**Supplementary Methods**

***Study population in St. Jude Lifetime Cohort Study (SJLIFE)***

Among 3,006 SJLIFE survivors with whole-genome sequencing (WGS) data, a total 2,370 survivors were available for further statistical analyses based on the following exclusion criteria (Supplementary Figure S1A): 1) survivors with non-European ancestry identified by admixture coefficient for the 1000 Genomes CEU population <80% (n=559); 2) survivors with excessive sample mean heterozygosity (n=14); 3) survivors with more than 2 missingness out of 12 selected single-nucleotide polymorphisms (SNPs) for the PRS calculation (n=2); 4) outliers with > 3X standard deviation from the mean of top three principal components (n=6); and 5) survivors with missing dose information for neck-RT (n=47) and for anthracyclines or epipodophyllotoxin (n=8).

***Study population in Childhood Cancer Survivor Study (CCSS)***

A total of 5,739 from the CCSS Original Cohort (diagnosed between 1970 and 1986) with imputed SNP data(1) and 2,998 from the CCSS Expansion Cohort (diagnosed between 1987 and 1999), for whom buccal/saliva samples underwent WGS, were available for the replication/validation analyses(2). A total of 4,671 survivors from the CCSS Original Cohort remained after excluding non-European ancestry individuals who had admixture coefficient for CEU population <80% (n=416) and individuals also enrolled in SJLIFE (n=652). A total of 2,428 survivors from the CCSS Expansion Cohort remained after applying the following exclusions: 1) failed the coverage and mapping QC (n=50); 2) unexpected duplicates (n=12); 3) samples with excessive heterozygosity (n=97); and 4) non-European ancestry individuals who had admixture coefficient for CEU population <80% (n=411). In combination, a total 6,416 CCSS survivors (4,188 from the Original Cohort and 2,228 from the Expansion Cohort) remained for analysis after further excluding survivors with missing dose information about neck-RT, anthracyclines or epipodophyllotoxin (n=683).

***Covariate selection***

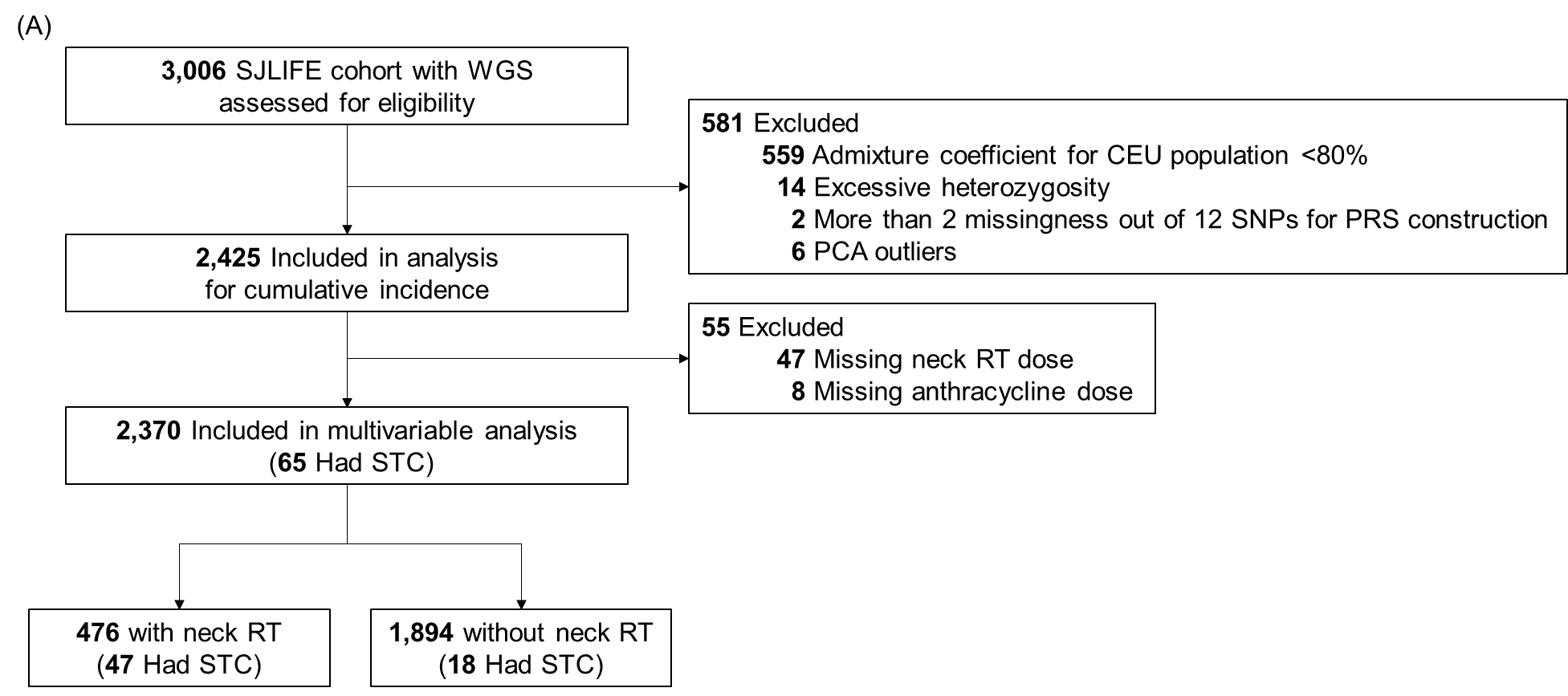
We employed the Fine and Gray proportional subdistribution hazards model to construct a clinical base model encompassing demographic and treatment variables in the SJLIFE study. With attained age, sex, and age at diagnosis in the model, we assessed STC risk in associations with each of the candidate treatment variables (neck-RT, anthracyclines(3), and epipodophyllotoxin) and the interaction between age and sex. Using the three treatment variables identified to be associated with STC risk, i.e., neck-RT dose (0, >0-<20 Gy, ≥20-<30 Gy, and ≥30 Gy), anthracyclines dose (0, tertiles [cutoffs: 87.5 and 198.7] among the exposed) and epipodophyllotoxin dose (0, tertiles [cutoff: 1472.7 and 5996.5] among the exposed), we derived eight treatment groups that represent multimodality treatment exposures. Through a genetic principal component analysis, we first generated the top ten eigenvectors. Based on the inflection point of the scree plot of eigenvalues, we chose to include the top three in the multivariable regression model evaluating each risk factor. However, after backward elimination, all three eigenvectors were subsequently dropped from the model because they were not statistically significantly associated with the subsequent thyroid cancer risk. Accordingly, the principal components were not included in the risk prediction model. The final clinical model included the following covariates: attained age; age at primary diagnosis; sex; and the derived 8-category treatment groups (Supplementary Table S2).

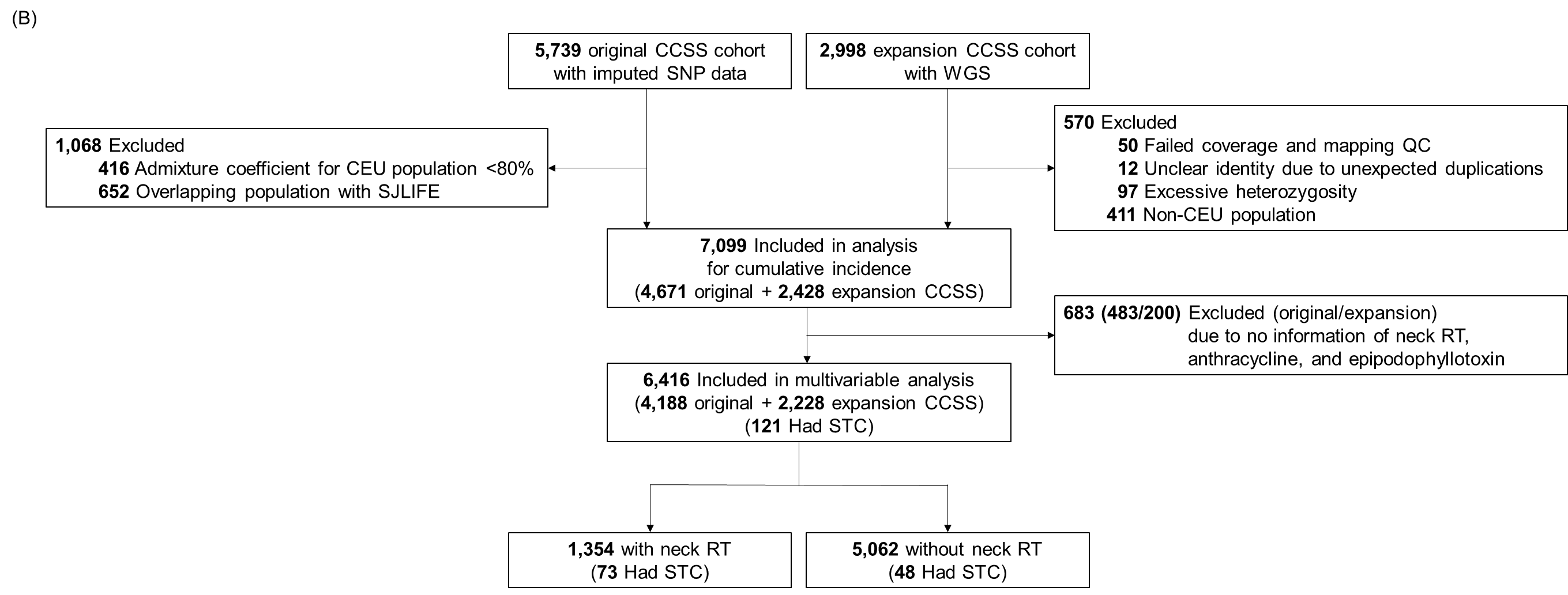
***Development and validation of base clinical model***

The base clinical model with the treatment groups and other clinical characteristics was built with the SJLIFE data (Supplementary Table S2). In this base model, compared to survivors with a primary cancer diagnosed at age 0-4 years, survivors diagnosed at age 5-9 years had a significantly decreased risk of STC (RR=0.28, 95% CI=0.10-0.78, *p*=0.015). Survivors with any of the seven combinatorial treatment exposures encompassing anthracyclines, epipodophyllotoxin, and neck-RT had statistically significantly increased rates of STC, compared to those without them, including the following: survivors exposed to any epipodophyllotoxin dose and anthracycline dose in the 2-3 tertiles without neck-RT (RR=5.08, 95% CI=1.95-13.23, *p*<0.001), neck-RT >0-<20 Gy without epipodophyllotoxin (RR=7.73, 95% CI=2.25-26.53, *p*=0.001), neck-RT ≥20-<30 Gy without epipodophyllotoxin (RR=14.30, 95% CI=6.92-29.57, *p*<0.001), neck-RT ≥30 Gy without epipodophyllotoxin (RR=5.69, 95% CI=2.17-14.90, *p*<0.001), neck-RT >0-<20 Gy with epipodophyllotoxin (RR=30.68, 95% CI=8.82-106.71, *p*<0.001), and neck-RT ≥20-<30 Gy with epipodophyllotoxin (RR=32.72, 95% CI=13.13-81.59, *p*<0.001), and neck-RT ≥30 Gy with epipodophyllotoxin (RR=13.06, 95% CI=2.86-59.64, *p*<0.001).

