0.13-7.70 | 1.00 | 0.19-5.11 | 1.40 | 0.42-4.70 | 1.49 | 0.45-4.91 |
| 100-199 | 1.34 | 0.85-2.10 | 2.49 | 1.10-5.65 | 1.04 | 0.27-4.02 | 2.23 | 1.12-4.43 | | |
| 200-299 | 2.60 | 1.80-3.75 | 1.42 | 0.54-3.74 | 0.97 | 0.13-7.55 | 2.79 | 1.39-5.59 | 1.74 | 0.76-3.96 |
| 300-399 | 1.96 | 1.30-2.97 | 4.82 | 2.16-10.75 | 3.51 | 1.02-12.10 | 1.60 | 0.68-3.74 | 1.50 | 0.35-6.34 |
| ≥400 | 2.22 | 1.46-3.39 | 6.73 | 2.54-17.83 | 5.49 | 1.97-15.25 | 2.42 | 0.90-6.49 | 1.84 | 0.24-14.00 |
| **Cumulative daunorubicin dose, mg/m²** | | | | | | | | | | |
| 0 | 1.0 | Ref. | 1.0 | Ref. | | | | | | |
| <100 | 0.47 | 0.11-1.89 | 2.28 | 0.83-6.27 | | | | | | |
| 100-199 | 0.47 | 0.16-1.40 | 3.00 | 1.05-8.60 | | | | | | |
| ≥200 | 0.83 | 0.40-1.70 | 4.06 | 0.82-20.17 | | | | | | |
| **Daunorubicin** | | | | | | | | | | |
| No | | | | | 1.0 | Ref. | 1.0 | Ref. | | |
| Yes | | | | | 1.53 | 0.49-4.79 | 1.92 | 0.57-6.38 | | |
| **Epirubicin** | | | | | | | | | | |
| No | | | | | 1.0 | Ref. | 1.0 | Ref. | | |
| Yes | | | | | 1.80 | 0.24-13.79 | 3.18 | 1.12-9.05 | | |
| **Chest radiotherapy field and dose** | | | | | | | | | | |
| No chest radiotherapy | 1.0 | Ref. | 1.0 | Ref. | | | 1.0 | Ref. | | |
| High-dose mantle (≥36 Gy) | 7.65 | 5.76-10.16 | 11.51 | 5.12-25.84 | | | 9.05 | 4.54-18.07 | | |
| Low-dose mantle (<36 Gy) | 4.04 | 2.72-6.00 | 8.40 | 3.95-17.87 | | | 2.06 | 0.47-9.14 | | |
| Mediastinal | 1.66 | 0.94-2.95 | 1.86 | 0.24-14.52 | | | 1.84 | 0.75-4.51 | | |
| TBI | 6.75 | 3.25-14.02 | 12.43 | 3.76-41.08 | | | 5.41 | 0.67-43.44 | | |
| Whole lung | 6.32 | 3.05-13.11 | 11.83 | 3.07-45.57 | | | 3.72 | 1.28-10.83 | | |
| Other | 1.37 | 0.78-2.40 | 2.65 | 0.85-8.23 | | | 7.43 | 4.53-12.17 | | |
| **Chest radiotherapy fields** | | | | | | | | | | |
| No chest radiotherapy | | | | | 1.0 | Ref. | | | | |
| Mantle | | | | | 8.11 | 2.99-21.95 | | | | |
| TBI & Whole lung | | | | | 15.43 | 4.65-51.27 | | | | |
| Other fields | | | | | 0.67 | 0.20-2.30 | | | | |
| **Chest radiotherapy fields** | | | | | | | | | | |
| Non-mantle | | | | | | | | | 1.0 | Ref. |
| Mantle | | | | | | | | | 2.80 | 1.18-6.63 |
| **Pelvic radiotherapy ≥5 Gy** | | | | | | | | | | |
| No | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. |
| Yes | 0.79 | 0.59-1.06 | 0.83 | 0.45-1.50 | 0.65 | 0.17-2.53 | 2.18 | 1.38-3.45 | 1.49 | 0.87-2.53 |
| **Age at primary childhood cancer diagnosis, yr** | | | | | | | | | | |
| <5 | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. |
| 5-9 | 1.62 | 0.83-3.18 | 0.97 | 0.27-3.45 | 0.48 | 0.16-1.45 | 1.10 | 0.57-2.11 | | |
| 10-14 | 2.61 | 1.49-4.57 | 3.30 | 1.19-9.16 | 0.93 | 0.36-2.41 | 1.86 | 1.06-3.28 | | |
| 15-21 | 2.50 | 1.43-4.38 | 2.08 | 0.71-6.05 | 1.36 | 0.47-3.92 | 2.17 | 1.09-4.30 | 0.64 | 0.30-1.36 |
| **CED[f], mg/m²** | | | | | | | | | | |
| None | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | | |

