Absolute risk prediction of second primary thyroid cancer among 5-year survivors of childhood cancer

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Abstract

Background: Survivors of a childhood cancer are at an elevated risk of developing thyroid cancer but their absolute risk of second primary thyroid cancer (SPTC) has not been quantified.

Methods: Using data from the Childhood Cancer Survivor Study (CCSS) and two nested case-control studies (Nordic CCSS; Late Effects Study Group), we developed three models to predict the absolute risk of SPTC in 5-year survivors of a childhood cancer: model M1 included self-reported risk factors only, model M2 added basic information about radiation and chemotherapy treatment obtained from medical records, and model M3 refined M2 by incorporating reconstructed dose of radiation to the thyroid gland. We assessed model performance in an independent cohort of French childhood cancer survivors.

Results: Selected predictive factors for M1 were birth year, age at diagnosis, gender, initial cancer type, and past thyroid nodule diagnosis. Treatment risk factors added to M2 were any radiation, radiation neck field, and any alkylating agent. For each model, prior thyroid nodule was the strongest risk factor (M1 RR = 11.9, M2 RR = 7.4, M3 RR = 8.6).

All models were well calibrated but models with treatment information (M2, M3) better discriminated cases from non-cases (M1 area under the curve (AUC) = 0.67 95% confidence interval (CI) = 0.61 to 0.74; M2 0.79 95% CI = 0.73 to 0.86; M3 0.77 95% CI = 0.70 to 0.83). M2 also provided the greatest separation in risk between cases and non-cases.

Conclusions: An absolute risk model for SPTC with basic information about prior treatment well differentiated low- from high-risk childhood cancer survivors.

Introduction

The incidence of childhood cancers in developed nations has been increasing at a modest but consistent rate (1). Owing to therapeutic advances, this rise in the pediatric cancer rate has coincided with a significant decline in mortality. More than 80% of five-year survivors of a childhood cancer who were diagnosed after 1970 are expected to be alive 30 years after the childhood cancer (2). Despite its short-term benefit for overall survival, the treatment for childhood cancers can have adverse late effects on the health of long-term survivors (3). Epidemiological studies have consistently shown that, in comparison to the general population, childhood cancer survivors have a higher risk of experiencing a fatal cardiac or pulmonary event, and are at a greater risk of developing a new primary malignancy (4-6).

Approximately 10% of subsequent primary malignancies among childhood cancer survivors are cancers of the thyroid gland (7). The excess risk of thyroid cancer is largely attributable to prior radiation therapy and the radiosensitivity of the thyroid gland. Studies of the radiation dose-response relationship have established that the risk of second primary thyroid cancer persists throughout adult life and is highest for those whose prior radiation therapy resulted in 15-30 Gray (Gy) of absorbed dose to the thyroid (8-9).

Previous studies of second primary thyroid cancer (SPTC) among childhood cancer survivors have focused on overall incidence (10-11), excess risk (7-8), and measures of relative risk (12-18). No study has yet quantified the absolute risk of SPTC. Absolute risk is the probability that an individual with a specific risk profile will develop disease by a given age in the presence of competing events (19). Absolute risk can most directly inform clinical decision-making and individual risk counseling, which makes it of primary importance to clinicians and patients (20). To be practically useful, however, a risk prediction tool should also be easy to administer in clinical settings. Prediction tools that have been established for breast cancer and

cardiovascular disease demonstrate the broad impact a validated absolute risk model can have on clinical practice (21-23).

Risk prediction for SPTC could be valuable because thyroid cancer is highly treatable yet current screening methods are known to result in many false-positives (24). False detection is of particular concern for survivors of childhood cancer who might be subject to more heightened monitoring than persons in the general population. To reduce unnecessary diagnostic procedures, there is a need for risk-tailored monitoring. Although the recommendation of the Children's Oncology Group is a yearly thyroid exam for all radiation-exposed childhood cancer survivors, the panel recognizes that the risk among these individuals is heterogeneous (25-26). An absolute risk model could be used to characterize this heterogeneity and, thereby, assist clinicians in appropriately matching the intensity of thyroid cancer screening to a patient's individual risk.

In this paper, we report the first absolute risk prediction models for SPTC in 5-year survivors of a childhood cancer. As it may not always be possible to obtain complete details about childhood treatment, we developed three models: one model included self-reported risk factors only, a second model included risk factors from self-report and medical record abstraction, and the third model considered all available risk information, including a computationally reconstructed radiation dose to the thyroid gland. With each model, the calculation of absolute risk involved the estimation of the relative risks of key predictors and the baseline incidence for both SPTC and competing events (thyroid removal, other second cancer, and death) in a dataset that combined outcomes of 5-year childhood cancer survivors from one large prospective cohort and two case-control studies. We validated each model in an independent cohort of childhood cancer survivors and compared their performance in correctly identifying low- and high-risk individuals.

Methods

Study populations. For model development, we combined data from a large ongoing cohort, the Childhood Cancer Survivor Study (CCSS) (27-28), and two case-control studies, the Late Effects Study Group (LESG) (14) and the Nordic Childhood Cancer Survivor Study (Nordic) (10, 29). CCSS participants are five-year survivors of childhood cancer treated between 1970 and 1986 at 26 medical centers in the United States and Canada, followed up to January 1, 2010 for the present analysis. LESG was a case-control study nested within a cohort of 9170 two-year survivors treated before age 18 between 1936 and 1979 at 13 US medical centers. Nordic was a nested case-control study of survivors diagnosed between 1960 and 1981, who were identified through national cancer registries of Denmark, Finland, Iceland, Norway, and Sweden. Subjects were eligible for inclusion in the study analysis if they were 1) alive and at-risk of developing SPTC 5 years after the childhood cancer diagnosis and 2) had a reconstructed dose of radiation absorbed by the thyroid gland. A childhood cancer was defined as a pathologically confirmed diagnosis of a malignant neoplasm before age 21. Second primary thyroid cancer was the first occurrence of a thyroid malignancy (ICD9 193.0-193.9 or ICDO3 site code 73.9, morphology less than 9000, and /3 behavior).

Predictors. Sources of information about risk factors for SPTC were categorized into three groups: patient self-report, chart review, or data reconstruction. Patient self-reported variables included demographic information, medical conditions, and health behaviors (Supplementary Table S1). Factors obtained from the medical record included the use of radiation therapy, body regions irradiated, and the use of each one of five classes of chemotherapeutic agents (alkylating agents, anthracyclines, bleomycin, epipodophyllotoxins, platinum agents). The period of inclusion for these treatment variables was the first ten years following the childhood cancer diagnosis. The one reconstructed risk factor considered in this study was the dose of radiation absorbed by the thyroid gland, which was estimated from

dosimetric models using anthropometric characteristics and data from radiotherapy records (30).