The base clinical model was validated in CCSS (Supplementary Table S7). Compared to survivors with a primary cancer diagnosed at age 0-4 years, a significantly decreased rate of STC was observed in survivors diagnosed at age ≥15 years (RR=0.41, 95% CI=0.22-0.77, *p*=0.006). Female survivors showed an increased rate of STC than male survivors (RR=1.75, 95% CI=1.20-2.55, *p*=0.004). Similarly, survivors with any of the seven combinatorial treatment exposures encompassing anthracyclines, epipodophyllotoxin, and neck-RT had statistically significantly increased rates of STC including the following: survivors exposed to neck-RT >0-<20 Gy without epipodophyllotoxin (RR=4.88, 95% CI=2.18-10.91, *p*<0.001), neck-RT ≥20-<30 Gy without epipodophyllotoxin (RR=7.73, 95% CI=4.64-12.88, *p*<0.001), neck-RT ≥30 Gy without epipodophyllotoxin (RR=4.47, 95% CI=2.69-7.54, *p*<0.001), and neck-RT >0-<20 Gy with epipodophyllotoxin (RR=8.64, 95% CI=2.08-35.91, *p*=0.003).

**Supplementary Figure S1. A consort diagram of the study population. (A) SJLIFE (B) CCSS**

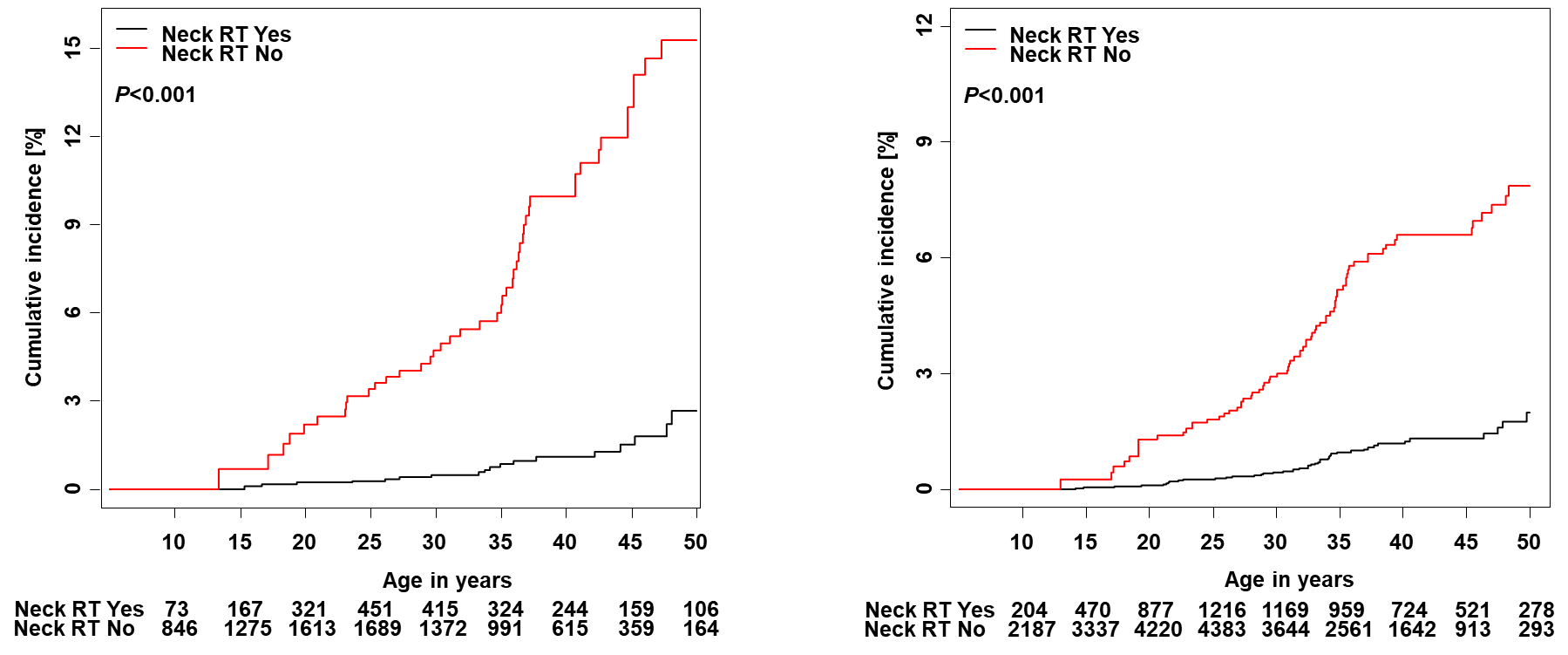




Abbreviations: St. Jude Lifetime (SJLIFE), CCSS (Childhood Cancer Survivor Study), whole-genome sequencing (WGS), SNP (single-nucleotide polymorphism, PRS (polygenic risk score), PCA (Principal component analysis), RT (radiation therapy), and STC (subsequent thyroid cancer)

**Supplementary Figure S2. Cumulative incidence of STC by neck-RT exposure. (A) SJLIFE (B) CCSS**

1. (B)



Abbreviations: STC (subsequent thyroid cancer), RT (radiation therapy), St. Jude Lifetime (SJLIFE), and CCSS (Childhood Cancer Survivor Study)

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| **Supplementary Table S1. Previously identified susceptibility loci associated with the risk of thyroid cancer** | | | | | | | | | |
| SNP | Region | Mapped gene | RA | RAF | OR | (95% CI) | Reported trait | Study | Exclusion criteria on SNP selection PRS |
| rs12129938 | 1q42.2 | *PCNXL2* | A | 0.80 | 1.32 | (1.20-1.43) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs11693806 | 2q35 | *DIRC3* | C | 0.32 | 1.43 | (1.33-1.54) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs6793295 | 3q26.2 | *LRRC34* | T | 0.80 | 1.23 | (1.15-1.33) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs10069690 | 5p15.33 | *TERT* | T | 0.28 | 1.20 | (1.12-1.29) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs73227498 | 5q22.1 | *EPB41L4A* | A | 0.87 | 1.37 | (1.23-1.49) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs2466076 | 8p12 | *NRG1* | G | 0.48 | 1.32 | (1.23-1.41) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs1588635 | 9q22.33 | *KRT18P13, FOXE1* | A | 0.40 | 1.69 | (1.59-1.82) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs7902587 | 10q24.33 | *LOC102724351, OBFC1* | T | 0.11 | 1.41 | (1.27-1.56) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs368187 | 14q13.2 | *LOC105370452* | G | 0.58 | 1.39 | (1.30-1.47) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs116909374 | 14q13.3 | *LOC107984003, RN7SKP21* | T | 0.03 | 1.81 | (1.57-2.08) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs2289261 | 15q22.33 | *SMAD3* | C | 0.68 | 1.23 | (1.15-1.32) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs56062135 | 15q22.33 | *SMAD3* | T | 0.25 | 1.24 | (1.16-1.34) | Thyroid cancer | Gudmundsson et al. 2017 | Included |
| rs4915076 | 1p13.3 | *VAV3* | T | 0.70 | 1.34 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs4649295 | 1q42.2 | *PCNXL2* | T | 0.82 | 1.45 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs966423 | 2q35 | *DIRC3* | C | 0.44 | 1.34 | (1.22-1.47) | Thyroid cancer | Gudmundsson et al. 2012 | In strong LD with rs11693806  which was included in another study with larger sample size |
| rs6759952 | 2q35 | *DIRC3* | T | 0.43 | 1.25 | (1.16-1.34) | Thyroid cancer | Köhler et al. 2013 | In strong LD with rs11693806  which was included in another study with larger sample size |
| rs12990503 | 2q35 | *DIRC3* | G | 0.63 | 1.38 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs9858271 | 3p14.2 | *LOC105377110* | G | 0.43 | 1.30 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs1874564 | 4q21.1 | *LOC107986291, LOC105377294* | G | 0.69 | 1.31 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs2439302 | 8p12 | *NRG1* | G | 0.35 | 1.36 | (1.23-1.50) | Thyroid cancer | Gudmundsson et al. 2012 | In strong LD with rs2466076  which was included in another study with larger sample size |
| rs6996585 | 8p12 | *NRG1* | G | 0.23 | 1.43 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs965513 | 9q22.33 | *KRT18P13, FOXE1* | A | 0.34 | 1.75 | (1.59-1.94) | Thyroid cancer | Gudmundsson et al. 2009 | In perfect LD with rs1588635  which was included in another study with larger sample size |
| rs965513 | 9q22.33 | *KRT18P13, FOXE1* | A | NR | 1.65 | (1.43-1.91) | Thyroid cancer | Takahashi et al. 2010 | In perfect LD with rs1588635  which was included in another study with larger sample size |
| rs965513 | 9q22.33 | *KRT18P13, FOXE1* | A | NR | 1.78 | NR | Thyroid cancer | Köhler et al. 2013 | Was included in another study has larger sample size |
| rs965513 | 9q22.23 | *KRT18P13, FOXE1* | A | 0.34 | 1.65 | (1.49-1.82) | Thyroid cancer | Mancikova et al. 2015 | Was included in another study has larger sample size |
| rs7037324 | 9q22.33 | *C9orf156* | A | 0.34 | 1.54 | (1.39-1.70) | Thyroid cancer | Mancikova et al. 2015 | In strong LD with rs1588635  which was included in another study with larger sample size |
| rs10122541 | 9q22.33 | *FOXE1, C9orf156* | G | 0.33 | 1.54 | (1.40-1.70) | Thyroid cancer | Mancikova et al. 2015 | In strong LD with rs1588635  which was included in another study with larger sample size |
| rs72753537 | 9q22.33 | *C9orf156* | C | 0.07 | 1.48 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs11175834 | 12q.14.3 | *LOC100507065, LOC105369807* | T | 0.15 | 1.36 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs34081947 | 14q13.2 | *LINC00609* | T | 0.41 | 1.25 | NR | Papillary thyroid cancer | Son et al. 2017 | Asian study |
| rs944289 | 14q13.3 | *PTCSC3, RN7SKP21* | T | 0.57 | 1.37 | (1.24-1.52) | Thyroid cancer | Gudmundsson et al. 2009 | In strong LD with rs368187  which was included in another study with larger sample size |
| rs116909374 | 14q13.3 | *LOC107984003, RN7SKP21* | T | 0.02 | 2.09 | (1.68-2.60) | Thyroid cancer | Gudmundsson et al. 2012 | Was included in another study has larger sample size |
| Abbreviations: SNP (single-nucleotide polymorphism), RA (risk allele), RAF (risk allele frequency), OR (odds ratio), NR (not reported), and PRS (polygenic risk score) | | | | | | | | | |

