Appendix

Material and methods

Source and organization of data

We described data acquisition in (1). For this analysis, we restricted data to doses <0.2 gray (Gy) and <0.1 Gy, resulting in the pooling of nine cohort studies with three diverse radiation sources, including treatment for cancer, treatment for benign diseases (tinea capitis, enlarged thymus, hemangioma and enlarged tonsils and adenoids) and Japanese atomic bomb survivors. Cases were those who developed incident thyroid cancer during follow-up, excluding non-melanoma skin cancer. For studies of benign diseases and atomic bomb survivors, thyroid cancer represented the first primary cancer, while for the cancer survivor cohorts, it represented the second primary cancer. For comparability across studies, we censored autopsy-identified thyroid cancers at date of death, but did not include them as cases.

There were minor differences in follow-up, numbers of patients and thyroid cancer cases in the pooled data from the individual studies in original publications (1). For most studies, person-time accrual started at first radiation exposure or at enrollment for non-exposed and continued until the earliest date of death, loss to follow-up, incident cancer or end of study. For the Atomic Bomb Survivors study, follow-up and case accrual started in 1958, 13 years after exposure. For the Childhood Cancer Survivor Study (CCSS) cohorts, follow-up started five years (CCSS-US) or three years (CCSS-Fr/UK) after first cancer (Appendix Table 1).

We analyzed data using Poisson regression and used study, sex, age at exposure (<1, 1-4, 5-9, 10-14, >15 years), calendar year of follow-up (<1935, 1935-1940,...,1995-1999,≥2000), time since exposure (<5, 5-9, 10-14, … , 45-49, ≥50 years), attained age (<10,10-14,…., 65-69, ≥70 years), exposure to chemotherapy (yes/no), thyroid radiation dose (0, >0-<0.005, 0.005-<0.01, 0.01-<0.02, ..., 0.19-<0.2 Gy) and number of radiation treatments (0, 1, ≥2), where one treatment represented all doses within six months, to cross-tabulate person-years. Regressions adjusted for study, sex and continuous age (age, age squared and the natural logarithm of age) and selected study-specific variables. For the Israel Tinea Capitis study, variables included country of origin (North Africa/Others) and comparison group (sibling/population). For the Rochester Thymus study, variables included the presence of goiter (yes/no) and Jewish religion (yes/no). For the Atomic Bomb Survivors study, variables included city of exposure (Hiroshima/Nagasaki), not in city at the time of the bombing (yes/no) and enrollment in the Adult Health Study (AHS) (yes/no). The latter variable accounted for surveillance-related differences in background thyroid cancer rates (2). For the CCSS cohorts, variables included type of first cancer (Hodgkin or other) and chemotherapy (yes/no) treatment. Since most radiation-exposed cases had only one treatment (84%), we assumed exposed patients with missing number of treatments had received one treatment. We computed person-years weighted means within each cell of the cross-tabulation for the continuous variables.

There were 142 non-exposed and 252 radiation-exposed thyroid cancer cases that accrued in 1,865,957 and 2,588,559 person-years of follow-up, respectively, for subjects with

doses <0.2 Gy (Appendix Table 1). For doses <0.1 Gy, in the radiation-exposed, there were 184 cases and 2,114,683 person-years of follow-up.

Appendix Table 1: Summary of cohort studies of thyroid cancer and external radiation exposure to the thyroid gland. Pooled data from nine cohorts with doses <0.2 Gy.