Model development

We developed three absolute risk models for SPTC using self-report data only (Model 1, M1); self-report and chart review (Model 2, M2); and all available risk factors including the reconstructed absorbed radiation dose to the thyroid (Model 3, M3). The absolute risk that a 5-year childhood cancer survivor develops SPTC between attained ages a_0 and a_1, given that the patient is alive and at-risk of SPTC at age a_0, is

$$\pi(a_0,a_1;x) = S(0,a_0;x)^{-1}\int_{a_0}^{a_1}\lambda_t(u;x)S(a_0,u;x)du \quad (1)$$

In Equation (1), $S(a,b;x)$ is the probability of event-free survival between [a,b),

$$S(a,b;x) = \exp\{-\int_{a}^{b}(\lambda_t(u;x)+\lambda_c(u;x))du\} \quad (2)$$

which is a function of hazard rates for SPTC (λ_t) and competing risks (λ_c). For all models and event types (i=t,c), the hazard had the general form

$$\lambda_j(u;x) = \lambda_{0j}(u)r_j(x) \quad (3)$$

where $\lambda_{0j}(u)$ is an unspecified baseline hazard and $r_j(x)$ is the relative risk model, which is a function of a vector of explanatory variables, x. Details of the relative risk models are described in the following section.

Relative risk models and estimation. For models M1 and M2, the relative risk was a Cox proportional hazards model, $r_j(x) = \exp\{x'\beta\}$. For M3, a non-linear excess relative risk (ERR) model was used to account for the complexity of the radiation dose-response relationship for SPTC (31). Previous investigations of the late effects of radiation have indicated a curvilinear relationship between the relative risk of thyroid cancer and radiation exposure to the thyroid gland. The relative risk increases up to approximately 20 Gy but declines at higher doses (8, 13, 32), a phenomenon attributed to a cell-killing effect. A linear-exponential-linear dose-response ERR model well describes this relationship (8, 33), and, thus, was used for M3,

$$r_t(x) = (1 + \gamma_0 x_d \exp\{\gamma_1 x_d\})\exp\{x_0'\beta\}. \quad (4)$$

In (4), x_d is the quantitative dose of radiation to the thyroid (Gy) and x_0 are additional predictors.

Because of the heterogeneous risk of competing events in this population, we also used a model-based method to estimate the competing event hazard function, λ_c. Competing events were thyroid removal, other second primary malignancy, or death. The relative risk followed a Cox proportional hazards model, $r_c(x) = \exp\{x'\eta\}$, with the same set of risk factors as the corresponding SPTC model. For M3, quantitative radiation dose was converted into a two-group categorical variable indicating ≤ 20 Gy or >20 Gy.

We used maximum likelihood to obtain pooled estimates of the relative risk model parameters from the combined cohort and case-control data, using a partial likelihood for the cohort data, with time in terms of age, and a logistic likelihood for the case-control data. For the SPTC relative risk models, the cohort outcome was the age at thyroid cancer diagnosis and non-events were censored at the minimum age when a competing event occurred or, if no competing event occurred, when they were last assessed. For risk factors that were only collected in the CCSS cohort, the case-control data contributed to the relative risk estimate

indirectly through the relative risks of the common risk factors. All analyses were performed with the R statistical programming language (34).

Variable selection. Variable selection for M1 and M2 proceeded from a base model including gender, age at first diagnosis, and separate indicators for any prior diagnosis of hyperthyroidism, hypothyroidism, thyroid enlargement, or thyroid nodules. Additional risk factors were added in a stepwise forward procedure using a significance level criterion of 10%. Because high correlation among predictors can result in unstable relative risk estimates, we kept the single strongest risk factor among the thyroid conditions of hypothyroidism, thyroid enlargement, or thyroid nodules. For the final stage of the model building, we examined all pairwise interactions and graphically checked for proportionality of relative risks. The ERR model M3 was a refinement of M2 which replaced the basic radiation variables with a dose-response curve based on the reconstructed dose of radiation absorbed by the thyroid gland.

Data on the age of first diagnosed benign thyroid conditions came from the CCSS cohort's baseline (1994-1996) and 2007 follow-up questionnaires (available at http://ccss.stjude.org/documents/questionnaires/). To account for the time-dependency of these factors in the relative risk calculations, the reported age of diagnosis was used to separate the person-time at risk according to condition status. Since ages were reported only in whole years, we supposed that there was an equal chance that a condition reported to have been diagnosed at age *A* occurred six months before or six months after turning age *A*, owing to rounding. As an approximation, we set the actual age of diagnosis to the midpoint of this interval.

Regarding the reporting of thyroid nodules among SPTC cases, there was concern that some nodule diagnoses occurred at the same time as the SPTC diagnosis and should not be considered predictive. We thus did not count nodule diagnoses that occurred within 12 months of the SPTC diagnosis, an interval chosen to account for the imprecision the self-reported age

at diagnosis. In a sensitivity analysis, we used an 18-month interval to determine how the choice of cutoff influenced the study's main findings.

Absolute risk estimation. Given the estimated relative risk, $\hat{r}_t(x)$, the estimator for the absolute risk of SPTC between ages a_0 and a_1 using formula (1) was

$$\hat{\pi}(a_0,a_1;x) = \{\hat{S}_t(a_0)^{\hat{r}_t(x)}\hat{S}_c(a_0)^{\hat{r}_c(x)}\}^{-1}\int_{a_0}^{a_1}\hat{S}_t(u)^{\hat{r}_t(x)}\hat{S}_c(u)^{\hat{r}_c(x)}\hat{r}_t(x)d\hat{\Lambda}_t(u), \quad (5)$$

conditional on covariate status at age a_0. The survival estimate, $\hat{S}_j(u)$ (j=t,c), and hazard increment, $d\hat{\Lambda}_t(u)$, were based on semiparametric estimators. Given event type j with distinct event times $t_{1j},\ldots,t_{nj}$, $n_j(t)$ the number of events at time t, and the at-risk indicator for the ith individual of the cohort equal to $\delta_{ij}(t)$, survival beyond time t was estimated as

$$\hat{S}_j(t) = \prod_{k:t_{kj}\le t}(1-\frac{n_j(t_{kj})}{\sum_i \delta_{ij}(t_{kj})\hat{r}_{ij}})$$

Here, $\hat{r}_{ij}$ is the ith subject's relative risk for event type j. The quantity $d\hat{\Lambda}_t(u) = \frac{1}{\sum_i \delta_{it}(u)\hat{r}_{it}}$ was the estimator for the hazard at observed event time u. For times not in $t_{1t},\ldots,t_{nt}$, $d\hat{\Lambda}_t(u)$ was zero. The absolute risk estimate of Equation (5) is a generalization of the semiparametric estimator of Benichou and Gail (19), using Breslow's estimator for the baseline hazard function (35).