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| **Supplementary Table S2. The multivariable base clinical model for STC risk in SJLIFEa** | | | |
| Selected variables | RR | (95% CI) | *P* |
| Age at diagnosis, years |  |  |  |
| 0-4 | 1.00 | (Ref.) |  |
| 5-9 | 0.28 | (0.10-0.78) | 0.015 |
| 10-14 | 1.21 | (0.62-2.23) | 0.55 |
| ≥15 | 0.62 | (0.28-1.23) | 0.17 |
| Sex |  |  |  |
| Men | 1.00 | (Ref.) |  |
| Women | 1.49 | (0.89-2.49) | 0.13 |
| Treatment group |  |  |  |
| None or others | 1.00 | (Ref.) |  |
| Epipodophyllotoxin & Anthracycline 2-3 tertiles without neck-RT | 5.08 | (1.95-13.23) | <0.001 |
| Neck-RT >0-<20 Gy without Epipodophyllotoxin | 7.73 | (2.25-26.53) | 0.001 |
| Neck-RT ≥20-<30 Gy without Epipodophyllotoxin | 14.30 | (6.92-29.57) | <0.001 |
| Neck-RT ≥30 Gy without Epipodophyllotoxin | 5.69 | (2.17-14.90) | <0.001 |
| Neck-RT >0-<20 Gy with Epipodophyllotoxin | 30.68 | (8.82-106.71) | <0.001 |
| Neck-RT ≥20-<30 Gy with Epipodophyllotoxin | 32.72 | (13.13-81.59) | <0.001 |
| Neck-RT ≥30 Gy with Epipodophyllotoxin | 13.06 | (2.86-59.64) | <0.001 |
| Abbreviations: STC (subsequent thyroid cancer) and RT (radiotherapy) | | | |
| aAdjusted for attained age modeled by restricted cubic splines | | | |

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| **Supplementary Table S3. Demographics and treatment characteristics between CEU and non-CEU survivors in SJLIFE and CCSS** | | | | | | |
|  | **SJLIFE** | | | **CCSS** | | |
|  | **CEU** | **non-CEU** |  | **CEU** | **non-CEU** |  |
|  | **(N=2,370)** | **(N=546)** |  | **(N=6,416)** | **(N=707)** |  |
|  | **N (%)** | **N (%)** | ***P*** | **N (%)** | **N (%)** | ***P*** |
| Age at diagnosis, years |  |  | 0.62 |  |  | <.001 |
| 0-4 | 922 (38.9%) | 213 (39.0%) |  | 2391 (37.3%) | 286 (40.5%) |  |
| 5-9 | 538 (22.7%) | 125 (22.9%) |  | 1423 (22.2%) | 189 (26.7%) |  |
| 10-14 | 532 (22.4%) | 132 (24.2%) |  | 1440 (22.4%) | 151 (21.4%) |  |
| ≥15 | 378 (15.9%) | 76 (13.9%) |  | 1162 (18.1%) | 81 (11.5%) |  |
| Sex |  |  | 0.07 |  |  | 0.94 |
| Men | 1,265 (53.4%) | 268 (49.1%) |  | 3058 (47.7%) | 338 (47.8%) |  |
| Women | 1,105 (46.6%) | 278 (50.9%) |  | 3358 (52.3%) | 369 (52.2%) |  |
| Race (Survey based) |  |  | <0.001 |  |  | <0.001 |
| White, non-Hispanic | 2,336 (98.6%) | 55 (10.1%) |  | 6024 (96.7%) | 43 (6.2%) |  |
| White, Hispanic | 22 (0.9%) | 20 (3.7%) |  | 68 (1.1%) | 48 (7.0%) |  |
| Other | 12 (0.5%) | 471 (86.3%) |  | 136 (2.2%) | 598 (86.8%) |  |
| Diagnosis |  |  | <0.001 |  |  | 0.09 |
| **Leukemia** | **868 (36.6%)** | **159 (29.1%)** |  | **1713 (26.7%)** | **212 (30.0%)** |  |
| Acute lymphoblastic leukemia | 802 (33.8%) | 142 (26.0%) |  | 1536 (23.9%) | 190 (26.9%) |  |
| Acute myeloid leukemia | 63 (2.7%) | 16 (2.9%) |  | 144 (2.2%) | 18 (2.5%) |  |
| Other leukemia | 3 (0.1%) | 1 (0.2%) |  | 33 (0.5%) | 4 (0.6%) |  |
| **CNS tumors** | **249 (10.5%)** | **58 (10.6%)** |  | **1160 (18.0%)** | **130 (18.3%)** |  |
| Astrocytoma or glioma | 123 (5.2%) | 29 (5.3%) |  | 720 (11.2%) | 71 (10.0%) |  |
| Medulloblastoma or PNET | 62 (2.6%) | 12 (2.2%) |  | 271 (4.2%) | 32 (4.5%) |  |
| Ependymoma | 25 (1.1%) | 8 (1.5%) |  | 169 (2.6%) | 27 (3.8%) |  |
| Other CNS tumors | 39 (1.6%) | 9 (1.6%) |  | 169 (3%) | 27 (4%) |  |
| **Lymphoma** | **474 (20.0%)** | **86 (15.8%)** |  | **1,373 (21.4%)** | **131 (18.6%)** |  |
| Hodgkin lymphoma | 289 (12.2%) | 55 (10.1%) |  | 849 (13.2%) | 67 (9.5%) |  |
| Non-Hodgkin lymphoma | 185 (7.8%) | 31 (5.7%) |  | 524 (8.2%) | 64 (9.1%) |  |
| **Sarcoma** | 306 (12.9%) | 82 (15.0%) |  | **1,028 (7.9%)** | **52 (7.4%)** |  |
| Ewing sarcoma | 84 (3.5%) | 5 (0.9%) |  | 194 (3.0%) | 11 (1.6%) |  |
| Osteosarcoma | 82 (3.5%) | 32 (5.9%) |  | 314 (4.9%) | 41 (5.8%) |  |
| Rhabdomyosarcoma | 76 (3.2%) | 24 (4.4%) |  |  |  |  |
| Non-rhabdomyosarcoma | 64 (2.7%) | 21 (3.8%) |  |  |  |  |
| Soft tissue sarcoma |  |  |  | 520 (8.1%) | 59 (8.3%) |  |
| **Embryonal** | **316 (13.3%)** | **102 (18.7%)** |  | **1108 (17.3%)** | **123 (17.4%)** |  |
| Wilms tumor | 152 (6.4%) | 54 (9.9%) |  | 621 (9.7%) | 75 (10.6%) |  |
| Neuroblastoma | 119 (5.0%) | 19 (3.5%) |  | 487 (7.6%) | 48 (6.8%) |  |
| Germ cell tumor | 45 (1.9%) | 29 (5.3%) |  |  |  |  |
| **Other** | 157 (6.6%) | 59 (10.8%) |  | 34 (0.5%) | 0 (0.0%) |  |
| Retinoblastoma | 66 (2.8%) | 31 (5.7%) |  |  |  |  |
| Hepatoblastoma | 16 (0.7%) | 3 (0.5%) |  |  |  |  |
| Melanoma | 15 (0.6%) | 3 (0.5%) |  |  |  |  |
| Carcinomas | 26 (1.1%) | 17 (3.1%) |  |  |  |  |
| Other | 34 (1.4%) | 5 (0.9%) |  | 34 (0.5%) | 0 (0.0%) |  |
| Radiation therapy |  |  |  |  |  |  |
| Neck RT dose, Gy |  |  | 0.12 |  |  | <0.001 |
| None | 1,894 (79.9%) | 448 (82.1%) |  | 5062 (78.9%) | 592 (83.7%) |  |
| >0-<20 | 59 (2.5%) | 6 (1.1%) |  | 175 (2.7%) | 17 (2.4%) |  |
| ≥20-<30 | 247 (10.4%) | 48 (8.8%) |  | 397 (6.2%) | 50 (7.1%) |  |
| ≥30 | 170 (7.2%) | 44 (8.1%) |  | 782 (12.2%) | 48 (6.8%) |  |
| Anthracycline dose, tertiles |  |  | 0.36 |  |  | <0.001 |
| None | 988 (41.7%) | 250 (45.8%) |  | 3784 (59.0%) | 353 (49.9%) |  |
| 1st tertile | 464 (19.6%) | 100 (18.3%) |  | 361 (5.6%) | 66 (9.3%) |  |
| 2nd tertile | 456 (19.2%) | 94 (17.2%) |  | 937 (14.6%) | 135 (19.1%) |  |
| 3rd tertile | 462 (19.5%) | 102 (18.7%) |  | 1334 (20.8%) | 153 (21.6%) |  |
| Epipodophyllotoxin dose, tertiles |  |  | 0.55 |  |  | <0.001 |
| None | 1,532 (64.6%) | 358 (65.6%) |  | 5693 (89.2%) | 578 (82.7%) |  |
| 1st tertile | 271 (11.4%) | 57 (10.4%) |  | 269 (4.2%) | 39 (5.6%) |  |
| 2nd tertile | 282 (11.9%) | 57 (10.4%) |  | 342 (5.4%) | 58 (8.3%) |  |
| 3rd tertile | 285 (12.0%) | 74 (13.6%) |  | 76 (1.2%) | 24 (3.4%) |  |
| Treatment group |  |  | 0.15 |  |  | <0.001 |
| Epipodophyllotoxin & Anthracycline 2-3 tertiles without Neck RT | 247 (10.4%) | 45 (8.2%) |  | 392 (6.1%) | 60 (8.5%) |  |
| Neck RT >0-<20 Gy without Epipodophyllotoxin | 39 (1.6%) | 3 (0.5%) |  | 132 (2.1%) | 12 (1.7%) |  |
| Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 194 (8.2%) | 40 (7.3%) |  | 360 (5.6%) | 41 (5.8%) |  |
| Neck RT ≥30 Gy without Epipodophyllotoxin | 135 (5.7%) | 38 (7.0%) |  | 741 (11.5%) | 45 (6.4%) |  |
| Neck RT >0-<20 Gy with Epipodophyllotoxin | 20 (0.8%) | 3 (0.5%) |  | 43 (0.7%) | 5 (0.7%) |  |
| Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 53 (2.2%) | 8 (1.5%) |  | 37 (0.6%) | 9 (1.3%) |  |
| Neck RT ≥30 Gy with Epipodophyllotoxin | 35 (1.5%) | 6 (1.1%) |  | 41 (0.6%) | 3 (0.4%) |  |
| None of the above | 1,647 (69.5%) | 403 (73.8%) |  | 4670 (72.8%) | 532 (75.2%) |  |

