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Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies

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The thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation. To provide insights into various modifying influences on risk, seven major studies with organ doses to individual subjects were evaluated. Five cohort studies (atomic bomb survivors, children treated for tinea capitis, two studies of children irradiated for enlarged tonsils, and infants irradiated for an enlarged thymus gland) and two case-control studies (patients with cervical cancer and childhood cancer) were studied. The combined studies include almost 120,000 people (approximately 58,000 exposed to a wide range of doses and 61,000 nonexposed subjects), nearly 700 thyroid cancers and 3,000,000 person years of follow-up. For persons exposed to radiation before age 15 years, linearity best described the dose response, even down to 0.10 Gy. At the highest doses (>10 Gy), associated with cancer therapy, there appeared to be a decrease or leveling of risk. For childhood exposures, the pooled excess relative risk per Gy (ERR/Gy) was 7.7 (95% CI = 2.1, 28.7) and the excess absolute risk per 10^4 PY Gy (EAR/10^4 PY Gy) was 4.4 (95% CI = 1.9, 10.1). The attributable risk percent (AR%) at 1 Gy was 88%. However, these summary estimates were affected strongly by age at exposure even within this limited age range. The ERR was greater ($P = 0.07$) for females than males, but the findings from the individual studies were not consistent. The EAR was higher among women, reflecting their higher rate of naturally occurring thyroid cancer. The distribution of ERR over time followed neither a simple multiplicative nor an additive pattern in relation to background occurrence. Only two cases were seen within 5 years of exposure. The ERR began to decline about 30 years after exposure but was still elevated at 40 years. Risk also decreased significantly with increasing age at exposure, with little risk apparent after age 20 years. Based on limited data, there was a suggestion that spreading dose over time (from a few days to >1 year) may lower risk, possibly due to the opportunity for cellular repair mechanisms to operate. The thyroid gland in children has one of the highest risk coefficients of any organ and is the only tissue with convincing evidence for risk at about 0.10 Gy.

INTRODUCTION

Studies of children treated with ionizing radiation for a variety of benign and malignant diseases have demonstrated that doses as low as 0.10 Gy or as high as 60 Gy can induce thyroid tumors *(1).* Most studies indicate that a linear dose response describes the data adequately and that tumor risk is higher in persons exposed during childhood. Despite the wealth of existing knowledge about radiation-induced thyroid cancer, many issues remain unresolved because of insufficient data in individual studies. With the recent publication of new studies and updates of previously published studies of thyroid cancer and radiation exposure, a pool of data is now available for expanded analyses.

A collaborative joint analysis was conducted of seven previously published studies (five cohort and two case-control) of acute external irradiation and thyroid cancer. The studies were conducted in several countries and include a wide range of doses, ages at exposure, times and reasons for exposure. Unlike a meta-analysis, which is based solely on published data, we analyzed the primary data using common definitions, statistical methods and assumptions. The major objectives were to assess (1) the shape of the dose-response relationship, (2) the effect of 'gender, (3) the influence of age at irradiation, (4) the temporal patterns of risk, in terms of age at risk and time since exposure. (5) the effect of fractionated exposures and (6) the influence of screening or clinical surveillance on risk estimates.

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TABLE I
Description of Study Subjects and Methods

Study/Place	References	Study population number (person years)[a] Exposed	Nonexposed	Percentage female	Method of cancer ascertainment	Years of exposure	Mean follow-up years (range)	Mean age at exposure (range)
			Cohort studies					
Atomic bomb (Japan)	*15, 41–44*	41,234[b] (859,475)[b]	38,738[b] (817,556)[b]	60	Tumor registries	1945	24 (1958–1987)	27 (all ages)
Thymus (Rochester)	*16, 36, 45, 46*	2,475 (87,556)	4,991 (176,133)	42	Mail questionnaires[c]	1926–1957	35 (1926–1987)	0.1 (0–1)
Tinea capitis (Israel)	*17, 39, 47–49*	10,834 (328,092)	16,226 (493,080)	51	Hospital records Tumor registry	1948–1960	30 (1950–1986)	7 (0–15)
Tonsils (MRH, Chicago)	*19, 50–52*	2,634 (88,100)	0 0	40	Clinical examinations Telephone interviews[c]	1939–1962	33 (1939–1990)	4 (0–15)
Tonsils (CHMC, Boston)	*18*	1,192 (34,527)	1,063 (31,474)	40	Mail questionnaires[c]	1938–1969	29 (1938–1981)	6 (0–18)
		Cases	Controls		Case-control studies			
Cervical cancer (International)	*20, 53–55*	43	81	100	Tumor registries and clinics	1926–1971	not applicable not applicable	53 (29–78)
Childhood cancer (International)	*21*	22	82	45	Medical records	1936–1979	not applicable not applicable	7 (0–18)

[a]Persons included in the present analysis (excludes people without follow-up or thyroid dose estimates).
[b]Exposed defined as ≥0.01 Sv to the thyroid, nonexposed defined as <0.01 Sv; person-years take migration adjustment into account.
[c]Information on thyroid cancers was verified by obtaining medical records.

MATERIALS AND METHODS

Study Populations

Published studies of thyroid cancer and external irradiation were reviewed and cohort studies with at least 1,000 irradiated subjects and individual estimates of the radiation dose to the thyroid were considered for possible inclusion in the pooled analysis. Five studies were identified that met these criteria. Few case-control studies of radiation-induced thyroid cancer have been published. We included the two that had more than 20 thyroid cancer cases and adequate dose information. Other studies of external radiation have been published, but they failed to meet at least one of the criteria described *(2-14).* Studies of exposure to internal radionuclides also are not considered.

The pooled analysis consists of seven studies. Four of the five cohort studies have internal, nonexposed comparison populations with over 20 years of follow-up: atomic bomb survivors in the Life Span Study (LSS)[1] *(15),* persons irradiated in infancy for an enlarged thymus gland *(16),* Israelis irradiated as children for tinea capitis *(17),* and children treated with radiotherapy for lymphoid hyperplasia at Children's Hospital Medical Center (CHMC) in Boston *(18).* In addition, a follow-up study of individuals irradiated at Michael Reese Hospital (MRH) in Chicago for enlarged tonsils and a variety of other benign head and neck conditions in childhood is included, although the study has no comparison population *(19).* Two nested case-control series contributed to some of the analyses: thyroid cancer cases and controls selected from a study of women receiving radiotherapy for cervical cancer *(20),* and from a cohort of childhood cancer patients participating in the Late Effects Study Group (LESG) *(21).* Exposed children (<15 years old) were included in all but the study of cervical cancer patients. Data on adult exposures were available from the studies of atomic bomb survivors and cervical cancer patients. The seven studies included in the analysis are described in more detail in Appendix 1 and summarized briefly in Tables 1 and II. Table III presents the major strengths and weaknesses of each of the studies. Figure la shows the number of thyroid cancers and Fig. lb shows the person years, or the number of control subjects in each study by dose category.

Statistical Analysis

Analyses of the original data sets were carried out on a microcomputer using the EPICURE statistical package *(22).* Because this is a pooled analysis, we used the same statistical models and variable categorization over studies whenever feasible. Consequently, our point estimates vary slightly from those reported in the original publications. but general inferences are similar.

Cohort studies. For every subject in each cohort we obtained dates of birth and exposure, type of exposure, number of exposures, individual thyroid dose estimates, thyroid cancer status and year of exit from the cohort. Data were summarized in multi-way tables defined by categories of sex, thyroid dose (grouped as 0, 0.01-0.09, 0.1-0.19, 0.2-0.29, 0.3-0.39, 0.4-0.49, 0.5-0.99, 1-1.99, 2-2.99, 3-3.99, 4-9.99, 10-19.99, 20-29.99, 30-39.99, 40-49.99, 50-59.99, 60+ Gy), age at exposure (grouped as <l, 1-4, 5-9,

[1]Abbreviations used: AHS, Adult Health Study; AR%, attributable risk percent: ATB, at the time of bombing; CHMC, Children's Hospital Medical Center; DS86, Dosimetry System 1986; EAR, excess absolute risk; ERR, excess relative risk; LESG, Late Effects Study Group; LSS, Life Span Study; MRH, Michael Reese Hospital; PY, person years; RERF, Radiation Effects Research Foundation.