Model validation

Data. The independent validation cohort was the France/United Kingdom Childhood Cancer Survivor Study (CCSS-France), an ongoing retrospective cohort whose participants were identified from eight centers in France and the UK (a subset of the British Childhood Cancer Survivor Study) (13). The original cohort includes 4096 3-year cancer survivors, diagnosed before age 16 between 1942 and 2008 with follow-up through 2009. We limited our validation to the 3254 French subjects since data on benign thyroid conditions were not available for the UK subjects. There were 2966 (91.1%) subjects who met inclusion criteria for the validation study. Among these participants, there were 39 SPTC cases (1.3%), 261 other second primary malignancies (8.8%), and 400 deaths before a second cancer (13.5%).

Analysis. The risk prediction used in evaluating model performance was the absolute risk of SPTC between the age at study entry (5 years after the age at first cancer diagnosis) and age at the end of follow-up (Dec. 31, 2009) for each model given the covariates at study entry. The status of prior thyroid nodule diagnosis was fixed at its value at the time of study entry.

Calibration refers to an absolute risk model's ability to accurately predict the number of disease events in a group of at-risk individuals (36). We assessed each model's calibration by determining how close the ratio of expected (E) events computed from the model to observed (O) events was to the value one, corresponding to perfect calibration. This was done overall and in subgroups defined by gender, first primary cancer diagnosis of Hodgkin lymphoma, age at first primary cancer diagnosis, and past radiation therapy. 95% CIs were constructed from a supposed Poisson distribution for the observed counts.

Each model's discriminatory ability was evaluated with the area under the curve (AUC). The AUC can be interpreted as the model's probability of predicting a higher risk for a randomly selected case than a randomly selected non-case and from 0.5 (worst discrimination) to 1 (best

discrimination). 95% CIs for differences between AUCs were constructed from bootstrap samples of the validation cohort.

Risk classification was assessed with the Net Reclassification Index (NRI) (37). The NRI quantifies a model's ability to correctly assign more cases to higher risk categories and more non-cases to lower risk categories in comparison to a reference model. We used the NRI to compare the risk reclassification among models M1, M2, and M3 for a 30 year-old childhood cancer survivor's projected risk of SPTC over 10 and 20-year projection lengths. After discussion among our study clinicians and considering that the lifetime risk of thyroid cancer in the general population is 1% (Table 36.12 of (38)), it was decided to use < 0.5%, 0.5-1.5%, and >1.5% as low, intermediate, and high risk, respectively.

To summarize these findings, we introduce the risk classification U-plot, a visual representation of the marginal improvement in risk stratification. This graphic is a side-by-side histogram of the predicted risk distribution of non-cases (on the left) and cases (on the right). The bars of the histogram indicate the percentage of individuals whose predicted risk is within the given interval. Better models have a more U-shaped plot because they place more non-cases in the lowest risk groups and more cases in the highest risk groups.

Results

Development data. A summary of a subset of demographic and treatment characteristics for the development dataset showed significant differences between cases and non-cases in past treatment history and diagnoses of benign thyroid conditions (Table 1). Cases were significantly more likely to have been treated with radiation or with an alkylating agent; to have had radiation exposure to the neck, and high doses of exposure (> 5 Gy) to the thyroid gland; to have a diagnosis of hypothyroidism, thyroid enlargement, or thyroid nodule. Of the 70 diagnoses

of thyroid nodules among SPTC cases in CCSS, 63 were reported before or at the age of the thyroid cancer diagnosis; 35 (56%) were classified as incident nodules using the 12-month cutoff (Supplementary Table S2).

Relative risk models. M1. The self-report relative risk model identified significant risk factors of SPTC for the self-reported variables of birth after 1970, age less than 15 years at FPC, an FPC diagnosis of Hodgkin lymphoma, female gender, and prior diagnosis of a thyroid nodule (Table 2). A past diagnosis of thyroid nodules was the strongest risk factor (RR 11.9 95% CI = 7.3 to19.2); the relative risks from all other factors ranged from 1.6-2.5. An FPC diagnosis of Hodgkin lymphoma and a lifetime thyroid nodules were each associated with a 70% increase in the risk of a competing event in a model with the M1 risk factors (Supplementary Table S3).

M2. When treatment variables from the medical record were considered, indicators of radiation, radiation therapy with a neck field, and the use of an alkylating agent were identified strong risk factors. Birth after 1970, age less than 15 years at FPC, female gender, and previous diagnosis of a thyroid nodule were significant predictors in the expanded model. The magnitude of the relative risks for these factors was similar to M1 but the relative risk of thyroid nodules was reduced by 40%. The competing risk model with the M2 factors found 1.6 to 2.1 relative risk associations with radiation and use of an alkylating agent (Supplementary Table S3).

M3. In an ERR model that included the dose of radiation to the thyroid gland, the relative risk associations of female gender and thyroid nodule diagnosis were still statistically significant risk factors, and treatment with an alkylating agent had borderline significance. The dose-response parameters of M3 indicated an increasing relative risk up to 15 Gy and a declining risk at higher doses. All treatment-related factors were strong risk factors in the competing risk model for M3 (Supplementary Table S3).

Some studies have found an interaction between radiation and certain chemotherapeutic agents on thyroid cancer risk (9). We examined whether the radiation dose-response curve differed for patients treated with an alkylating agent by allowing an additional factor to be added to the linear dose term (γ_0) of the ERR model. This parameter was not significantly different from zero (0.4 95% CI = -2.0 to 2.8), indicating no interaction. We also investigated whether the dose-response relationship changed with time from diagnosis by adding a linear term for periods of risk 10 years or more beyond the childhood cancer diagnosis. This parameter was no different from zero (0.2 95% CI = -1.9 to 2.4). When we re-estimated each relative risk model using a different time-scale (years from first cancer rather than age), the magnitude of the relative risk estimates were unchanged, which was further evidence that the relative risk estimates were independent of time over the projection intervals considered in this paper.

Example projections. A selection of projections for hypothetical low and high-risk profiles of a 30-year-old childhood cancer survivor demonstrate the extensive range and heterogeneity of thyroid cancer risk in this population. All models predict a less than 1% 20-year SPTC risk for a male survivor without past radiation exposure or evidence of thyroid nodules (Profile A, Table 3). For a female survivor of Hodgkin lymphoma who had a 20 Gy radiation exposure to the thyroid gland and a past thyroid nodule (Profile C), this risk is 23-30%. Because M1 does not include treatment-related risk factors it cannot distinguish individuals who differ only in their treatment history. M1 predicts the same risk for Profile B and Profile C individuals who differ only in prior exposure to radiation. However, M2 and M3 suggest that a there is a 15% absolute risk difference between these risk types.

Validation. Cases and non-cases of the CCSS and CCSS-France cohorts differed on most baseline characteristics (Table 4). Most notably, SPTC cases in the validation cohort were all under the age of 15 when diagnosed with a childhood cancer, had a significantly lower median dose of exposure to the thyroid, and significantly fewer diagnoses of thyroid nodules.

There was no evidence of significant bias in the overall calibration of models M1-M3 (Table 5). Comparisons of expected and observed counts within subgroups showed that all models tended to predict fewer cases for subjects in the validation cohort who were born after 1970 or whose first cancer was Hodgkin lymphoma. Calibration in the subgroup of individuals over the age of 15 years at first cancer diagnosis or with a prior thyroid nodule could not be evaluated because the number of cases was too low.

