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## Polygenic Risk Score Improves Risk Stratification and Prediction of Subsequent Thyroid Cancer after Childhood Cancer

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### Abstract

**Background:**—Subsequent thyroid cancer (STC) is one of the most common malignancies in childhood cancer survivors. We aimed to evaluate the polygenic contributions to STC risk and potential utility in improving risk prediction.

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**Data sharing statement:** The St. Jude Lifetime Cohort Study data are accessible through the St. Jude Cloud (<https://stjude.cloud>) through the link of cancer survivorship. The Childhood Cancer Survivor Study data are accessible through the dbGaP (<https://www.ncbi.nlm.nih.gov/gap/>) with the accession number: phs001327.v2.p1.

**Methods:** A polygenic risk score (PRS) was calculated from 12 independent single-nucleotide polymorphisms associated with thyroid cancer risk in the general population. Associations between PRS and STC risk were evaluated among survivors from St. Jude Lifetime Cohort (SJLIFE) and were replicated in survivors from Childhood Cancer Survivor Study (CCSS). A risk prediction model integrating the PRS and clinical factors, initially developed in SJLIFE, and its performance were validated in CCSS.

**Results:** Among 2,370 SJLIFE survivors with a median follow-up of 28.8 (interquartile range [IQR]=21.9–36.1) years, 65 (2.7%) developed STC. Among them, the standardized PRS was associated with an increased rate of STC (relative rate [RR]=1.57, 95% CI=1.24–1.98,  $p<0.001$ ). Similar associations were replicated in 6,416 CCSS survivors among whom 121 (1.9%) developed STC during median follow-up of 28.9 (IQR=22.6–34.6) years (RR=1.52, 95% CI=1.25–1.83,  $p<0.001$ ). A risk prediction model integrating the PRS with clinical factors showed better performance than the model considering only clinical factors in SJLIFE ( $p=0.004$ , AUC=83.2% vs. 82.1%, at age 40), which was further validated in CCSS ( $p=0.010$ , AUC=72.9% vs. 70.6%).

**Conclusions:** Integration of the PRS with clinical factors provided a statistically significant improvement in risk prediction of STC, although the magnitude of improvement was modest.

**Impact:** PRS improves risk stratification and prediction of STC, suggesting its potential utility for optimizing screening strategies in survivorship care.

## Keywords

Polygenic risk score; Subsequent thyroid cancer; Childhood cancer; Survivorship

## INTRODUCTION

Following the successful treatment of childhood cancer, survivors often experience subsequent malignancies requiring further therapy and clinical care. Of these, the most common endocrine malignancy observed in survivors of childhood cancer are subsequent thyroid cancers (STC),(1) which accounts for approximately 10% of all subsequent malignancies.(2) The predominant form of STC is differentiated thyroid cancer, which includes both papillary and follicular carcinoma.(3) Among childhood cancer survivors, occurrence of STC has been reported largely attributable to radiotherapy (RT) for childhood cancer that exposes the thyroid gland.(4) Importantly, STC occurrence also demonstrates a dose-related increase in risk that declines after 30Gy.(5) Therefore, periodic surveillance for thyroid cancer among childhood cancer survivors treated with neck-RT is highly recommended.(6) However, debate remains over the necessity and benefit of routine STC screening with ultrasonography versus routine palpation, considering STC's favorable prognosis as well as potential harms associated with discovery of benign thyroid nodules. In recently published consensus recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group and the PanCareSurFup Consortium, the expert panel found no evidence to support superiority of one screening modality over the other, and therefore recommended shared decision making between the health care provider and survivor to make this determination.(7) As such, both clinical practitioners and survivors of childhood cancer may benefit from methods to enhance precision in risk stratification and

individual risk prediction via the integration of genetic susceptibility of STC with clinical risk factors such as childhood cancer treatment exposures and doses.

Polygenic contributions to the risk of *de novo* thyroid cancer in the general population have been studied by genome-wide association studies (GWAS), resulting in the identification of 12 independent common risk alleles within populations of European ancestry (without known exposure to radiotherapy or chemotherapy).(8–13) Notably, the estimated effect sizes (i.e., per-allele odds ratios (ORs)) range between 1.20 and 1.81, which are relatively larger than most cancer GWAS findings. For example, the effect size for 172 common breast cancer risk loci ranges between 1.03 and 1.31.(14) This difference points to an allelic architecture of genetic susceptibility for thyroid cancer, involving a smaller number of risk loci, some of which may have higher estimated effect sizes as compared to other more common adult carcinomas (e.g., breast,(15) colon,(16) and prostate(17)).

We hypothesized that the polygenic risk score (PRS) based on all the common risk alleles, which were identified within the general population presumably without exposure to radiotherapy or chemotherapeutic agents for *de novo* thyroid cancer risk, could be informative for assessing the risk of STC among survivors of childhood cancer. In this study, we established a risk prediction model by integrating a PRS with commonly used clinical risk factors identified among survivors in the St. Jude Lifetime Cohort (SJLIFE).(18) We further validated our integrated prediction model within an independent cohort of survivors from Childhood Cancer Survivors Study (CCSS).(19)

## MATERIALS AND METHODS

### Study population and data collection

The SJLIFE study is a retrospective cohort study initiated in 2007 with prospective clinical follow-up and ongoing enrollment of 5-year survivors of all childhood cancer who were treated at St. Jude Children's Research Hospital (SJCRH) since its establishment in 1962.(18) Among 3,006 SJLIFE survivors with whole-genome sequencing (WGS) data as previously described(14), a total 2,370 survivors were available for further statistical analyses based on the exclusion criteria (Supplementary Methods, Supplementary Figure S1A). The demographic and clinical characteristics including treatment information were abstracted from the self-reported questionnaires and patients' medical records, respectively. Subsequent malignancies including STC were clinically ascertained. The current report of SJLIFE is based on follow-up through 2018. All SJLIFE study participants provided written informed consent. The SJLIFE study protocol was approved by the Institutional Review Board (IRB) at SJCRH.

