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Long-Term Follow-up for Brain Tumor Development after Childhood Exposure to Ionizing Radiation for Tinea Capitis

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Ionizing radiation is an established risk factor for brain tumors, yet quantitative information on the long-term risk of different types of brain tumors is sparse. Our aims were to assess the risk of radiation-induced malignant brain tumors and benign meningiomas after childhood exposure and to investigate the role of potential modifiers of that risk. The study population included 10,834 individuals who were treated for tinea capitis with X rays in the 1950s and two matched nonirradiated groups, comprising population and sibling comparison groups. The mean estimated radiation dose to the brain was 1.5 Gy. Survival analysis using Poisson regression was performed to estimate the excess relative and absolute risks (ERR, EAR) for brain tumors. After a median follow-up of 40 years, an ERR/Gy of 4.63 and 1.98 (95% CI = 2.43–9.12 and 0.73–4.69) and an EAR/Gy per 10^4 PY of 0.48 and 0.31 (95% CI = 0.28–0.73 and 0.12–0.53) were observed for benign meningiomas and malignant brain tumors, respectively. The risk of both types of tumors was positively associated with dose. The estimated ERR/Gy for malignant brain tumors decreased with increasing age at irradiation from 3.56 to 0.47 ($P = 0.037$), while no trend with age was seen for benign meningiomas. The ERR for both types of tumor remains elevated at 30-plus years after exposure.

INTRODUCTION

The carcinogenic effect of ionizing radiation is well established (*1–4*). Nevertheless, the fact that brain and meninges tissues are also sensitive to radiation was accepted relatively late compared to other solid tumors. Several follow-up studies demonstrating the influence of ionizing radiation on the brain refer to ''brain tumors'' without differentiating between benign and malignant neoplasms or to the type of tissue involved (meninges, glial cells, etc.) (*5–7*). In addition, specific features of the effect of radiation on the brain such as the risk over time and the dose–response curve have not been fully studied and need further investigation.

Between 1948 and 1960, about 20,000 Israeli individuals, particularly children, were treated with ionizing radiation to the head area for tinea capitis, a benign fungal disease of the scalp. This population was composed mostly of newly arrived immigrants from North Africa and to a lesser extent from the Middle East.

In 1968, our group initiated a comprehensive follow-up of a cohort comprised of irradiated individuals and two comparison groups to determine possible delayed radiation effects. 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 (*4*). This pattern was observed repeatedly in additional follow-ups (*8, 9*). The high relative risk (RR) observed for meningioma (RR = 9.5; 95% CI = 3.5–25.7) was especially striking; a RR of 2.6 was seen for glioma (95% CI = 0.8–8.6) (*8*).

The aim of the present report is to assess the risk of radiation-induced malignant brain tumors and benign meningiomas over a long follow-up period of about 40 years. In this analysis, we have investigated the role of age at irradiation, individual dose, latent period, attained age, gender and ethnic origin on the risk of developing brain tumors after childhood exposure to ionizing radiation.

METHODS

The tinea capitis cohort includes 10,834 irradiated subjects, an equal number of nonirradiated persons derived from the national population registry and individually matched to the exposed subjects by age (±2 years), gender, country of birth and year of immigration, and 5,392 nonirradiated siblings. This latter group was matched to the exposed group using wider categories: gender (when possible), age (±5 years), country of birth, and year of immigration. Since both disease and treatment often involved complete families, this group could be located in only about 50% of the cohort (*4*).

The therapeutic procedure followed the Adamson-Kienbock technique.

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

The hair had been shaved and the remaining hair was removed through a waxing process. Subsequently, the scalp area was divided into five fields, each being treated on one of five consecutive days.

The irradiation was performed with a 75–100 kV superficial therapy X-ray machine. The air exposure at a focused skin distance of 25–30 cm ranged between 350–400 R per field according to age. Most patients received one course of therapy (5 consecutive days). About 9% of the patients received two or more courses. Dosimetric studies were conducted years later (*10*) using one of the original X-ray machines and a head phantom construction of a skull of a 7-year-old child over which a layer of tissue-equivalent material was molded. Based on the latter dosimetry, individual average doses to different organs were estimated for each irradiated case. These assessments accounted for age and gender (which were highly correlated with size of the child), center of irradiation, number of treatments, and probable head movements during treatment (*8*).

Doses were calculated for different areas of the brain; the lowest average dose was for the back and front of the lower plane (mean 1.1 Gy), whereas the highest dose was for the front of the upper plane (mean 1.8 Gy). The mean average dose to the brain for all irradiated individuals was 1.5 Gy (range 1.0–6.0 Gy). The respective estimated doses for children who received one (about 91% of the cohort) and more than one course of therapy were 1.4 Gy (range 1.0–2.0 Gy) and 3.0 Gy (range 2.0–6.0 Gy), respectively (*8, 10*).

