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Risk of Thyroid Cancer after Childhood Exposure to Ionizing Radiation for Tinea Capitis*

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Background: The thyroid gland is known to be sensitive to the carcinogenic effect of ionizing radiation, especially in children. The role of potential modifiers of the risk and latency period effects needs further investigation. We examined the effect of low doses of ionizing radiation (4.5–49.5 cGy) on the risk of developing thyroid cancer after long latent periods of up to 54 yr after childhood exposure.

Methods: The study population included 10,834 individuals irradiated against tinea capitis in the 1950s and two matched nonirradiated groups (general population and siblings) for comparison. Cancer statistics and vital status data were obtained from national registries, updated to December 2002. Excess relative and absolute risks [excess relative risk per gray (ERR/Gy), excess absolute risk (EAR)] were estimated using Poisson regression for survival analysis.

Results: Within the study period, 159 cases of thyroid cancer were diagnosed. Total ERR/Gy and excess absolute risk per gray per 10^4 person-years for developing thyroid cancer reached 20.2 (95% confidence interval 11.8–32.3) and 9.9 (95% confidence interval 5.7–14.7), respectively. The risk was positively associated with dose and negatively associated with age at exposure. ERR/Gy was significantly elevated 10–19 yr after exposure, peaking at 20–30 yr, and decreasing dramatically (although still significantly elevated) 40 yr after exposure.

Conclusions: Our findings agree with patterns of risk modification seen in most studies of radiation-induced thyroid cancer, although risk per unit dose seems higher. Our data show that 40 yr after irradiation, ERR decreases dramatically, although remaining significantly elevated. The hypothesis of different genetic susceptibility of the Jewish population deserves further exploration. **(*J Clin Endocrinol Metab* 91: 4798–4804, 2006)**

THE THYROID GLAND is highly sensitive to the carcinogenic effect of ionizing radiation, especially in children (1–5). On the basis of a pooled analysis comprising almost 120,000 people and 3 million person-years (PY), Ron *et al.* (6) estimated the influence of various modifying factors on the risk of developing thyroid cancer (TC) after exposure to ionizing radiation. This quantitative summary was published in 1995 and incorporated all available studies that met the inclusion criteria: exposure to external radiation, adequate individual dose information, at least 1000 irradiated subjects for prospective studies, and more than 20 cases for case-control studies. The mean follow-up periods in the five pooled studies ranged between 24 and 33 yr. The pooled excess relative risk per gray (ERR/Gy) was 7.7 [95% confidence interval (CI) 2.1–28.7] for persons exposed before age 15 yr; the estimated risk was strongly affected by age at exposure (the data on adult exposure were limited and not convincing), was greater for females than males (although with borderline significance, $P = 0.07$), and whereas still elevated 40 yr after the exposure, it began to decline after about 30 yr. The authors concluded that linearity best describes the dose-response curve for dose ranges of 0.10 Gy up to more than 10 Gy, in which a leveling off in the risk appeared to occur (6).

The tinea capitis cohort is one of the studies included in this pooled analysis. The cohort was initiated in 1965 to investigate the possible health outcomes of irradiation treatment given to children in Israel to cure tinea capitis, a fungal infection of the scalp. This treatment was given in an organized way during the 1950s by the Israeli Ministry of Health to more than 20,000 individuals in Israel (mainly children, newly arrived immigrants from North Africa and to a lesser extent from the Middle East) and an additional unknown number of people abroad (7).

The cohort comprised irradiated individuals and two comparison groups: general population and siblings. In the first follow-up, updated to December 1972, it was found that radiation caused at least a doubling of the incidence rates of head and neck tumors, especially those of the brain and thyroid gland (8). This pattern was repeatedly observed in additional follow-ups (1, 9). The last publication on TC risk, updated for malignant TC to 1986 and for benign tumors to 1980, showed a relative risk of 4.0 (95% CI 2.3–7.9), and 2.0 (95% CI 1.3–3.0) for these tumors, respectively (1). This last report on the tinea capitis cohort gave a mean follow-up period of 30 yr.

The aim of the present report was to add 16 yr of follow-up

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* This paper is dedicated to the memory of the late Dr. Baruch Modan, who was the initiator and leader of the tinea capitis studies in Israel for more than 30 yr.