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| **Supplementary Table S4. Cumulative incidence of STC by PRS tertiles and age.** | | | | | | | | | | | | | | | | | |
| Age at follow-up | PRS in SJLIFE | | | | | | | | | | PRS in CCSS | | | | | | |
| Tertile 1 | | | Tertile 2 | | | Tertile 3 | | Tertile 1 | | | | Tertile 2 | | | Tertile 3 | |
| CI | (95% CI) | CI | | (95% CI) | CI | | (95% CI) | | CI | (95% CI) | CI | | (95% CI) | CI | | (95% CI) |
| Overall survivors | | | | | | | | | | | | | | | | | |
| 30 years old | 0.4 | (0.0-0.9) | 1.2 | | (0.3-2.0) | 2.1 | | (1.0-3.3) | | 0.4 | (0.0-0.9) | 1.1 | | (0.3-2.0) | 2.1 | | (1.0-3.3) |
| 40 years old | 1.6 | (0.4-2.8) | 2.8 | | (1.3-4.2) | 4.8 | | (2.9-6.6) | | 1.6 | (0.4-2.8) | 2.7 | | (1.3-4.2) | 4.8 | | (2.9-6.6) |
| 50 years old | 2.7 | (0.8-4.5) | 6.7 | | (3.3-10.0) | 8.1 | | (5.0-11.2) | | 2.7 | (0.8-4.5) | 6.7 | | (3.3-10.0) | 8.1 | | (5.0-11.2) |
| Survivors with neck-RT | | | | | | | | | | | | | | | | | |
| 30 years old | 2.5 | (0.0-7.1) | 4.0 | | (0.0-7.9) | 7.6 | | (3.1-11.8) | | 0.9 | (0.0-1.8) | 4.4 | | (1.9-6.9) | 3.3 | | (1.3-5.3) |
| 40 years old | 5.4 | (0.0-10.9) | 10.0 | | (4.1-15.6) | 14.1 | | (7.9-19.9) | | 3.6 | (1.7-5.5) | 7.5 | | (4.4-10.5) | 8.6 | | (5.5-11.6) |
| 50 years old | 9.1 | (1.4-16.1) | 14.2 | | (6.7-21.1) | 22.0 | | (13.4-29.7) | | 4.2 | (2.0-6.3) | 9.6 | | (5.7-13.3) | 10.0 | | (6.4-13.4) |
| Survivors without neck-RT | | | | | | | | | | | | | | | | | |
| 30 years old | 0.2 | (0.0-0.6) | 0.6 | | (0.0-1.3) | 0.6 | | (0.0-1.3) | | 0.1 | (0.0-0.2) | 0.3 | | (0.0-0.6) | 0.9 | | (0.4-1.4) |
| 40 years old | 0.2 | (0.0-0.6) | 0.6 | | (0.0-1.3) | 1.8 | | (0.4-3.2) | | 0.1 | (0.0-0.2 | 1.1 | | (0.5-1.7) | 1.8 | | (1.0-2.6) |
| 50 years old | 0.8 | (0.0-1.7) | 4.5 | | (0.5-8.4) | 2.6 | | (0.5-4.6) | | 0.1 | (0.0-0.2) | 1.6 | | (0.4-2.7) | 3.7 | | (1.7-5.7) |
| Abbreviations: STC (subsequent thyroid cancer), PRS (polygenic risk factor), SJLIFE (St. Jude Lifetime Cohort Study), CCSS (Childhood Cancer Survivor Study), CI (cumulative incidence) and RT (radiation therapy) | | | | | | | | | | | | | | | | | |