For replication/validation of findings from SJLIFE, data from survivors in the CCSS cohort, a multicenter retrospective cohort study with prospective follow-up, was used.(19,20) A total of 6,416 (4,188 original + 2,228 expansion) CCSS cohort were available for analyses after the exclusions (Supplementary Methods, Supplementary Figure S1B). The demographic and clinical characteristics were obtained in CCSS from self- or proxy-reported questionnaires, death certificate, and medical records. Treatment data included all treatments received within the first five years following childhood cancer diagnosis. Subsequent malignancies

including STC were identified by self-reported questionnaires and subsequently confirmed by pathology reports. The CCSS survivors were followed up through 2019. The CCSS study participants provided the informed consent and the study protocol was approved by the IRB at each participating center.

### SNP extraction and PRS calculation

A total of 32 single-nucleotide polymorphism (SNP) associations with thyroid cancer risk in the general population were downloaded from NHGRI-EBI GWAS catalog on December 8<sup>th</sup>, 2019(21) (Supplementary Table S1), many of which are highly correlated. We subsequently excluded studies using individuals from non-European ancestry. If multiple studies have reported association findings for the same SNP or SNPs with strong pairwise linkage disequilibrium (LD,  $r^2 > 0.8$ ), estimates from the study with the largest sample size were used. A total of 12 SNPs (rs11693806, rs2466076, rs1588635, rs368187, rs116909374, rs12129938, rs6793295, rs73227498, rs7902587, rs2289261, and rs56062135) remained after curation. The PRS was calculated as a weighted sum of the number of risk alleles carried by an individual, in which their weights were taken as the natural logarithm of the estimated ORs of the corresponding loci, and then standardized as a z-score with a mean of 0 and a standard deviation (SD) of 1. To compare cumulative incidence curves for groups with different genetic risks, the PRS was categorized into tertiles (cutoffs: 2.73 and 3.33).

### Statistical analysis

The cumulative incidence of STC by age was estimated for SJLIFE and CCSS survivors in each tertile of the PRS. Death was considered as a competing risk event. Gray's method (22) was used to evaluate statistical significance of the differences in cumulative incidence curves across three tertiles. We employed the Fine and Gray proportional subdistribution hazards model (23) to construct a clinical base model encompassing demographic and treatment variables in the SJLIFE study (Supplementary Methods). 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). Then, the standardized PRS was added as a continuous independent variable to the final clinical model to formulate the full integrated model. The adjusted subdistribution hazard ratio was reported as relative rate (RR). The RR of STC by one SD increase in the PRS was estimated by the maximum likelihood method and its inference including 95% confidence intervals (CIs) and p-values were calculated using the standard large-sample inference methods. The analyses were also stratified by the neck-RT exposure status. In order to evaluate model-predicted lifetime risk, we estimated the cumulative incidence of STC at age of 20, 30, 40 and 50 years for each risk profile (n=192 profiles) comprised of the combinations of sex (2 categories), age-at-diagnosis (4), treatment combinations (8), and PRS tertiles (3). A replication analysis of the integrated model was conducted with the CCSS data using the integrated model from SJLIFE including the same definitions of variables and adjusting for the same set of covariates: the purpose of this replication analysis was to examine the consistency between SJLIFE and CCSS regarding the associations of the PRS with the STC rate.

To evaluate risk prediction performance of the SJLIFE models, we considered the final clinical model and the integrated model (the final clinical model plus the PRS) of SJLIFE

and validated in CCSS. We estimated time-dependent receiver operating characteristic (ROC) curves(24) and compared predictive power by time-specific area under the ROC curves (AUCs) and its weighted average, Harrell's Concordance (C) statistic(25), between the two models at ages of 40 and 50 years. Data analysis and visualization were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA) and R 3.5.1(26). All statistical tests were two-sided and  $p$ -value<0.05 was set as the threshold for statistical significance.

## RESULTS

### Characteristics of study populations

Among 2,370 SJLIFE survivors (median time from diagnosis: 28.8 years, interquartile range [IQR]: 21.9–36.1 years), 65 (2.7%) were subsequently diagnosed with thyroid cancer (Table 1). The median age at primary cancer diagnosis and follow-up was 7.1 years (IQR: 3.1–13.1 years) and 36.6 years (IQR: 30.3–44.1 years), respectively. A total of 1,265 (53.4%) were male. Childhood cancer diagnoses comprised leukemia (36.6%), central nervous system (CNS) tumors (10.5%), lymphoma (20.0%), sarcoma (12.9%), and non-CNS embryonal tumors (16.5%). For radiotherapy, 20.1% survivors received neck-RT. For chemotherapy potentially impacting STC risk, 58.3%, and 35.4% survivors were exposed to anthracyclines, and epipodophyllotoxins, respectively.

Among 6,416 CCSS survivors (median time from diagnosis: 28.9 years, IQR: 22.6–34.6), 121 (1.9%) survivors were subsequently diagnosed with thyroid cancer. The median age at primary cancer diagnosis was 7.5 years (IQR: 3.3–13.6 years) and the median follow-up was 36.5 years (IQR: 30.2–44.2 years). A total of 3,058 (47.7%) were male. Childhood cancer diagnoses comprised leukemia (26.7%), central nervous system (CNS) tumors (18.1%), lymphoma (21.4%), sarcoma (16.0%), and non-CNS embryonal tumors (17.3%). Regarding the treatment variables required for the replication analysis in the CCSS, 21.1%, 41.0% and 11.3% survivors were exposed to neck-RT, anthracyclines and epipodophyllotoxins, respectively.

We further tested the difference of several characteristics including age at diagnosis, sex, primary diagnosis, treatment exposures and treatment group between survivors included in the analysis versus those excluded (Supplementary Table S3). We found that primary diagnosis was significantly different ( $P<0.001$ ) in SJLIFE, whereas age at diagnosis, treatment exposures, and treatment group were significantly different ( $P<0.001$ ) in CCSS.