Abbreviations: AT, Ataxia telangiectasia; CI, confidence interval; EAR, excess absolute risk; ERR/Gy, excess relative risk per gray; LRT, likelihood ratio test; PY, person-years; TC, thyroid cancer.

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after the last update of this cohort and assess the excess relative and absolute risks of radiation-induced TC over a long follow-up period updated to December 2002. In this analysis, we investigated the role of individual dose, age at irradiation, attained age, gender, ethnic origin, and especially the effect of the latent period on the risk of developing TC after childhood exposure to ionizing radiation.

Subjects and Methods

Study population

The tinea capitis cohort included 10,834 subjects irradiated in Israel, an equal number of nonirradiated persons derived from the national population registry, individually matched to the exposed subjects by age (± 2 yr), gender, country of birth, and year of immigration and 5,392 nonirradiated siblings matched for gender, when possible, and age ± 5 yr. Because both disease and treatment often involved complete families, this group could be located in only about 50% of the cohort (8).

Exposure to radiation and dosimetry

The therapeutic procedure followed the Adamson-Kienbock technique. The heads were shaved and the remaining hair removed through a waxing process. Subsequently the scalp area was divided into five fields, each treated on one of 5 consecutive days.

The irradiation was performed with a 75- to 100-kV superficial therapy x-ray machine. The air exposure at a focus-skin distance of 25–30 cm ranged between 350 and 400 roentgens/field, depending on age. Most patients received one course of therapy (5 consecutive days), and about 9% of the patients received two or more courses. On the basis of a dosimetry study that was conducted in the 1960s (11), individual average doses to different organs were estimated for each irradiated case. These assessments took into account age and gender (highly correlated with the size of the child), center of irradiation, number of treatments, and probable head movements during treatment (1).

The mean average dose to the thyroid gland for all irradiated individuals was 9.3 cGy (range 4.5–49.5 cGy). The estimated doses for children who received one course (about 91% of the cohort) or more than one course of therapy were 8.4 cGy (range 4.5–16.5 cGy) and 18.4 cGy (range 9.0–49.5 cGy), respectively (1).

Data collection

Information on tumor development was obtained from the Israeli Cancer Registry and included cases diagnosed up to and including December 2002. This registry was established in 1960 and is notified by law of all malignant tumors. According to a recent survey, the completeness of this registry is 95% for malignant tumors (12). Each tumor diagnosis was ascertained through medical documents (pathology, surgery, and hospitalization records). Vital status was updated to December 2002 through the Israeli Population Registry.

Additional details on the methodological aspects of this study are available in previous publications (8, 13). The study was approved by the Chaim Sheba Medical Center Review Board Committee.

Statistical methods

We estimated the effect of irradiation on TC development in terms of ERR and excess absolute risk (EAR). The analysis was carried out essentially as described in a previous publication (13), and the models used are described in the *Appendix*, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

We performed Poisson regression to estimate and compare the risks in the irradiated cohort *vs.* the two nonirradiated cohorts combined, including matching variables in all the models. We combined the two unexposed cohorts (population and siblings) because: 1) the rates of TC in the two comparison groups were lower than the rates among the exposed; and 2) the observed to expected ratio of TCs in the sibling and population comparison groups did not differ (17:19.2, compared with 39:38.8, $P = 0.66$).

For irradiated persons, the period of observation was defined as starting from the date of exposure and for nonirradiated persons starting from the date of exposure of their irradiated matched pair. End of follow-up was defined as thyroid tumor diagnosis, death, or December 31, 2002, whichever occurred first.

For the Poisson analysis, the data were arranged as a multiway table with each cell corresponding to a separate combination of the categorized variables: gender; age at irradiation (categorized as nonirradiated, <5 yr, 5–9 yr, and ≥10 yr); latency, defined as time since exposure (categorized as nonirradiated, <10, 10–19, 20–29, 30–39, and ≥40 yr); ethnic origin (Middle-Eastern born, North African born, and Israeli born); and attained age (categorized in 2-yr age groups). The time scale was defined by attained age. The fine categorization by attained age was necessary for studying the time-dependent covariates. The number of events, number of PY, and mean value of estimated radiation dose were calculated for each cell and constituted the input to the Poisson model.

