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

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Appendix

A1. Absolute risk formulation.

The absolute risk of a five-year childhood cancer survivor developing SPTC between attained ages a_0 and a_1, given the set of risk factors x, is

$$\pi(a_0, a_1; x) = S(0, a_0; x)^{-1} \int_{a_0}^{a_1} \lambda_t(u; x) S(a_0, u; x) du. \qquad \text{(A.E1)}$$

In Equation (A.E1), λ_t denotes the hazard rate for SPTC, S(a,b;x) is the probability of event-free survival between [a,b),

$$S(a, b; x) = \exp\{-\int_a^b (\lambda_t(u; x) + \lambda_c(u; x)) du\} \qquad \text{(A.E2)}$$

that accounts for competing events through the competing risk hazard λ_c. Given the estimated relative risk, $\hat{r}_t(x)$, the estimator for the absolute risk of SPTC in (A.E1) is

$$\hat{\pi}(a_0, a_1; x) = \{\hat{S}_t(a_0)^{\hat{r}_t(x)} \hat{S}_c(a_0)^{\hat{r}_c(x)}\}^{-1} \int_{a_0}^{a_1} \hat{S}_t(u)^{\hat{r}_t(x)} \hat{S}_c(u)^{\hat{r}_c(x)} \hat{r}_t(x) \hat{\lambda}_t(u) du. \qquad \text{(A.E3)}$$

We let the distinct event times for event type j be $t_{1j},\ldots,t_{nj}$, $n_j(t)$ the number of events of type j at time t, and $\delta_{ij}(t)$ the at-risk indicator for the ith individual of the cohort. Letting $\hat{r}_{ij}$ denote the ith subject's relative risk for event type j, survival beyond time t for event type j is estimated as

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

The quantity $\hat{\lambda}_t(u) = (\sum_i \delta_{it}(u)\hat{r}_{it})^{-1}$ is the estimator for the hazard at the event time u. For times not in $t_{1t},\ldots,t_{nt}$, $\hat{\lambda}_t(u)$ is zero. The absolute risk estimate of (A.E3) is a generalization of the semiparametric estimator of Benichou and Gail (20), using Breslow's estimator for the baseline hazard function.

A2. Excess relative risk model

For models M1 and M2, the relative risk model 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 (33). Investigations of the late effects of radiation have indicated a curvilinear relative risk relationship for the radiation absorbed dose to the thyroid gland. The relative risk increases up to approximately 20 Gy but declines at higher doses, a phenomenon attributed to a cell-killing effect (8, 13, 15, 46). To capture this relationship, M3 used a linear-exponential-linear ERR (35, 36) dose-response model M3 was

$$r_t(x) = (1 + \exp\{\gamma_1 x_d\} \sum_j \gamma_{0j} x_{dj}) \exp\{x_0'\beta\}. \qquad \text{(A.E4)}$$

In Equation (A.E4), x_d is the quantitative radiation absorbed dose to the thyroid (Gy) and x_0 are additional predictors. While γ_1 was constant, a separate linear

effect γ_0 was estimated for each of the four age-at-diagnosis groups <5, 5-9, 10-14, and ≥15 years. This parameterization was chosen because age at diagnosis has been previously shown to be an important modifier of the radiation dose-response effect on SPTC risk (34).

A3. Variable selection

Variable selection was based on the CCSS cohort alone. It proceeded from a base model including gender and age at diagnosis of first childhood cancer for models M1. The base model for M2 added radiation (yes/no). M3 was comprised of all variables selected from model M2 with any radiation-related variables replaced by the reconstructed dose model. Linearity of the continuous factors on the log hazard scale was investigated with Kaplan-Meier plots of the CCSS SPTC outcomes and log-rank tests comparing curves in subgroups defined by the continuous variable. This guided the coding of continuous variables prior to any model fitting.

Candidate risk factors were added to the base models in a stepwise forward procedure using a significance level criterion of 10%. Because highly correlated predictors can result in unstable relative risk estimates, we retained the single strongest risk factor among types of thyroid dysfunction. For the final stage of the model building, we examined all pairwise interactions and graphically checked for proportionality of relative risks. In simulation studies, we estimated that this procedure could identify 5 true predictors among the candidates with 85% power and 9 predictors with 66% power, when each

predictor had a relative risk of 1.5. Given 5 to 10 identified predictors, the power to detect a pairwise interaction with relative risks of 1.5 among them was estimated to range from 50 to 60%.