TABLE 11
Summary of Radiation Exposure Conditions by Study

Study	Type of exposure	Field size (cm)	Energy	Mean thyroid dose[a] (Gy) (range)	Fractionation	Type of dosimetry
Atomic bomb	Nuclear explosions	Whole body	MeV X rays, slow and fast neutrons	0.27 (0.01-3.99)	None	Organ-specific doses estimated based on individual exposure and shielding history, computer models of radiation yield and attenuation by materials and tissue.
Thymus	X-ray therapy	Ranged from 3 x 5 to 10 x 10	75-200 kVp	1.36 (0.03-11)	1 to 11 (>85% had <=2) given in 1 week	Individual doses estimated based on primary beam location, beam quality and the source-to-skin distance.
Tinea capitis	X-ray therapy	Depended on head size	70-100 kVp	(0.04-0.5)	5 given daily[b]	Individual doses estimated based on phantom measurements taking treatment conditions and age at irradiation into account.
Tonsils (MRH)	X-ray therapy	6 x 8; 8 x 10; 10 x 10	200 kVp	0.59 (0.01-5.8)	3 given weekly[c]	Individual doses estimated based on phantom measurements taking treatment conditions and age at irradiation into account.
Tonsils (CHMC)	X-ray therapy	5 x 7; 6 x 7; 6 x 8	250 kVp	0.24 (0.03-0.55)	2 given weekly[d]	Individual doses estimated based on phantom measurements taking treatment conditions and age at irradiation into account.
Cervical cancer	X-ray therapy and/or radium implants	Large variation	Ortho- or megavoltage	0.11 (0.01-0.24)	Varied (>50% treated 5 days per week for 30 days)	Individual doses estimated based on phantom measurements and usual treatment conditions.
Childhood cancer	X-ray therapy	Large variation	Ortho- or megavoltage	12.50 (l-76)	Large variation	Individual doses estimated based on phantom measurements and treatment conditions taking age, height, weight, body surface area and estimated thyroid gland size into account.

[a]Among exposed subjects.
[b]Approximately 9% of the exposed patients had repeat treatments more than 1 year after first treatment.
[c]Approximately 12% of the exposed patients had additional treatments usually more than 6 months after first treatment.
[d]Approximately ll% of the exposed patients had additional treatments.

10-14. 15–19. 20–29, 30-39. 40-49, 50-59. 60+ years), calendar time (grouped in 5-year intervals from January 1, 1905 through December 31, 1987) and time since exposure (grouped in 5-year intervals). Additional variables were included for specific studies, e.g. country of origin for the Israel tinea capitis study and inclusion in the Adult Health Study (AHS) for the atomic bomb survivor study. For the atomic bomb survivors. we analyzed the data separately for two age-at-exposure groups: <15 years old at the time of the bombings (ATB) and >=15 ATB. For each cell of the cross-classification, the number of observed thyroid cancers, the number of person-years, and person-year-weighted average values for dose. attained age, age at exposure and time since exposure were computed.

Poisson regression methods for analysis of cohort time-to-exposure data were used to analyze each data set and all data combined. Person-years of observation were computed from the date of first radiation treatment. or the date of study entry for the comparison subjects. until the date of thyroid cancer diagnosis. date of death or the date of the end of the follow-up. whichever occurred first. We fitted both relative and absolute excess risk models using AMFIT, a program for the analysis of general rate models with grouped cohort data *(22).* Maximum likelihood parameter estimates, score tests for nested models and likelihood-based confidence intervals were computed *(23).* At times, the lower confidence bound for the dose–response estimate could not be determined when it was less than zero.

We assume that the disease rate, $r(x,z,d)$, depends on the estimated radiation dose d, a vector of covariates x which describe the background disease rate and covariates z which affect the dose-response relationship. For the relative risk models. components of x include indicator variables for strata defined by categories of calendar year interval, attained age and gender. For the absolute risk model. all indicator variables for categories of age were replaced with two continuous variables (age and natural logarithm of age). Under a relative risk model, r can be written as a

TABLE III
Strengths and Limitations of Included Studies

Study	Strengths	Limitations
A-bomb	Large exposed and nonexposed population which includes people of all ages and both sexes; not selected because of disease or occupation; wide range of doses estimated by comprehensive individual dosimetry system: thyroid cancer ascertainment through population-based tumor registries: histological confirmation for 93% of the cancers; long follow-up including lifetime for some subjects	No cancer incidence information for the first 13 years following exposure or for nonresidents of Hiroshima or Nagasaki; possible effects of thermal or mechanical injury and trauma following the bombings; possible "survival of the fittest" effect; males of military age may have had physical conditions which excluded them from active service; possible underestimation of neutrons may slightly overestimate risk estimates; doses uncertain for highly exposed individuals
Thymus	No underlying disease: sibling comparison group; individual dosimetry: long follow-up; some fractionated exposures; information on other risk factors: pathology slide review of most thyroid cases	Cancer ascertainment through mailed questionnaire may lead to under- or biased reporting; publicity concerning radiation-induced thyroid cancer may influence medical surveillance of exposed; only newborns were treated; small number of thyroid cancers, especially among the nonexposed; dosimetry uncertain
Tinea capitis	Large exposed population; two nonexposed groups; underlying disease does not cause late medical effects: nearly complete thyroid cancer ascertainment through national cancer registry and national survey of pathology departments; virtually complete vital status follow-up through national population registry: individual dosimetry: cancers validated through pathology review or medical records	Limited range of ages and doses; dosimetry uncertain due to possible patient movement: persons who contracted tinea capitis may differ in unknown ways from siblings or other comparison subjects who did not: publicity concerning radiation-induced thyroid cancer may influence medical surveillance of exposed
Tonsils (MRH)	Large exposed population: large number of thyroid cancers; individual dosimetry; cancers verified through medical records; underlying disease does not cause late effects	No nonexposed; many of the subjects were screened for thyroid disease so asymptomatic cancers ascertained: orientation of the radiation field is unclear for 70% of cohort causing uncertainty in the thyroid dose estimates; only 69% of potential subjects could be traced for follow-up; only childhood exposures
Tonsils (CHMC)	Nonexposed comparison group with same condition as exposed. but treated with surgery: individual dosimetry; cancers verified through medical records	Small number of thyroid cancers, none among nonexposed: orientation of the radiation field is unclear causing uncertainty in the thyroid dose estimates; cancer ascertainment through mailed questionnaire may lead to under-or biased reporting: publicity concerning radiation-induced thyroid cancer may influence medical surveillance of exposed
Cervical cancer	Cases and controls selected from large international cohort so no response bias; one of few studies with adult exposures; individual dosimetry; cancers were validated	Almost no nonexposed; only adult women: limited range of doses; the underlying disease may affect results; cannot estimate absolute risk without extrapolating from cohort study; possible detection bias
Childhood cancer	Cases and controls selected from large cohort so no response bias: individual dosimetry; only study with very high doses: cancers were validated	Almost no nonexposed; only childhood exposures; the underlying disease or other treatments may affect results; cannot estimate absolute risk without extrapolating from cohort study; possible referral bias

product of the background disease rate among nonexposed, denoted $r_o(x)$, and a dose-response function, $h(z,d)$. If the dose–response function, h, is linear in dose alone, the model is the linear excess relative risk (ERR) model, $r(x,d) = r_o(x)\,(1 + ßd)$, where ß is the parameter which measures the unit increase in excess relative risk per Gy (ERR/Gy) (model 1). Deviations from this linear model are evaluated by fitting the linear-quadratic model. $r(x,d) = r_o(x)\,(1 + ßd + \theta d^2)$ (model 2), and to reflect cell killing at high doses we also fitted the linear-exponential dose-response model, $r(x,d) = r_o(x)\,(1 + ßd)e^{-\theta d}$, where θ is a parameter which measures the nonlinear deviation of the dose-response relationship (model 3). A test of nonlinearity in the dose–response relationship is carried out using a score test of the null hypothesis $\theta = O$.

To evaluate whether the dose–response trend. β, varies within categories of other factors, such as age at exposure, time since exposure and gender, suppose z, which maybe a component of x. has J categories with indicator variables $Z_1,...,Z_J$ which take values one or zero depending on whether the subject is in the J th category or not. Variation of the dose response across levels of z is assessed by fitting model (1) and comparing its deviance with a model that includes J dose–response parameters, namely, $r(x,z,d) = r_o(x)\,[1 + ßd \exp(\gamma_1 z_1 + \ldots + \gamma_J z_J)$, where β is the ERR/Gy at the referent category (model 4). This model is over-parameterized, so one of the -y parameters, usually γ_1, is fixed at zero. The $\exp(\gamma)$ values represent the modification of the ERR/Gy for specific categories of the factor. Under the null hypothesis of no effect modification. the difference in the