Information on tumor development was obtained from the Israeli Cancer Registry and included cases diagnosed up to and including December 1996. This registry was established in 1960 and is notified by law of all malignant tumors and benign meningiomas. According to a recent survey, the completeness of this registry is 95% and 75.7% for malignant brain tumors and benign meningiomas, respectively (*11*). To validate the diagnoses, we ascertained each tumor diagnosis through medical documents (pathology, surgery and hospitalization records). Vital status was updated to December 1996 through the Israeli Population Registry.

For each individual, the following information was available: year of birth, gender, country of birth, year of immigration to Israel, year of irradiation, place and number of irradiations, topography, morphology, date of tumor diagnosis, and date of death when relevant. More details on the methodological aspects of this study are available in previous publications (*4, 8*). The study was approved by the Chaim Sheba Medical Center review board committee.

STATISTICAL METHODS

We estimated the effect of radiation on brain tumor development in terms of excess relative risk (ERR) and excess absolute risk (EAR).

The ERR for the exposure is the ratio of the difference between the rates in the exposed and unexposed groups to the rate in the unexposed group. The ERR per dose is defined assuming that the ERR is proportional to the dose and represents the ERR for a unit dose of radiation.

The absolute risk is defined as the probability that a disease-free individual in a specified group will develop a given disease over a specified interval (*12*). The absolute risk is presented for 1 year multiplied by 10^4 to avoid leading zeroes. The EAR is the difference between the absolute risks in the irradiated and nonirradiated groups, and the EAR per dose is defined assuming that the EAR is proportional to the dose and represents the EAR for a unit dose of radiation.

We performed Poisson regression to estimate and compare the risks in the irradiated cohort and the two nonirradiated cohorts combined, including matching variables in all the models. Poisson regression is the standard way of conducting survival analysis in radiation epidemiology cohorts (*7*) and was used in the previous analyses of the tinea capitis data (*13*).

We analyzed the data as unmatched, following the approach of Shafer *et al.* (*14*), who stated that, because of the small number of outcomes among the siblings' comparison group in the tinea capitis cohort, ''it is unlikely that correctly accounting for sibling dependence, which would greatly complicate the analysis, will make any difference compared with the analysis, which used all matching variables as covariates.''

We combined the two unexposed cohorts (population and siblings) because (1) the number of tumors in the sibling comparison group (three and five for benign meningiomas and malignant brain tumors, respectively) were too small for separate analysis, (2) the rates of malignant brain tumors and benign meningiomas in the two comparison groups were lower than the rates among the exposed, and (3) the observed numbers in the sibling and population comparison groups of both malignant brain tumors and benign meningiomas did not differ significantly from the expected [5 and 8 compared to 5.3 and 7.7 for malignant brain tumors ($P = 0.59$) and 3 and 11 compared to 5.71 and 8.29 for benign meningiomas ($P = 0.14$)].

We fitted ERR and EAR models for the average effect of a cohort. The model for ERR was

$$R(c, X) = T0(X)\cdot(1 + \mathrm{ERR}\cdot c).$$

The model for EAR was

$$R(c, X) = T0(X) + \mathrm{EAR}\cdot c.$$

In both models, $c = 0$ for nonexposed, $c = 1$ for exposed, and X is a list of stratification variables [gender, 2-year age groups, and ethnic origin (North African, Middle Eastern, Israeli born)]. The baseline risk $T0(X)$ was estimated separately for all combinations of the values of the stratification variables.

For estimating the ERR and EAR per dose, we used the same models as above, but with c now replaced by d as the estimated dose. Thus the model for ERR was

$$R(d, X) = T0(X)\cdot(1 + \beta_R\cdot d),$$

and for EAR it was

$$R(d, X) = T0(X) + \beta_A\cdot d,$$

where β_R and β_A were the ERR per dose and EAR per dose, respectively. Thus the estimation of ERR and EAR per dose assumed a linear dose–response model. Many authors (*9, 15–17*) have recommended and used such a model in radiation epidemiology. We also compared the linear dose response with the linear-quadratic model, which is usually regarded as the possible alternative (*7, 13*). We chose the form of $1 + \beta \cdot$ dose in the ERR model and not $1 + \exp(\beta) \cdot$ dose to allow the ERR estimate to be negative, should the data so dictate (*18*, pp. 195–200).

For studying the effect of an additional categorized variable z (like age group at irradiation) on the dose response, we used the model for ERR,

$$R(d, X, z) = T0(X)\cdot(1 + \beta_R\cdot d\cdot z),$$

and for EAR,

$$R(d, X, z) = T0(X) + \beta_A\cdot d\cdot z.$$

Here z is a vector of dummy variables and β is a (row) vector of the coefficients. The variables z related to radiation treatment (age at irradiation and latent period) were defined as zero in the nonexposed cohort. For example, the variable ''age at first irradiation'' had four levels: nonirradiated, less than 5 years, 5 to 9 years, and 10+ years, from which three dummy variables were formed. The corresponding vector β_R or β_A consisted of three coefficients. With suitable coding of the dummy variables, the values of the β coefficients represent ERR per dose or EAR per dose for a given category in comparison to the base category.