### Cumulative incidence of STC by neck-RT and PRS tertiles

The cumulative incidence curves of STC showed statistically significant differences by PRS tertiles among SJLIFE survivors ( $p=0.002$ , Figure 1A). Survivors with PRS in the third tertile had the highest cumulative incidence compared to survivors >25 years old with a PRS in the second or the first tertile. Among SJLIFE survivors (Supplementary Table S4), the cumulative incidence for those with PRS in the first, second and third tertiles were 0.4% (95% CI=0.0–0.9), 1.2% (95% CI=0.3–2.0), and 2.1% (95% CI=1.0–3.3) by age 30 years, 1.6% (95% CI=0.4–2.8), 2.8% (95% CI=1.3–4.2), 4.8% (95% CI=2.9–6.6), by age 40 years, and 2.7% (95% CI=0.8–4.5), 6.7% (95% CI=3.4–10.0), 8.1% (95% CI=5.0–11.2) by age 50

years, respectively. Among 65 SJLIFE survivors who developed STC, 9 had a PRS in the first tertile, 23 in the second tertile and 33 in the third tertile. When stratified by neck-RT, the cumulative incidence of STC showed statistically significant differences by neck-RT exposure among SJLIFE survivors ( $p<0.001$ , Supplementary Figure S2A, Supplementary Table S5). Furthermore, the cumulative incidence of STC differed across PRS tertiles in survivors exposed to neck-RT ( $p=0.013$ , Figure 1B) but not in survivors without neck-RT exposure ( $p=0.29$ , Figure 1C). The cumulative incidence was as high as 22.0% by age 50 years for SJLIFE survivors who were previously exposed to neck-RT and had PRS in the third tertile (Supplementary Table S4).

A similar pattern of cumulative incidence of STC by PRS tertiles was observed among CCSS survivors ( $p<0.001$ , Figure 2A). Among the CCSS survivors (Supplementary Table S4), the cumulative incidences of STC for survivors with PRS in the first, second and third tertiles were 0.3% (95% CI=0.0–0.5), 1.0% (95% CI=0.5–1.5), 1.4% (95% CI=0.8–1.9) by age 30 years, 1.4% (95% CI=0.8–2.0), 2.5% (95% CI=1.6–3.3), 3.5% (95% CI=2.5–4.5) by age 40 years, and 1.6% (95% CI=0.9–2.4), 3.5% (95% CI=2.2–4.9), 5.2% (95% CI=3.6–6.8) by age 50 years, respectively. Among 121 CCSS survivors who developed STC, 22 had a PRS in the first tertile, 40 in the second tertile and 59 in the third tertile. When stratified by neck-RT, the cumulative incidence of STC showed statistically significant differences by neck-RT exposure among CCSS survivors ( $p<0.001$ , Supplementary Figure S2B, Supplementary Table S5). Furthermore, statistically significant differences of cumulative incidence across the PRS tertiles were observed among survivors previously exposed to neck-RT ( $p=0.040$ , Figure 2B) and survivors not exposed to neck-RT ( $p<0.001$ , Figure 2C). CCSS survivors exposed to neck-RT showed a distinct pattern where survivors with a PRS in the second tertile had the highest incidence before age 35 years but survivors with a PRS in the third tertile became the highest incidence group after age 35 years. The cumulative incidence was as high as 10.0% by age 50 years for CCSS survivors who were previously exposed to neck-RT and had a PRS in the third tertile (Supplementary Table S4).

In addition, we calculated the model-predicted lifetime risk (cumulative incidence) of STC at age of 20, 30, 40 and 50 years for each risk profile ( $n=192$  profiles). (Supplementary Table S6).

### Association of the PRS with STC risk

The base clinical model with the treatment groups and other clinical characteristics was built with the SJLIFE data (Supplementary Table S2). The base clinical model was validated in CCSS (Supplementary Table S7). We assessed whether the PRS based on the 12 SNPs was associated with the risk of developing STC among childhood cancer survivors (Table 2). In SJLIFE, the PRS was statistically significantly associated with an increased rate of STC among all survivors (RR=1.57, 95% CI=1.24–1.98,  $p<0.001$ ) and among survivors with prior neck-RT exposure (RR=1.68, 95% CI=1.29–2.18,  $p<0.001$ ). However, no significant association was observed among survivors with no prior neck-RT exposure. The associations between the PRS and STC rates were replicated in CCSS overall (RR=1.52, 95% CI=1.25–

1.83,  $p<0.001$ ), survivors with neck-RT (RR=1.42, 95% CI=1.09–1.85,  $p=0.009$ ) and survivors without prior neck-RT (RR=1.66, 95% CI=1.26–2.20,  $p<0.001$ ) (Table 3).

### Evaluation of a risk prediction model of STC with the PRS included

We first compared two risk prediction models of STC: a base clinical model considering the treatment groups and other clinical characteristics and an integrated model additionally including the PRS (Table 4). In the SJLIFE survivors, the integrated model with the PRS performed better than the base clinical model at age of 40 years ( $C$ -statistic=84.2%, AUC=0.83 vs.  $C$ -statistic=82.8%, AUC=0.82,  $p=0.004$ ) and at age of 50 years ( $C$ -statistic=83.4%, AUC=0.82 vs.  $C$ -statistic=82.1%, AUC=0.81,  $p=0.022$ ). The CCSS replication data showed better performance of the integrated model with the PRS than the base clinical model at age of 40 years ( $C$ -statistic=73.0%, AUC=0.73 vs.  $C$ -statistic=70.7%, AUC=0.71,  $p=0.010$ ) and age of 50 years ( $C$ -statistic=72.7%, AUC=0.72 vs.  $C$ -statistic=70.5%, AUC=0.69,  $p=0.006$ ).

## DISCUSSION

Implementation of precision care that focuses surveillance and interventions on populations at high risk of adverse outcomes represents a priority among multidisciplinary health care professionals monitoring childhood cancer survivors. Our study demonstrates that the PRS constructed from thyroid cancer associated genetic variants established in the general population can effectively identify survivors with high STC risk, although the risk prediction model integrating the PRS with cancer treatment risk factors only provided a marginal improvement over risk prediction of STC utilizing a clinical model that includes cancer therapy exposures. Nonetheless, these findings, which were validated in an independent cohort of childhood cancer survivors, provide a basis for future addition of newly discovered thyroid cancer risk loci that could eventually be useful for identifying individuals at the highest and lowest risk for STC and inform future discussions regarding risk-based surveillance strategies.