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 in whole years, we supposed a condition reported to have been diagnosed at age A was equally likely to have occurred six months before or six months after turning age A. As an approximation, we set the age of diagnosis to the midpoint of this interval.

A4. Missing data

Multiple imputation (37) was used to handle missing data for the case-control data, namely thyroid nodules and neck irradiation, and, for 75% of LESG, birth year. Because the entry period for LESG ended in 1979, participants diagnosed at age 9 or greater were born before 1970, which allowed us to reconstruct birth year category (≤1970 or >1970) for 26 (25%) of LESG participants. For the imputation procedure, a matched subset from the CCSS cohort was identified for each case-control subject, using the matching variables of case status, gender, age at diagnosis, first cancer diagnosis, and radiation absorbed dose, coded as a six-group categorical variable. In each imputed data set, missing data for case-

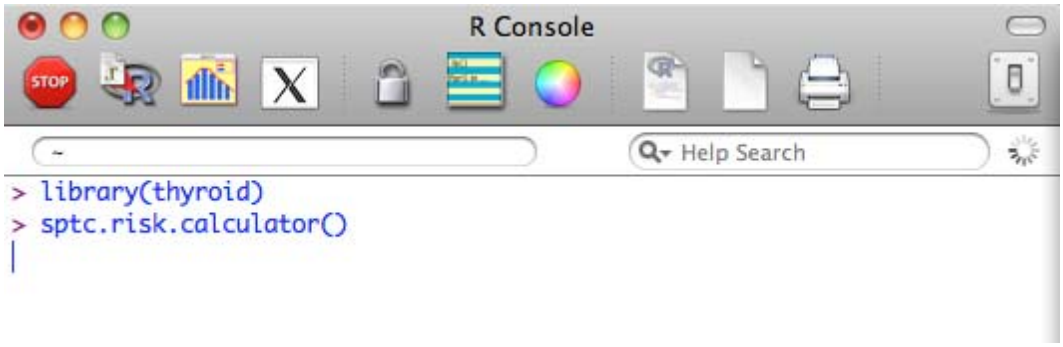
control subjects were imputed with the data from a CCSS participant who was randomly selected from their matched set. The relative risk estimates of the main analyses were based on 100 imputed datasets. We computed standard errors for the imputation based relative risk estimates following the approach by Rubin (1987, *Multiple Imputation for Nonresponse in Surveys*. J. Wiley & Sons, New York). In sensitivity analyses, we compared the multiply-imputed relative risk estimates to the relative risk estimates estimated from the cohort data only and report our findings in supplementary material (Tables S4-S6).

A5. Risk prediction software

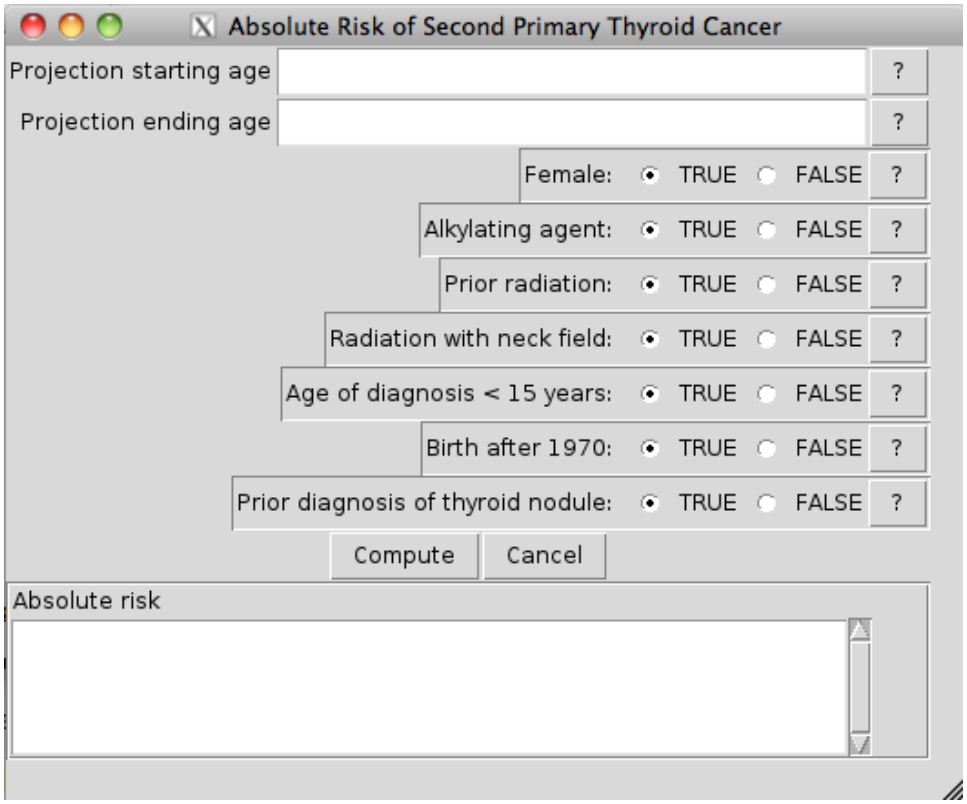
We have written a package in the R language for calculating risk predictions and 95% confidence intervals for the M2 model described in the main text. An installation of the R version 2.15 or higher is required. R is freely available at http://cran.r-project.org/. The risk prediction package is can be downloaded freely at http://dceg.cancer.gov/bb/ where instructions for installation are also provided.