				Non-exposed		Exposed				
	Calendar years of:								Age at:	
Study: Place (reference)	Exposure	Cs accrual	%Female	Cs	P-yrs	Cs	P-yrs	Dose (gray)[a]	Exposure [a]	Dx [b]
Medical radiation: cancer treatment										
CCSS-Fr/UK: France, UK (3)	1942-2000	1946-2009	44	3	22,749	5	15,301	0.07	5.5 (0-19)	37 (27-57)
CCSS-US: USA and Canada (4)	1970-1986	1975-2006	49	9	61,707	3	15,741	0.09	7.5 (0-19)	27 (11-62)
Medical radiation: benign disease treatment										
Thymus: Rochester, USA (5)	1926-1957	1935-2008	49	7	208,347	1	28,051	0.13	0.1 (0-6)	44
Tinea Capitis: Israel (6)	1943-1960	1944-2007	50	54	733,027	132	587,600	0.08	7.2 (0-19)	38 (11-62)
Tonsils (MRH): Chicago, USA (7)	1939-1962	1939-2007	42	0	0	1	5,201	0.08	3.0 (0-15)	27
Hemangioma: Stockholm, Sweden (8)	1920-1959	1958-2005	67	0	0	22	520,100	0.05	0.5 (0-1)	44 (20-77)
Hemangioma: Göteborg, Sweden (9)	1930-1965	1958-2005	66	0	0	12	414,592	0.05	0.5 (0-1)	33 (13-57)
Hemangioma (IGR): France (10)	1940-1973	1942-2007	71	2	33,477	6	115,524	0.01	1.0 (0-19))	32 (27-36)
Environmental exposure										
Atomic Bomb Survivors [c]: Japan (11, 12)	1945	1958-2002	52	67	806,648	70	886,449	0.03	8.8 (0-19)	53 (21-73)
Pooled data	1926-2000	1935-2009	51	142	1,865,957	252 [d]	2,588,559	0.05	4.9 (0-19)	42 (11-77)

Cs, cases; P-yrs, person-years; gray (Gy); Dx, diagnosis of thyroid cancer; CCSS, Childhood Cancer Survivors Study; MRH, Michael Reese Hospital; IRG, (*Institut Gustave-Roussy)*; France (Fr); United Kingdom (UK); United States of America (USA)

[a] Person-years weighted mean among radiation exposed for doses <0.2 Gy.

[b] Ages at incidence of thyroid cancer.

[c] Ages at exposure <20 years. Exposed defined as ≥0.01 gray to the thyroid.

[d] For <0.1 Gy, there were 184 exposed thyoid cancer cases from CCSS-Fr/UK UK (3), CCSS-USA (4), Tinea Capitis (6), Hemangioma: Stockholm (8), Hemangioma: Göteborg (9), Hemangioma: France (10) and Atomic Bomb Survivors Japan (11).

Models for thyroid cancer risk

We modeled the thyroid cancer incidence rate, $\mathrm{r}(x, d, c)$, using a vector of explanatory variables, *x*, which varied with analysis but generally included study, sex, attained age, year of birth and other factors, an indicator variable for CCSS patients with chemotherapy exposure, *c*, and thyroid radiation dose, *d*. Previous analysis determined that an additive model best described the joint association of radiation exposure and treatment with chemotherapy (*c* =1 if yes and *c* =0 if no). In an additive relationship for two factors (radiation dose and chemotherapy), often termed non-synergistic, the incidence rate for exposure to both factors, $\mathrm{r}(x, d, c)$, equals the sum of the incidence rate in the absence of both factors, $\mathrm{r}(x, 0, 0)$, and the individual excess rates at the referent level of the other, $\{\mathrm{r}(x, d, 0) - \mathrm{r}(x, 0, 0)\}$ and $\{\mathrm{r}(x, 0, c) - \mathrm{r}(x, 0, 0)\}$ (13, 14), expressed symbolically as

$$\mathrm{r}(x, d, c) = \mathrm{r}(x, 0, 0) + \{\mathrm{r}(x, d, 0) - \mathrm{r}(x, 0, 0)\} + \{\mathrm{r}(x, 0, c) - \mathrm{r}(x, 0, 0)\}$$