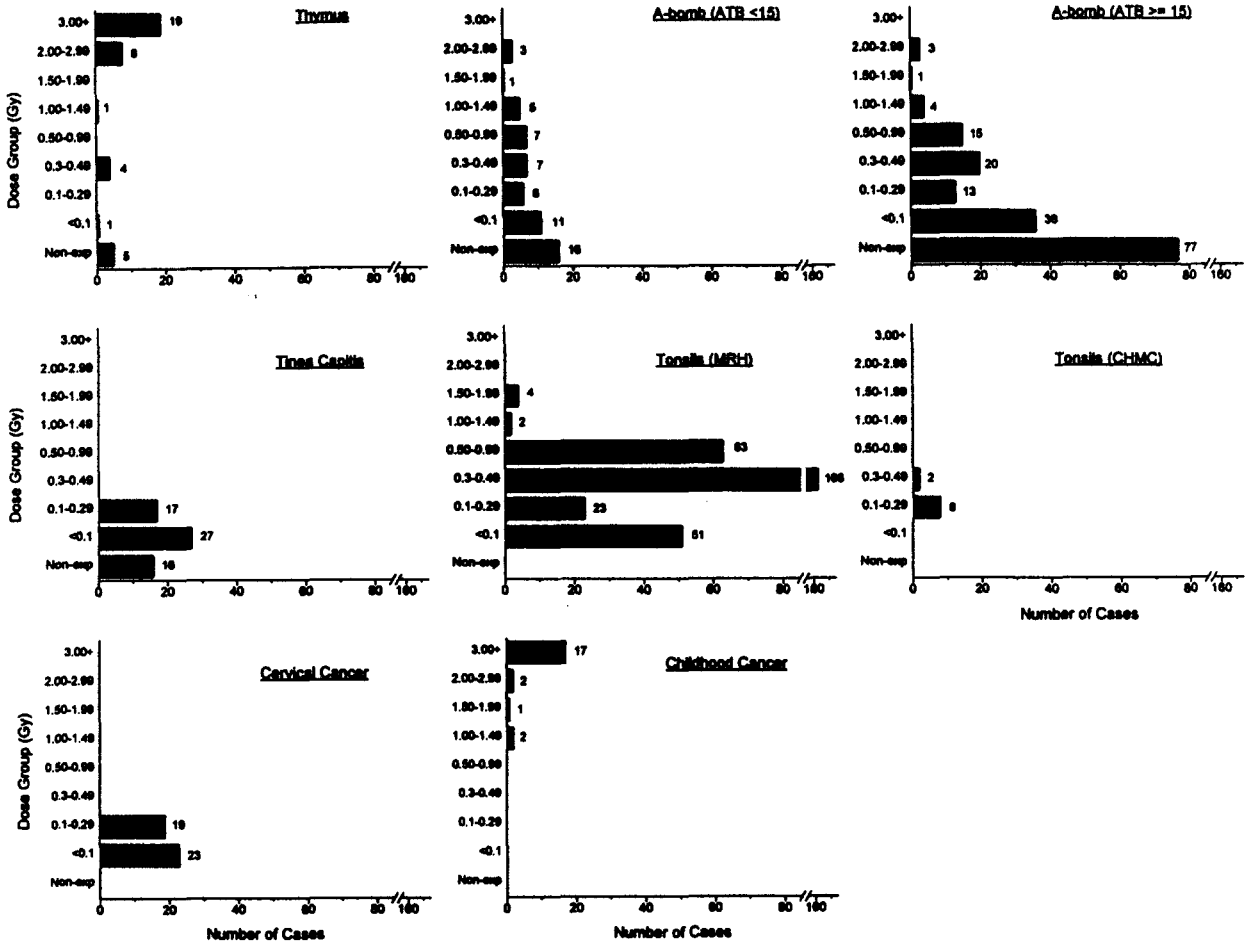

FIG. 1a. Number of thyroid cancer cases by dose category for individual studies.

model deviances is asymptotically a x^2 distribution with $J - 1$ degrees of freedom. A significant P value indicates that the effect of radiation on incidence of thyroid cancer is not homogeneous across levels of z.

The excess absolute risk (EAR) model is a model in which the effect of radiation, denoted $g(z,d)$, adds to the background thyroid cancer rate. A linear dose-response model takes the form $r(x,d) = r_0(x) + ßd$, where the dose-response parameter β is the excess absolute disease rate per Gy (EAR/Gy).

Case-control studies. Variable categorizations were defined as described for the cohort analysis. In the two matched case-control studies, PECAN, a computer program *(22)* for conditional logistic regression analysis, was used to estimate the ERR/Gy (model 1) and modifying factors (model 4), in much the same way as the relative risk regressions for the cohort studies.

Pooled analysis. The pooled analysis was limited to the cohort studies and was based on Poisson regression methods as described above. For this analysis, the data were cross-classified further by cohort. Because of the large difference in radiation effects after childhood or adult exposure, the data were restricted to subjects under age 15 years at exposure. Model (1) was modified by replacing ß with cohort-specific dose-response parameters. Summary estimates of ERR/Gy and EAR/Gy were obtained as the weighted mean of the individual estimates, with the inverse variances as weights. This approach weights each study by the amount of information contributed, i.e. number of cases and person years. No attempt at a subjective weighting for study quality was made. A random effects model *(24)* was used to compute the confidence interval of the pooled risk estimate. The variance for the parameter estimate includes two terms, variation within study and variation between studies. The wider confidence interval obtained using this method reflects the additional uncertainty involved in calculating a pooled risk estimate when there is considerable variation in the individual risk estimates. The contribution of each study to the pooled risk estimates was assessed by an influence analysis, in which pooled ERR and EAR estimates are obtained, omitting a single cohort one at a time.

RESULTS

Analysis of Individual Studies

Tables IVa and IVb provide the distribution of thyroid cancers in the seven study populations by gender, time and age factors, and number of radiation exposures. In the cohort studies (Table IVa), 436 thyroid cancers occurred among individuals exposed to radiation before the age of 15 years and 92 were diagnosed among persons exposed at or after age 15 years. The majority of cases exposed during childhood (70.9%) came from the MRH tonsil study. Only cervical cancer patients and some atomic bomb survivors were exposed during adulthood. Thyroid cancer incidence

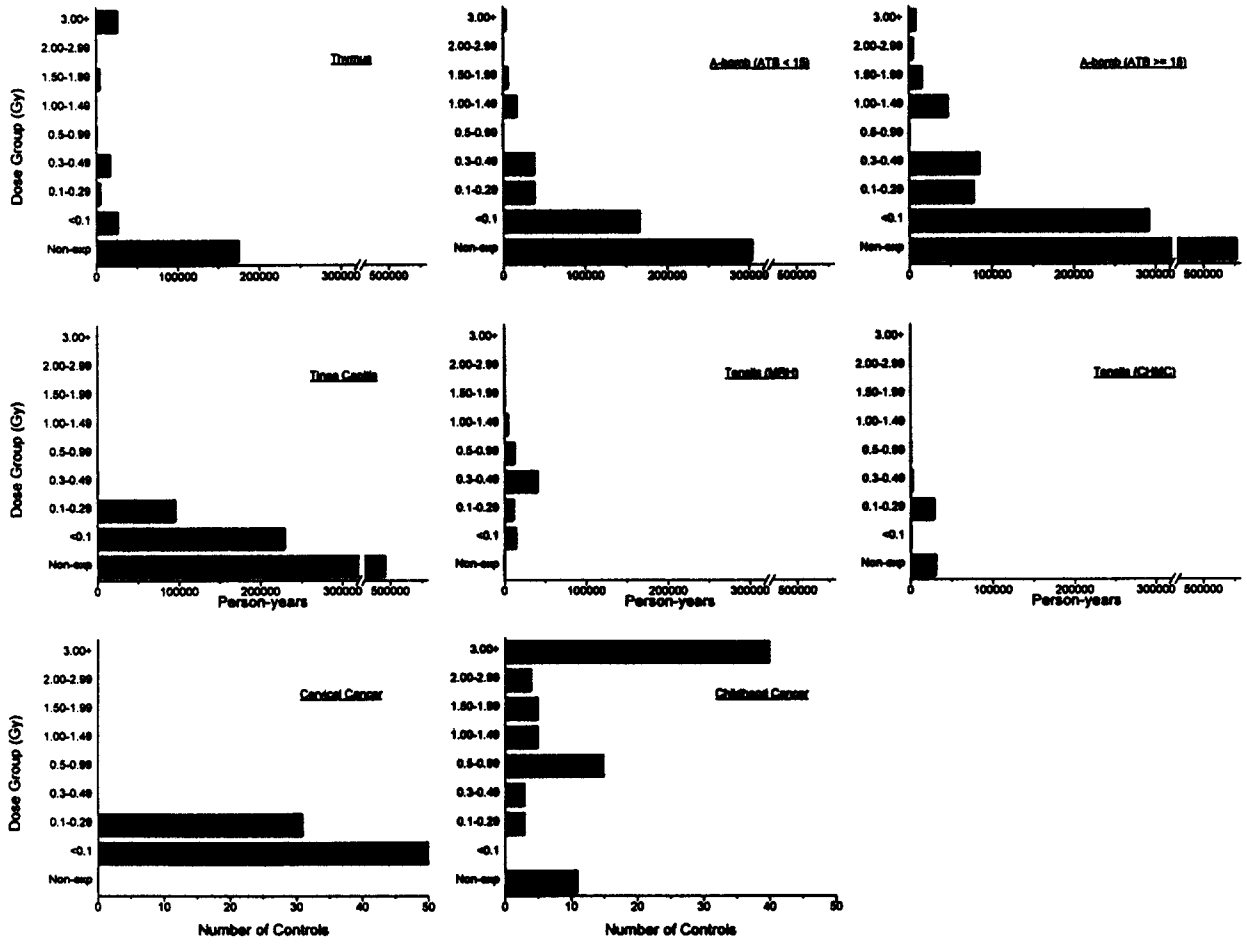

FIG. lb. Number of person years (cohort studies) or controls (case-control studies) by dose category for individual studies.

rates were considerably higher for females than males, and they increased with attained age. Higher crude thyroid cancer rates were seen among the exposed individuals than the nonexposed in all variable categories. A larger difference between the rates in the exposed and nonexposed individuals was observed in the persons exposed during childhood than those exposed as adults.