All calculations were performed using the AMFIT program of the Epicure software package (14). The overall *P* value for each category of a given variable was derived from the likelihood ratio test (LRT), obtained by comparing the model with and without the relevant dummy variable. The significance of linear trends was tested using the LRT. Occasionally when the profile likelihood was nearly flat, the lower boundary for the dose response estimates could not be determined (see Ref. 14, pp. 56–57).

Results

Table 1 presents the characteristics of the irradiated population, showing approximately equal numbers of males and females and a preponderance of subjects of North African origin (59%). The follow-up period ranged from 1 to 54 yr (median 46 yr); the mean age at irradiation was 7.1 ± 3.1 yr (range <1 yr to 15 yr) and the mean age at end of follow-up was 52.1 ± 7 (range 19–68 yr).

TABLE 1. Distribution of the study irradiated cases (n = 10,834) by demographic and radiation-related characteristics

	n	%
Demographic characteristics		
Gender		
Males	5298	48.9
Females	5536	51.1
Birth year		
1934–1944	1892	17.5
1945–1949	3985	36.8
1950–1959	4957	45.7
Ethnic origin		
Israel	2331	21.5
Middle East	2137	19.7
North Africa	6366	58.8
Year of immigration		
1948–1951	3188	37.5
1952–1955	3052	35.9
1956–1959	2263	26.6
Radiation-related characteristics		
Follow-up period (yr)		
Range	1–54	
Median	46	
Age at irradiation		
0–4	2513	23.2
5–9	5888	53.9
≥10	2583	22.9
No. of irradiations		
1	9814	90.6
2	904	8.4
3	110	1.0
4	6	0.1
Dose to thyroid (cGy)		
Range	4.5–49.5	
Median	8.7	

Overall, 159 cases of TC (103 in irradiated, 56 in nonirradiated) were diagnosed during the study period. There were no pairs of irradiated and nonirradiated matched siblings who both developed TC. In all groups the papillary and mixed tumors were the most frequent histological types, comprising 79.6 and 78.6% of all tumors in the irradiated and nonirradiated groups, respectively. The follicular type comprised 14.6 and 12.5% of the tumors in these groups, respectively (data not shown).

The number of PY observed for the calculation of the risk of developing TC in the study groups was: 487,233 in the irradiated group, 490,803 in the nonirradiated population group, and 243,271 in the nonirradiated siblings (Table 2). The crude incidence rates of TC per 10^4 PY were very similar between the two control groups ($0.79/10^4$ PY and $0.70/10^4$ PY for population and sibling groups, respectively, $P = 0.7$). This similarity remained when rates were subdivided by gender ($P > 0.5$ for both males and females). Therefore, as mentioned in *Subjects and Methods*, the two nonexposed groups were combined in subsequent analyses.

As shown in Table 3, the crude incidence rates of TC per 10^4 PY in the study groups showed substantially higher rates of tumors among the irradiated group as compared with the two nonexposed groups combined ($2.11/10^4$ PY, compared with $0.76/10^4$ PY, respectively, $P < 0.001$). In both groups the rates of TC were about 3-fold in females, compared with males. A significant positive trend with attained age was observed among both exposed and nonexposed individuals ($P < 0.001$).

The total ERR/Gy for developing TC after irradiation was 20.2 (95% CI 11.8–32.3). For all categories of gender, ethnic origin, attained age, age at irradiation, number of irradiations, and latent period, the ERR/Gy demonstrated a significantly higher risk for this tumor among the irradiated *vs.* the nonirradiated comparison group (Tables 3 and 4).

The risk for developing thyroid tumors was positively associated with dose. The ERR by quintiles of dose was 1.6 (95% CI 0.6–3.1) for doses of 4.5–5.9 cGy, rising to 4.2 (95% CI 2.3–6.9) for doses of more than 11 cGy (P for trend $<$ 0.001). The ERR for low doses ($<$10 cGy) was 1.19 (95% CI 0.53–2.15), whereas the ERR for higher doses ($\geq$10 cGy) was 3.53 (95% CI 1.99–5.80) (data not shown). Compared with the linear dose model, the linear-quadratic dose-response model did not improve the goodness of fit for the risk for either the whole range of doses or doses less than 10 cGy (LRT, $P = 0.75$ and 0.3, respectively) (Fig.1). We therefore proceeded with a linear model in the analysis, as recommended in the literature (15, 16).