For irradiated persons, the period of observation was defined 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 considered as brain tumor diagnosis, death or end of December 1996, whichever occurred first.

For the Poisson analysis, the data were arranged as a multi-way table with each cell corresponding to a separate combination of the categorized variables: gender, age at irradiation (categorized as nonirradiated, <5 years, 5–9 years and ≥ 10 years), latency defined as time since exposure (categorized as nonirradiated, <20, 20–29 and ≥ 30 years), ethnic origin

TABLE 1
Distribution of the Irradiated Cases in Study (n = 10,834) by Demographic and Radiation-Related Characteristics

Demographic characteristics			Radiation-related characteristics		
	n	Percent			
Gender			Follow-up period (years)		
Male	5298	48.9	Range	1–48	
Female	5536	51.1	Median	40	
Birth year			Age at irradiation	*n*	percent
1934–1944	1892	17.5	0–4	2513	23.2
1945–1949	3985	36.8	5–9	5888	53.9
1950–1959	4957	45.7	≥10	2583	22.9
Ethnic origin			Number of irradiations	*n*	percent
Middle East	2137	19.7	1	9814	90.6
North Africa	6366	58.8	2	904	8.4
Israel	2331	21.5	3	110	1.0
			4	6	0.1
Year of immigration					
1948–1951	3188	37.5	Dose to brain (Gy)		
1952–1955	3052	35.9	Range	0.98–6.0	
1956–1959	2263	26.6	Median	1.38	

(Middle-Eastern born, North African born and Israeli born), and attained age (categorized in 2-year age groups). The time scale was defined as attained age. The fine categorization by attained age was necessary for studying the time-dependent covariates. In other cohort studies, investigators have included both attained age and calendar year in the stratification because incidence rates were known to vary appreciably according to both of these variables. Calendar year was not included in the analysis as a stratification variable because the quite narrow range of year of birth (83% between 1945–1959) induced a high correlation between calendar year and attained age. Thus, in our study, stratifying by one of these variables was sufficient to adjust for the other. The number of events, number of person years (PY), and mean estimated radiation dose were calculated for each cell and became the input to the Poisson model.

All calculations were performed using the AMFIT program of the Epicure software package (*18*).

Maximum likelihood parameter estimates and likelihood-based confidence intervals were computed. Occasionally the lower bound for the dose–response estimates could not be determined (*13*). This occurs when the profile likelihood is nearly flat (*18*, pp. 56–57).

The overall P value for a category of a given variable was derived from the likelihood ratio test obtained by comparing the model with and without the dummy variable of interest. The significance of linear trends was tested using the likelihood ratio test.

For testing the assumption about linear dependence of the risk on dose, we compared the goodness of fit of the linear model $T0(X) \cdot (1 + \beta \cdot d)$ with the linear-quadratic model $T0(X) \cdot (1 + \beta_1 \cdot d + \beta_2 \cdot d^2)$ using the likelihood ratio test.

RESULTS

Table 1 presents the characteristics of the irradiated population, showing approximately equal numbers of males and females and a predominance of those of North African origin (59%). The follow-up period ranged from 1 to 48 years; the mean age at irradiation was 7.1 ± 3.1 years (range <1–15). The maximal dose to the brain for the entire cohort reached 6 Gy, with a median of 1.38 Gy.

A total of 1,069,450 and 1,069,043 person years was observed for the calculation of the risk of malignant brain tumors and benign meningiomas, respectively. Overall, 81 cases of benign meningiomas (67 irradiated and 14 nonirradiated) and 44 cases of malignant brain tumors (31 irradiated and 13 nonirradiated) were diagnosed during the study period. Table 2 shows the specific histological types of the malignant brain tumors diagnosed. Most (75%) of these tumors were of neuroepithelial tissue origin; five cases of malignant meningiomas and four hemangiopericytomas (all of them in the irradiated group) were also included. Fibrous, meningothelial and transitional were the most frequent histological types of benign meningiomas.

The crude incidence rates per 10^4 PY of brain tumors in the study groups showed substantially higher rates of both malignant and benign brain tumors among the irradiated group compared to the two nonexposed groups. As mentioned in the Statistical Methods, the two nonexposed groups were combined in further analyses. The rates of $1.57/10^4$ PY and $0.22/10^4$ PY among the exposed and nonexposed groups yielded a very high crude ERR of 6.35 (95% CI = 3.26–12.63) for benign meningiomas. For malignant brain tumors, we found a crude ERR of 2.94 (95% CI = 1.08–6.98) based on total rates of $0.73/10^4$ PY and $0.19/10^4$ PY among the irradiated and the nonirradiated groups, respectively (data not shown).