In the current study, it is evident that the PRS can stratify survivors with different STC risk levels as observed in the distinct cumulative incidence curves corresponding to PRS tertiles, in both SJLIFE and CCSS. The magnitude of differences in cumulative incidence is substantial. For instance, by age of 40 years, SJLIFE survivors with a PRS in the third tertile had a 6-fold increased STC rate compared to survivors with a PRS in the first tertile suggesting that survivors with a PRS in the third tertile may benefit more from a recommendation of imaging screening to facilitate early diagnosis. The rate of STC increased by 1.5-fold per standard deviation change of the PRS after adjusting for other clinical risk factors. The effect sizes for the PRS differed little between survivors with and without radiation exposure to neck. Moreover, we found the prediction model integrating the PRS with clinical risk factors had small but statistically significant improvement of accuracy in predicting STC risk over the model considering only clinical risk factors across the entire age range in SJLIFE. The improved performance was further validated using CCSS study.

Clinically, if we follow the surveillance guideline for carriers of pathogenic/likely pathogenic germline variants in *PTEN* gene(27–29), using a 35% lifetime risk as the

threshold for recommendation of ultrasonography surveillance (USS) for STC may be reasonable. To illustrate the value of considering PRS, take male survivors at age of 50 years (Supplementary Table S6D) as an example: for those diagnosed between 0 and 4 years and treated with Neck RT <20 Gy plus epipodophyllotoxin, considering PRS would exclude approximately one-third of survivors who would have met criteria for USS without the additional consideration of the PRS; for those diagnosed between 0 and 4 years and treated with Neck RT between 20 and 30 Gy plus epipodophyllotoxin, considering PRS would exclude approximately two-thirds from USS; for those diagnosed between 10 and 14 years and treated with Neck RT <30 Gy plus epipodophyllotoxin, considering PRS would exclude approximately one-third from USS; for those diagnosed 15 years old and treated with Neck RT < 20 Gy plus epipodophyllotoxin, considering PRS would include an additional one-third for USS.

We previously showed that the PRS based on established breast cancer risk loci identified from the general population (i.e., by comparing *de novo* breast cancer cases vs. non-cancer controls) was associated with risk of subsequent breast cancer among survivors of childhood cancer.(14) Our current study further generalizes this paradigm by demonstrating that the PRS based on the 12 SNPs previously discovered by thyroid cancer GWAS studies could inform STC risk in survivors of childhood cancer. Notably, the effect of each of the 12 SNPs was attenuated towards null when analyzing the STC among survivors of childhood cancer, possibly due to the strong effects of prior cancer treatment and different host genetics (Supplementary Table S8). A methodological study evaluating the generalizability of GWAS findings among childhood cancer survivors suggested that cancer treatments, including chemotherapy and RT, produce persistent changes on the methylome affecting methylation levels of CpG sites near disease/trait-associated genes and alter the expression of underlying genes or expressivity of risk alleles(30). However, despite the attenuated effect size observed in each SNP for STC risk in survivors of childhood cancer, joint contributions of all 12 SNPs in the PRS were still useful in risk stratification and prediction.

In general population case-control samples from UK Biobank, Liyanarachchi *et al.* reported that the top decile (91–100%) of the PRS, built by 10 SNPs identified from previous GWAS, conferred a 6.9-fold higher risk of thyroid cancer compared to the bottom decile (0–10%), and adding the 10-SNP PRS to the model significantly improved predictive ability with AUC of 0.69–0.75(31). There are few studies to evaluate the polygenic contributions for subsequent malignancies among survivors of childhood cancer(14,32) and one study for clinical prediction model, specifically for STC.(33) Our risk prediction model integrating the PRS, generated by the 12-GWAS SNPs, with the treatment exposure groups, improved the performance with AUC of 0.72–0.83, which was slightly better than the previously reported clinical model with AUC of 0.71–0.80.(33)

This study has several limitations. First, even though we included all survivors five or more years from the completion of primary diagnoses, they are still relatively young, with a median attained age of 36.6 years in SJLIFE and 36.5 years in CCSS. The young age of our cohorts is especially pertinent considering that thyroid cancer incidence increases with age in the general population and is most prevalent in the 65-to-74 age group.(34) Hence, longer follow-up is warranted to comprehensively evaluate the effect of the PRS



on STC. Second, we did not have neck-RT dose for everyone, and we did not consider low dose scattering from nearby radiation fields. Third, since the study population was restricted to survivors of European ancestry, further validation in other race/ethnic groups is needed. We compared the difference of STC incidence between CEU survivors (i.e., survivors of European ancestry) (N=2,370 SJLIFE and 6,416 CCSS) and non-CEU survivors (i.e., survivors of other or mixed ancestries) excluded from the analysis (N=546 SJLIFE and 707). In SJLIFE, 65 of 2,370 CEU survivors (2.7%) and 4 of 546 non-CEU survivors (0.7%) developed STC and CEU survivors had 3.2-fold increased risk for STC than non-CEU survivors (RR=3.2, 95% CI=1.2–8.9,  $p=0.02$ ) in multivariable analysis adjusted for age at diagnosis, attained age, and sex, and 2.7-fold increased risk when additionally adjusted for treatment group (RR=2.7, 95% CI=1.0–7.4,  $p=0.06$ ). In CCSS, 121 of 6,416 CEU survivors (1.9%) and 8 of 707 non-CEU survivors (1.1%) developed STC but this was not statistically significant ( $p=0.34$ ). Because non-CEU survivors represent a mixed population and a relatively small proportion of STC incidence, we had insufficient statistical power, to include non-CEU population in this analysis. Lastly, heterogeneity exists between SJLIFE, the discovery study, and CCSS, the replication study. It is notable that the incidence of STC is lower in CCSS than SJLIFE (especially among survivors with prior neck-RT exposure), potentially due to under reporting in CCSS, which relies on self-report and subsequent confirmation by pathology report. Nevertheless, our study is the largest ( $N_{\text{total}}=8,786$ ) and the first to study the polygenic contributions to STC risk among childhood cancer survivors.