As shown in Table 3, the ERR/Gy did not differ significantly between categories of gender, ethnic origin, and attained age, meaning that no interaction was found between dose of irradiation and these variables regarding the risk of developing TC. However, although not statistically significant, the ERR/Gy for subjects of North African origin was higher than for those of Israeli or Middle Eastern origin (28.2 *vs.* 13.6 and 13.4, $P = 0.15$, respectively). The association between irradiation and the development of TC was modified by age at irradiation ($P = 0.02$ by LRT); the highest ERR/Gy was noted for subjects exposed in the youngest age group (33.9 *vs.* 12.9 and 21.1, for age groups $<$5, 5–9, and 10+, respectively, P for $<$5 *vs.* 5+ = 0.01) (Table 4).

In the first 10 yr after the exposure, only five cases occurred among the irradiated group, compared with four in both nonexposed groups. The first case of TC recorded occurred in a 14-yr-old irradiated person 4 yr after the irradiation; the second occurred in a 20-yr-old nonirradiated sibling 8 yr after the irradiation of his matched irradiated sibling (data not shown). Significantly elevated ERR/Gy was first noticed for latent periods of 10–19 yr after exposure, reaching about 29 in the 20–30 yr after exposure. A dramatic decrease in the ERR was observed 40 yr after exposure ($P = 0.04$ for 40+ *vs.* 10–39 yr). No difference in the ERR was found relative to the number of irradiations.

The ERR/Gy for papillary and follicular tumors was 20.5 (95% CI 11.0–34.8) and 27.8 (95% CI 6.1.–89.0). However, this difference was not statistically significant ($P = 0.8$).

Table 5 describes the EAR for TC by attained age and gender showing a total EAR estimate of 9.9/Gy per 10^4 PY. The EAR/Gy per 10^4 PY was about 4-fold greater for females, compared with males ($P = 0.001$). The EAR/Gy per 10^4 PY rose from about 9 to about 19–24 after attained age of 40 yr ($P = 0.02$).

Discussion

In this study we assessed the role of childhood exposure to external low doses of ionizing radiation (4.5–49.5 cGy) in the development of TC after long latent periods of up to 54 yr. This study adds 16 more years of follow-up and 100 newly diagnosed cancers to the previous report on this cohort (1).

In agreement with previous studies (2, 17–21), we confirmed that the thyroid gland in children is highly sensitive to the carcinogenic effect of ionizing radiation. Yet the ERR/Gy of 20.2 (95% CI 11.8–32.3) that we found is 2–18 times higher than that reported in comparable studies (6). The present estimate nevertheless falls well within the CI of the overall estimate derived from the pooled analysis (2.1–28.7).

A possible explanation for the high risk estimate seen in our study could be an error in individual estimates of dose to the thyroid gland (*e.g.* due to the extensive movement of the child or a deviation from the routine guidelines of the treatment). Schaffer *et al.* (22) and Lubin *et al.* (23), who investigated the impact of such uncertainties in the tinea

TABLE 2. Number, PY, and rates per 10^4 PY by study group

	Exposed			Population			Siblings		
	n	PY	Rate per 10^4 PY	n	PY	Rate per 10^4 PY	n	PY	Rate per 10^4 PY
Total	103	487,233	2.11	39	490,803	0.79	17	243,271	0.70
Males	22	243,271	0.92	8	239,143	0.34	5	127,453	0.39
Females	81	249,370	3.25	31	251,660	1.23	12	115,818	1.04

TABLE 3. Rates per 10^4 PY, ERR/Gy, and 95% CIs for malignant thyroid by selected demographic variables