The risk for developing both types of tumors was positively associated with dose (P for trend <0.001 and 0.04 for benign meningiomas and malignant brain tumors, respectively). For benign meningiomas, the ERR was 2.64 for doses ≤1.2 Gy, rising to 18.82 for doses more than 2.6 Gy. For malignant brain tumors the ERR were 1.66 and 4.81 for these same groups of doses.

Compared to the linear dose model, the linear-quadratic

TABLE 2
Malignant Brain Tumors[a] in the Study Population by Morphology

	Irradiated cases	Sibling comparison group	Population comparison group
A. Tumors of neuroepithelial tissue			
1) Astrocytic tumors			
Astrocytoma (94003, 94203, 94213[b])	11	1	3
Glioblastoma multiforme (94403, 94413[c])	4	3	3
2) Oligodendroglial tumors			
Oligodendroglioma (94503)	1	1	—
3) Ependymal tumors			
Ependymoma (93913)	1	—	—
4) Neuronal and mixed neuronal glial tumors			
Ganglioglioma (95053[d])	1	—	—
5) Glioma not otherwise specified (93803)	3	—	1
B. Tumors of the meninges			
1) Tumors of meningothelial cells			
Anaplastic/malignant meningioma (95303)	5	—	—
2) Malignant neoplasms			
Hemangiopericytoma (91503)	4	—	—
C. Clinical diagnosis confirmation only	1	—	1
TOTAL	31	5	8

[a] Including low-grade diffuse gliomas.

[b] One case of pilocytic astrocytoma. This diagnosis was considered malignant up to 1.1.2001 (at the time of original diagnosis) and will continue to be considered as malignant according to *International Classification of Disease*, 3rd ed. In addition, this patient was treated by surgery and radiotherapy. Two years later, she represented with clinical deterioration [psychiatric epidose (epilepsy)]. Although the clinical deterioration might have been due to radiation necrosis, a diagnosis of a diffuse astrocytoma cannot be ruled out.

[c] Including one case of giant cell glioblastoma (among a sibling control).

[d] This diagnosis is usually considered as uncertain behavior; however, this case was classified as malignant by the pathologist according to the specific characteristics seen in the slide.

model showed a significantly better fit for benign meningiomas (likelihood ratio test $P = 0.03$). The use of a linear-quadratic dose–response model did not significantly improve the goodness of fit for malignant brain tumors (likelihood ratio test $P = 0.7$). In both cases, linear and linear-quadratic models were very close up to 2.7 Gy (where 95% of the observations were) (Fig. 1a and b); therefore, we proceeded with a linear model in the analysis, as recommended in the literature (*15, 16*).

Table 3 presents a dose–response analysis of the variables of interest adjusted for attained age and matching variables for benign meningiomas showing a significant ERR/Gy of 4.63 for developing this tumor after irradiation. For all categories of gender, place of birth, age at irradiation and latent period, the ERR/Gy demonstrated significantly higher risk for benign meningiomas among the irradiated cohort compared to the nonirradiated group. No interaction was found between irradiation and gender, ethnic origin, age at irradiation, or latent period. The estimated ERR/Gy remained close to the overall value (4.63) for the different categories of age at irradiation. The data suggest that the excess risk for benign meningioma continues after a long latent period, reaching an estimated ERR/Gy of 5.21 when 30 years or more have passed since the exposure.

Combining all meningiomas (81 benign and 5 malignant), the ERR/Gy reached 5.01 (95% CI 2.66–9.80). The addition of these five malignant meningioma cases did not change the effect of radiation seen for gender, place of birth, age at irradiation, and latent period on the development of benign meningiomas. All of these malignant meningioma cases occurred amongst individuals who were irradiated below age 10 [three below age 5 compared to 11 out of the 67 benign meningiomas in this age-at-irradiation category ($P = 0.047$)]. No differences in the distribution of gender, ethnic origin and latent period were noticed between malignant and benign meningiomas (not shown).

Table 4 presents the ERR/Gy for malignant brain tumors by selected demographic and radiation-related variables. While gender, place of birth and latent period did not seem to modify the association between irradiation and the development of malignant brain tumors, an inverse association was seen for these tumors with age at irradiation. The estimated ERR/Gy for malignant brain tumors decreased with increasing age at irradiation from 3.56 to 0.47 ($P = 0.037$ when comparing the ERR/Gy between the youngest and the oldest age-at-irradiation categories). Adjusted for the background variables, this trend was statistically significant ($P = 0.03$).