Discrimination significantly improved with the inclusion of treatment risk factors: M2 had an AUC of 0.79, a 0.12 (95% CI = 0.05 to 0.20) improvement over M1 (AUC 0.67 95% CI = 0.61 to 0.74). M3 had an AUC of 0.77 (95% CI = 0.70 to 0.83), a 0.09 (95% CI = 0.01 to 0.17) improvement over M1. There was no statistically significant difference in the discriminatory ability of models M2 and M3 (AUC difference 0.03 95% CI = -0.02 to 0.08).

When compared to M1, both M2 and M3 significantly improved the 10-year SPTC risk classification of non-cases (M2 vs. M1 NRI (non-cases) 0.59 95% CI = 0.56 to 0.63l; M3 vs. M1 NRI (non-cases) 0.60 95% CI = 0.57 to 0.63). While M1 placed only 3% of non-cases in the lowest risk category, M2 and M3 placed 65% and 60% in this category (Figure 1), and the improvement in classification of M2 over M3 was significant (M2 vs. M3 NRI (non-cases) 0.02 95% CI = 0.004 to 0.04). Though the differences were more modest, M2 also performed the best in the risk classification of cases (M1 vs. M2 NRI (cases) 0.10 95% CI = -0.14 to 0.35; M2 versus M3 95% CI = -0.02, 0.33). Whereas M1 and M3 placed 23.1% and 38.5% of the validation cohort cases into the highest risk category, M2 predicted that 53.8% had the highest risk. These differences were suggestive but not statistically significant. Similar results were found for 20-year projections (Supplementary Figure S1).

Discussion

We have developed the first absolute risk prediction models for SPTC in 5-year survivors of a childhood cancer. In our assessment of three models, differing in what treatment information they included, all models were well calibrated and had greater discriminatory ability than established cancer prediction models (39). A model which included the risk factors gender, birth after 1970, age less than 15 years at the time of the childhood cancer diagnosis, prior diagnosis of a thyroid nodule, past radiation therapy, radiation with a neck field, and past use of an alkylating agent (M2) had the best overall performance. This model significantly improved discrimination and risk classification as compared to a model without treatment risk factors (M1) and improved risk classification among cases when compared to a model that also included the quantitative dose of radiation exposure to the thyroid gland (M3).

We have shown that complex exposure models can be incorporated into absolute risk predictions. However, a main finding of our study is that the inclusion of the nonlinear effects of the radiation dose of exposure to the thyroid did not improve discriminatory ability or risk classification performance compared to a model that had qualitative information on past radiotherapy, namely, whether any radiation treatment had been used to treat the childhood cancer and whether this therapy included a neck field. This finding could be explained, in part, by the lower levels of radiation exposure in the CCSS-France validation cohort. 75% of the CCSS-France cohort cases who received radiation had less than 16 Gy, which is near the peak 15 Gy of the dose-response curve. Few of the radiation exposed subjects were within the range of the dose-response curve where the differences in the risk distributions of M2 and M3 would be greatest.

The good performance of M2 has important practical implications. Because the risk profile for M2 could be determined from patient self-report, it might be feasible to implement M2 as a risk prediction tool for clinician-guided individual risk counseling. A limitation is that information about the treatment of the childhood cancer might be difficult for some individuals to

recall given their youth at the time of treatment. In a study of 635 childhood cancer survivors, Kadan-Lottick and colleagues found that after a median of 21 years from the time of diagnosis 3.5% of the survivors could not provide a first primary diagnosis and 8% did not know whether they had received radiation therapy (40). This study did not ask about fields of radiation. Chart review could recover most treatment information, though some persons might still have incomplete profiles. Research is needed to investigate the importance of these logistical barriers and to consider whether the use of a model without treatment information would be warranted in persons for whom sufficient treatment history is unavailable.

One reason for these unknowns is that no risk prediction tool has ever been specifically developed for childhood cancer survivors. Second primary thyroid cancer could make a valuable first case for prediction-based monitoring since thyroid cancer has a number of available screening methods and, when detected early, is highly amenable to treatment. The Children's Oncology Group currently recommends a yearly thyroid exam for irradiated childhood cancer survivors (25). Yet, given the high false-positive rate of current screening approaches and the wide range of risk we observed in our study cohorts, more targeted strategies may be justified. For example, based on 10-year risk projections in the CCSS samples, a substantial portion of survivors (65% based on M2 estimates) had an absolute risk under 0.5%. This risk is less than half the lifetime risk of thyroid cancer in the general population and might warrant a lower frequency of screening (40). Risk-based considerations like this will not only be useful to physicians, they could also inform the development of national guidelines such as the US Preventive Services Task Force's guidance for thyroid cancer screening that is presently under revision (41).

All of the study's models were validated in an independent cohort of childhood cancer survivors. This is the strongest test of a prediction model's performance. It is an additional strength that our validation sample came from a different country and cases were identified

through a different mechanism (national disease registry) than the model development data as it suggests that these models might be generalized to the larger population of Western childhood cancer survivors treated before the 1990s.

There were some limitations to our study. Since we did not have sufficient detail about the clinical monitoring of the individuals in the studies used for model development, we could not determine what influence screening practices might have had on the risk associated with self-reported medical conditions. For the development of model M3, we did not consider other functional forms for the ERR curve but limited our study to the form that fit the data well in more extensive radiation dose-response studies in similar cohorts (8, 32-33).

For validation, the small number of cases in CCSS-France reduced the precision of our assessment of performance in subgroups. Also, characteristics of thyroid nodule diagnoses in the CCSS-France prevented a thorough evaluation of the model performance among subjects with a prior nodule. In CCSS, 55.5% of nodule diagnoses occurred within 12 months of a thyroid cancer diagnosis, while in CCSS-France 87.2% did. As a consequence, the relative risk association in this cohort was approximately half that used in the developed models (Supplementary Table S4). To investigate the sensitivity of our conclusions to the nodule risk factor, we excluded diagnoses within 18 months of SPTC. This resulted in the exclusion of an additional 14.3% of case diagnoses and weakened the risk association in all models (Supplementary Table S5). This resulted in a non-significant increase in the expected to observed counts for M2 (1.28 95% CI = 0.94 to 1.76) and a similar AUC (0.81 95% CI = 0.74 to 0.87) (Supplementary Table S6).

Although this sensitivity analysis provides some reassurance that our main conclusions are robust to differences in thyroid nodule diagnosis in the development and validation cohorts, this will need further confirmation in cohorts in which screening for nodules followed a

systematic schedule and diagnostic data were collected prospectively. Also, as survivors from later birth cohorts begin to reach older adulthood, it will be important to conduct further validation studies to determine how improvements in radiotherapy beginning in the 1990s might impact the applicability of these models to later treatment cohorts.