	Exposed		Nonexposed		ERR/Gy	95% CI
	n	Rate per 10^4 PY	n	Rate per 10^4 PY		
Total	103	2.11	56	0.76	20.2	11.8–32.3
Gender[a]						
Males	22	0.92	13	0.35	17.3	3.6–46.8
Females	81	3.25	43	1.17	21.1	11.5–35.6
Ethnic origin[b]						
Israel	13	1.27	8	0.52	13.6	1.3–46.5
Middle East	24	2.31	27	0.63	13.4	3.3–32.1
North Africa	66	2.43	21	1.36	28.2	14.2–51.7
Attained age, yr[c]						
<20	13	0.94	6	0.29	27.1	5.3–94.4
20–29	20	1.88	11	0.69	18.0	3.5–51.3
30–39	23	2.19	11	0.69	23.4	6.7–61.7
40–49	31	3.12	15	1.02	23.0	8.1–53.2
50+	16	4.21	13	2.13	10.9	−1.0–37.7

[a] ERR: males *vs.* females, $P = 0.7$.
[b] ERR: North Africa *vs.* Israel and Middle East, $P = 0.15$.
[c] Linear trend for ERR, $P = 0.3$.

capitis studies, concluded that the measurement error in dosimetry has a minimal effect on dose-response estimation and inference.

Ron *et al.* (6) explained this higher risk assessment seen in the tinea study by possible methodological, ethnic, socioeconomic, and/or medical system differences existing between studies. An increased genetic susceptibility of our study population might be a plausible explanation for this phenomenon. The ataxia telangiectasia mutated (ATM) protein is activated primarily in response to double-strand breaks (known to be the major cytotoxic lesion caused by ionizing radiation) and plays a central role in subsequent initiation of signaling pathways (24). The AT gene is responsible for the autosomal recessive disorder ataxia telangiectasia (AT), characterized by cerebellar degeneration, immunodeficiency, and cancer predisposition (25). Studies dating back to the early 1970s suggested an elevated incidence of cancer in AT patients' blood relatives who are probably heterozygous (26). In the community of North African Jews in Israel, to which more than half of our cohort belongs, a founder mutation (designated 103C→T) for the AT gene was found (27). The frequency of this founder mutation in the above-mentioned population is about 1.2%, making this gene a possible candidate to explain such an effect (27).

Data from the Rochester study also suggested that Jewish subjects appeared to be at higher radiogenic risk than others ($P = 0.003$) (28).

The EAR per 10^4 PY Gy seen in our results (9.9, 95% CI 5.7–14.7) is also more than twice as high as the estimates derived from the pooled analysis (4.4, 95% CI 1.9, 10.1). This is compatible with the nature of the EAR, which reflects background rates, and with the fact that Israel presents higher rates of TC, compared with most Western countries. The increase in EAR seen with attained age and especially the sharp increase at ages 40+ yr is compatible with the peak in incidence rates of TC occurring at 40–60 yr (29).

TABLE 4. Rates per 10^4 PY, ERR/Gy, and 95% CIs for malignant thyroid by radiation and clinical related variables

	Exposed		ERR/Gy	95% CI	*P*
	n	Rate per 10^4 PY			
Age at irradiation, yr[a]					
<5	33	2.95	33.9	18.6–57.2	0.02
5–9	44	1.68	12.9	5.2–24.4	
10+	26	2.30	21.1	6.5–43.2	
Latent period[b]					
<10	5	0.49	16.4	−74.9	0.4
10–19	20	1.87	23.9	7.8–55.1	
20–29	25	2.37	28.9	11.5–59.9	
30–39	30	2.88	27.1	11.9–52.0	
40+	23	3.36	9.7	1.2–24.3	
No. of irradiations					
1	89	2.02	21.2	11.8–34.7	0.6
2+	14	3.02	17.8	7.0–35.1	
Histological type[c]					
Papillary[d]	82	1.69	20.5	11.0–34.8	
Follicular	15	0.31	27.8	6.1–89.0	
Other	6	0.12	11.4	−4.0–67.5	

[a] <5 *vs.* 5–9, $P = 0.006$; 5–9 *vs.* 10+, $P = 0.3$; <5 *vs.* 5+, $P = 0.01$; P for linear trend for the three age groups = 0.07.
[b] <10 *vs.* 10 +, $P = 0.7$; 10–39 *vs.* 40+, $P = 0.04$.
[c] $P = 0.8$ (for papillary *vs.* follicular).
[d] Including mixed tumors (papillary carcinoma and follicular variant).