The highest risk (ERR/Gy of 2.94) was seen in the first 20 years after irradiation, followed by an estimated ERR/

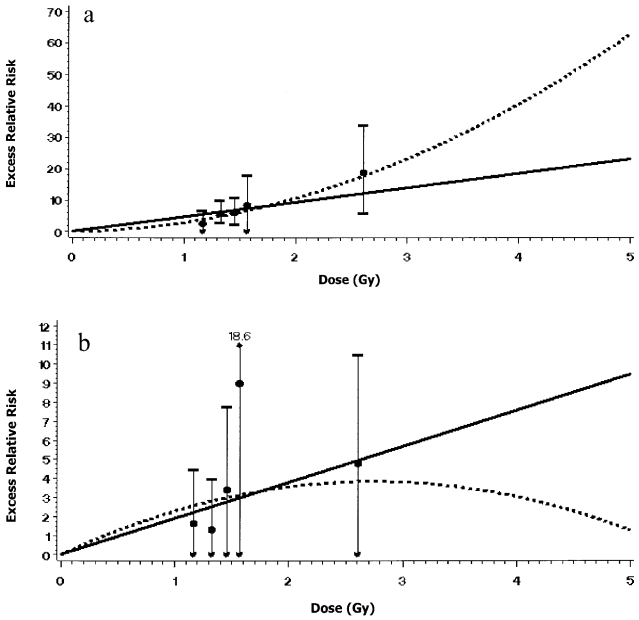

FIG. 1. Panel a: Excess relative risk (ERR) by quintiles of dose for benign meningiomas; linear and linear-quadratic models (adjusted for matching variables). (♥) The lower confidence limit is negative. Likelihood ratio test of linear-quadratic compared to linear models: $P = 0.03$. The comparison group includes population and siblings. (———) linear; (·····) linear-quadratic; ●) observed. Panel b: Excess relative risk (ERR) by quintiles of dose for malignant brain tumors; linear and linear-quadratic models (adjusted for matching variables). (♥) The lower confidence limit is negative. Likelihood ratio test of linear-quadratic compared to linear models: $P = 0.07$. The comparison group includes population and siblings. (———) linear; (·····) linear-quadratic; ●) observed.

Gy of 1.21 for the latent period of 20–29 years and 2.05 for the latent period of 30 years or more. This change in ERR between the categories of follow-up period was not statistically significant. Nevertheless, the distribution of diagnoses by latency shows differences between malignant brain tumors and benign meningiomas ($P = 0.06$). While the majority of benign meningiomas (74.6%) were diagnosed 30 years or more after the exposure and only 8.9% were diagnosed in the first 20 years, only 54.8% of the malignant brain tumors were diagnosed with long latency of 30+ years and about a quarter were diagnosed within the first 20 years of follow-up.

Table 5 presents the EAR/10^4 PY for malignant brain tumors and benign meningiomas by latent period, showing an EAR estimate of 0.31 and 0.48 per Gy/10^4 PY for malignant brain tumor and benign meningiomas, respectively. For both types of tumors, the EAR showed a positive association, with latent period increasing from 0.14 to 0.74 and from 0.18 to 2.03/Gy/10^4 PY for malignant brain tumor and benign meningiomas, respectively (P for trend <0.001).

DISCUSSION

In general, the results presented here are in line with the previous analysis of the tinea capitis cohort that showed an RR of 2.6 (95% CI 0.8–8.6) for glioma and of 9.5 (95% CI 3.5–25.7) for meningiomas (*8*). The current report adds 16 more years of follow-up and includes estimation of the ERR and EAR per radiation unit using a survival analysis method.

TABLE 3
Rates/10^4 Person Years (PY) among Exposed, Excess Relative Risk per Gray (ERR/Gy), and 95% Confidence Intervals (CI) for Benign Meningiomas by Selected Demographic and Radiation-Related Variables

	PY (10^4)	Exposed no.	Rate/10^4 PY	ERR/Gy[a]	95% CI	P for homogeneity
Total	42.7	67	1.57	4.63	2.43–9.12	
Gender						
Male	20.8	28	1.34	4.97	1.91–14.20	
Female	21.9	39	1.78	4.37	1.82–10.97	0.85
Ethnic origin						
Middle East	8.7	22	2.52	6.27	2.03–22.87	
North Africa	25.1	34	1.35	4.00	1.63–10.12	0.82
Israel	8.9	11	1.24	3.97	0.61–29.10	
Age at irradiation[b]						
<5	9.8	11	1.12	4.48	1.60–11.01	
5–9	23.0	36	1.57	5.03	2.49–10.26	0.81
10+	9.9	20	2.01	4.11	1.71–9.16	
Latent period (years)[b]						
<20	21.0	6	0.30	4.46	0.80–18.43	
20–29	10.6	11	1.04	3.29	1.03–8.97	0.68
30+	11.2	50	4.47	5.21	2.51–11.11	

[a] Unexposed include population and siblings; adjusted for matching variables.
[b] P for trend for ERR/Gy nonsignificant.