In summary, this study demonstrates that the PRS, generated from thyroid cancer risk loci identified in the general population, can further enhance STC risk stratification among childhood cancer survivors, beyond cancer-treatment factors. As more clinical indicators and new thyroid cancer-related loci are identified, we anticipate that findings from research like ours will enable more precise identification of survivors at highest and lowest risk for STC, and thus, begin to inform development of personalized surveillance strategies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data and materials availability:

Z.W. and Y.Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Abbreviation list

AUCs	Area under the ROC curves
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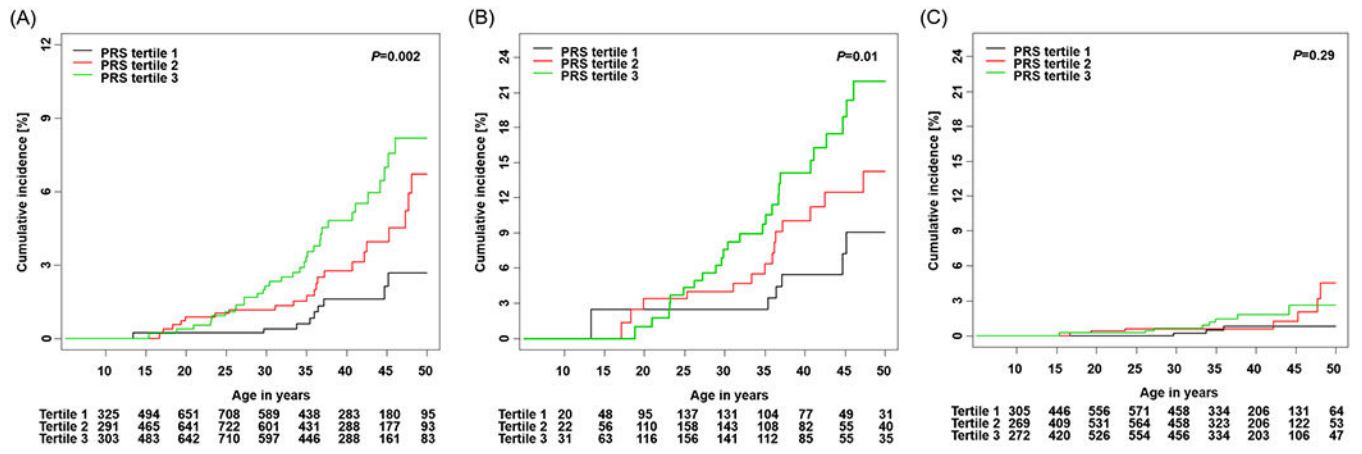
<b>CCSS</b>	Childhood Cancer Survivor Study
<b>C</b>	Concordance
<b>CI</b> s	Confidence intervals
<b>GWAS</b>	Genome-wide association studies
<b>IQR</b>	Interquartile range
<b>LD</b>	Linkage disequilibrium
<b>OR</b> s	Odds ratios
<b>PRS</b>	Polygenic risk score
<b>RT</b>	Radiotherapy/radiation therapy
<b>ROC</b>	Receiver operating characteristic
<b>RR</b>	Relative rate
<b>SNP</b>	Single-nucleotide polymorphism
<b>SD</b>	Standard deviation
<b>SJCRH</b>	St. Jude Children's Research Hospital
<b>SJLIFE</b>	St. Jude Lifetime Cohort
<b>STC</b>	Subsequent thyroid cancer
<b>USS</b>	Ultrasonography surveillance
<b>WGS</b>	Whole-genome sequencing

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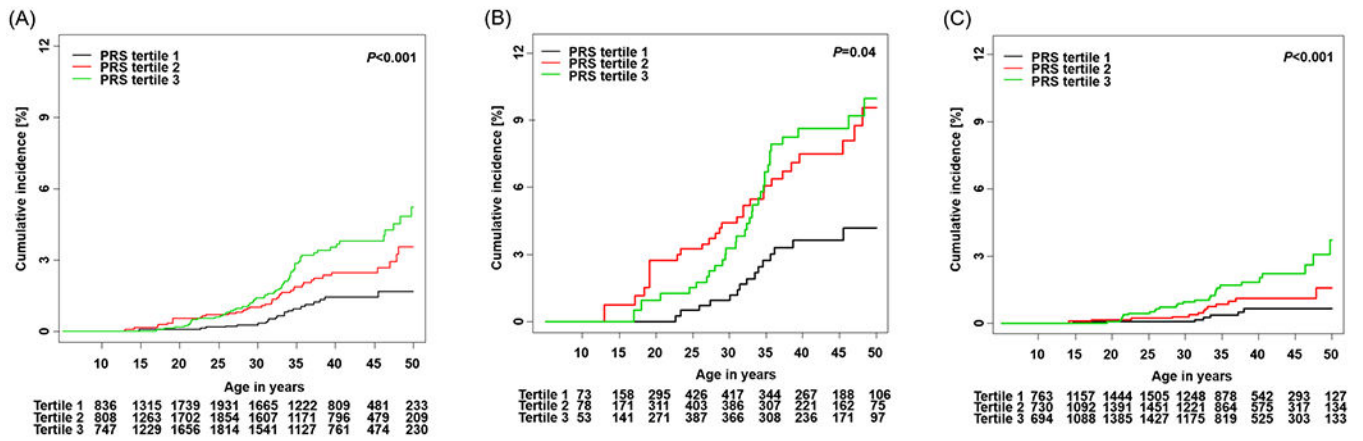
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**Figure 1.** Cumulative incidence of STC by PRS tertiles in SJLIFE. (A) Overall survivors (B) Survivors with neck-RT (C) Survivors without neck-RT



**Figure 2.**

Cumulative incidence of STC by PRS tertiles in CCSS. (A) Overall survivors (B) Survivors with neck-RT (C) Survivors without neck-RT