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Figure 1. Risk classification U-plot for the 10-year projected risk of second primary thyroid cancer for a 30 year-old survivor (CCSS-France validation cohort; n=2966, events=39).

Table 1: Summary characteristics of the analytic sample stratified by study and second primary thyroid cancer (SPTC) case status. All cells are No. (%) unless stated otherwise.

	Non-cases			SPTC Cases		
	CCSS	LESG	Nordic	CCSS	LESG	Nordic
	n = 11873	*n* = 82	*n* = 36	*n* = 124	*n* = 22	*n = 13*
Female[†,§]	5609 (47)	54 (66)	27 (75)	86 (69)	14 (64)	10 (77)
Type of first cancer[†,‡,§]						
Bone cancer	1000 (8)	4 (5)	3 (8)	11 (9)	0 (0)	1 (8)
CNS	1540 (13)	3 (4)	7 (19)	16 (13)	1 (5)	0 (0)
HL	1514 (13)	15 (18)	1 (3)	39 (31)	5 (23)	5 (38)
Kidney (Wilms)	1045 (9)	21 (26)	2 (6)	2 (2)	4 (18)	1 (8)
Leukemia	4058 (34)	NA[a]	7 (29)	33 (27)	NA	2 (15)
Neuroblastoma	805 (7)	27 (33)	1 (3)	8 (6)	7 (32)	0 (0)
NHL	878 (7)	5 (6)	1 (3)	6 (5)	2 (9)	1 (8)
Soft tissue sarcoma	1033 (9)	3 (4)	2 (6)	9 (7)	1 (5)	0 (0)
Other	0 (0)	4 (5)	12 (33)	0 (0)	2 (9)	3 (23)
Age at diagnosis[†,‡,§], years						
<5	4846 (41)	51 (62)	12 (33)	33 (27)	11 (50)	3 (23)
5-9	2599 (22)	15 (18)	6 (17)	27 (22)	5 (23)	2 (15)
10-14	2346 (20)	11 (13)	4 (11)	50 (40)	4 (18)	2 (15)
15+	2082 (18)	5 (6)	14 (39)	14 (11)	2 (9)	6 (46)
Year of birth[†,‡,§]						
Before 1970	4435 (37)	.[b]	30 (83)	55 (44)	.	11 (85)
1970-1986	7438 (63)	.	6 (17)	69 (56)	.	2 (15)
Radiation [c,†, §]	7896 (67)	71 (87)	17 (47)	112 (90)	22 (100)	12 (92)
Radiation [c,d,†, §] [Gy], median (IQR)	1.1 (0.47, 20.20)	3.3 (0.88, 19.97)	0.72 (0.17, 3.68)	20.35 (10.00, 30.69)	11.7 (4.41, 26.03)	7.43 (1.75, 21.23)
Chemotherapy [c,†,‡]	9569 (81)	42 (51)	16 (44)	102 (82)	12 (55)	9 (69)
Alkylating agent [c,†,‡, §]	6405 (54)	27 (33)	8 (22)	84 (68)	9 (41)	5 (38)
Variables only collected in CCSS						
Other chemotherapy [c]						
Bleomycin [c]	702 (6)			10 (8)		
Anthracyclines [c]	4886 (41)			43 (35)		
Platinum agent [c]	725 (6)			6 (5)		
Epipodophyllotoxins [c]	1125 (9)			12 (10)		
Radiation to neck [c, §]						
Yes	2888 (24)			88 (71)		
No	8984 (76)			36 (29)		
Missing	1 (0)			0 (0)		
Age of last known vital status[§], years						
<21	1357 (11)			20 (16)		
21-34	6015 (51)			81 (65)		

35-44	3537 (30)	21 (17)
45+	964 (8)	2 (2)
Number of visits to physician [e, §]		
None	4 (0)	0 (0)
1-6	6677 (56)	65 (52)
7-20	2077 (18)	34 (27)
20+	1372 (12)	9 (7)
Missing	1743 (15)	16 (13)
Years since last physical exam [e, §]		
< 1	5306 (45)	63 (51)
1-4	3253 (28)	32 (26)
5+	904 (8)	12 (10)
Never	575 (5)	4 (3)
Missing	1835 (15)	13 (10)
Ever smoked[§]		
Yes	2601 (22)	29 (23)
No	8691 (73)	94 (76)
Unsure	81 (1)	1 (1)
Missing	500 (4)	0 (0)
Use of any thyroid medication [c, §]		
Yes	1021 (9)	49 (40)
No	10335 (87)	68 (55)
Unsure	76 (1)	0 (0)
Missing	441 (4)	7 (6)
Overactive thyroid (in lifetime) [f, §]		
Yes	301 (3)	12 (10)
No	11372 (96)	105 (85)
Unsure	176 (2)	6 (6)
Missing	24 (0)	1 (1)
Underactive thyroid (in lifetime) [f, §]		
Yes	1314 (11)	45 (36)
No	10338 (87)	63 (56)
Unsure	198 (2)	8 (8)
Missing	23 (0)	1 (1)
Thyroid nodules (in lifetime) [f, §]		
Yes	478 (4)	70 (56)
No	11181 (94)	46 (37)
Unsure	182 (2)	7 (6)
Missing	32 (0)	1 (1)
Thyroid enlargement (in lifetime) [f, §]		
Yes	390 (3)	56 (45)
No	11261 (95)	62 (50)
Unsure	178 (2)	5 (4)

Missing	50 (0)	1 (1)

a Leukemia cases were excluded from LESG

b Variable was not collected for this study

c During 10 years following first cancer, determined from medical record

d Reconstructed dose

e During previous two years; self-report on baseline questionnaire

f Combined self-report on baseline questionnaire and 2007 follow-up

† Comparing non-cases between studies, p-value < .05; Wilcoxon test for continuous; χ^2 for categorical

‡ Comparing cases between studies, p-value < .05; Wilcoxon test for continuous; χ^2 for categorical

§ Comparing combined cases and non-cases, p-value < .05; Wilcoxon test for continuous; χ^2 for categorical

Table 2: Multivariable relative risk estimates for models of second primary thyroid cancer risk (SPTC) in childhood cancer survivors (n=12150, 159 events).