As expected, thyroid cancers were detected more frequently among screened persons or those examined as part of a special clinical program than among persons not included in these types of programs (Table V). Among nonexposed individuals included in the atomic bomb survivor study who are members of the AHS biennial clinical examination program, the rate of thyroid cancer was 2.5 times higher than among those not in the program. In the MRH tonsil cohort, the age- and sex-adjusted thyroid cancer rate was about seven times higher after 1974, when thyroid cancer screening programs were introduced in the United States, than before 1974. However; the large difference in thyroid cancer incidence did not influence the slope of the dose response significantly m either the atomic bomb survivors (test for homogeneity of dose response; $P = 0.86$) or MRH patients (test for homogeneity of dose response; $P = 0.39$), and therefore the following analyses are presented for the cohorts as a whole.

Based on a linear model, both the excess relative risks and the absolute excess risks demonstrate a strong association between radiation and thyroid cancer in each of the studies of childhood exposure for which a stable risk estimate could be obtained (Table VI). A finite risk estimate could not be calculated for the CHMC tonsil study because no thyroid cancers occurred among the nonexposed, the number of cases was small, and the range of exposures was narrow. Thus this study was used only in the pooled analysis. Under the relative risk model, the point estimate for the Israeli tinea capitis study was more than three times larger than the estimate from the other cohorts, but the instability of all the estimates resulted. in wide confidence intervals which generally overlapped. Motivated by the high point estimate of the tinea capitis study, supplemental analyses were conducted to try to characterize the excess relative risk better. Since this study had two comparison groups

TABLE IVa
Number of Thyroid **Cancer Cases and Crude** Rates (per 10,000 Person-Years)
for All Cohort Studies within **Categories of Several Variables**

	Thymus			A-bomb (<15 years ATB)			A-bomb (≥15 years ATB)			Tinea capitis			Tonsils (MRH)[a]		Tonsils (CHMC)[b]	
	Cases[c]	Exp[d] $n = 33$	N-exp[d] $n = 5$	Cases[c]	Exp[d] $n = 40$	N-exp[d] $n = 16$	Cases[c]	Exp[d] $n = 92$	N-exp[d] $n = 77$	Cases	Exp[d] $n = 44$	N-exp[d] $n = 16$	Cases[c]	Exp[d] $n = 309$	Cases[c]	Exp[d] $n = 10$
Overall	38	3.8	0.3	56	1.4	0.5	169	1.7	1.4	60	1.3	0.3	309	35.1	10	2.9
Gender																
Male	15	3.0	0.0	10	0.5	0.2	26	0.9	0.6	12	0.4	0.2	161	30.9	4	1.9
Female	23	4.8	0.6	46	2.4	0.8	143	2.1	1.7	48	2.2	0.5	148	41.1	6	4.4
Attained age (years)																
<20	12	2.5	0.0	—	—	—	—	—	—	12	0.7	0.1	37	9.1	1	0.6
20–29	12	4.4	0.5	10	0.8	0.3	0	0	0	28	2.0	0.4	101	40.0	5	4.5
30–39	8	5.2	0.4	14	1.0	0.5	10	1.9	0.7	19	1.7	0.6	142	86.1	3	5.1
40–49	5	11.8	1.1	21	2.1	0.4	17	1.0	1.2	1	1.6	0.0	27	52.3	1	16.4
50–59	1	0.0	4.5	11	3.6	1.8	48	2.2	1.2	—	—	—	2	46.4	—	—
≥60							94	1.6	1.7	—	—	—	—	—	—	—
Time since exposure or entry into cohort (years)																
<15	5	1.4	0.0	2	0.7	0	28	2.2	1.6	17	0.8	0.2	24	6.1	1	0.6
15–19	7	6.0	0.0	10	1.2	0.7	33	1.9	1.0	12	1.7	0.4	36	28.1	3	5.2
20–24	6	4.4	0.4	5	0.8	0.2	28	1.7	1.1	12	2.5	0.9	46	37.5	1	1.9
25–29	6	4.5	0.5	7	0.9	0.5	29	1.8	1.4	8	1.3	0.3	118	112.7	4	10.1
≥30	14	6.4	0.8	32	2.2	0.7	51	1.3	1.7	3	2.2	0.0	85	63.8	1	5.1
Age at exposure or entry into cohort (years)																
<1	38	3.8	0.3	—	—	—	—	—	—	—	—	—	25	35.5	1	17.6
1–4	—	—	—	17	1.2	0.3	—	—	—	21	2.1	0.1	211	40.4	2	2.5
5–9	—	—	—	16	1.5	0.6	—	—	—	28	1.1	0.4	62	26.4	5	2.3
10–14	—	—	—	23	1.7	0.7	—	—	—	11	0.9	0.4	11	20.3	2	4.2
15–19	—	—	—	—	—	—	28	1.9	0.8	—	—	—	—	—	—	—
20–29	—	—	—	—	—	—	37	1.4	1.4	—	—	—	—	—	—	—
30–39	—	—	—	—	—	—	38	1.5	1.1	—	—	—	—	—	—	—
≥40	—	—	—	—	—	—	66	2.0	1.8	—	—	—	—	—	—	—
Number of treatment courses																
1	11	2.4	—	—	—	—	—	—	—	39	1.3	—	273	34.6	10	3.3
≥2	22	5.2	—	—	—	—	—	—	—	5	1.6	—	36	38.7	0	0.0

[a]Thyroid cancer rates for exposed only. No nonexposed subjects.
[b]Thyroid cancer rates for exposed only. No cases were observed among nonexposed.
[c]Cases included in the present analysis (excludes people without thyroid dose estimates).
[d]Crude rate/10,000 person-years for exposed (Exp) and nonexposed (N-exp) subjects. *n* is the number of thyroid cancer cases.

(siblings and matched general population comparisons), we evaluated the dose response using each group separately. We found no significant difference, although the point estimate (ERR/Gy = 22.5) was lower when the exposed subjects were compared with the siblings. We also fitted a variant of model (1) which allowed an intercept different from one, namely, $RR = \theta^{I(d>0)}(1 + \beta \times d)$, where I is an indicator for exposure and θ estimates the intrinsic difference between exposed and nonexposed (Fig. 2a). Under this model, the ERR/Gy was 6.6 with a 95% CI of <0.0, 346.8 with θ estimated as 1.9 with a 95% CI of 1.0, 3.5. This ERR/Gy estimate was closer to the other studies, but the θ estimate was not significantly different from one, suggesting that this model and model (1) fit the data equally well. We did similar analyses for the other studies, but none of the results changed substantially.

The plots in Fig. 2a show the fit of the linear dose-response models to the observed data. With the possible exception of the childhood cancer survivor study, the linear model appears to fit the data quite well. In the childhood cancer survivor study there was some suggestion that a linear-exponential model may fit the data better than a linear model; however, there was no statistically significant improvement in fit. Visually, the linear-exponential model appears to better capture the substantial increased risk for persons treated with more than 2 Gy compared with those treated with less than 2 Gy, and the apparent flattening of the ERR at the very high dose levels.

TABLE IVb
Number of Thyroid Cancer Cases and Percentage of Exposed Subjects for Case-Control Studies within Variable Categories

	Cervical cancer[a]				Childhood cancer[a,b]			
	Number of subjects		Percentage dose ≥ 0.05 Gy		Number of subjects		Percentage dose ≥ 2.0 Gy	
	Cases	Controls	Case	Controls	Cases	Controls	Cases	Controls
Overall	43	81	88.4	84.0	22	82	86.4	51.2
Gender								
Male	–	–	–	–	8	28	87.5	45.2
Female	43	81	88.4	84.0	14	54	85.7	54.6
Attained age (years)								
<20	–	–	–	–	12	52	83.3	50.0
20–29	–	–	–	–	10	29	90.0	51.5
30–39	1	1	100.0	100.0	0	1		100.0
40–49	4	7	100.0	71.4	–	–	–	–
50–59	7	17	100.0	88.2	–	–	–	–
≥60	31	56	83.9	85.7	–	–	–	–
Time since exposure (years)								
<15	27	51	88.9	86.3	15	60	93.3	61.7
15–19	6	13	83.3	92.3	4	11	75.0	26.7
20–24	6	13	83.3	69.2	2	7	50.0	14.3
25–29	3	3	100.0	66.7	1	4	100.0	50.0
≥30	1	1	100.0	100.0	–	–	–	–
Age at exposure (years)								
<1	–	–	–	–	4	18	75.0	55.6
1–4	–	–	–	–	7	33	71.4	27.3
5–9	–	–	–	–	5	15	100.0	57.9
10–19	–	–	–	–	6	16	100.0	87.5
20–29	1	1	100.0	100.0	–	–	–	–
30–39	9	17	100.0	76.5	–	–	–	–
≥40	33	63	84.9	85.7	–	–	–	–

[a]Subjects included in the present analysis (excludes people without doses).
[b]Excludes four controls with no matched cases.