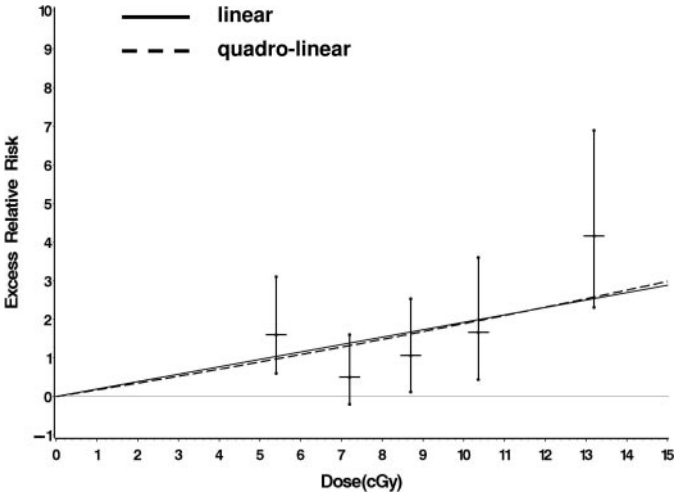

FIG. 1. Dose-response association for thyroid cancer: ERR and 95% confidence limits by quintiles of dose and linear and linear-quadratic curves. Likelihood ratio test of fit of linear-quadratic *vs.* linear models: $P > 0.75$, adjusted for gender, place of birth, and birth year.

Latency

TC was the first solid tumor found to have a significantly increased incidence among A-bomb survivors (30). In most studies, the minimal latency periods reported are 5–10 yr, and the excess of TC becomes more pronounced 10–15 yr after irradiation (28, 31). Shorter intervals were observed after the Chernobyl accident (4, 32). In our cohort a significant ERR was observed starting from 10 yr after the irradiation.

The determination of the temporal sequence for developing thyroid neoplasm after irradiation is not fully known because no population has yet been followed up throughout its lifetime. In a recent report on the A-bomb survivors, an elevated risk for thyroid tumors was shown 55–58 yr after the exposure (5). It is important to mention that the more aggressive forms of all differentiated TCs appear in older patients (17). This emphasizes the importance of long-term cohort studies that could determine the risk for the maximal follow-up period. An analysis of the latent period in consecutively diagnosed TC patients overcame this problem. Kikuchi *et al.* (33) evaluated this issue in 171 radiation-associated thyroid tumors patients and found a mean latency period of 28.4 and 34.1 yr for malignant and benign tumors, respectively.

In our results the ERR/Gy increased to a maximum at 20–39 yr after irradiation. However, there is no indication that the radiation effect disappears, even 40 yr after the exposure. Ron *et al.* (6) showed that the excess risk peaked at 15–19 yr after the exposure, with a leveling off in the risk from 30 yr after irradiation.

TABLE 5. EAR per gray per 10^4 PY and 95% CI for TC by attained age

	EAR per gray per 10^4 PY	95% CI
Total	9.9	5.7–14.7
Gender[a]		
Males	4.8	1.0 –9.7
Females	19.4	11.9–28.0
Attained age (yr)[b]		
<20	4.6	0.1–11.2
20–29	10.5	2.5–21.2
30–39	10.9	1.3–22.9
40–49	18.9	7.7–32.7
50+	23.7	0–56.2

[a] $P = 0.001$.
[b] Linear trend, $P < 0.001$; <40 *vs.* 40+, $P = 0.02$.

Age at exposure

ERR for most cancers seems to decrease with increasing age at exposure (2, 13, 18, 32, 34). Our finding of a highest risk for TC among those exposed in the youngest age group is biologically plausible and in line with other studies (5, 6, 35, 36). In a thorough review on the induction of TC in humans by ionizing radiation, Shore (31) compared the risk estimates from studies of juvenile and adult irradiation. He found lower risk estimates after adult exposure by about a factor of 9 than those after juvenile irradiation. A recent study on the A-bomb survivors also showed no significant dose-response relationship for TC among age at exposure of 20 yr or older (5).