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| **Supplementary Table S5. Cumulative incidence of STC by neck-RT and age.** | | | | | | | | |
| Age at follow-up | SJLIFE | | | | CCSS | | | |
| Survivors with neck-RT | | Survivors without neck-RT | | Survivors with neck-RT | | Survivors without neck-RT | |
| CI | (95%\_CI) | CI | (95%\_CI) | CI | (95%\_CI) | CI | (95%\_CI) |
| 30 years old | 4.7 | (0.0-7.1) | 0.5 | (0.0-7.8) | 2.9 | (0.0-1.8) | 0.4 | (1.9-6.9) |
| 40 years old | 10.0 | (0.0-10.9) | 1.1 | (4.1-15.4) | 6.6 | (1.7-5.5) | 1.2 | (4.4-10.5) |
| 50 years old | 15.3 | (1.4-16.1) | 2.6 | (6.6-21.0) | 7.9 | (2.0-6.3) | 2.0 | (5.7-13.3) |
| Abbreviations: STC (subsequent thyroid cancer), SJLIFE (St. Jude Lifetime Cohort Study), CCSS (Childhood Cancer Survivor Study), CI (cumulative incidence), 95%\_CI (95% confidence interval), and RT (radiation therapy). | | | | | | | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Supplementary Table S6. Model-predicted lifetime risk of STC at age of 20, 30, 40, and 50 years by sex in SJLIFE** | | | | | |
| **(A) Male survivors at age of 20 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 0.1 (0.0 - 0.2) | 0.1 (0.1 - 0.4) | 0.2 (0.1 - 0.6) | 0.2 (0.1 - 0.4) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.4 (0.2 - 1.1) | 0.7 (0.3 - 1.7) | 1.0 (0.4 - 2.6) | 0.8 (0.3 - 2.2) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.7 (0.3 - 1.7) | 1.0 (0.4 - 2.6) | 1.6 (0.6 - 4.0) | 1.2 (0.4 - 3.4) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.3 (0.5 - 3.4) | 2.0 (0.8 - 5.1) | 3.1 (1.2 - 7.8) | 2.2 (0.8 - 6.1) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 0.5 (0.2 - 1.3) | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.1) | 0.9 (0.3 - 2.5) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 3.3 (1.3 - 8.1) | 4.9 (2.0 - 12.1) | 7.6 (3.0 - 18.2) | 4.7 (1.7 - 12.7) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 2.6 (1.0 - 6.5) | 3.9 (1.6 - 9.7) | 6.0 (2.4 - 14.7) | 5.0 (1.8 - 13.5) |
| 0-4 | None of the above | 1.2 (0.5 - 3.1) | 1.9 (0.7 - 4.7) | 2.9 (1.1 - 7.2) | 2.0 (0.7 - 5.6) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.0 (0.0 - 0.1) | 0.0 (0.0 - 0.1) | 0.1 (0.0 - 0.2) | 0.0 (0.0 - 0.1) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.1 (0.0 - 0.3) | 0.2 (0.1 - 0.5) | 0.3 (0.1 - 0.7) | 0.2 (0.1 - 0.6) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.2 (0.1 - 0.5) | 0.3 (0.1 - 0.7) | 0.4 (0.2 - 1.1) | 0.3 (0.1 - 1.0) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.4 (0.1 - 0.9) | 0.6 (0.2 - 1.4) | 0.9 (0.3 - 2.2) | 0.6 (0.2 - 1.8) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 0.1 (0.1 - 0.4) | 0.2 (0.1 - 0.6) | 0.3 (0.1 - 0.9) | 0.3 (0.1 - 0.7) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 0.9 (0.4 - 2.3) | 1.4 (0.5 - 3.5) | 2.2 (0.9 - 5.4) | 1.3 (0.5 - 3.8) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.7 (0.3 - 1.8) | 1.1 (0.4 - 2.8) | 1.7 (0.7 - 4.3) | 1.4 (0.5 - 4.0) |
| 5-9 | None of the above | 0.3 (0.1 - 0.9) | 0.5 (0.2 - 1.3) | 0.8 (0.3 - 2.0) | 0.6 (0.2 - 1.6) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 0.1 (0.0 - 0.3) | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.7) | 0.2 (0.1 - 0.5) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.5 (0.2 - 1.3) | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.2) | 1.0 (0.3 - 2.7) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.1) | 1.9 (0.7 - 4.7) | 1.5 (0.5 - 4.1) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.6 (0.6 - 4.0) | 2.4 (1.0 - 6.1) | 3.7 (1.5 - 9.2) | 2.7 (1.0 - 7.4) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 0.6 (0.2 - 1.6) | 0.9 (0.4 - 2.4) | 1.5 (0.6 - 3.7) | 1.1 (0.4 - 3.0) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 3.9 (1.5 - 9.6) | 5.9 (2.3 - 14.3) | 9.0 (3.6 - 21.3) | 5.6 (2.0 - 15.2) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 3.1 (1.2 - 7.7) | 4.7 (1.9 - 11.5) | 7.2 (2.9 - 17.3) | 6.0 (2.2 - 16.1) |
| 10-14 | None of the above | 1.5 (0.6 - 3.7) | 2.2 (0.9 - 5.6) | 3.4 (1.4 - 8.5) | 2.4 (0.9 - 6.8) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 0.1 (0.0 - 0.1) | 0.1 (0.0 - 0.2) | 0.1 (0.1 - 0.3) | 0.1 (0.0 - 0.3) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.3 (0.1 - 0.7) | 0.4 (0.2 - 1.1) | 0.6 (0.3 - 1.6) | 0.5 (0.2 - 1.4) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.4 (0.2 - 1.0) | 0.6 (0.2 - 1.6) | 1.0 (0.4 - 2.4) | 0.8 (0.3 - 2.1) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.8 (0.3 - 2.1) | 1.2 (0.5 - 3.1) | 1.9 (0.8 - 4.8) | 1.4 (0.5 - 3.9) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 0.3 (0.1 - 0.8) | 0.5 (0.2 - 1.2) | 0.7 (0.3 - 1.9) | 0.6 (0.2 - 1.6) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 2.0 (0.8 - 5.0) | 3.0 (1.2 - 7.6) | 4.7 (1.9 - 11.5) | 2.9 (1.0 - 8.1) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 1.6 (0.6 - 4.0) | 2.4 (1.0 - 6.1) | 3.7 (1.5 - 9.2) | 3.1 (1.1 - 8.6) |
| 15+ | None of the above | 0.7 (0.3 - 1.9) | 1.1 (0.4 - 2.9) | 1.8 (0.7 - 4.4) | 1.3 (0.4 - 3.5) |
| **(B) Male survivors at age of 30 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 1.4 (0.6 - 3.1) | 2.2 (1.0 - 4.7) | 3.3 (1.5 - 7.2) | 2.6 (1.2 - 5.4) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 2.8 (1.3 - 6.1) | 4.3 (2.0 - 9.2) | 6.6 (3.0 - 14.0) | 4.7 (2.2 - 9.8) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 1.1 (0.5 - 2.4) | 1.7 (0.8 - 3.7) | 2.6 (1.2 - 5.6) | 1.9 (0.9 - 4.0) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 6.9 (3.2 - 14.5) | 10.3 (4.8 - 21.3) | 15.5 (7.4 - 31.0) | 9.8 (4.7 - 19.8) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 5.5 (2.5 - 11.7) | 8.3 (3.8 - 17.3) | 12.5 (5.9 - 25.5) | 10.4 (5.0 - 21.0) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 2.6 (1.2 - 5.6) | 3.9 (1.8 - 8.5) | 6.1 (2.8 - 12.9) | 4.3 (2.0 - 9.0) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.7) | 0.5 (0.2 - 1.0) | 0.3 (0.2 - 0.7) |
| 0-4 | None of the above | 0.9 (0.4 - 2.1) | 1.4 (0.7 - 3.2) | 2.2 (1.0 - 4.9) | 1.7 (0.8 - 3.6) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.4 (0.2 - 0.9) | 0.6 (0.3 - 1.3) | 0.9 (0.4 - 2.1) | 0.7 (0.3 - 1.6) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.8 (0.4 - 1.7) | 1.2 (0.6 - 2.7) | 1.9 (0.9 - 4.1) | 1.3 (0.6 - 2.9) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.3 (0.1 - 0.7) | 0.5 (0.2 - 1.0) | 0.7 (0.3 - 1.6) | 0.5 (0.3 - 1.1) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.9 (0.9 - 4.2) | 3.0 (1.4 - 6.4) | 4.6 (2.1 - 9.8) | 2.9 (1.3 - 6.0) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 1.5 (0.7 - 3.4) | 2.4 (1.1 - 5.1) | 3.6 (1.7 - 7.8) | 3.0 (1.4 - 6.4) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 0.7 (0.3 - 1.6) | 1.1 (0.5 - 2.4) | 1.7 (0.8 - 3.7) | 1.2 (0.6 - 2.6) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.1 (0.0 - 0.1) | 0.1 (0.0 - 0.2) | 0.1 (0.1 - 0.3) | 0.1 (0.0 - 0.2) |
| 5-9 | None of the above | 0.3 (0.1 - 0.6) | 0.4 (0.2 - 0.9) | 0.6 (0.3 - 1.4) | 0.5 (0.2 - 1.0) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 1.7 (0.8 - 3.7) | 2.6 (1.2 - 5.6) | 4.0 (1.8 - 8.6) | 3.1 (1.5 - 6.5) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 3.4 (1.5 - 7.3) | 5.1 (2.4 - 10.9) | 7.8 (3.6 - 16.5) | 5.6 (2.7 - 11.7) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 1.3 (0.6 - 2.9) | 2.0 (0.9 - 4.4) | 3.1 (1.4 - 6.7) | 2.3 (1.1 - 4.8) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 8.1 (3.8 - 17.1) | 12.2 (5.7 - 24.9) | 18.2 (8.7 - 35.9) | 11.7 (5.7 - 23.4) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 6.5 (3.0 - 13.8) | 9.8 (4.6 - 20.3) | 14.8 (7.0 - 29.7) | 12.5 (6.0 - 24.8) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 3.1 (1.4 - 6.7) | 4.7 (2.2 - 10.1) | 7.2 (3.3 - 15.2) | 5.2 (2.5 - 10.7) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.2 (0.1 - 0.5) | 0.4 (0.2 - 0.8) | 0.6 (0.3 - 1.2) | 0.4 (0.2 - 0.9) |
| 10-14 | None of the above | 1.1 (0.5 - 2.5) | 1.7 (0.8 - 3.8) | 2.7 (1.2 - 5.8) | 2.0 (1.0 - 4.3) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 0.9 (0.4 - 1.9) | 1.3 (0.6 - 2.9) | 2.1 (0.9 - 4.5) | 1.6 (0.8 - 3.4) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.7 (0.8 - 3.8) | 2.7 (1.2 - 5.8) | 4.1 (1.9 - 8.8) | 3.0 (1.4 - 6.2) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.7 (0.3 - 1.5) | 1.0 (0.5 - 2.3) | 1.6 (0.7 - 3.5) | 1.2 (0.6 - 2.5) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 4.2 (1.9 - 9.1) | 6.4 (3.0 - 13.6) | 9.8 (4.6 - 20.3) | 6.2 (3.0 - 12.8) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 3.4 (1.5 - 7.3) | 5.1 (2.4 - 11.0) | 7.8 (3.6 - 16.5) | 6.6 (3.2 - 13.6) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 1.6 (0.7 - 3.5) | 2.4 (1.1 - 5.3) | 3.7 (1.7 - 8.1) | 2.7 (1.3 - 5.7) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.1 (0.1 - 0.3) | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.6) | 0.2 (0.1 - 0.4) |
| 15+ | None of the above | 0.6 (0.3 - 1.3) | 0.9 (0.4 - 1.9) | 1.4 (0.6 - 3.0) | 1.1 (0.5 - 2.3) |
| **(C) Male survivors at age of 40 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 2.2 (1.0 - 4.8) | 3.3 (1.5 - 7.2) | 5.1 (2.4 - 11.0) | 3.9 (1.7 - 8.6) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 3.3 (1.5 - 7.1) | 5.0 (2.3 - 10.7) | 7.6 (3.5 - 16.0) | 5.8 (2.6 - 12.7) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 6.5 (3.0 - 13.7) | 9.7 (4.5 - 20.3) | 14.7 (6.9 - 29.6) | 10.5 (4.8 - 22.3) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 2.5 (1.2 - 5.5) | 3.9 (1.8 - 8.4) | 5.9 (2.7 - 12.7) | 4.3 (1.9 - 9.5) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 15.2 (7.2 - 30.6) | 22.3 (10.8 - 42.8) | 32.4 (16.3 - 58.0) | 21.2 (10.0 - 41.7) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 12.3 (5.8 - 25.1) | 18.2 (8.7 - 35.8) | 26.7 (13.2 - 49.7) | 22.5 (10.6 - 43.8) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 5.9 (2.7 - 12.7) | 8.9 (4.2 - 18.7) | 13.5 (6.4 - 27.5) | 9.6 (4.4 - 20.5) |
| 0-4 | None of the above | 0.5 (0.2 - 1.0) | 0.7 (0.3 - 1.5) | 1.1 (0.5 - 2.4) | 0.8 (0.3 - 1.7) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.6 (0.3 - 1.3) | 0.9 (0.4 - 2.1) | 1.4 (0.7 - 3.2) | 1.1 (0.5 - 2.5) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.9 (0.4 - 2.0) | 1.4 (0.6 - 3.1) | 2.2 (1.0 - 4.7) | 1.7 (0.7 - 3.8) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 1.8 (0.8 - 4.0) | 2.8 (1.3 - 6.1) | 4.3 (2.0 - 9.3) | 3.1 (1.4 - 6.8) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.7 (0.3 - 1.6) | 1.1 (0.5 - 2.4) | 1.7 (0.8 - 3.7) | 1.2 (0.5 - 2.8) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 4.5 (2.1 - 9.6) | 6.8 (3.1 - 14.3) | 10.3 (4.8 - 21.3) | 6.5 (2.9 - 14.1) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 3.6 (1.6 - 7.7) | 5.4 (2.5 - 11.6) | 8.3 (3.8 - 17.3) | 6.9 (3.1 - 15.0) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 1.7 (0.8 - 3.7) | 2.6 (1.2 - 5.6) | 3.9 (1.8 - 8.5) | 2.8 (1.3 - 6.3) |
| 5-9 | None of the above | 0.1 (0.1 - 0.3) | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.7) | 0.2 (0.1 - 0.5) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 2.6 (1.2 - 5.7) | 4.0 (1.8 - 8.6) | 6.1 (2.8 - 13.0) | 4.7 (2.1 - 10.3) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 3.9 (1.8 - 8.4) | 5.9 (2.7 - 12.6) | 9.0 (4.2 - 18.9) | 7.0 (3.2 - 15.2) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 7.7 (3.6 - 16.2) | 11.5 (5.4 - 23.7) | 17.3 (8.2 - 34.2) | 12.6 (5.8 - 26.2) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 3.0 (1.4 - 6.6) | 4.6 (2.1 - 9.9) | 7.1 (3.3 - 14.9) | 5.2 (2.3 - 11.4) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 17.9 (8.6 - 35.4) | 26.1 (12.8 - 48.7) | 37.4 (19.1 - 64.5) | 25.0 (12.0 - 47.9) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 14.5 (6.9 - 29.3) | 21.3 (10.3 - 41.1) | 31.0 (15.5 - 56.0) | 26.5 (12.7 - 50.2) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 7.1 (3.3 - 14.9) | 10.6 (5.0 - 21.9) | 15.9 (7.6 - 31.9) | 11.5 (5.3 - 24.3) |
| 10-14 | None of the above | 0.5 (0.2 - 1.2) | 0.8 (0.4 - 1.8) | 1.3 (0.6 - 2.8) | 0.9 (0.4 - 2.1) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 1.3 (0.6 - 2.9) | 2.0 (0.9 - 4.5) | 3.2 (1.4 - 6.8) | 2.4 (1.1 - 5.4) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 2.0 (0.9 - 4.4) | 3.1 (1.4 - 6.7) | 4.7 (2.2 - 10.1) | 3.7 (1.6 - 8.1) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 4.0 (1.8 - 8.6) | 6.1 (2.8 - 12.9) | 9.2 (4.3 - 19.3) | 6.7 (3.0 - 14.5) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.6 (0.7 - 3.4) | 2.4 (1.1 - 5.2) | 3.7 (1.7 - 7.9) | 2.7 (1.2 - 6.0) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 9.6 (4.5 - 20.0) | 14.3 (6.8 - 28.9) | 21.3 (10.3 - 41.1) | 13.8 (6.4 - 28.6) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 7.7 (3.6 - 16.2) | 11.5 (5.4 - 23.7) | 17.3 (8.2 - 34.3) | 14.6 (6.8 - 30.1) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 3.7 (1.7 - 7.9) | 5.6 (2.6 - 11.9) | 8.5 (3.9 - 17.8) | 6.1 (2.8 - 13.3) |
| 15+ | None of the above | 0.3 (0.1 - 0.6) | 0.4 (0.2 - 0.9) | 0.7 (0.3 - 1.5) | 0.5 (0.2 - 1.1) |
| **(D) Male survivors at age of 50 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 4.3 (1.9 - 9.7) | 6.4 (2.8 - 14.4) | 9.8 (4.4 - 21.4) | 7.4 (3.6 - 15.2) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 6.3 (2.8 - 14.2) | 9.5 (4.2 - 20.9) | 14.4 (6.5 - 30.5) | 11.1 (5.4 - 22.1) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 12.3 (5.5 - 26.4) | 18.2 (8.3 - 37.5) | 26.8 (12.6 - 51.7) | 19.5 (9.8 - 37.0) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 4.9 (2.2 - 11.2) | 7.5 (3.3 - 16.6) | 11.3 (5.1 - 24.5) | 8.3 (4.0 - 16.8) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 27.7 (13.1 - 53.1) | 39.2 (19.3 - 68.7) | 53.7 (28.2 - 83.5) | 37.3 (19.8 - 62.9) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 22.7 (10.5 - 45.2) | 32.6 (15.6 - 60.2) | 45.7 (23.1 - 76.0) | 39.2 (20.9 - 65.3) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 11.3 (5.1 - 24.5) | 16.8 (7.6 - 35.0) | 24.9 (11.6 - 48.7) | 18.0 (8.9 - 34.4) |
| 0-4 | None of the above | 0.9 (0.4 - 2.1) | 1.4 (0.6 - 3.2) | 2.1 (0.9 - 4.9) | 1.5 (0.7 - 3.2) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 1.2 (0.5 - 2.8) | 1.8 (0.8 - 4.2) | 2.8 (1.2 - 6.5) | 2.1 (1.0 - 4.5) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.8 (0.8 - 4.2) | 2.7 (1.2 - 6.3) | 4.2 (1.8 - 9.6) | 3.3 (1.5 - 6.8) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 3.6 (1.6 - 8.2) | 5.4 (2.4 - 12.2) | 8.3 (3.7 - 18.3) | 5.9 (2.8 - 12.2) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.4 (0.6 - 3.2) | 2.1 (0.9 - 4.9) | 3.3 (1.4 - 7.5) | 2.4 (1.1 - 5.0) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 8.6 (3.8 - 18.9) | 12.9 (5.8 - 27.5) | 19.2 (8.8 - 39.3) | 12.3 (6.0 - 24.3) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 6.9 (3.0 - 15.3) | 10.3 (4.6 - 22.5) | 15.6 (7.0 - 32.7) | 13.1 (6.4 - 25.7) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 3.3 (1.4 - 7.5) | 5.0 (2.2 - 11.2) | 7.6 (3.4 - 16.9) | 5.4 (2.6 - 11.2) |
| 5-9 | None of the above | 0.3 (0.1 - 0.6) | 0.4 (0.2 - 0.9) | 0.6 (0.3 - 1.4) | 0.4 (0.2 - 0.9) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 5.1 (2.2 - 11.4) | 7.7 (3.4 - 17.0) | 11.6 (5.2 - 25.0) | 8.9 (4.3 - 18.0) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 7.5 (3.3 - 16.7) | 11.3 (5.0 - 24.4) | 17.0 (7.7 - 35.2) | 13.2 (6.5 - 26.1) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 14.5 (6.5 - 30.7) | 21.4 (9.8 - 43.0) | 31.1 (14.8 - 58.1) | 23.1 (11.7 - 42.8) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 5.9 (2.6 - 13.2) | 8.9 (3.9 - 19.5) | 13.4 (6.0 - 28.5) | 9.9 (4.8 - 19.9) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 32.2 (15.4 - 59.6) | 44.8 (22.6 - 75.0) | 60.2 (32.7 - 88.4) | 43.1 (23.4 - 69.8) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 26.5 (12.4 - 51.3) | 37.6 (18.4 - 66.7) | 51.8 (27.0 - 81.8) | 45.2 (24.7 - 72.2) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 13.4 (6.0 - 28.5) | 19.8 (9.0 - 40.2) | 28.9 (13.7 - 54.9) | 21.3 (10.7 - 40.0) |
| 10-14 | None of the above | 1.1 (0.5 - 2.5) | 1.6 (0.7 - 3.8) | 2.5 (1.1 - 5.8) | 1.8 (0.9 - 3.8) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 2.6 (1.1 - 6.0) | 4.0 (1.7 - 9.1) | 6.1 (2.7 - 13.7) | 4.7 (2.2 - 9.7) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 3.9 (1.7 - 8.9) | 5.9 (2.6 - 13.3) | 9.1 (4.0 - 19.9) | 7.1 (3.4 - 14.4) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 7.7 (3.4 - 17.1) | 11.6 (5.2 - 24.9) | 17.3 (7.9 - 35.9) | 12.7 (6.2 - 25.0) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 3.0 (1.3 - 7.0) | 4.6 (2.0 - 10.5) | 7.1 (3.1 - 15.8) | 5.2 (2.5 - 10.8) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 18.0 (8.2 - 37.0) | 26.2 (12.3 - 50.8) | 37.5 (18.3 - 66.7) | 25.2 (12.8 - 46.1) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 14.5 (6.5 - 30.7) | 21.4 (9.8 - 43.0) | 31.1 (14.8 - 58.1) | 26.6 (13.6 - 48.3) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 7.1 (3.1 - 15.8) | 10.6 (4.7 - 23.1) | 16.0 (7.2 - 33.4) | 11.6 (5.7 - 23.1) |