	Relative Risk[a] (95% CI)			Subgroup Characteristics		
Risk factor	M1	M2	M3	Event (%/N)	% Irradiated	Mean Dose (Gy)
Birth year after 1970	1.55 (1.01, 2.37)	1.83 (1.21, 2.76)	1.25 (0.74, 2.12)	69 (0.9/7507)	62.9	6.44
Age at FPC < 15 years	2.52 (1.43, 4.45)	2.40 (1.36, 4.24)	1.75 (0.83, 3.72)	137 (1.4/10027)	66.4	8.5
Hodgkin lymphoma FPC	2.37 (1.59, 3.56)			49 (3.1/1579)	93.9	34.95
Female	1.75 (1.23, 2.49)	2.23 (1.56, 3.18)	1.93 (1.21, 3.10)	110 (1.9/5800)	65.6	11.24
Thyroid nodules (in lifetime)[b]	11.86 (7.34, 19.17)	7.38 (4.60, 11.85)	8.64 (4.77, 15.64)	28 (5.5/506)	90.5	26.49
Any alkylating agent [c]		1.59 (1.12, 2.24)	1.60 (0.99, 2.57)	98 (1.5/6538)	71.2	12.12
Any radiation [c]		2.60 (1.34, 5.02)		146 (1.8/8130)	100	11.17
Neck radiation field [c]		6.57 (4.12, 10.49)		88 (3/2967)	100	28.11
Radiation dose (linear) [d,e]			1.72 (0.75, 3.90)			
Radiation dose (exponential) [d,e]			-0.065 (-0.045, -0.093)			

FPC, first primary cancer

a All estimates were adjusted for other reported risk factors

b Self-reported 'Yes' at baseline or 2007 follow-up; diagnoses within 12 months of SPTC excluded

c Within 10 years of FPC

d Computationally reconstructed radiation dose (Gy) to thyroid

e Relative to no exposure, 10 Gy exposure has an excess relative risk of 8.96 95% CI (2.47, 15.45)

Table 3: Example 10- and 20-year risk projections for second primary thyroid cancer for a 30 year-old childhood cancer survivor.

Risk factor	Factor in model (Y/N) [M1, M2, M3]	Profile A		Profile B		Profile C	
Birth year after 1970	[Y,Y,Y]	N		Y		Y	
Age at FPC < 15 years	[Y,Y,Y]	Y		Y		Y	
Hodgkin lymphoma FPC	[Y,N,N]	N		Y		Y	
Female	[Y,Y,Y]	N		Y		Y	
Thyroid nodules (in lifetime)	[Y,Y,Y]	N		Y		Y	
Any alkylating agent for FPC	[N,Y,Y]	N		Y		Y	
Any radiation	[N,Y,N]	N		Y		Y	
Neck radiation field	[N,Y,N]	N		N		Y	
Radiation dose to thyroid	[N,N,Y]	0 Gy		0.5 Gy		20.0 Gy	
	Model	10 year	20 year	10 year	20 year	10 year	20 year
	M1	0.50%	0.69%	23.93%	29.58%	23.93%	29.58%
	M2	0.05%	0.08%	4.26%	6.30%	17.62%	22.84%
	M3	0.13%	0.20%	5.39%	7.55%	19.33%	24.17%

Table 4: Summary characteristics of the model development (CCSS) and validation (CCSS-France) cohorts stratified by second primary thyroid cancer (SPTC) status. All cells are No. (%) unless stated otherwise.

	Non-cases		SPTC Cases	
	CCSS-US *N* = 11873	CCSS-France *N* = 2927	CCSS-US *N* = 124	CCSS-France *N* = 39
Female	5609 (47)	1279 (44)	86 (69)	24 (62)
Type of first cancer[a,†,‡]				
CNS	1540 (13)	426 (15)	16 (13)	2 (5)
HL	1514 (13)	198 (7)	39 (31)	11 (28)
Kidney (Wilms)	1045 (9)	621 (21)	2 (2)	7 (18)
Neuroblastoma	805 (7)	416 (14)	8 (6)	7 (18)
NHL	878 (7)	328 (11)	6 (5)	5 (13)
Other	6091 (51)	938 (32)	53 (43)	7 (18)
Age at diagnosis[†], years				
<5	4846(41)	1542 (53)	33 (27)	11 (28)
5-9	2599 (22)	699 (24)	27 (22)	14 (36)
10-14	2346 (20)	592 (20)	50 (40)	13 (36)
15+	2082 (18)	90 (3)	14 (11)	0 (0)
Year of birth[†,‡]				
Before 1970	4435 (37)	1341 (46)	55 (44)	24 (62)
1970-1986	7438 (63)	1575 (54)	69 (56)	15 (38)
Radiation[b,c,†,‡] [Gy], median (IQR)	1.1 (0.5, 20.3)	0.7 (0.2, 5.6)	20.4 (10.0, 30.7)	6.5 (1.1, 16.3)
Radiation[c,†]	7896 (67)	2049 (70)	112 (90)	36 (92)
Radiation to neck[c]	2888 (24)	761 (26)	88 (71)	29 (74)
Chemotherapy[c,†]	9569 (81)	2173 (74)	102 (82)	28 (72)
Missing	0 (14)	0 (0)	0 (0)	0 (0)
Alkylating agent[c,†]	6405 (54)	1437 (49)	84 (68)	19 (49)
Other chemotherapy[c]				
Bleomycin[c,†]	702 (6)	161 (6)	10 (8)	5 (13)
Anthracyclines[c,†]	4886 (41)	933 (32)	43 (35)	11 (28)
Platinum agent[c,†]	725 (6)	181 (6)	6 (5)	2 (5)
Epipodophyllotoxins[c,†]	1125 (9)	80 (3)	12 (10)	1 (3)
Ever Smoked[d,†,‡]	1170 (10)	947 (32)	12 (10)	17 (44)
Use of hypothyroid medication[†]	948 (8)	179 (6)	43 (38)	14 (58)
Overactive thyroid[d,†]	303 (3)	46 (2)	10 (9)	5 (21)
Underactive thyroid[d,†]	1316 (11)	115 (4)	42 (37)	4 (17)
Thyroid nodules[d]	480 (4)	121 (4)	66 (58)	11 (46)
Thyroid enlargement[d,e,‡]	391 (3)	39 (1)	53 (46)	2 (8)

a Leukemia cases were excluded from CCSS-France
b Reconstructed dose
c During 10 years following first cancer, determined from medical record
d In lifetime; self-report on baseline questionnaire
e CCSS-France assessed goitre; CCSS enlargement or swelling

† Comparing non-cases, p-value < .05; Wilcoxon test for continuous; χ^2 for categorical
‡ Comparing cases, p-value < .05; Wilcoxon test for continuous; χ^2 for categorical

Table 5: Comparison of model calibration based on the CCSS-France validation cohort (n=2966, events= 39).