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

**Table 1.**

Demographics and treatment characteristics in SJLIFE and CCSS

Characteristics	SJLIFE						CCSS					
	Total (N=2,370, 100%)		Survivors with STC (N=65, 2.7%)		Survivors without STC (N=2,305, 97.3%)		Total (N=6,416, 100%)		Survivors with STC (N=121, 1.9%)		Survivors without STC (N=6,295, 98.1%)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age at diagnosis, years												
0-4	922	(38.9%)	19	(29.2%)	903	(39.2%)	2,391	(37.3%)	30	(24.8%)	2,361	(37.5%)
5-9	538	(22.7%)	5	(7.7%)	533	(23.1%)	1,423	(22.2%)	21	(17.4%)	1,402	(22.3%)
10-14	532	(22.4%)	25	(38.5%)	507	(22.0%)	1,440	(22.4%)	47	(38.8%)	1,393	(22.1%)
15	378	(15.9%)	16	(24.6%)	362	(15.7%)	1,162	(18.1%)	23	(19.0%)	1,139	(18.1%)
Sex												
Men	1,265	(53.4%)	27	(41.5%)	1,238	(53.7%)	3,058	(47.7%)	41	(33.9%)	3,017	(47.9%)
Women	1,105	(46.6%)	38	(58.5%)	1,067	(46.3%)	3,358	(52.3%)	80	(66.1%)	3,278	(52.1%)
Diagnosis												
Leukemia	868	(36.6%)	19	(29.2%)	849	(36.8%)	1,713	(26.7%)	25	(20.7%)	1,688	(26.8%)
Acute lymphoblastic leukemia	802	(33.8%)	16	(24.6%)	786	(34.1%)	1,536	(23.9%)	21	(17.4%)	1,515	(24.1%)
Acute myeloid leukemia	63	(2.7%)	3	(4.6%)	60	(2.6%)	144	(2.2%)	1	(0.8%)	143	(2.3%)
Other leukemia	3	(0.1%)	-	(0.0%)	3	(0.1%)	33	(0.5%)	3	(2.5%)	30	(0.5%)
CNS tumors	249	(10.5%)	5	(7.7%)	244	(10.6%)	1,160	(18.1%)	19	(15.7%)	1,141	(18.1%)
Astrocytoma or glioma	123	(5.2%)	-	(0.0%)	123	(5.3%)	720	(11.2%)	5	(4.1%)	715	(11.4%)
Medulloblastoma or PNET	62	(2.6%)	4	(6.2%)	58	(2.5%)	271	(4.2%)	8	(6.6%)	263	(4.2%)
Ependymoma	25	(1.1%)	1	(1.5%)	24	(1.0%)						
Other CNS tumors	39	(1.6%)	-	(0.0%)	39	(1.7%)	169	(2.6%)	6	(5.0%)	163	(2.6%)
Lymphoma	474	(20.0%)	32	(49.2%)	442	(19.2%)	1,373	(21.4%)	43	(35.5%)	1,330	(21.1%)
Hodgkin lymphoma	289	(12.2%)	30	(46.2%)	259	(11.2%)	849	(13.2%)	38	(31.4%)	811	(12.9%)
Non-Hodgkin lymphoma	185	(7.8%)	2	(3.1%)	183	(7.9%)	524	(8.2%)	5	(4.1%)	519	(8.2%)
Sarcoma	306	(12.9%)	3	(4.6%)	303	(13.1%)	1,028	(16.0%)	20	(16.5%)	1,008	(16.0%)
Ewing sarcoma	84	(3.5%)	2	(3.1%)	82	(3.6%)	194	(3.0%)	5	(4.1%)	189	(3.0%)
Osteosarcoma	82	(3.5%)	-	(0.0%)	82	(3.6%)	314	(4.9%)	10	(8.3%)	304	(4.8%)

Characteristics	SJLIFE						CCSS					
	Total (N=2,370, 100%)		Survivors with STC (N=65, 2.7%)		Survivors without STC (N=2,305, 97.3%)		Total (N=6,416, 100%)		Survivors with STC (N=121, 1.9%)		Survivors without STC (N=6,295, 98.1%)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Rhabdomyosarcoma	76	(3.2%)	1	(1.5%)	75	(3.3%)						
Non-rhabdomyosarcoma	64	(2.7%)	-	(0.0%)	64	(2.8%)						
Soft tissue sarcoma												
Non-CNS Embryonal	401	(16.5%)	5	(7.7%)	396	(16.8%)	520	(8.1%)	5	(4.1%)	515	(8.2%)
Wilms tumor	152	(6.4%)	1	(1.5%)	151	(6.6%)	1108	(17.3%)	12	(9.9%)	1096	(17.4%)
Neuroblastoma	119	(5.0%)	1	(1.5%)	118	(5.1%)	621	(9.7%)	5	(4.1%)	616	(9.8%)
Germ cell tumor	45	(1.9%)	1	(1.5%)	44	(1.9%)	487	(7.6%)	7	(5.8%)	480	(7.6%)
Retinoblastoma	66	(2.8%)	2	(3.1%)	64	(2.8%)						
Hepatoblastoma	16	(0.7%)	-	(0.0%)	16	(0.7%)						
Others												
Melanoma	15	(0.6%)	-	(0.0%)	15	(0.7%)						
Carcinomas	26	(1.1%)	-	(0.0%)	26	(1.1%)						
Other	34	(1.4%)	1	(1.5%)	33	(1.4%)	34	(0.5%)	2	(1.7%)	32	(0.5%)
Radiation therapy												
Neck-RT dose, Gy												
None	1,894	(79.9%)	18	(27.7%)	1,876	(81.4%)	5,062	(78.9%)	48	(39.7%)	5,014	(79.7%)
>0-<20	59	(2.5%)	6	(9.2%)	53	(2.3%)	175	(2.7%)	9	(7.4%)	166	(2.6%)
20-<30	247	(10.4%)	31	(47.7%)	216	(9.4%)	397	(6.2%)	28	(23.1%)	369	(5.9%)
30	170	(7.2%)	10	(15.4%)	160	(6.9%)	802	(12.5%)	36	(29.8%)	766	(12.2%)
Chemotherapy												
Anthracycline dose, tertiles												
None	988	(41.7%)	30	(46.2%)	958	(41.6%)	3,784	(59.0%)	72	(59.5%)	3,712	(59.0%)
1st tertile	464	(19.6%)	2	(3.1%)	462	(20.0%)	361	(5.6%)	5	(4.1%)	356	(5.7%)
2nd tertile	456	(19.2%)	19	(29.2%)	437	(19.0%)	937	(14.6%)	13	(10.7%)	924	(14.7%)
3rd tertile	462	(19.5%)	14	(21.5%)	448	(19.4%)	1,334	(20.8%)	31	(25.6%)	1,303	(20.7%)
Epidodophy/lotoxin dose, tertiles												
None	1,532	(64.6%)	43	(66.2%)	1,489	(64.6%)	5,693	(88.7%)	112	(92.6%)	5,581	(88.7%)
1st tertile	271	(11.4%)	10	(15.4%)	261	(11.3%)	269	(4.2%)	2	(1.7%)	267	(4.2%)