We rewrote the additive model as

$$\mathrm{r}(x, d, c) = \mathrm{r}_0(x)\,\{1 + \mathrm{ERR}(d) + \theta\, c\} \qquad (1)$$

where $\mathrm{r}_0(x)=\mathrm{r}(x, 0, 0)=\exp(\varphi\, x)$ was the thyroid cancer incidence rate among non-radiation, non-chemotherapy exposed individuals with φ a vector of parameters, ERR(*d*) was the radiation-associated excess relative risk (ERR) and θ was the excess relative risk of chemotherapy. For doses <0.2 Gy, we fitted a linear model, ERR(*d*) = β *d*, to the data and examined departures from linearity using power

$$\mathrm{r}(x, d, c) = \mathrm{r}_0(x)\,\{1 + \beta\, d^{\delta} + \theta\, c\}$$

and linear-exponential

$$\mathrm{r}(x, d, c) = \mathrm{r}_0(x)\,\{1 + \beta d \exp(\delta d) + \theta\, c\}$$

forms; results were similar and we reported P-values only for the former. We computed a likelihood-based 95% confidence interval (CI) for estimates of β.

A threshold dose designates a dose below which there is no apparent radiation effect. We conducted a profile search to find the maximum likelihood estimate of the threshold under a linear model, namely, ERR(*d*) = β $(d - \eta)_+$, where $(d - \eta)_+ = \max(0, d - \eta)$ with η the unknown threshold. Finally, we also employed a less restrictive semi-parametric modeling

approach and fitted a restricted cubic spline with 4-knots with knots identified using the AIC and a grid search (15, 16).

For a categorical effect modifier *z* with J levels,$(\sum_j \beta_j z_j)$ replaced β, where z_j was an indicator variable and β_j was the ERR/Gy for the j^{th} category, i.e.,

$$r(x, d, z, c) = r_0(x) \{1 + (\sum_j \beta_j d z_j) + \theta c\} \quad (2)$$

We evaluated sex, age at radiation exposure, attained age, time since exposure and number of radiation treatments as potential modifiers of dose effects and evaluated effect modification with a likelihood ratio tests which compared deviances for Appendix equations 1 and 2. We also fitted models that included continuous modifiers, i.e., ERR(*d*, *z*) = β *d* g(*z*), where we identified the best fitting model using ln{g(.)} and $z, z^2, \ln(z) \text{ and } \ln(z)^2$.

The best-fitting model across the full range of radiation doses in excess of 70 Gy was the following (1):