Under the absolute risk model, the highest point estimate was seen in the Israeli tinea capitis study. It was about 2.5 times higher than the point estimate for the other studies. As shown in Table V, when calendar year is used as a surrogate measure for screening, the incidence of thyroid cancer increased about 7-fold in the screened MRH subjects. When calendar year is included in the risk model, the EAR is $2.4/10^4$ PY Gy (95% CI = undetermined, 10.4) before 1974 and 45.2 (95% CI = -3.2, 89.0) after 1974. Thus the average EAR of $3.0/10^4$ PY Gy does not characterize the risk well, given the wide variation over calendar time. [The value $0.17/10^4$ PY cGy as reported in the original paper *(19)* was a misprint and should have been $0.017/10^4$ PY cGy]. The childhood cancer study was of the case-control design so that an absolute risk could not be determined directly. Shore *(1),* however, provided an estimate of $0.4/10^4$ PY Gy based on incidence data available from the cohort which generated the cases. Because the ERR and the EAR models are not nested models, direct comparisons really cannot be made. However, in all but the Rochester thymus study, the deviances were slightly lower using the relative risk model than the absolute risk model, but due to the large number of degrees of freedom, it is inappropriate to suggest that either simple model is preferable.

Only the atomic bomb survivor and cervical cancer studies provided data on adult exposure. Based on these limited data, the evidence for an effect of radiation in thyroid carcinogenesis was not convincing (Fig. 2b). The point estimate of the ERR/Gy for atomic bomb survivors above age 15 ATB (mean age =36 years) was 0.4 (95% CI = -0.1, 1.2). For cervical cancer patients, who had a mean age at treatment of 53 years, the ERR/Gy (34.9) was very high, but the confidence intervals around each of the data points were large, the dose response was not statistically significant, and the confidence interval around the overall point estimate of the dose response was extremely wide (95% CI

TABLE V
Thyroid Cancer Rates by Degree of Medical Surveillance

	Normal medical care[a]		Heightened medical surveillanc[a]	
	cases	Rate	cases	Rate
Tonsils (MRH)	109	15.6	200	109.6
Males	49	11.8	112	105.6
Females	60	21.1	88	115.1
A-bomb	153	1.1	72	2.8
Males	23	0.4	13	1.4
Females	130	1.5	59	3.6

[a]For the tonsil study, normal medical care includes cases diagnosed before thyroid screening began (<1974) and heightened medical surveillance means after screening began (>=1974). Thyroid cancer rates are attained age adjusted for a subject aged 30-34 years. For the atomic bomb survivors, normal medical care includes cases diagnosed among members of the LSS cohort not included in the special clinical program, i.e. as part of their usual medical care. Heightened medical surveillance includes cases diagnosed among members of the Adult Health Study, a program which provides biennial clinical examinations by RERF doctors who are aware of the association between thyroid cancer and radiation exposure.

= –2.2, ∞). similar to the results for excess relative risk, there was no evidence of a significant EAR among the atomic bomb survivors exposed above age 15 years. We did not estimate the EAR for the cervical cancer study because of its case-control design.

Table VII shows the variation in the ERR/Gy by several factors. The entries are the proportional modifications to the ERR/Gy relative to the referent category, i.e. the exp(γ) values in model (4). Generally, the excess relative risks for radiation effects appeared similar for females and males; only the thymus study exhibited differential effects, with males more sensitive to radiation than females. The thymus study also was the only one that showed significant variation in risk by attained age, although similar, nonsignificant patterns were observed for atomic bomb survivors (<15 years ATB) and cervical cancer patients. Results from the MRH tonsil study indicated heterogeneity in risk with time since exposure, but the pattern was not consistent, whereas in the thymus study risk appeared to decrease over time, but the variation was not statistically significant. An excess risk was observed during the last follow-up period in all studies. In fact, 30 years or more after exposure the study-specific ERRs/Gy were still above 3 (data not shown). Although tests for homogeneity were not statistically significant, risks appeared to decrease with increasing age at exposure in all studies except the childhood cancer study. Among the atomic bomb survivors, the only study with data from all age groups, the pattern of decreasing risk with increasing age at exposure was seen in the cohort of persons exposed before age 15 and those exposed after age 15. Although the overall dose response was not significant in the adult cohort and the results were not statistically significant, the individual ERR/Gy point estimates were positive until age 40+.

Three studies allowed a limited evaluation of fractionation; however, the length of time between fractions, dose per fraction and reason for fractionation differed in each study. In the thymus study, 51%. of the patients had all their exposure at one time, 39% had 2 dose fractions, and 10% had 3-11 fractions. Of those with fractionated exposure, 49% had an average interval between fractions of 1-2 days and 51% had an interval of 3 days to several months. In both the tinea capitis and MRH tonsil studies, all patients received their exposure in fractions. In the tinea capitis study, one treatment course consisted of 5 fractions with a l-day interval

TABLE VI
Excess Relative Risk per Gy (ERR/Gy) and Excess Absolute Risk per 10^4PY Gy (EAR/10^4PY Gy)

	Excess relative risk model				Excess absolute risk model				
	ERR/Gy	95% CI	*P* value for nonlinearity	Deviance	EAR/10^4 PY Gy	95% CI	*P* value for nonlinearity	Deviance	Degrees of freedom
Exposure <15 years old									
Thymus	9.1	(3.6, 28.8)	0.41	172.8	2.6	(1.7, 3.6)	0.67	168.8	1610
A-bomb (<15 ATB)	4.7	(1.7, 10.9)	0.41	276.1	2.7	(1.2, 4.6)	0.98	280.3	1390
Tinea capitis	32.5	(14.0, 57.1)	0.45	295.8	7.6	(2.7, 13.0)	0.77	312.9	3156
Tonsils (MRH)	2.5	(0.6,26.0)	0.24	1054.1	3.0[a]	(0.5, 17.1)	0.02	1069.3	6748
Childhood cancer[b]	1.1	(0.4,29.4)	0.09						
Exposure >=15 years old									
Cervical cancer	34.9	(-2.2, -)	0.81						
A-bomb (>=15 ATB)	0.4	(-0,1, 1.2)	0.38	714.3	0.4	(-0.1, 1.4)	0.70	715.8	3985

[a]This is the average excess absolute risk, however, the EAR/1O^{4}PY Gy was 2,4 (95% CI = undetermined, 10.4) for follow-up until 1974 and 45.2 (95% CI = -3.2, 89.0) for follow-up after 1974. The EAR/10^4PY Gy estimates in this study are subject to large variability because of the influence of extreme dose points. These points, however, appeared to have little influence on the ERR/Gy.

[b]ERR/Gy estimates baaed on setting doses under 2 Gy to the mean dose of 0.74 Gy.

[c]ERR/Gy estimates based on regression of category-specific mean doses. It can be seen that the point estimate is not significant and the confidence interval is extremely large.