Characteristics	SJLIFE						CCSS					
	Total (N=2,370, 100%)		Survivors with STC (N=65, 2.7%)		Survivors without STC (N=2,305, 97.3%)		Total (N=6,416, 100%)		Survivors with STC (N=121, 1.9%)		Survivors without STC (N=6,295, 98.1%)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
2nd tertile	282	(11.9%)	6	(9.2%)	276	(12.0%)	342	(5.3%)	6	(5.0%)	336	(5.3%)
3rd tertile	285	(12.0%)	6	(9.2%)	279	(12.1%)	76	(1.2%)	1	(0.8%)	75	(1.2%)
Treatment group												
Epipodophyllotoxin & Anthracycline 2-3 tertiles without neck-RT	247	(10.2%)	7	(10.8%)	240	(10.2%)	392	(6.1%)	5	(4.1%)	387	(6.1%)
Neck-RT >0-<20 Gy without Epipodophyllotoxin	39	(1.6%)	3	(4.6%)	36	(1.5%)	132	(2.1%)	7	(5.8%)	125	(2.0%)
Neck-RT 20-<30 Gy without Epipodophyllotoxin	294	(12.1%)	22	(33.8%)	172	(7.3%)	360	(5.6%)	27	(22.3%)	333	(5.3%)
Neck-RT 30 Gy without Epipodophyllotoxin	135	(5.6%)	8	(12.3%)	127	(5.4%)	741	(11.5%)	36	(29.8%)	705	(11.2%)
Neck-RT >0-<20 Gy with Epipodophyllotoxin	20	(0.8%)	3	(4.6%)	17	(0.7%)	43	(0.7%)	2	(1.7%)	41	(0.7%)
Neck-RT 20-<30 Gy with Epipodophyllotoxin	53	(2.2%)	9	(13.8%)	44	(1.9%)	37	(0.6%)	1	(0.8%)	36	(0.6%)
Neck-RT 30 Gy with Epipodophyllotoxin	35	(1.4%)	2	(3.1%)	33	(1.4%)	41	(0.6%)	-	(0.0%)	41	(0.7%)
PRS												
None of the above	1,647	(67.9%)	11	(16.9%)	1,636	(69.3%)	4,670	(72.8%)	43	(35.5%)	4,627	(73.5%)
1st tertile	791	(33.4%)	9	(13.8%)	782	(33.9%)	2,201	(34.3%)	22	(18.2%)	2,179	(34.6%)
2nd tertile	789	(33.3%)	23	(35.4%)	766	(33.2%)	2,132	(33.2%)	40	(33.1%)	2,092	(33.2%)
3rd tertile	790	(33.3%)	33	(50.8%)	757	(32.8%)	2,083	(32.5%)	59	(48.8%)	2,024	(32.2%)
	Median	(IQR)	Median	(IQR)	Median	(IQR)	Median	(IQR)	Median	(IQR)	Median	(IQR)
Age at diagnosis, years	7.1	(3.1-13.1)	12.0	(4.2-14.9)	6.9	(3.1-13.1)	7.5	(3.3-13.6)	11.1	(5.0-14.3)	7.4	(3.2-13.6)
Age at follow-up, years	36.6	(30.3-44.1)	42.2	(37.7-48.6)	36.5	(30.1-43.9)	36.5	(30.2-44.2)	42.6	(36.7-49.3)	36.4	(30.1-44.1)
Length of follow-up, years	28.8	(21.9-36.1)	31.6	(26.7-37.9)	28.8	(21.9-36.1)	28.9	(22.6-34.6)	32.5	(25.7-38.4)	28.8	(22.5-34.5)

Abbreviations: SJLIFE (St. Jude Lifetime cohort study), CCSS (Childhood Cancer Survivor Study), STC (subsequent thyroid cancer), CNS (central nervous system), PNET (primitive neuroectodermal tumor), RT (radiotherapy), PRS (polygenic risk score), IQR (interquartile range)

**Table 2.**

Multivariable model fits for STC rates in association with the standardized PRS and clinical risk factors in SJLIFE.<sup>a</sup>