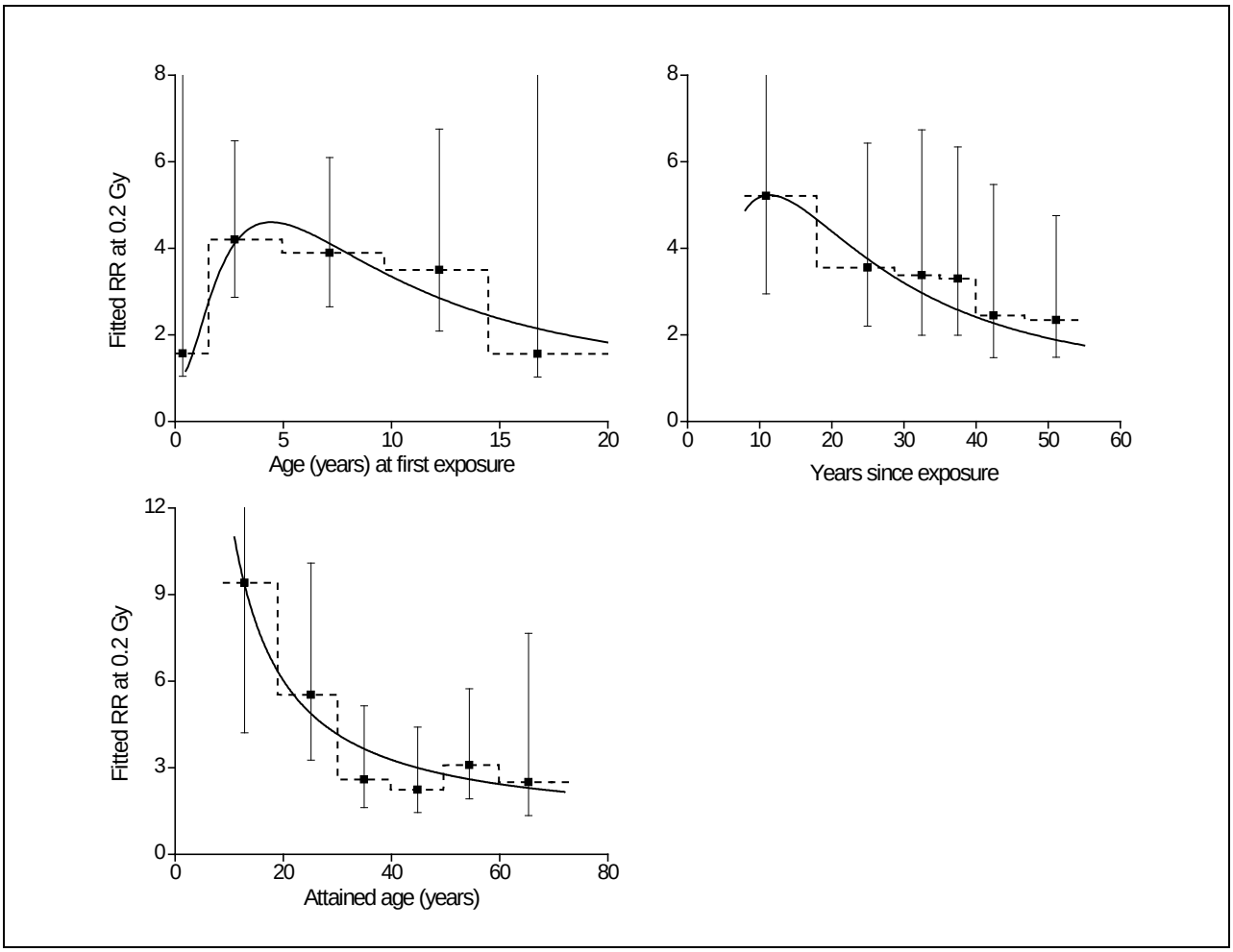
$$ERR(d) = \beta d \exp\{\gamma_1 d + \gamma_2 d^2 + \gamma_3 \ln(d)\} \quad (3)$$

We fitted equation 3 to the nine studies using all doses to compute downward extrapolations for comparison of fitted RRs at 0.2 Gy with estimates from models that we developed in restricted data. We note that equation 3 embedded a linear, $\gamma_1 = \gamma_2 = \gamma_3 = 0$ model.

We smoothed the log-RRs in Figure 1 using a procedure similar to Pierce and Preston (17). For a 5-point moving average, we used the log RRs with prior weights of 0.10, 0.25, 0.30, 0.25, 0.10 and used the covariance matrix with weights assumed fixed to obtain standard errors.

Results – effect modification

Table 2 provides the fitted relative risk (RR) at 0.2 Gy overall and for categories of various potential effect modifiers. Age at first exposure, time since exposure and attained age were of particular note. Appendix Figure 1 shows the category-specific fitted estimates at 0.2 Gy (solid symbol) and fitted models using continuous variables for the modifiers (solid line).



Appendix Figure 1: Fitted relative risks (RR) at 0.2 Gy based on a linear excess RR model with additive adjustment for use of chemotherapy accounting for effect modification by categories of age in years at first radiation exposure, years since first radiation exposure and attained age in categories (solid symbol) ($RR_{0.2\ Gy}$ in main text Table 2 with 95% CI) and with a best fitting model based on the Akaike Information Criterion using continuous variables (solid line). Data pooled from nine cohort studies and limited to <0.2 Gy.

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