TABLE 4
Rates/10^4 Person Years (PY) among Exposed, Excess Relative Risk per Gray (ERR/Gy), and 95% Confidence Intervals (CI) for Malignant Brain Tumors by Selected Demographic and Radiation-Related Variables

	PY (10^4)	Exposed no.	Rate/10^4 PY	ERR/Gy[a]	95% CI	*P* for homogeneity
Total	42.8	31	0.73	1.98	0.73–4.69	
Gender						
Male	20.9	19	0.91	2.11	0.56–6.45	0.86
Female	21.9	12	0.55	1.79	0.25–7.03	
Ethnic origin						
Middle East	8.7	6	0.69	1.40	−0.16–9.34	
North Africa	25.1	22	0.88	2.16	0.66–6.08	0.93
Israel	8.9	3	0.34	2.14	0.03–55.20	
Age at irradiation[b,c]						
<5	9.8	8	0.82	3.56	0.96–9.91	
5–9	23.0	18	0.78	2.24	0.75–5.54	0.09
10+	9.9	5	0.50	0.47	−2.74[d]	
Latent period (years)[e]						
<20	20.2	8	0.41	2.94	0.39–13.95	
20–29	10.6	6	0.57	1.21	−0.02–4.60	0.65
30+	11.7	17	1.45	2.05	0.55–5.73	

[a] Unexposed include population and siblings; adjusted for matching variables.
[b] ERR/Gy for age at irradiation <5 compared to 10+, $P = 0.037$; 5–9 compared to 10+, $P = 0.07$.
[c] P for trend for ERR/Gy = 0.03.
[d] Likelihood confidence interval has no lower bound.
[e] P for trend for ERR/Gy nonsignificant.

The advantages of this study include a relatively large irradiated population well validated for the exposure, two nonexposed comparison groups (matched for gender, age and place of birth), 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 only cause underestimation of the true association. The possibility of a detection bias, due to ascertainment of more tumors among persons with a history of irradiation, may be a concern. However, such a bias is less likely in our analysis, since (1) the irradiated population was not offered a screening program and (2) the present analysis includes cases diagnosed up to December 1996, while the compensation law, which may have encouraged irradiated persons to seek testing, was passed only in 1995. Moreover, the annual incident cases diagnosed during 1993–1996 were stable for both malignant tumors and benign meningiomas.

Among the limitations of this study are the restricted range of ages and doses involved and the use of estimated dosimetry rather than measurements performed for each child (see Statistical Methods section). This may yield inaccuracies (e.g. due to extensive movement of the child or a deviation from the routine guidelines of the treatment) that could, in principle, influence the results. However, Shaffer *et al.*, who investigated the impact of such uncertainties in the tinea capitis studies, concluded that the measurement error in dosimetry has a negligible effect on dose–response estimation and inference (*14*). Another limitation is that in the tinea capitis study the notion of fractionation could not be analyzed. According to the therapeutic protocol for tinea capitis, each course was of an identical dose. Therefore, children who received more than one course of treatment were in fact exposed to a larger cumulative dose. This is in contrast to other experimental and clinical studies in which the total dose is fixed while fractionation leads to smaller doses per single exposure (*19*).

TABLE 5
Excess Absolute Risk (EAR) and 95% Confidence Intervals (CI) for Malignant Brain Tumor and Benign Meningioma by Latent Period

Latent period (years)[b]	Malignant brain tumor		Meningioma	
	EAR/Gy per 10^4 PY[a]	95% CI	EAR/Gy per 10^4 PY[a]	95% CI
<20	0.14	0–0.38	0.18	0.04–0.39
20–29	0.37	0.06–0.75	0.55	0.20–1.05
30+	0.74	0.30–1.24	2.03	1.24–2.97
Total	0.31	0.12–0.53	0.48	0.28–0.73

[a] Unexposed includes population and siblings; adjusted for matching variables.
[b] P for trend <0.001 for both tumor types.

The data we have presented provide further evidence that brain and meninges tissues are highly sensitive to radiation carcinogenesis (*5–8*). Our results also imply that after exposure to ionizing radiation, differences may exist between factors affecting the risk for malignant brain tumors and those for benign meningiomas. While young age at irradiation was found to be associated with a higher RR for developing a malignant brain tumor, the ERR/Gy for benign meningioma appeared to be unaltered with age within the age range studied. The RR for developing either type of tumor remained elevated at 30+ years after irradiation. Dose–response association was seen for both tumors, and no evidence was seen for interaction between irradiation and either gender or ethnic origin.