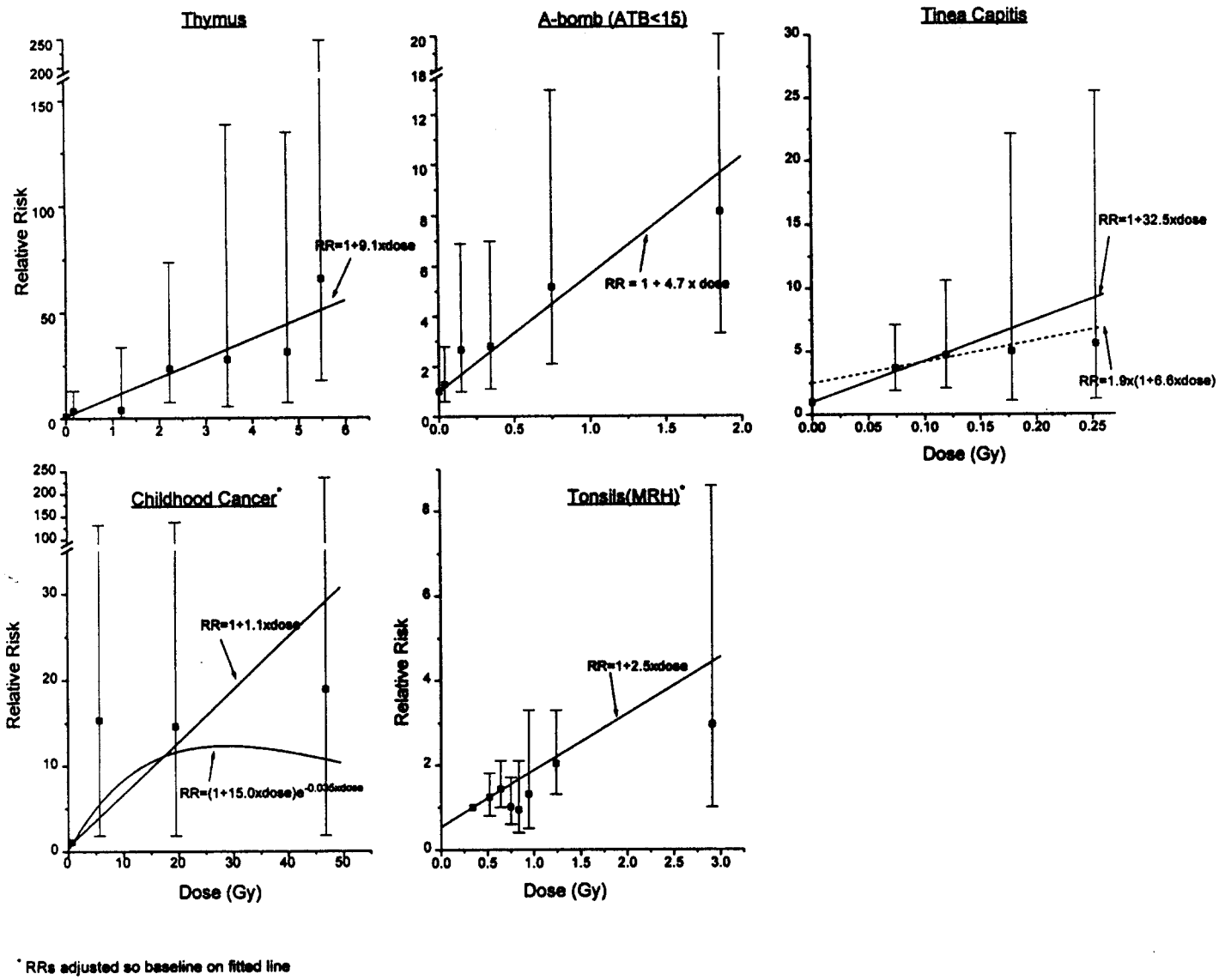

FIG. 2a. Fitted dose response of data from studies of childhood (<15 years) exposure.

between them. A typical treatment course at MRH consisted of 3 fractions at weekly intervals. Since almost all patients had the standard therapy regimen, we were able to evaluate fractionation only by examining patients who received multiple treatment courses. In general, treatment courses were separated by at least 6 months for the MRH patients and 1 year for the tinea capitis patients. Although fractionation was defined differently in the three studies and the results were not statistically significant, the pattern of risk was very similar. The ERRs/Gy were about 30% lower in each study when exposure was fractionated (Table VII).

Pooled Analysis

To estimate risk patterns better, we pooled the data from the five cohort studies of persons irradiated before age 15 [atomic bomb survivors, thymus, tinea capitis and the two tonsil studies (MRH, CHMC)]. A comparison of the contribution of cases and person years from each of the studies shows that the pooled analysis is heavily influenced by the large number of cases from MRH and person years from the tinea capitis and atomic bomb survivor studies (Figs. la and b). It can also be seen that the dose range is rather limited in most of the individual studies, there is not much dose overlap among the studies, and the high-dose cases come predominately from the thymus study.

Combining the data from the five studies, the pooled ERR/Gy from model (1) was 7.7 (95% CI = 2.1, 28.7) (Fig. 3). A test for homogeneity of the ERR/Gy across studies showed that the individual point estimates differed significantly ($P < 0.001$). (Note the CI based on a fixed

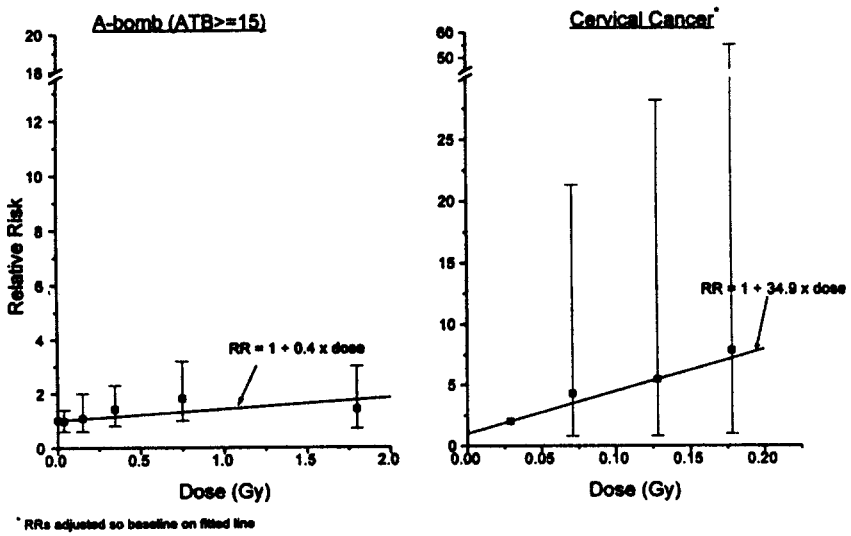

FIG. 2b. Fitted dose response of data from studies of adult (>=15 years) exposure.

effects model was narrower, 4.9, 12.0.) We also computed the pooled ERR/Gy using model (4), allowing for the non-zero ERR at zero dose. The risk was lower (ERR/Gy = 3.8, 95% CI = 1.4, 10.7), and the intercept value for θ was 1.4. The difference in the ERR/Gy across cohorts was no longer significant (P = 0.08). The fitted linear dose-response curves appear to underestimate the risk at low doses and overestimate the risk at high doses (Fig. 3); however, tests for curvilinearity were not significant. The model-based average pooled AR% for exposed subjects was 80%, and it is estimated that for persons exposed to 1 Gy it would be 88%. For the individual studies, the AR% among the exposed subjects ranged from about 35% to 90%.

To evaluate the impact of individual studies on the overall ERR, we carried out an influence analysis by computing the weighted ERR/Gy five times, omitting data from each cohort in turn and using data from the four remaining studies. None of the cohorts had a statistically significant influence on the overall ERR/Gy estimate, although the MRH tonsil and Israel tinea capitis studies had the greatest influence on the summary estimate. When the data from MRH were removed, the point estimate increased from 7.7 to 12.2 (95% CI = 3.9, 37.8). When the tinea capitis study was similarly removed, the risk estimate decreased from 7.7 to 3.8 (95% CI = 1.4, 9.9). The decrease was from 3.8 with an intercept of 1.4 to 2.5 (intercept 1,6) when the ERR/Gy was adjusted for exposure status.

Figure 4 shows the ERR/Gy estimates and their 95% CI on the logarithmic scale. It can be seen that three ERR/Gy estimates are within the pooled random effects confidence interval. The tinea capitis study risk estimate was similar to those of the other studies when the indicator of exposure status was included in the model. Because the childhood cancer study employed a case-control design, it was not included in the pooled risk estimate, but the ERR/Gy appeared to level off at high doses.

The ERR/Gy was nearly twice as high for females than males, although the difference did not reach statistical significance (P = 0.07). The ERR/Gy decreased with increasing age at exposure and was highest for persons exposed to radiation before age 5 (Table VIII). For the first 5 years after exposure there was no excess risk and only two thyroid cancers occurred among the exposed subjects. The ERR/Gy was highest about 15 years after exposure, but still in excess 40 or more years after exposure.

Three studies contributed data on fractionated exposures. Taking into account the limitations of the data described previously, the pooled risk estimate was greater for persons treated with radiation in a single exposure than those treated with multiple exposures or treatments. When the analysis was limited to fractions of <l Gy (325 cases with 1 fraction and 22 with multiple), <0.5 Gy (134 cases with 1 fraction and 11 with multiple), or a total dose of <6 Gy (373 cases with 1 fraction and 11 with multiple), the ratio of the ERR/Gy for fractionated to single exposure treatments was always 0.7.

The pooled EAR/10^4PY Gy was 4.4 (95% CI = 1.9, 10.1). When the data from MRH after the initiation of the screening program began were removed from the analysis, the pooled EAR was 4.1 (95% CI = 1.6, 10.0).