**Supplementary Table 5 | Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors in each cohort[a]**

| | CCSS[b] | | SJLIFE[b] | | DCCSS-LATER[c] | | FCCSS[d] | | DHL[e] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** |
| <6000 | 0.78 | 0.55-1.11 | 0.96 | 0.45-2.08 | 0.73 | 0.18-2.99 | 1.04 | 0.57-1.90 | | |
| 6000-17999 | 1.11 | 0.86-1.45 | 0.74 | 0.40-1.36 | 1.40 | 0.57-3.42 | 0.93 | 0.54-1.62 | | |
| ≥18000 | 1.61 | 1.00-2.59 | 0.43 | 0.14-1.38 | 1.49 | 0.51-4.31 | 1.05 | 0.46-2.39 | | |

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; DCCSS-LATER = Dutch Childhood Cancer Survivor Study LATER; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; Gy = Gray; HR = Hazard ratio; SBC = Subsequent breast cancer; SJLIFE = St. Jude Lifetime Cohort Study; TBI = Total Body Irradiation; yr = year

[a]The results of the multivariable Cox proportional hazard regression analyses in the Swiss Childhood Cancer Survivor Study (SCCSS) are not provided due to low numbers in the case-cohort data.

[b]The model included cumulative doxorubicin and daunorubicin dose (categorical variables), chest radiotherapy field and dose (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[c]The model included cumulative doxorubicin dose (categorical variable), daunorubicin (yes/no), epirubicin (yes/no), chest radiotherapy fields (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[d]The model included cumulative doxorubicin dose (categorical variable), daunorubicin (yes/no), epirubicin (yes/no), chest radiotherapy field and dose (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[e]The model included cumulative doxorubicin dose (categorical variable), chest radiotherapy fields (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), and age at primary childhood cancer diagnosis (categorical variable).

[f]Cyclophosphamide Equivalent Dose calculation: CED ($mg/m^2$) = 1.0 (cumulative cyclophosphamide dose ($mg/m^2$)) + 0.244 (cumulative ifosfamide dose ($mg/m^2$)) + 0.857 (cumulative procarbazine dose ($mg/m^2$)) + 14.286 (cumulative chlorambucil dose ($mg/m^2$)) + 15.0 (cumulative BCNU (carmustine) dose ($mg/m^2$)) + 16.0 (cumulative CCNU (lomustine) dose ($mg/m^2$)) + 40 (cumulative melphalan dose ($mg/m^2$)) + 50 (cumulative Thio-TEPA (thiotepa) dose ($mg/m^2$)) + 100 (cumulative nitrogen mustard dose ($mg/m^2$)) + 8.823 (cumulative busulfan dose ($mg/m^2$)).

**Supplementary Table 6 | Subsequent breast cancer ascertainment/validation process for each participating study**

| | Subsequent breast cancer | |
|---|---|---|
| **Studies** | **Ascertainment** | **Validation** |
| CCSS | Record linkage to the National death index;<br><br>Initial self- or proxy-reports | Medical records including pathology reports |
| SJLIFE | Record linkage to the Cancer registry follow-up and the National Death Index;<br><br>Prospective follow-up at St. Jude with breast imaging, self-report or next of kin reported | Medical records including pathology reports |
| DCCSS-LATER | Medical records;<br><br>Record linkage to the Population-based Netherlands Cancer Registry and the Nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA [Dutch Pathology Registry]) | Pathology reports |
| FCCSS | Hospital clinical files and Long term follow-up visits;<br><br>Record linkage to the National death certificate data and the National Public and Private Hospital and National Health Insurance Database;<br><br>Self-completed questionnaire | Pathology reports |
| SCCSS | Medical records including pathology reports;<br><br>Record linkage to the Cantonal cancer registries and the Cause-of death statistics;<br><br>Self-report | Medical records including pathology reports |
| DHL | Medical records and Questionnaires sent to general practitioners;<br><br>Record linkage to the Population-based Netherlands Cancer Registry | Pathology reports |

CCSS = Childhood Cancer Survivor Study; system; DCCSS-LATER = Dutch Childhood Cancer Survivor Study LATER; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study

**Supplementary Table 7 | Selection procedures for chemotherapeutic agents other than anthracyclines and alkylating agents in multivariable Cox proportional hazard regression analyses for subsequent breast cancer risk among female five-year childhood cancer survivors[a]**