Once installed, the following commands are issued to load the package and to invoke the graphical user interface for second primary thyroid cancer risk calculator.

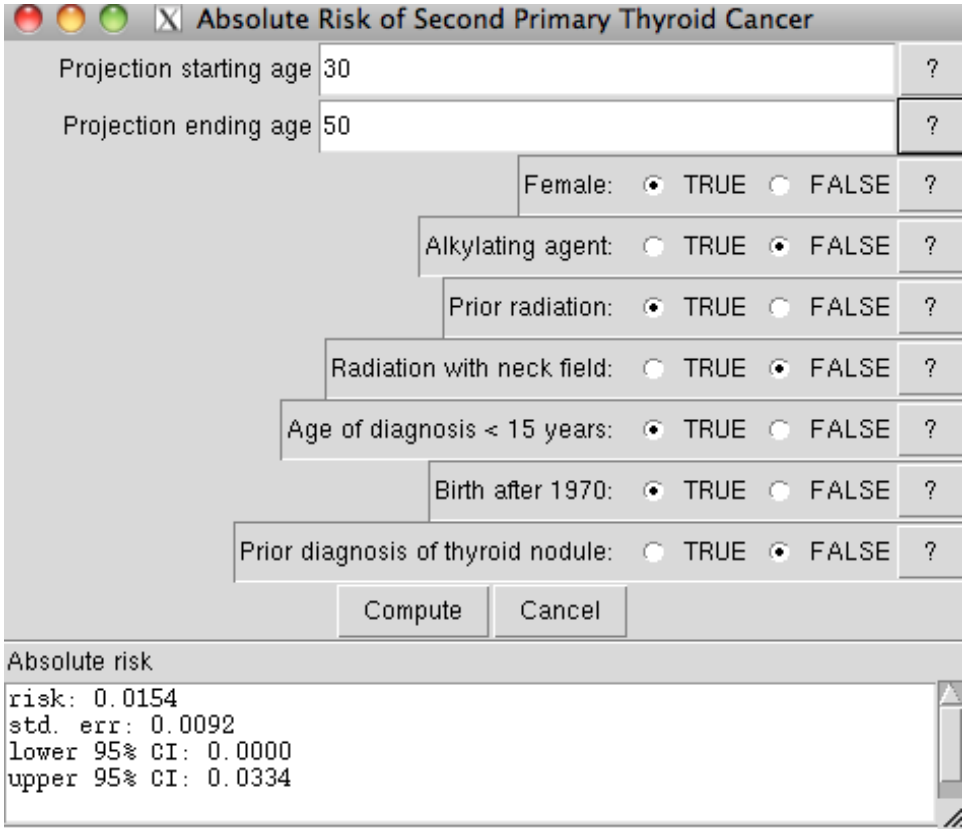
Step 1. Load package into R and invoke the SPTC risk calculator.



The following interface will appear.



Step 2. Input the starting age and ending age for the projection interval and the patient characteristics at the beginning of the projection interval. Select compute.



The output provides the estimated SPTC risk, its standard error, and the lower and upper 95% confidence limits (lower and upper 95%CI). All values are given as probabilities. A normal approximation is used for constructing the 95% confidence intervals that are truncated at zero to avoid negative lower limits.