DISCUSSION

A pooled analysis of seven studies of radiation-induced thyroid cancer allowed a more detailed evaluation of dose response and effect modification than was previously possible. The pooled ERR/Gy estimate was 7.7. Even using a random effects model to compute the CI, the lower bound

TABLE VII
Modifiers of Excess Relative Risk per Gy (ERR/Gy) by Several Categorical Variables[a]

Category	Thymus	A-bomb (<15 ATB)	A-bomb (≥15 ATB)	Tinea capitis	Tonsils (MRH)	Cervical cancer[b]	Childhood cancer[c]
			Gender				
Male	∞	2.9	0.2	0.2	1.8		0.6
Female	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**	N.A.	**1.0**
P[d]	0.03	0.39	0.57	0.17	0.66		0.91
			Attained age				
<20	10.4			0.8	0.3		**1.0**
20–29	3.2	1.1		1.1	0.7		∞
30–39	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**		
40–49	0.6	0.8	3.7		0.3	∞	
50–59		0.3	4.3			**1.0**	
≥60			<0			0.5	
P	0.04	0.87	0.32	0.94	0.19	0.23	0.18
			Time since exposure				
<15	**1.0**	∞	**1.0**	**1.0**	**1.0**	∞	**1.0**
15–19	1.2	**1.0**	6.0	0.8	5.8	**1.0**	∞
20–24	0.5	2.5	0.3	1.0	4.1		
25–29	0.3	1.3	2.7	0.3	4.9		
≥30	0.1	1.8	0.0	1.0	3.9		
P	0.14	0.91	0.66	0.63	0.03	0.44	0.19
			Age at exposure				
<1	N.A.				**1.0**		0.0
1–4		**1.0**		**1.0**	0.5		**1.0**
5–9		0.6		0.4	0.5		2.3
10–14		0.2		0.3	0.0		4.8
15–19			**1.0**				
20–29			0.6				
30–39			0.6			**1.0**	
≥40			<0			0.0	
P		0.14	0.09	0.15	0.22	0.43	0.31
			Number of fractions or treatment courses				
1	**1.0**			**1.0**	**1.0**		
≥2	0.7			0.6	0.7		
P	0.38			0.31	0.25		

[a]Table entries are the ERR/Gy for designated categories relative to referent category. Referent category in bold.
[b]ERR/Gy estimates based on regression of category-specific mean doses.
[c]ERR/Gy estimates based on setting doses under 2 Gy to the mean dose of 0.74 Gy.
[d]*P* value for likelihood ratio test of homogeneity of ERR/Gy across categories.

was still 2.1. The magnitude of the risk clearly shows that, along with the breast and bone marrow, the thyroid is highly sensitive to radiation. An increased risk was observed over a wide range of doses and a linear dose response characterized the data well. Since only the childhood cancer study included people exposed to extremely high radiation doses, we could not formally assess the importance of cell killing, but based on its 22 cases there was a suggestion that the excess risk may level off at very high doses.

The most recent National Academy of Sciences report (BEIR V) on the health effects of ionizing radiation *(25)* analyzed the data from the Rochester thymus study and the Israel tinea capitis study. Restricting the analysis to thyroid cancers occurring 5 years or more after exposure, they reported a highly significant dose response with no significant difference in the ERR that was dependent on gender in either study. Overall the magnitude of the risk in the two studies differed, but when a subgroup of the tinea capitis cohort (persons born in Israel and irradiated after age 5 years) was compared to the Rochester series, the difference was no longer statistically significant. As a result, the BEIR V committee recommended a relative risk model based on the tinea capitis subgroup described above. At 1 Gy, this model predicts an ERR of 7.3.

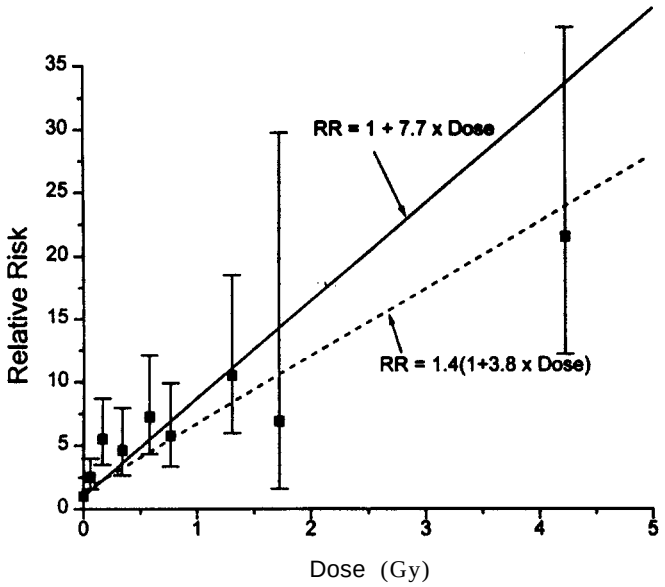

FIG. 3. Pooled fitted dose response of data from cohort studies of childhood (<15 years) exposure. The solid line represents the dose response based on model (1) $[r(x,d) = r_o(x)(1 + ßd)]$ and the dotted line **represents the dose response based on** a variant of model (1) which **allowed an intercept different** from one.

As described in Table III, all studies have strengths and weaknesses. However, the analysis demonstrated that no single study had undue influence on the overall risk estimate. The MRH study is unique in that it has no nonexposed population and that a large number of patients were screened for thyroid disease. Yet the ERR/Gy estimate did not differ significantly from the other studies and the patterns of risk were similar to those observed in the other studies. Two studies had high ERR/Gy point estimates: the Israel tinea capitis study and the cervical cancer patients. The cervical cancer study includes only adult patients, so the large risk is particularly unusual and it is likely due to chance and/or to the statistical instability caused by having very few nonexposed patients. The tinea capitis risk is more difficult to explain. We analyzed the data using the two comparison groups separately, but the results were essentially the same. Adjustment for possible intrinsic differences between exposed and nonexposed subjects reduced the ERR/Gy estimate substantially and made it fall within the confidence interval of the pooled estimate (Fig. 4). Methodological, ethnic, socioeconomic and/or medical system differences may partly explain the high tinea capitis study risk, but at present no readily explainable factor has been identified. Another possibility is dose error. If the doses were as little as 15% higher, the ERR/Gy point estimate would fall

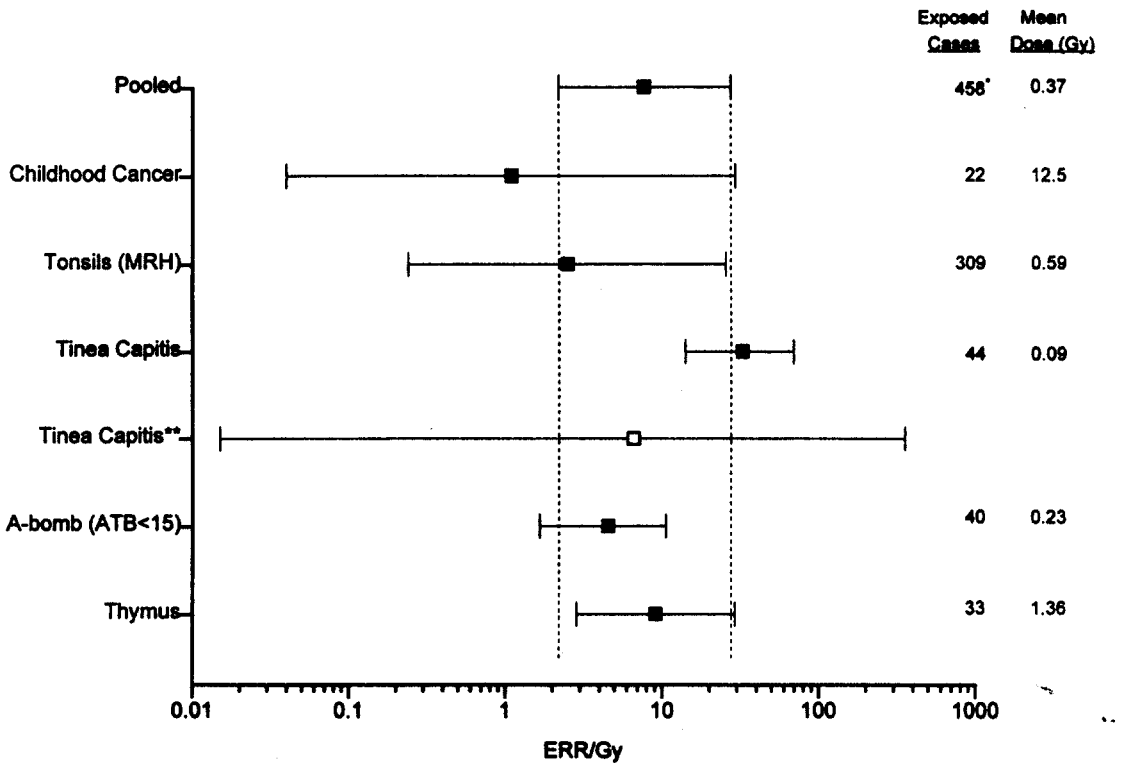

FIG. 4. Point estimates and 95% confidence intervals of the ERR/Gy for studies of childhood (<15 years) exposure in relation to the pooled **estimate** and confidence interval. *The number of pooled cases includes the cases for the individual studies shown in the plot and the 10 cases from the CHMC tonsil study. **ERR/Gy adjusted for non-zero intercept. Lower confidence interval is <0.

TABLE VIII
Pooled Analysis of Cohort Studies of Persons Exposed before Age 15 Years: Modifiers of Excess Relative Risk per Gy (ERR/Gy)

Variable	Categories	Number of cases	Modifying effect[a]	*P* value[b]
Gender	**Male**	202	0.5	0.07
	Female	271	**1.0**	
Attained age (years)	**<20**	62	**1.0**	0.15
	20–29	146	0.5	
	30–39	192	0.1	
	40+	73	0.0	
Time since exposure (years)	**<5**	2	<0	<0.001
	5–9	21	1.3	
	10–14	26	**1.0**	
	15–19	68	2.2	
	20–24	78	1.5	
	25–29	143	2.1	
	30–34	71	0.7	
	35–39	41	0.3	
	40+	23	1.0	
Age at first exposure (years)	**<1**	64	**1.0**	0.004
	1–4	251	1.0	
	5–9	111	0.5	
	10–14	47	0.2	
Number of treatments	**1**	373	**1.0**	0.18
	2+	63	0.7	

[a]Table entries are the ERR/Gy for designated categories relative to referent category. Referent category is in bold.