| 15+ | None of the above | 0.6 (0.2 - 1.3) | 0.8 (0.4 - 2.0) | 1.3 (0.6 - 3.0) | 0.9 (0.4 - 2.0) |
| **(E) Female survivors at age of 20 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 0.7 (0.3 - 1.7) | 1.0 (0.4 - 2.6) | 1.6 (0.6 - 3.9) | 1.2 (0.4 - 3.3) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.0 (0.4 - 2.5) | 1.5 (0.6 - 3.8) | 2.3 (0.9 - 5.9) | 1.8 (0.6 - 5.0) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 2.0 (0.8 - 5.0) | 3.0 (1.2 - 7.5) | 4.7 (1.9 - 11.4) | 3.3 (1.2 - 9.0) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.0) | 1.8 (0.7 - 4.6) | 1.3 (0.5 - 3.7) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 4.8 (1.9 - 11.9) | 7.3 (2.9 - 17.6) | 11.1 (4.5 - 25.9) | 6.9 (2.5 - 18.3) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 3.9 (1.5 - 9.5) | 5.8 (2.3 - 14.2) | 8.9 (3.6 - 21.2) | 7.3 (2.7 - 19.4) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 1.8 (0.7 - 4.6) | 2.8 (1.1 - 6.9) | 4.3 (1.7 - 10.5) | 3.0 (1.1 - 8.3) |
| 0-4 | None of the above | 0.1 (0.1 - 0.4) | 0.2 (0.1 - 0.5) | 0.3 (0.1 - 0.8) | 0.2 (0.1 - 0.7) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.2 (0.1 - 0.5) | 0.3 (0.1 - 0.7) | 0.4 (0.2 - 1.1) | 0.3 (0.1 - 0.9) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.3 (0.1 - 0.7) | 0.4 (0.2 - 1.1) | 0.7 (0.3 - 1.7) | 0.5 (0.2 - 1.4) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 0.6 (0.2 - 1.4) | 0.8 (0.3 - 2.1) | 1.3 (0.5 - 3.3) | 0.9 (0.3 - 2.6) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.2 (0.1 - 0.5) | 0.3 (0.1 - 0.8) | 0.5 (0.2 - 1.3) | 0.4 (0.1 - 1.1) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 1.4 (0.5 - 3.4) | 2.1 (0.8 - 5.2) | 3.2 (1.3 - 8.0) | 2.0 (0.7 - 5.5) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 1.1 (0.4 - 2.7) | 1.7 (0.7 - 4.2) | 2.6 (1.0 - 6.4) | 2.1 (0.8 - 5.9) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 0.5 (0.2 - 1.3) | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.0) | 0.9 (0.3 - 2.4) |
| 5-9 | None of the above | 0.0 (0.0 - 0.1) | 0.1 (0.0 - 0.1) | 0.1 (0.0 - 0.2) | 0.1 (0.0 - 0.2) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 0.8 (0.3 - 2.0) | 1.2 (0.5 - 3.1) | 1.9 (0.7 - 4.7) | 1.4 (0.5 - 4.0) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.2 (0.5 - 3.0) | 1.8 (0.7 - 4.6) | 2.8 (1.1 - 7.0) | 2.2 (0.8 - 6.0) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 2.4 (0.9 - 5.9) | 3.6 (1.4 - 8.9) | 5.5 (2.2 - 13.5) | 3.9 (1.4 - 10.8) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.9 (0.4 - 2.3) | 1.4 (0.6 - 3.5) | 2.2 (0.9 - 5.4) | 1.6 (0.6 - 4.4) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 5.8 (2.3 - 14.0) | 8.7 (3.5 - 20.6) | 13.1 (5.4 - 30.1) | 8.3 (3.0 - 21.7) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 4.6 (1.8 - 11.3) | 6.9 (2.8 - 16.8) | 10.5 (4.3 - 24.8) | 8.8 (3.2 - 23.0) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 2.2 (0.9 - 5.4) | 3.3 (1.3 - 8.2) | 5.1 (2.0 - 12.4) | 3.6 (1.3 - 9.9) |
| 10-14 | None of the above | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.6) | 0.4 (0.2 - 1.0) | 0.3 (0.1 - 0.8) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 0.4 (0.2 - 1.0) | 0.6 (0.2 - 1.6) | 1.0 (0.4 - 2.4) | 0.7 (0.3 - 2.1) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.6 (0.2 - 1.5) | 0.9 (0.4 - 2.4) | 1.4 (0.6 - 3.6) | 1.1 (0.4 - 3.1) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 1.2 (0.5 - 3.1) | 1.9 (0.7 - 4.7) | 2.9 (1.1 - 7.1) | 2.1 (0.7 - 5.7) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.5 (0.2 - 1.2) | 0.7 (0.3 - 1.8) | 1.1 (0.4 - 2.8) | 0.8 (0.3 - 2.3) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 3.0 (1.2 - 7.4) | 4.5 (1.8 - 11.1) | 6.9 (2.8 - 16.7) | 4.3 (1.6 - 11.8) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 2.4 (0.9 - 5.9) | 3.6 (1.4 - 8.9) | 5.5 (2.2 - 13.5) | 4.6 (1.7 - 12.6) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 1.1 (0.4 - 2.8) | 1.7 (0.7 - 4.3) | 2.6 (1.0 - 6.6) | 1.9 (0.7 - 5.2) |
| 15+ | None of the above | 0.1 (0.0 - 0.2) | 0.1 (0.1 - 0.3) | 0.2 (0.1 - 0.5) | 0.1 (0.1 - 0.4) |
| **(F) Female survivors at age of 30 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 1.4 (0.6 - 3.1) | 2.2 (1.0 - 4.7) | 3.3 (1.5 - 7.2) | 2.5 (1.2 - 5.3) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 2.1 (1.0 - 4.6) | 3.2 (1.5 - 7.0) | 5.0 (2.3 - 10.6) | 3.8 (1.8 - 7.9) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 4.2 (1.9 - 9.1) | 6.4 (2.9 - 13.5) | 9.7 (4.5 - 20.2) | 6.9 (3.3 - 14.2) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.6 (0.8 - 3.6) | 2.5 (1.1 - 5.5) | 3.9 (1.8 - 8.3) | 2.8 (1.3 - 5.9) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 10.1 (4.7 - 20.9) | 15.0 (7.1 - 30.2) | 22.3 (10.8 - 42.7) | 14.2 (6.9 - 28.0) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 8.1 (3.8 - 17.0) | 12.1 (5.7 - 24.8) | 18.1 (8.7 - 35.7) | 15.1 (7.4 - 29.5) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 3.9 (1.8 - 8.3) | 5.9 (2.7 - 12.5) | 8.9 (4.2 - 18.6) | 6.3 (3.0 - 13.0) |
| 0-4 | None of the above | 0.3 (0.1 - 0.7) | 0.5 (0.2 - 1.0) | 0.7 (0.3 - 1.5) | 0.5 (0.2 - 1.1) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.4 (0.2 - 0.9) | 0.6 (0.3 - 1.3) | 0.9 (0.4 - 2.0) | 0.7 (0.3 - 1.5) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 0.6 (0.3 - 1.3) | 0.9 (0.4 - 2.0) | 1.4 (0.6 - 3.1) | 1.1 (0.5 - 2.3) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 1.2 (0.5 - 2.6) | 1.8 (0.8 - 3.9) | 2.8 (1.3 - 6.1) | 2.0 (0.9 - 4.2) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 0.5 (0.2 - 1.0) | 0.7 (0.3 - 1.5) | 1.1 (0.5 - 2.4) | 0.8 (0.4 - 1.7) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 2.9 (1.3 - 6.3) | 4.4 (2.0 - 9.5) | 6.8 (3.1 - 14.3) | 4.2 (2.0 - 8.8) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 2.3 (1.1 - 5.0) | 3.5 (1.6 - 7.6) | 5.4 (2.5 - 11.5) | 4.5 (2.1 - 9.4) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 1.1 (0.5 - 2.4) | 1.7 (0.8 - 3.6) | 2.6 (1.2 - 5.6) | 1.8 (0.9 - 3.9) |
| 5-9 | None of the above | 0.1 (0.0 - 0.2) | 0.1 (0.1 - 0.3) | 0.2 (0.1 - 0.4) | 0.1 (0.1 - 0.3) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 1.7 (0.8 - 3.7) | 2.6 (1.2 - 5.6) | 4.0 (1.8 - 8.5) | 3.0 (1.4 - 6.4) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 2.5 (1.2 - 5.5) | 3.8 (1.8 - 8.3) | 5.9 (2.7 - 12.6) | 4.6 (2.2 - 9.5) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 5.0 (2.3 - 10.7) | 7.6 (3.5 - 15.9) | 11.5 (5.4 - 23.6) | 8.3 (4.0 - 16.9) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 2.0 (0.9 - 4.3) | 3.0 (1.4 - 6.5) | 4.6 (2.1 - 9.9) | 3.4 (1.6 - 7.1) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 11.9 (5.6 - 24.4) | 17.7 (8.4 - 34.9) | 26.0 (12.8 - 48.6) | 16.9 (8.3 - 32.8) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 9.6 (4.5 - 19.9) | 14.3 (6.8 - 28.8) | 21.3 (10.3 - 41.0) | 18.0 (8.8 - 34.5) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 4.6 (2.1 - 9.9) | 7.0 (3.2 - 14.7) | 10.6 (4.9 - 21.9) | 7.6 (3.6 - 15.5) |
| 10-14 | None of the above | 0.4 (0.2 - 0.8) | 0.5 (0.2 - 1.2) | 0.8 (0.4 - 1.8) | 0.6 (0.3 - 1.3) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 0.9 (0.4 - 1.9) | 1.3 (0.6 - 2.9) | 2.0 (0.9 - 4.5) | 1.6 (0.7 - 3.3) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.3 (0.6 - 2.8) | 2.0 (0.9 - 4.3) | 3.1 (1.4 - 6.6) | 2.4 (1.1 - 5.0) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 2.6 (1.2 - 5.6) | 3.9 (1.8 - 8.5) | 6.0 (2.8 - 12.8) | 4.4 (2.1 - 9.1) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.0 (0.5 - 2.2) | 1.5 (0.7 - 3.4) | 2.4 (1.1 - 5.2) | 1.8 (0.8 - 3.7) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 6.3 (2.9 - 13.3) | 9.5 (4.4 - 19.7) | 14.3 (6.8 - 28.8) | 9.1 (4.4 - 18.5) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 5.0 (2.3 - 10.7) | 7.6 (3.5 - 16.0) | 11.5 (5.4 - 23.6) | 9.7 (4.7 - 19.6) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 2.4 (1.1 - 5.2) | 3.6 (1.7 - 7.8) | 5.6 (2.6 - 11.8) | 4.0 (1.9 - 8.3) |
| 15+ | None of the above | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.6) | 0.4 (0.2 - 0.9) | 0.3 (0.1 - 0.7) |
| **(G) Female survivors at age of 40 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 3.3 (1.5 - 7.1) | 4.9 (2.3 - 10.6) | 7.6 (3.5 - 16.0) | 5.7 (2.6 - 12.5) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 4.9 (2.2 - 10.5) | 7.4 (3.4 - 15.5) | 11.2 (5.2 - 23.0) | 8.5 (3.9 - 18.3) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 9.5 (4.4 - 19.9) | 14.2 (6.7 - 28.7) | 21.2 (10.2 - 40.9) | 15.2 (7.1 - 31.2) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 3.8 (1.7 - 8.2) | 5.7 (2.6 - 12.3) | 8.8 (4.1 - 18.3) | 6.4 (2.9 - 13.8) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 21.9 (10.6 - 42.1) | 31.5 (15.8 - 56.7) | 44.4 (23.4 - 72.7) | 29.9 (14.5 - 55.2) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 17.8 (8.5 - 35.2) | 25.9 (12.7 - 48.5) | 37.2 (19.0 - 64.3) | 31.5 (15.4 - 57.6) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 8.8 (4.1 - 18.4) | 13.1 (6.2 - 26.7) | 19.6 (9.4 - 38.2) | 14.0 (6.5 - 29.0) |
| 0-4 | None of the above | 0.7 (0.3 - 1.5) | 1.0 (0.5 - 2.3) | 1.6 (0.7 - 3.5) | 1.1 (0.5 - 2.6) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 0.9 (0.4 - 2.0) | 1.4 (0.6 - 3.1) | 2.2 (1.0 - 4.7) | 1.6 (0.7 - 3.7) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 1.4 (0.6 - 3.0) | 2.1 (1.0 - 4.6) | 3.2 (1.5 - 7.0) | 2.5 (1.1 - 5.5) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 2.7 (1.3 - 5.9) | 4.2 (1.9 - 9.0) | 6.4 (2.9 - 13.5) | 4.5 (2.0 - 10.0) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 1.1 (0.5 - 2.3) | 1.6 (0.7 - 3.6) | 2.5 (1.1 - 5.5) | 1.8 (0.8 - 4.1) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 6.6 (3.1 - 14.1) | 10.0 (4.6 - 20.7) | 15.0 (7.1 - 30.2) | 9.5 (4.3 - 20.2) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 5.3 (2.4 - 11.3) | 8.0 (3.7 - 16.8) | 12.1 (5.7 - 24.8) | 10.1 (4.6 - 21.4) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 2.5 (1.1 - 5.5) | 3.8 (1.7 - 8.2) | 5.9 (2.7 - 12.5) | 4.2 (1.9 - 9.2) |
| 5-9 | None of the above | 0.2 (0.1 - 0.4) | 0.3 (0.1 - 0.6) | 0.5 (0.2 - 1.0) | 0.3 (0.1 - 0.7) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 3.9 (1.8 - 8.4) | 5.9 (2.7 - 12.5) | 9.0 (4.2 - 18.8) | 6.9 (3.1 - 14.9) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 5.8 (2.7 - 12.4) | 8.7 (4.1 - 18.3) | 13.2 (6.2 - 26.9) | 10.2 (4.7 - 21.7) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 11.3 (5.3 - 23.2) | 16.7 (8.0 - 33.3) | 24.7 (12.1 - 46.6) | 18.1 (8.5 - 36.4) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 4.5 (2.1 - 9.7) | 6.8 (3.2 - 14.5) | 10.4 (4.8 - 21.5) | 7.6 (3.5 - 16.5) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 25.6 (12.5 - 48.0) | 36.4 (18.6 - 63.2) | 50.4 (27.3 - 78.8) | 34.9 (17.3 - 62.1) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 20.9 (10.1 - 40.4) | 30.2 (15.0 - 54.8) | 42.7 (22.3 - 70.8) | 36.7 (18.3 - 64.5) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 10.4 (4.8 - 21.5) | 15.4 (7.3 - 31.0) | 22.9 (11.1 - 43.7) | 16.7 (7.8 - 33.9) |
| 10-14 | None of the above | 0.8 (0.4 - 1.8) | 1.3 (0.6 - 2.7) | 1.9 (0.9 - 4.2) | 1.4 (0.6 - 3.1) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 2.0 (0.9 - 4.4) | 3.1 (1.4 - 6.6) | 4.7 (2.2 - 10.1) | 3.6 (1.6 - 8.0) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 3.0 (1.4 - 6.5) | 4.6 (2.1 - 9.8) | 7.0 (3.2 - 14.8) | 5.4 (2.4 - 11.8) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 5.9 (2.7 - 12.6) | 8.9 (4.2 - 18.7) | 13.5 (6.4 - 27.4) | 9.8 (4.5 - 20.8) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 2.3 (1.1 - 5.1) | 3.5 (1.6 - 7.7) | 5.4 (2.5 - 11.6) | 4.0 (1.8 - 8.9) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 14.0 (6.6 - 28.4) | 20.6 (10.0 - 40.0) | 30.1 (15.0 - 54.7) | 19.8 (9.3 - 39.4) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 11.3 (5.3 - 23.3) | 16.8 (8.0 - 33.3) | 24.7 (12.1 - 46.7) | 21.0 (9.9 - 41.4) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 5.4 (2.5 - 11.6) | 8.2 (3.8 - 17.3) | 12.4 (5.8 - 25.4) | 9.0 (4.1 - 19.2) |
| 15+ | None of the above | 0.4 (0.2 - 0.9) | 0.6 (0.3 - 1.4) | 1.0 (0.5 - 2.2) | 0.7 (0.3 - 1.6) |
| **(G) Female survivors at age of 50 years old** | | | | | |
| Age at primary diagnosis | Treatment group | PRS (1st tertile) | PRS (2nd tertile) | PRS (3rd tertile) | Overall |
| 0-4 | Anthracycline 2-3 tertiles without Neck RT | 6.3 (2.8 - 14.1) | 9.5 (4.2 - 20.8) | 14.3 (6.4 - 30.3) | 10.9 (5.3 - 21.7) |
| 0-4 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 9.4 (4.1 - 20.5) | 14.0 (6.3 - 29.6) | 20.8 (9.5 - 41.9) | 16.0 (7.9 - 31.1) |
| 0-4 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 17.9 (8.1 - 36.8) | 26.0 (12.2 - 50.5) | 37.3 (18.2 - 66.4) | 27.6 (14.2 - 49.7) |
| 0-4 | Neck RT ≥30 Gy without Epipodophyllotoxin | 7.3 (3.2 - 16.2) | 11.0 (4.9 - 23.8) | 16.5 (7.5 - 34.3) | 12.1 (5.9 - 24.0) |
| 0-4 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 38.5 (18.9 - 67.9) | 52.5 (27.4 - 82.4) | 68.5 (39.2 - 93.2) | 50.0 (27.9 - 77.1) |
| 0-4 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 32.0 (15.3 - 59.4) | 44.6 (22.5 - 74.8) | 60.0 (32.6 - 88.2) | 52.3 (29.5 - 79.3) |
| 0-4 | Neck RT ≥30 Gy with Epipodophyllotoxin | 16.5 (7.5 - 34.4) | 24.1 (11.2 - 47.5) | 34.8 (16.8 - 63.2) | 25.6 (13.0 - 46.6) |
| 0-4 | None of the above | 1.3 (0.6 - 3.1) | 2.1 (0.9 - 4.7) | 3.2 (1.4 - 7.2) | 2.2 (1.1 - 4.7) |
| 5-9 | Anthracycline 2-3 tertiles without Neck RT | 1.8 (0.8 - 4.1) | 2.7 (1.2 - 6.2) | 4.2 (1.8 - 9.5) | 3.2 (1.5 - 6.6) |
| 5-9 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 2.7 (1.2 - 6.2) | 4.1 (1.8 - 9.3) | 6.3 (2.7 - 14.0) | 4.8 (2.3 - 9.9) |
| 5-9 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 5.3 (2.3 - 12.0) | 8.0 (3.5 - 17.7) | 12.1 (5.4 - 26.1) | 8.7 (4.2 - 17.6) |
| 5-9 | Neck RT ≥30 Gy without Epipodophyllotoxin | 2.1 (0.9 - 4.8) | 3.2 (1.4 - 7.2) | 4.9 (2.1 - 11.0) | 3.6 (1.7 - 7.4) |
| 5-9 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 12.6 (5.6 - 27.0) | 18.6 (8.5 - 38.2) | 27.4 (12.9 - 52.6) | 17.7 (8.8 - 34.0) |
| 5-9 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 10.1 (4.5 - 22.1) | 15.1 (6.8 - 31.7) | 22.4 (10.3 - 44.7) | 18.8 (9.4 - 35.8) |
| 5-9 | Neck RT ≥30 Gy with Epipodophyllotoxin | 4.9 (2.1 - 11.0) | 7.4 (3.2 - 16.3) | 11.2 (5.0 - 24.2) | 8.0 (3.8 - 16.2) |
| 5-9 | None of the above | 0.4 (0.2 - 0.9) | 0.6 (0.2 - 1.3) | 0.9 (0.4 - 2.1) | 0.6 (0.3 - 1.3) |
| 10-14 | Anthracycline 2-3 tertiles without Neck RT | 7.5 (3.3 - 16.6) | 11.2 (5.0 - 24.3) | 16.9 (7.7 - 35.0) | 13.0 (6.3 - 25.6) |
| 10-14 | Neck RT >0-<20 Gy without Epipodophyllotoxin | 11.1 (4.9 - 24.0) | 16.4 (7.4 - 34.2) | 24.3 (11.3 - 47.8) | 19.0 (9.5 - 36.2) |
| 10-14 | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 21.0 (9.6 - 42.3) | 30.2 (14.4 - 56.9) | 42.8 (21.4 - 72.8) | 32.4 (16.9 - 56.5) |
| 10-14 | Neck RT ≥30 Gy without Epipodophyllotoxin | 8.7 (3.8 - 19.1) | 13.0 (5.8 - 27.7) | 19.4 (8.9 - 39.5) | 14.4 (7.1 - 28.2) |
| 10-14 | Neck RT >0-<20 Gy with Epipodophyllotoxin | 44.1 (22.1 - 74.2) | 58.9 (31.8 - 87.5) | 74.8 (44.8 - 96.0) | 56.8 (32.7 - 83.2) |
| 10-14 | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 36.9 (18.0 - 65.9) | 50.6 (26.2 - 80.7) | 66.5 (37.6 - 92.2) | 59.1 (34.4 - 85.1) |
| 10-14 | Neck RT ≥30 Gy with Epipodophyllotoxin | 19.4 (8.9 - 39.5) | 28.1 (13.2 - 53.7) | 40.0 (19.8 - 69.7) | 30.0 (15.5 - 53.2) |
| 10-14 | None of the above | 1.6 (0.7 - 3.7) | 2.4 (1.1 - 5.6) | 3.8 (1.6 - 8.6) | 2.7 (1.3 - 5.6) |
| 15+ | Anthracycline 2-3 tertiles without Neck RT | 3.9 (1.7 - 8.9) | 5.9 (2.6 - 13.2) | 9.0 (4.0 - 19.8) | 6.9 (3.3 - 14.1) |
| 15+ | Neck RT >0-<20 Gy without Epipodophyllotoxin | 5.8 (2.5 - 13.1) | 8.8 (3.9 - 19.3) | 13.3 (5.9 - 28.2) | 10.3 (5.0 - 20.7) |
| 15+ | Neck RT ≥20-<30 Gy without Epipodophyllotoxin | 11.3 (5.0 - 24.5) | 16.8 (7.6 - 34.9) | 24.8 (11.6 - 48.6) | 18.2 (9.1 - 34.8) |
| 15+ | Neck RT ≥30 Gy without Epipodophyllotoxin | 4.5 (2.0 - 10.3) | 6.8 (3.0 - 15.3) | 10.4 (4.6 - 22.6) | 7.7 (3.7 - 15.7) |
| 15+ | Neck RT >0-<20 Gy with Epipodophyllotoxin | 25.7 (12.0 - 50.0) | 36.5 (17.8 - 65.4) | 50.6 (26.2 - 80.7) | 35.1 (18.5 - 60.1) |
| 15+ | Neck RT ≥20-<30 Gy with Epipodophyllotoxin | 21.0 (9.6 - 42.3) | 30.3 (14.4 - 56.9) | 42.8 (21.4 - 72.9) | 36.9 (19.6 - 62.5) |
| 15+ | Neck RT ≥30 Gy with Epipodophyllotoxin | 10.4 (4.6 - 22.7) | 15.5 (7.0 - 32.5) | 23.0 (10.6 - 45.6) | 16.8 (8.3 - 32.4) |
| 15+ | None of the above | 0.8 (0.4 - 1.9) | 1.3 (0.5 - 2.9) | 1.9 (0.8 - 4.5) | 1.4 (0.7 - 3.0) |
| Abbreviations: STC (subsequent thyroid cancer), PRS (polygenic risk scsore), SJLIFE (St. Jude Lifetime cohort study), and RT (radiotherapy). | | | | | |