Characteristics	Overall survivors			Survivors with neck-RT			Survivors without neck-RT		
	RR	(95% CI)	P	RR	(95% CI)	P	RR	(95% CI)	P
Age at diagnosis, years									
0-4	1.00	(Ref.)		1.00	(Ref.)		1.00	(Ref.)	
5-9	0.28	(0.10-0.78)	0.015	0.26	(0.07-1.03)	0.06	0.33	(0.07-1.50)	0.15
10-14	1.20	(0.64-2.23)	0.58	1.46	(0.64-3.34)	0.37	0.67	(0.21-2.09)	0.49
15	0.61	(0.31-1.20)	0.15	0.74	(0.32-1.71)	0.49	0.47	(0.12-1.82)	0.28
Sex									
Men	1.00	(Ref.)		1.00	(Ref.)		1.00	(Ref.)	
Women	1.50	(0.89-2.53)	0.13	1.17	(0.63-2.17)	0.62	2.97	(1.05-8.39)	0.039
Treatment group									
Anthracycline dose in the 2-3 tertiles with Epipodophyllotoxin without neck-RT									
Neck-RT >0-<20 Gy without Epipodophyllotoxin	4.81	(1.83-12.65)	0.001	-	-		5.23	(1.82-15.03)	0.002
Neck-RT 20-<30 Gy without Epipodophyllotoxin	7.25	(2.08-25.32)	0.002	1.00	(Ref.)		-	-	
Neck-RT 30 Gy without Epipodophyllotoxin	14.55	(7.03-30.09)	<0.001	1.95	(0.60-6.36)	0.27	-	-	
Neck-RT >0-<20 Gy with Epipodophyllotoxin	5.61	(2.14-14.74)	<0.001	0.73	(0.19-2.76)	0.65	-	-	
Neck-RT 20-<30 Gy with Epipodophyllotoxin	35.94	(10.20-126.56)	<0.001	4.52	(0.94-21.76)	0.06	-	-	
Neck-RT 30 Gy with Epipodophyllotoxin	28.50	(11.19-72.60)	<0.001	3.56	(0.96-13.19)	0.06	-	-	
None of the above	13.32	(2.96-60.01)	<0.001	1.72	(0.29-10.13)	0.55	-	-	
Standardized PRS <sup>b</sup> , continuous (per one standard deviation)	1.00	(Ref.)		1.68	(1.29-2.18)	<0.001	1.36	(0.85-2.15)	0.24

Abbreviations: PRS (polygenic risk score), STC (subsequent thyroid cancer), RT (radiotherapy), RR (relative rate), and SJLIFE (St. Jude Lifetime Cohort Study).

<sup>a</sup> Adjusted for attained age modeled by restricted cubic splines.

<sup>b</sup> Standardized PRS was calculated as a weighted sum of the number of risk alleles carried by survivors and standardized by a mean of 0 and a SD of 1.

**Table 3.**

Multivariable model fits for STC rates in association with the standardized PRS and clinical risk factors in CCSS<sup>a</sup>

Characteristics	Overall survivors			Survivors with neck-RT			Survivors without neck-RT		
	RR	(95% CI)	P	RR	(95% CI)	P	RR	(95% CI)	P
Age at diagnosis, years									
0-4	1.00	(Ref.)		1.00	(Ref.)		1.00	(Ref.)	
5-9	0.70	(0.40-1.23)	0.21	0.83	(0.40-1.91)	0.65	0.46	(0.18-1.17)	0.10
10-14	0.92	(0.56-1.50)	0.74	0.90	(0.46-1.86)	0.77	0.79	(0.35-1.77)	0.57
15	0.40	(0.21-0.75)	0.004	0.25	(0.10-0.61)	<0.001	0.82	(0.36-1.89)	0.65
Sex									
Men	1.00	(Ref.)		1.00	(Ref.)		1.00	(Ref.)	
Women	1.69	(1.15-2.47)	0.007	1.51	(0.93-2.45)	0.10	2.17	(1.17-4.05)	0.015
Treatment group									
Anthracycline 2-3 tertiles without neck-RT	2.21	(0.88-5.57)	0.09	-			2.19	(0.87-5.54)	0.10
Neck-RT >0-<20 Gy without Epipodophyllotoxin	5.04	(2.25-11.28)	<0.001	1.00	(Ref.)		-		
Neck-RT 20-<30 Gy without Epipodophyllotoxin	8.07	(4.84-13.47)	<0.001	1.66	(0.72-3.83)	0.23	-		
Neck-RT 30 Gy without Epipodophyllotoxin	4.49	(2.68-7.52)	<0.001	1.03	(0.45-2.36)	0.94	-		
Neck-RT >0-<20 Gy with Epipodophyllotoxin	8.76	(2.14-35.88)	0.003	1.77	(0.36-8.73)	0.48	-		
Neck-RT 20-<30 Gy with Epipodophyllotoxin	3.76	(0.51-27.47)	0.19	0.81	(0.10-6.72)	0.85	-		
Neck-RT 30 Gy with Epipodophyllotoxin	-			-			-		
None of the above	1.00	(Ref.)					1.00	(Ref.)	
Standardized PRS <sup>b</sup> , continuous (per one standard deviation)	1.52	(1.25-1.83)	<0.001	1.42	(1.09-1.85)	0.009	1.66	(1.26-2.20)	<0.001

Abbreviations: PRS (polygenic risk score), STC (subsequent thyroid cancer), RT (radiotherapy), RR (relative rate), and CCSS (Childhood Cancer Survivor Study)

<sup>a</sup> Adjusted for attained age modeled by restricted cubic splines

<sup>b</sup> Standardized PRS was calculated as a weighted sum of the number of risk alleles carried by survivors and standardized by a mean of 0 and a SD of 1

Comparison of risk prediction models for STC between the base clinical model and the integrated model including the PRS

**Table 4.**

	SJLIFE discovery			CCSS replication <sup>c</sup>		
	Clinical model <sup>a</sup>	Integrated model <sup>b</sup>	P	Clinical model <sup>a</sup>	Integrated model <sup>b</sup>	P
Age at 40 years			0.004			0.010
C-statistic	82.8%	84.2%		70.7%	73.0%	
AUC	0.82	0.83		0.71	0.73	
Age at 50 years			0.022			0.006
C-statistic	82.1%	83.4%		70.5%	72.7%	
AUC	0.81	0.82		0.69	0.72	

Abbreviations: STC (subsequent thyroid cancer), PRS (polygenic risk score), SJLIFE (St. Jude Lifetime Cohort Study), CCSS (Childhood Cancer Survivor Study), and AUC (area under curve)

<sup>a</sup>The base clinical model included age at diagnosis, attained age modeled by restricted cubic splines, sex, and combined treatment group

<sup>b</sup>The integrated model included PRS on top of the clinical model

<sup>c</sup>The CCSS replication analysis used the exact same model as SJLIFE discovery including the regression coefficients and variable definitions