	Subgroup [n]	Observed	Expected/Observed (95% CI)		
			M1	M2	M3
Overall	[2966]	39	0.85 (0.62, 1.17)	0.87 (0.64, 1.19)	0.81 (0.59, 1.11)
Birth year after 1970	Y [1589]	14	1.28 (0.76, 2.16)	1.26 (0.75, 2.13)	1.05 (0.62, 1.77)
	N [1377]	25	0.61 (0.41, 0.91)	0.65 (0.44, 0.96)	0.67 (0.46, 1.00)
Age at FPC < 15 years	Y [2876]	39	0.84 (0.62, 1.15)	0.86 (0.63, 1.17)	0.79 (0.58, 1.08)
Hodgkin lymphoma FPC	Y [209]	11	0.22 (0.12, 0.39)	0.53 (0.29, 0.95)	0.51 (0.28, 0.91)
	N [2757]	28	1.10 (0.76, 1.60)	1.01 (0.69, 1.46)	0.93 (0.64, 1.34)
Female	Y [1303]	24	0.80 (0.54, 1.20)	0.89 (0.60, 1.33)	0.77 (0.52, 1.15)
	N [1663]	15	0.94 (0.56, 1.55)	0.83 (0.50, 1.38)	0.86 (0.52, 1.43)
Thyroid nodules[a]	N [2965]	39	0.85 (0.62, 1.17)	0.87 (0.63, 1.19)	0.80 (0.59, 1.01)
Any alkylating agent	Y [1456]	19	0.85 (0.54, 1.33)	1.05 (0.67, 1.64)	0.97 (0.62, 1.52)
	N [1510]	20	0.86 (0.55, 1.33)	0.70 (0.45, 1.09)	0.66 (0.42, 1.02)
Any radiation	Y [2085]	36	0.68 (0.49, 0.94)	0.89 (0.64, 1.23)	0.79 (0.57, 1.09)
	N [881]	3	2.99 (0.96, 9.27)	0.68 (0.22, 2.12)	1.03 (0.33, 3.20)
Neck radiation field	Y [786]	29	0.32 (0.22, 0.46)	0.85 (0.59, 1.22)	0.65 (0.45, 0.93)
	N [2180]	10	2.40 (1.29, 4.46)	0.93 (0.50, 1.73)	1.28 (0.69, 2.37)
Radiation dose > 10 Gy	Y [405]	11	0.43 (0.24, 0.78	1.16 (0.64, 2.10)	1.12 (0.62, 2.03)
	N [2561]	28	1.02 (0.70, 1.47)	0.76 (0.52, 1.09)	0.68 (0.47, 0.99)

Factors in the model are shaded

a Diagnosis status at the beginning of the projection interval.

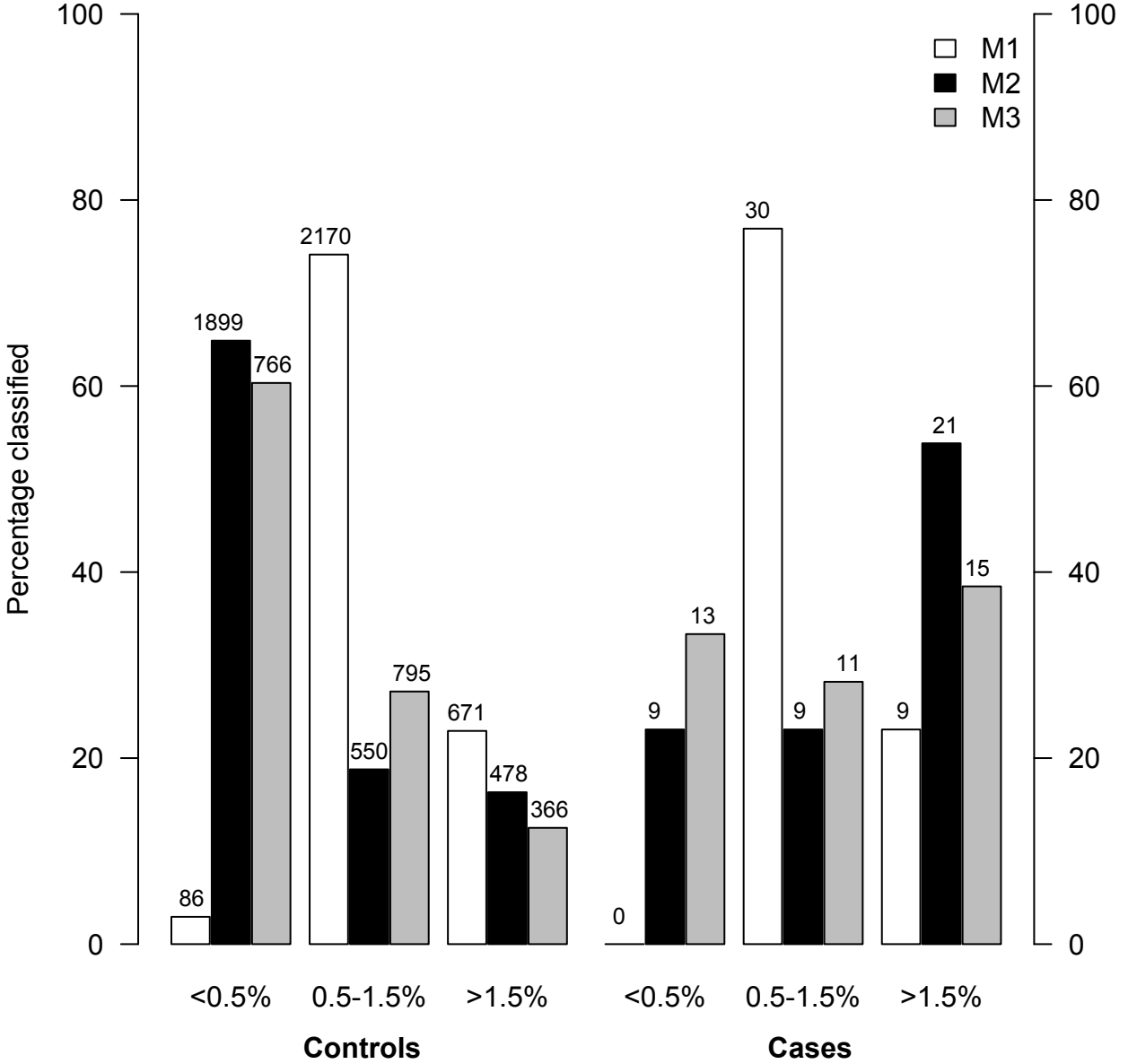
100
80
60
40
20
0
Percentage classified
M1
M2
M3
86
1899
766
2170
550
795
671
478
366
0
9
13
30
9
11
9
21
15
<0.5%
0.5-1.5%
>1.5%
Controls
<0.5%
0.5-1.5%
>1.5%
Cases

Table S1: Factors included in variable selection procedure for relative risk models.