Based on 88 meningiomas and 43 gliomas, the latest results of the studies of the A-bomb survivors for brain tumors reported an ERR_{Sv} of 0.6 (95% CI −0.01 to 1.8) for meningiomas and an ERR_{Sv} of 0.6 (95% CI −0.2 to 2.0) for gliomas (*20*). These risk estimates are much lower than the 5.01/Gy for meningiomas (malignant and benign) and 1.98/Gy for malignant brain tumors observed in our study. Moreover, while excess risk for meningioma development was a relatively early finding in the tinea capitis cohort, being demonstrated about 20 years after the exposure (*4*), evidence of a high incidence of meningiomas among the A-bomb survivors was first presented in 1994 for Nagasaki (*21, 22*) and in 1997 for Hiroshima (*23*). The observation that the excess of brain tumors was noticed so much earlier in the tinea capitis cohort was explained by Sadamori *et al.* (*22*) to result from the much higher exposure of the tinea capitis cohort compared to that of most of the A-bomb survivors, even those who were less than 2.5 km from the hypocenter. Indeed, compared to a minimum dose of 0.98 Gy in the tinea capitis cohort, only about 7.6% (6,000 individuals) of the Life Span Study survivors had brain doses of over 0.5 Sv and only 3.5% of the survivors had dose estimates greater than 1 Sv. Approximately 40% of the A-bomb survivor cohorts had virtually no exposure (a weighted brain dose of less than 0.005 Sv) (*20*). The explanation of Sadamori *et al.* is also in line with the results of Soffer *et al.* (*24*), who suggested that the latent period observed after exposure to high doses is considerably shorter than after exposure to low doses. The observation that major differences still exist in the level of risk of brain tumors after adjustment for doses and after long latent periods in the tinea capitis and A-bomb cohorts needs further consideration. The discrepancy might also result from the dissimilarity in the age distribution of the two cohorts and supports the notion that risk varies with age at exposure (see later in the Discussion). It is also possible that one has yet to see the full effect of radiation on brain tumors in the A-bomb cohort and that future follow-up will show an increase in their rates to the level seen in our study. Other possible explanations for the discrepancy include a higher genetic susceptibility to ionizing radiation among the Jewish population or a lower detection rate of brain tumors in the Japanese population.

It is worth mentioning that according to the A-bomb analysis, the highest risk was observed for schwannomas (ERR_{Sv} = 4.5; 95% CI 1.9–9.2) (*20*). Nerve sheath tumors of the head and neck were also found to be in excess in a previous analysis of our cohort (RR = 33.1; 95% CI 9.4–116.5) (*8*). Unfortunately, since this generally benign tumor is not indicated in the Israeli Cancer Registry, we could not include it in the present report.

Data from a pooled analysis of a 35-year follow-up of two Swedish cohorts of infants who were exposed to ^{226}Ra treatment for hemangiomas (n = 28,008) are more comparable with our results (*7*). Based on 86 brain tumors combined, the ERR/Gy was 2.7 (95% CI 1.0–5.6), in line with our findings.

Both of these studies support our finding of a dose–response association. Sadamori *et al.* and Shintani *et al.* demonstrated a high correlation between distance from the hypocenter of the bomb and rate of meningiomas (*22, 23*). The latest results of the A-bomb study also indicate good agreement with a linear dose response for nervous system tumors (other than schwannoma) (*20*). The Swedish study (7) also found the best fit for a linear dose–response model. In this cohort, although the mean exposure was very low (7 cGy, range 0–11.5 Gy), for children who developed brain tumors, the mean doses were 1.02 Gy and 31 cGy for glioma and meningioma, respectively.

The shape of the dose–response curve, especially in the low-dose range, is one of the most crucial issues in radiation research, and it has important practical implications with regard to radiation protection guidelines. Generally, the linear model is considered most appropriate for carcinogens that are DNA reactive and induce mutations (*25*). Most guidelines for solid tumors are now largely based on a linear, no-threshold dose–response curve as a simple and convenient method to optimize procedures and regulations (*16, 26–28*). These models accord well with the effects observed for doses of 100 mGy up to 4 Gy, when lethal effects begin to distort the curve (*17*). Pierce and Preston (*28*) evaluated the dose–response curve focusing on the A-bomb survivors with doses of less than 0.5 Sv. Their results provide useful risk estimates for doses as low as 0.05 Sv. According to their data, there is no evidence that linear risk estimates from a wider dose range overestimate low-dose risks, and there is considerable evidence that the linear risk estimates are appropriate for research purposes.

Our tinea capitis data analysis indicates that, while the linear-quadratic model did not significantly improve the goodness of fit for malignant brain tumors, it gave a significantly better fit than the linear model for benign meningiomas. However, for the latter tumor, both models gave the same prediction up to 2 Gy; the discrepancy was observed only for the highest quintile of exposure (mean 2.7 Gy). Extrapolation of our results to doses outside the range of our data should be interpreted with caution. We do not

consider this finding as conclusive, but we record it here to allow comparison with future studies.