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| **Supplementary Table S7. Validation of the multivariable clinical model for STC risk in CCSSa** | | | |
| Selected variables | RR | (95% CI) | *P* |
| Age at diagnosis, years |  |  |  |
| 0-4 | 1.00 | (Ref.) |  |
| 5-9 | 0.72 | (0.41-1.27) | 0.26 |
| 10-14 | 0.94 | (0.58-1.54) | 0.82 |
| ≥15 | 0.41 | (0.22-0.77) | 0.006 |
| Sex |  |  |  |
| Men | 1.00 | (Ref.) |  |
| Women | 1.75 | (1.20-2.55) | 0.004 |
| Treatment group |  |  |  |
| None or others | 1.00 | (Ref.) |  |
| Epipodophyllotoxin & Anthracycline 2-3 tertiles without neck-RT | 2.23 | (0.88-5.65) | 0.09 |
| Neck-RT >0-<20 Gy without Epipodophyllotoxin | 4.88 | (2.18-10.91) | <0.001 |
| Neck-RT ≥20-<30 Gy without Epipodophyllotoxin | 7.73 | (4.64-12.88) | <0.001 |
| Neck-RT ≥30 Gy without Epipodophyllotoxin | 4.47 | (2.69-7.54) | <0.001 |
| Neck-RT >0-<20 Gy with Epipodophyllotoxin | 8.64 | (2.08-35.91) | 0.003 |
| Neck-RT ≥20-<30 Gy with Epipodophyllotoxin | 4.13 | (0.56-30.37) | 0.16 |
| Neck-RT ≥30 Gy with Epipodophyllotoxin | - |  | - |
| Abbreviations: STC (subsequent thyroid cancer) and RT (radiotherapy) | | | |
| aAdjusted for attained age modeled by restricted cubic splines. | | | |