Variable	Candidate for which models	Cohort only
Female	M1,M2,M3	No
Race	M1,M2,M3	Yes
BMI	M1,M2,M3	Yes
Type of first cancer	M1,M2,M3	No
Date of birth	M1,M2,M3	No
Age at diagnosis for first primary cancer	M1,M2,M3	No
Physician visits	M1,M2,M3	Yes
Cancer-related physician visits	M1,M2,M3	Yes
Last physical exam	M1,M2,M3	Yes
Ever smoked	M1,M2,M3	Yes
Current smoker	M1,M2,M3	Yes
Thyroid medication	M1,M2,M3	Yes
Hypothyroid medication	M1,M2,M3	Yes
Overactive thyroid medication	M1,M2,M3	Yes
Overactive thyroid	M1,M2,M3	Yes
Underactive thyroid	M1,M2,M3	Yes
Thyroid nodules	M1,M2,M3	Yes
Thyroid enlargement	M1,M2,M3	Yes
Growth hormone deficiency	M1,M2,M3	Yes
Injection of growth hormone	M1,M2,M3	Yes
Other hormone problem	M1,M2,M3	Yes
Birth control use	M1,M2,M3	Yes
Estrogen/progesterone medication	M1,M2,M3	Yes
Parity	M1,M2,M3	Yes
Any first degree relative with cancer	M1,M2,M3	Yes
No. of first degree relatives with cancer	M1,M2,M3	Yes
Any first degree relative with thyroid cancer	M1,M2,M3	Yes
No. of first degree relatives with thyroid cancer	M1,M2,M3	Yes
Radiation for FPC (Y/N)	M2,M3	No
Eleven body regions of radiation exposure for FPC (Y/N)	M2, M3	Yes
Chemotherapy for FPC	M2,M3	No
Alkylating agents for FPC	M2,M3	No
Bleomycin for FPC	M2,M3	Yes
Anthracyclines for FPC	M2,M3	Yes
Platinum agents for FPC	M2,M3	Yes
Epipodophyllotoxins for FPC	M2,M3	Yes
Radiation dose (Gray) for FPC	M3	No

FPC, first primary cancer

Table S2: Years from nodule diagnosis to second primary thyroid cancer in CCSS cohort (n=63).

Years	No.	%
[0, 0.5)	17	26.9
[0.5, 1)	18	28.6
[1, 1.5)	9	14.3
[1.5, 5)	12	19.0
[5, 10)	5	7.9
≥ 10	2	3.2

Table S3: Relative risks for second primary thyroid cancer competing events (minimum time to other second primary cancer, thyroid removal, or death) [n=12150, event=2483].

Risk factor	M1	M2	M3
Birth year after 1970	0.70†	0.74†	0.73†
Age at FPC < 15 years	0.84†	0.81†	0.81†
Hodgkin disease FPC	1.74†		
Female	0.99	1.04	1.04
Thyroid nodules (in lifetime)[b]	1.69†	1.44†	1.45†
Any alkylating agent for FPC[c]		1.60†	1.65†
Any radiation for FPC[c]		2.06†	2.27†
Neck radiation field[c]		1.77†	
Radiation > 20 Gray			1.62†

FPC, first primary cancer
a All estimates were adjusted for other reported risk factors
b Self-reported 'Yes'; 12-month incident nodule diagnoses excluded
c Within 10 years of FPC
† P-value < .01

Table S4: Multivariable relative risk estimates for models of second primary thyroid cancer risk in validation cohort of childhood cancer survivors (n=2966, events=39).

	Relative Risk[a] (95% CI)			Subgroup Characteristics		
Risk factor	M1	M2	M3	Event (%/N)	% Irradiated	Mean Dose (Gray)
Birth year after 1970	1.06 (0.52, 2.16)	1.28 (0.62, 2.66)	1.30 (0.62, 2.73)	14 (0.9/1589)	58.2	4.78
Age at FPC < 15 years	NE			39 (1.4/2876)	70.0	5.65
Hodgkin disease FPC	4.21 (2.03, 8.71)			11 (5.3/209)	94.3	20.33
Female	1.90 (0.97, 3.67)	1.86 (0.97, 3.57)	1.79 (0.90, 3.58)	24 (1.8/1303)	72.3	5.55
Thyroid nodules (in lifetime)[b]	4.16 (1.53, 11.31)	3.93 (1.49, 10.40)	3.66 (0.56, 23.75)	5 (5/101)	84.2	9.89
Any alkylating agent [c]		1.07 (0.56, 2.06)	0.96 (0.42, 2.22)	98 (1.5/6538)	71.2	12.12
Any radiation[c]		1.25 (0.32, 4.96)		146 (1.8/8130)	100.0	11.17
Neck radiation field[c]		7.14 (3.03, 16.78)		88 (3/2967)	100.0	28.11
Radiation dose (linear)[d,e]			1.25 (0.03, 54.09)			
Radiation dose (exponential)[d,e]			-0.069 (-0.006, -0.782)			

FPC, first primary cancer; NE, not estimable

a All estimates were adjusted for other reported risk factors

b Self-reported 'Yes' at baseline or follow-up; 12-month incident nodule diagnoses excluded

c Within 10 years of FPC

d Computationally reconstructed radiation dose (Gray) to thyroid

e Relative to no exposure

Table S5: **Sensitivity analysis.** Multivariable relative risk estimates for models of second primary thyroid cancer risk in childhood cancer survivors using 18-month cutoff for incident nodules (n=12150, 159 events).

	Relative Risk[a] (95% CI)			Subgroup Characteristics		
Risk factor	M1	M2	M3	Event (%/N)	% Irradiated	Mean Dose (Gray)
Birth year after 1970	1.44 (0.94, 2.20)	1.03 (0.68, 1.56)	2.74 (1.61, 4.69)	69 (0.9/7507)	62.9	6.44
Age at FPC < 15 years	2.97 (1.69, 5.24)	7.85 (4.45, 13.85)	1.51 (0.62, 3.66)	137 (1.4/10027)	66.4	8.50
Hodgkin disease FPC	2.69 (1.81, 4.01)			49 (3.1/1579)	93.9	34.95
Female	1.90 (1.34, 2.70)	2.27 (1.60, 3.24)	1.85 (1.21, 2.83)	110 (1.9/5800)	65.6	11.24
Thyroid nodules (in lifetime)[b]	6.29 (3.62, 10.92)	0.56 (0.34, 0.97)	3.21 (1.40, 7.36)	19 (3.8/497)	90.3	26.56
Any alkylating agent [c]		1.51 (1.07, 2.13)	1.37 (0.93, 2.01)	98 (1.5/6538)	71.2	12.12
Any radiation[c]		3.34 (1.73, 6.45)		146 (1.8/8130)	100.0	11.17
Neck radiation field[c]		3.99 (2.51, 6.35)		88 (3/2967)	100.0	28.11
Radiation dose (linear)[d,e]			1.56 (0.67, 3.62)			
Radiation dose (exponential)[d,e]			-0.049 (-0.034, -0.072)			

FPC, first primary cancer

a All estimates were adjusted for other reported risk factors

b Self-reported 'Yes' at baseline or 2007 follow-up; 18-month incident nodule diagnoses excluded

c Within 10 years of FPC

d Computationally reconstructed radiation dose (Gray) to thyroid

e Relative to no exposure, 10 Gray exposure has an excess relative risk of 9.53 95% CI (2.31, 16.75)

Table S6: **Sensitivity analysis.** Model calibration and discrimination in CCSS-France validation cohort using 18-month cutoff for incident nodules (n=2966, events= 39).

Model	E/O (95% CI)	AUC (95% CI)
M1	0.93 (0.68, 1.27)	0.68 (0.61, 0.74)
M2	1.29 (0.94, 1.76)	0.81 (0.74, 0.87)
M3	0.84 (0.62, 1.15)	0.73 (0.67, 0.80)