Gender

The incidence rates of TC are higher in females, compared with males. This might explain our observation of an EAR about 4-fold higher in females, compared with males ($P = 0.001$), yet it is not clear whether the thyroid gland of females is more susceptible to the carcinogenic effect of ionizing radiation. The higher ERR/Gy seen in our data for females, compared with males (21.2 *vs.* 17.3, respectively), was not statistically significant. In the pooled analysis, the combined ERR was greater for females than males, with marginal statistical significance ($P = 0.07$). However, the findings from the individual studies were not consistent (6).

Dose response

In radiation studies, one of the more important issues that have profound practical implications for determination of radiation protection guidelines is the shape of the dose-response curve, especially regarding low doses, in which most of the medical diagnostic exposure occurs. According to our data, significant ERRs are shown for low doses of 4 to less than 10 cGy. The tinea capitis study provides risk estimates directly interpolated for doses of 4–50 cGy. Extrapolation of our results to doses outside the range of our data should be interpreted with caution. Most radiation studies were based on cohorts exposed to higher doses (*e.g.* among the seven studies quoted in the pooled analysis, the doses in the tinea study are between 1.2 and 140 times lower than doses for cervical cancer and childhood cancer, respectively). As mentioned above, the linear model fits our data over the whole range of doses as well as for doses of less than 10 cGy, and the linear quadratic model did not significantly improve the goodness of fit. This is in line with other solid tumor studies in general as well as those dealing with TC in particular (2, 5, 17, 18, 31, 37).

There is a fair amount of data derived from *in vivo* animal

experiments, suggesting that fractionated exposure is less carcinogenic than acute exposure. At this time, the human data are not adequate to fully address this issue (21, 38). Unfortunately, considering the strong relationship between dose and fractionation in our cohort, we could not examine this issue.

Histological type

Our results did not show significant differences between the ERR/Gy of papillary and follicular cancers. This similarity should be taken with caution because many of the diagnoses of the latter have been made decades ago, before the understanding that some follicular cancers are in fact follicular variants of papillary cancers.

Screening

Screening for nodular thyroid disease has a pronounced effect on ascertainment. Therefore, although no screening programs to detect early TC among the irradiated population exist in Israel, the possibility of a detection bias should be considered. An attempt to screen the irradiated population was made in Israel in the early 1980s. No cancers were detected among 443 persons who complied with the program (39).

Our data did not show a rise in the relative risk of developing TC between the exposed and nonexposed subjects, despite wide publicity (in the late 1980s) (1) and after the introduction of the compensation law in 1994 (7). A comparison of the incidence rates between the irradiated population and their population of nonexposed controls showed a relatively stable rate ratio over time.

Limitations

Among the possible limitations of this study are the heterogeneity in the validation of the diagnosis because we did not perform pathological review. It is worth mentioning that a histological review made in the 1980s by Ron *et al.* (10) on 59 samples of this cohort suggested that the discrepancy between the original hospital and study review diagnoses was not statistically significant and did not affect the conclusions regarding radiation exposure risk.

Among the advantages of this study are the relatively large irradiated population, well validated for the exposure, two individually matched nonexposed comparison groups, a high ascertainment rate of tumor and vital status through national registries, and the availability of estimated individual dosimetry. Due to the verification of exposure through original treatment records, any misclassification of the exposure (exposed/unexposed) must result from unknown exposure among the supposedly nonirradiated comparison groups. Such misclassification, if it exists, would cause only underestimation of the true association.

In conclusion, this report adds more data on the long-term effects of childhood exposure to ionizing radiation. In general, our findings are compatible with the patterns of risk modification seen in most studies of radiation-induced TC, although the risk per unit dose appears to be higher. The hypothesis of different host susceptibility factors that might exist in the Jewish population should be further explored in special genetic epidemiological studies.

Most studies have demonstrated risks after acute thyroid doses of 0.5 Gy to several grays (31). Our study is the largest of the few studies that have evaluated the effect of external thyroid doses of the order of 0.1 Gy. The carcinogenic effects of low-level radiation must be considered in the planning of safety measures against potential public health hazards.

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