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| **Supplementary Table S8. Adjusted associations of the 12 SNPs included in the PRS construction with STC risk in SJLIFEa** | | | | | | | | | |
| SNP | Overall survivors | | | Survivors with neck-RT | | | Survivors without neck-RT | | |
| RR | (95% CI) | *P* | RR | (95% CI) | *P* | RR | (95% CI) | *P* |
| rs12129938 | 1.42 | (0.89-2.26) | 0.14 | 1.34 | (0.78-2.32) | 0.29 | 2.02 | (0.66-6.23) | 0.22 |
| rs11693806 | 1.23 | (0.82-1.85) | 0.33 | 1.24 | (0.78-1.96) | 0.36 | 1.18 | (0.44-3.14) | 0.74 |
| rs6793295 | 1.10 | (0.72-1.67) | 0.65 | 1.19 | (0.70-2.02) | 0.53 | 0.89 | (0.45-1.76) | 0.74 |
| rs10069690 | 1.43 | (0.97-2.11) | 0.07 | 1.68 | (1.05-2.67) | 0.03 | 0.98 | (0.45-2.13) | 0.96 |
| rs73227498 | 1.09 | (0.64-1.86) | 0.76 | 0.89 | (0.48-1.65) | 0.71 | 2.59 | (0.66-10.20) | 0.17 |
| rs2466076 | 1.39 | (0.97-1.98) | 0.07 | 1.56 | (1.07-2.27) | 0.02 | 0.99 | (0.42-2.34) | 0.96 |
| rs1588635 | 1.23 | (0.84-1.80) | 0.28 | 1.08 | (0.66-1.78) | 0.77 | 1.58 | (0.85-2.92) | 0.15 |
| rs7902587 | 1.03 | (0.53-1.99) | 0.94 | 1.47 | (0.73-2.98) | 0.28 | - |  | >.99 |
| rs368187 | 0.99 | (0.69-1.43) | 0.97 | 1.15 | (0.75-1.76) | 0.53 | 0.68 | (0.35-1.34) | 0.27 |
| rs116909374 | 2.37 | (1.09-5.19) | 0.03 | 2.50 | (0.96-6.50) | 0.06 | 1.93 | (0.43-8.66) | 0.39 |
| rs2289261 | 1.45 | (0.98-2.15) | 0.07 | 1.55 | (0.98-2.46) | 0.06 | 1.35 | (0.69-2.65) | 0.39 |
| rs56062135 | 1.04 | (0.67-1.60) | 0.86 | 1.08 | (0.62-1.88) | 0.79 | 0.93 | (0.50-1.75) | 0.83 |
| Abbreviations: SNP (single-nucleotide polymorphism), PRS (polygenic risk score), STC (subsequent thyroid cancer), SJLIFE (St. Jude Lifetime Cohort Study), RT (radiotherapy), and RR (relative rate) | | | | | | | | | |
| aAdjusted for age at diagnosis, attained age modeled by restricted cubic splines, sex, and the treatment group | | | | | | | | | |

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