Young age at irradiation is known as a risk factor for several tumors (e.g. breast, thyroid) (*13, 29*). The development of the nervous system continues from conception to maturity. After birth, the brain continues to grow dramatically, from an average weight of about 400 g at birth to about 1000 g by the end of the first postnatal year. Growth of the brain and myelination continue, at a much slower rate than before, until the age of 12–15 years (*30*). Therefore, a higher risk of malignant brain tumors, especially of gliomas, among those irradiated at a younger age is biologically plausible. An association of young age at exposure and development of meningiomas was reported by Preston-Martin *et al.*, who found a positive association between early exposure to full-mouth series of dental X rays and the development of meningiomas (*31*). The A-bomb data (*20*) showed a weak, statistically nonsignificant effect of age at exposure for nervous system tumors other than schwannomas (P for trend = 0.06), with people exposed before age 20 years having higher estimated risks. For this younger age group the ERR was 1.3 (95% CI 0.01–4.5) and 1.2 (95% CI 0.3–2.9) for meningiomas and nervous system tumors excluding schwannoma, respectively.

Including a relatively narrow range of young ages (mean 6 months, range 1 day to 81 months), Karlsson *et al.* (*7*) also found a negative association between age at radiation treatment and the development of brain tumors. We have demonstrated an inverse association with age at exposure in our study only for malignant brain tumors, while for benign meningiomas, the RR did not appear to vary with age at irradiation, within the age range of our study (≤15 years). Moreover, significantly more malignant meningiomas developed in the youngest age at irradiation group compared with benign meningiomas (P = 0.047). These findings are in line with Soffer *et al.* (*24*), who suggested that very young individuals are more susceptible to the carcinogenic effect of ionizing radiation and are at greater risk of developing malignant tumors thereafter.

In agreement with Karlsson *et al.* (*7*), we did not find evidence for interaction between radiation and gender. Data from the A-bomb study indicate a greater ERR_{Sv} among males than females for nervous system tumors other than schwannoma (*20*) but a higher RR for females for combined solid tumors (*2*).

While our results show that the excess risk for developing benign meningiomas and malignant brain tumors remains elevated 30 and more years after the exposure, our data do not demonstrate a clear trend of ERR with time since exposure, neither for malignant brain tumors nor for benign meningiomas. Nevertheless, while 25% of the malignant brain tumors were diagnosed in the first 20 years, the majority (75%) of benign meningiomas were diagnosed 30 years or more after the exposure (P = 0.06). Similarly, in a small series (*32*) of 808 individuals who received radium treatment for adenoid hypertrophy after an estimated dose to the brain of 0.15–0.4 Gy, the three malignant brain tumors occurred within the first 25 years after irradiation, and the four benign brain tumors were diagnosed 35 years or more after the exposure. In the Swedish study, out of 13 intracranial tumors that were diagnosed at a young age (≤20 years), 10 were gliomas. These observations may imply that the induction period after irradiation may be shorter for malignant tumors compared to benign tumors. Alternatively, it is possible that benign tumors may develop over the same period as malignant brain tumors but are diagnosed later due to their slower progression and longer asymptomatic periods. Therefore, while it is evident that the latent period for both tumors may persist for more than 30 years after the exposure, differences in the clinical symptomatology may result in earlier detection of malignant brain tumors.

The EAR and ERR models generally provided an equally good fit to our data. The results in Tables 3, 4 and 5 indicate that the ERR model has a relatively stable pattern over time, whereas the EAR appears to rise with time since exposure, since the incidence of tumors increases with age. The same rise in the EAR over time was seen in the Swedish study even though the EARs were high compared to our study [EAR/Gy per 10^4 PY of 2.1 (95% CI 0.3–4.4) for all brain tumors compared to 0.31 (95% CI 0.12–0.53) and 0.48 (95% CI 0.28–0.73) for malignant brain tumors and meningiomas, respectively]. Moreover, whereas the ERR is not biased by undetected cases arising from incomplete registration at the National Cancer Registry, as long as the detection rate is similar between exposed and nonexposed, the EAR is biased by such undetected cases. Nevertheless, for health planning, it is more meaningful to translate the results into EAR terms, since this conveys the increase in the absolute numbers of cases arising from the exposure.

Exposure of the brain to high-dose therapeutic radiation is not uncommon (e.g. by treatment for benign intracranial arteriovenous malformation or for treatment of leukemia). Moreover, the exposure of the brain to low-dose radiation may grow with time, with the expanded use of new techniques of pediatric and adult computed tomography (CT) and scans. This may lead to increases in cumulative lifetime exposure. The results presented herein contribute quantitative information on the risk of brain tumor development after an exposure of the meninges and brain tissues to ionizing radiation and indicate that after such childhood exposure the risk persists throughout into adulthood and middle age.

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ERRATUM

In the paper ‘‘Long-Term Follow-up for Brain Tumor Development after Childhood Exposure to Ionizing Radiation for Tinea Capitis’’ by Siegal Sadetzki, Angela Chetrit, Laurence Freedman, Marilyn Stovall, Baruch Modan and Ilya Novikov, Vol. **163**, No. 4, pp. 424–432, 2005:

On p. 428, in the legend to Fig. 1, the *P* value is incorrect. The text should read: ‘‘Likelihood ratio test of linear-quadratic compared to linear models: $P = 0.7$.’’