| | | | Base model | | Base model + Epipodophyllotoxins | | Base model + Vinca alkaloids | | Base model + Platinum compounds | | Base model + Antimetabolites | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. SBC (n)[b] | Total (n) | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| **Cumulative doxorubicin dose, mg/m²** | | | | | | | | | | | | |
| 0 | 431 (55.1%) | 11,170 (62.4%) | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. |
| <100 | 16 (2.0%) | 912 (5.1%) | 1.76 | 0.88-3.51 | 1.71 | 0.86-3.41 | 1.79 | 0.90-3.58 | 1.75 | 0.88-3.49 | 1.77 | 0.89-3.52 |
| 100-199 | 69 (8.8%) | 1,795 (10.0%) | 1.77 | 1.30-2.42 | 1.73 | 1.27-2.36 | 1.82 | 1.33-2.49 | 1.76 | 1.29-2.40 | 1.78 | 1.31-2.42 |
| 200-299 | 67 (8.6%) | 1,026 (5.7%) | 2.50 | 1.85-3.40 | 2.43 | 1.79-3.31 | 2.59 | 1.90-3.54 | 2.49 | 1.84-3.37 | 2.51 | 1.85-3.41 |
| 300-399 | 64 (8.2%) | 1,012 (5.7%) | 2.33 | 1.68-3.23 | 2.21 | 1.59-3.08 | 2.39 | 1.72-3.34 | 2.32 | 1.67-3.23 | 2.36 | 1.69-3.29 |
| ≥400 | 58 (7.4%) | 779 (4.4%) | 2.78 | 1.99-3.88 | 2.73 | 1.96-3.82 | 2.83 | 2.02-3.96 | 2.78 | 1.99-3.88 | 2.84 | 2.02-4.00 |
| Unknown | 77 (9.8%) | 1,209 (6.8%) | - | - | - | - | - | - | - | - | - | - |
| **Cumulative daunorubicin dose, mg/m²** | | | | | | | | | | | | |
| 0 | 684 (87.5%) | 14,630 (81.7%) | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. | 1.0 | Ref. |
| <100 | 7 (0.9%) | 623 (3.5%) | 0.98 | 0.46-2.09 | 0.91 | 0.42-1.95 | 1.01 | 0.47-2.18 | 0.98 | 0.46-2.09 | 1.02 | 0.47-2.22 |
| 100-199 | 16 (2.0%) | 953 (5.3%) | 0.98 | 0.55-1.75 | 0.93 | 0.53-1.64 | 1.01 | 0.57-1.81 | 0.98 | 0.55-1.75 | 1.03 | 0.56-1.88 |
| ≥200 | 17 (2.2%) | 645 (3.6%) | 1.22 | 0.69-2.17 | 1.14 | 0.64-2.03 | 1.24 | 0.69-2.20 | 1.22 | 0.68-2.16 | 1.28 | 0.71-2.32 |
| Unknown | 58 (7.4%) | 1,052 (5.9%) | - | - | - | - | - | - | - | - | - | - |
| **Epipodophyllotoxins** | | | | | | | | | | | | |
| No | 611 (78.1%) | 13,434 (75.0%) | | | 1.0 | Ref. | | | | | | |
| Yes | 78 (10.0%) | 3,346 (18.7%) | | | 1.33 | 0.98-1.80 | | | | | | |
| Unknown | 93 (11.9%) | 1,123 (6.3%) | | | - | - | | | | | | |
| **Vinca alkaloids** | | | | | | | | | | | | |
| No | 269 (34.4%) | 6,194 (34.6%) | | | | | 1.0 | Ref. | | | | |
| Yes | 420 (53.7%) | 10,586 (59.1%) | | | | | 0.86 | 0.68-1.09 | | | | |
| Unknown | 93 (11.9%) | 1,123 (6.3%) | | | | | - | - | | | | |
| **Platinum compounds** | | | | | | | | | | | | |
| No | 642 (82.1%) | 14,219 (79.4%) | | | | | | | 1.0 | Ref. | | |
| Yes | 47 (6.0%) | 2,561 (14.3%) | | | | | | | 0.99 | 0.68-1.44 | | |
| Unknown | 93 (11.9%) | 1,123 (6.3%) | | | | | | | - | - | | |
| **Antimetabolites** | | | | | | | | | | | | |
| No | 504 (64.5%) | 10,376 (58.0%) | | | | | | | | | 1.0 | Ref. |
| Yes | 185 (23.7%) | 6,404 (35.8%) | | | | | | | | | 0.92 | 0.72-1.18 |
| Unknown | 93 (11.9%) | 1,123 (6.3%) | | | | | | | | | - | - |

CI = Confidence interval; HR = Hazard ratio; No. = number; SBC = Subsequent breast cancer

[a]The base multivariable model included cumulative doxorubicin dose (categorical variable), cumulative daunorubicin dose (categorical variable), epirubicin (yes/no), age at primary cancer diagnosis (categorical variable), the combination of the chest radiation field and the associated maximum dose (categorical variable), pelvic radiation dose ≥5 Gy (yes/no), and alkylating agent cumulative exposure (cyclophosphamide equivalent dose, categorical variable). Because there is only evidence for associations between anthracyclines and alkylating agents on SBC risk, we applied the following selection procedure to evaluate other chemotherapeutic agents: we added binary indicators for epipodophyllotoxins, vinca alkaloids, platinum compounds, and antimetabolites to the base model; if addition of each variable changed any HRs of doxorubicin dose and/or daunorubicin dose by >10% compared to a model without the variable, it was included in the final models.

[b]One survivor had a SBC prior to five years after primary cancer.