[b]*P* value for likelihood ratio test of homogeneity of ERR/Gy across categories.

within the confidence interval of the pooled estimate, as well as three of the four other childhood studies. Finally, Hazen *et al. (26)* suggested that the combination of radiation exposure to both the thyroid and pituitary glands maybe particularly effective in inducing thyroid cancer.

Results on gender differences in sensitivity for developing radiation-induced thyroid cancer have been inconsistent *(1).* Higher ERRs/Gy for women than men have been reported from some studies, but the opposite effect has also been noted. In the joint analysis, the ERR was higher for females than for males, but the difference was not statistically significant. Because of the greater risk of spontaneous thyroid cancer in females, the absolute radiogenic excess was also larger for females than males.

A trend for decreasing risk with increasing age at irradiation has frequently *(1,15,17,19,27),* but not always *(10)* been reported. This pattern was observed in each of the individual studies. The joint analysis strengthened these findings and suggests a greater radiation effect in humans during periods of rapid cell proliferation during development of the thyroid gland.

Data on adult exposures were available from only two studies, and more data on adults clearly are needed. **However,** overall the results essentially were negative, as are studies of adults exposed to ^{131}I *(28,29).* Shore *(1)* estimated thyroid cancer risk in a study of 124 persons exposed as adults *(2)* and three studies of mixed childhood and adult exposure *(5,8,14).* The studies are small and only a mean dose is available. The ERR/Gy estimates ranged from 0.0 to 1.2, which is considerably smaller than the estimates found in cohorts irradiated during childhood.

How long the excess risk of radiation-induced thyroid cancer will persist is a question that has particular relevance for persons irradiated many years ago and also for their clinicians. Some studies have suggested a continuing decline in risk 40 years or more after exposure *(1, 30).* In the pooled analysis, the excess risk peaked 15-19 years after radiation exposure, then declined, although an excess at 40+ years was still apparent. Since the two largest cohorts (atomic bomb survivors and MRH) have little follow-up after 40 years, it will take additional years of observation until lifetime risks can be characterized accurately.

In light of the early reports of a dramatic increase in thyroid cancer among children living in Belarus *(31, 32),* it is of note that in our pooled data only two thyroid cancers developed among the exposed subjects less than 5 years after exposure, although there were more than 81,000 person-years of follow-up.

The effects of fractionated radiation exposure on the thyroid gland have not been clearly established. Fractionation effects have been examined by interval between fractions for the induction of several types of solid tumors (lung, ovary, skin) in animals *(33-35).* These studies indicate that the critical length of time between fractions in terms of a dose-sparing effect for carcinogenesis is <=24 h. In addition, cellular DNA repair processes are known to operate within minutes for single-strand DNA damage and within hours for double-strand damage. These data suggest that the intervals between fractions in our studies should be sufficient to see a dose-sparing effect if one exists.

Three of the studies (thymus, tinea capitis and MRH) included in our analysis had some type of fractionated exposures. The interval between fractions ranged from 1 day to several years. About one-half of the thymus patients received their treatment in fractionated exposures, whereas the tinea capitis and MRH patients received two different types of fractionated exposures: all patients received fractionated exposures as part of the standard therapy regimen, and about 10% of the patients also received more than one course of treatment. Therefore, we were able to evaluate fractionation associated with the number of treatment courses. In the pooled analysis, because of the relatively small number of person years in the >2-fraction category, we analyzed the data using two fractionation groupings (1, 2+). Individually the three studies showed a consistently lower risk for fractionated exposures; about a 30% reduction in ERR/Gy for persons whose total dose was accumulated during two or more exposures. Earlier analysis *(36)* of

the thymus study did not show this sparing effect of fractionated exposure when three categories of fractionation were used (1, 2, >2). When the data were pooled, the ratio of the ERR/Gy for fractionated to single exposure was 0.7 (95% CI = 0.5, 1.1) and the *P* value for the test of significance was 0.18. To the extent that information about fractionated exposures delivered at relatively high dose rates is relevant, the data suggest the dose and dose-rate effectiveness factor may be about 1.5.

Pooled analyses of epidemiological studies have become more common recently, and the methods are still evolving. Advantages and limitations of the technique are currently being discussed *(37, 38).* Heterogeneity among studies, various levels of study quality and selection bias have been cited as problems associated with pooled analyses. To try to prevent some of these problems, we restricted the analysis to studies of external radiation that met population or case size requirements and had adequate thyroid dose information, Yet the studies included comprised various population groups and different comparison populations, and they employed a range of methods for cancer ascertainment and follow-up. We tried to include all studies that met the inclusion criteria, and since the circle of radiation epidemiologists is small, the likelihood of unknown studies is minimal.

Because we observed heterogeneity among the different studies, likelihood-based confidence intervals were obtained for the individual studies, but a random-effects model was used to calculate the confidence interval for the pooled analysis. The random-effects model takes potential heterogeneity between studies into account so that a wider confidence interval is obtained than when a fixed-effects model is used *(24).* In our analysis, the range of the confidence interval based on a random-effects model (2.1, 28.7) was more than double that based on a fixed-effects model (4.9, 12.0).

The relatively small overlap in dose in the various studies is a limitation of the pooled analysis. The only high-dose exposures were among children, and only the Rochester thymus and atomic bomb survivors studies included a wide range of exposure.

In these data, there is little direct information about the error in estimated individual doses. Pottern *et al. (18)* report that there is ±50% uncertainty in the dose estimates for the CHMC tonsil study. The doses for the MRH tonsil study could be ±30% if all of the rectangular fields had been in one direction or the other. In the tinea capitis study, slight head movement was shown to increase the mean thyroid dose estimate by 50%, from 0.06 to 0.09 Gy *(39).* Pierce *et al. (40)* suggest that there might be as much as 35% error in the dose estimates for the atomic bomb survivors and that this magnitude of error could result in a 10-15% underestimate of the ERR/Gy for cancer incidence in this cohort.

Papillary (including mixed papillary-follicular) cancers comprised 97, 87, 85 and 70% of the cancers occurring among the atomic bomb survivors, MRH patients, tinea capitis patients and thymus patients, respectively. We did not evaluate radiation risk in terms of histological type because the number of nonpapillary cancers was small. Combining data from several published studies, Shore *(1)* reported an increased risk of radiation-induced follicular thyroid cancer. However, the level of risk was lower than the risk of developing papillary carcinoma. A causal association between radiation and anaplastic carcinoma has not been demonstrated. The number of these fatal cancers is small in exposed populations, precluding any separate risk assessment at this time. As the study subjects reach the natural ages for developing follicular and anaplastic thyroid cancers, it is likely that their frequency will increase, and further follow-up of the cohorts will permit an evaluation of radiation effects for these cell types.

In conclusion, a pooled analysis of seven studies provided a method for studying several issues regarding radiation-induced thyroid cancer. The ERR/Gy was elevated in each of the studies of childhood exposure, and the pooled estimate clearly demonstrated that the thyroid gland is highly sensitive to the carcinogenic effects of radiation. In the joint analysis, females had a higher risk than males, but the findings were not consistent in the individual studies. No excess risk was seen in the first 5 years after exposure. Among those exposed as children, there was a clear increased risk 5 to 9 years after exposure which persisted for the entire follow-up period. The excess relative risk was most apparent among persons irradiated before age 5. Among the cervical cancer patients and atomic bomb survivors exposed after age 15, the ERR/Gy was not significantly elevated.

APPENDIX
Description of Studies Included in the Pooled Analysis

1. The Life Span Study of Atomic Bomb Survivors

The Life Span Study (LSS) is a cohort of approximately 94,000 atomic bomb survivors and 26,000 persons who resided in Hiroshima or Nagasaki shortly after the bombings. The LSS has been followed since the mid-1950s, first by the Atomic Bomb Casualty Commission and subsequently by the Radiation Effects Research Foundation (RERF). As described in a recent RERF report *(15),* thyroid cancer incidence diagnosed between 1958–1987 was determined among the 79,972 atomic bomb survivors who were alive and free of cancer as of January 1, 1958 and who have DS86 dose estimates of less than 4 Gy kerma. This is the only study that includes people of both sexes who were exposed at all ages. First primary thyroid cancers (excluding occult cancer) were ascertained through the Nagasaki and Hiroshima tumor registries *(41).* Of the 225 thyroid cancers identified among the LSS cohort, 93%. were confirmed histologically, 4% were diagnosed Clinically, and 3%. were ascertained through death certificates. The Adult Health Study (AHS) is a companion study which includes a sub-

sample of approximately 20% of the LSS. The AHS participants are clinically examined biennially by RERF doctors. To evaluate the possible effect of intense medical surveillance, analyses were done separately by AHS status.

Survivors of the bombs in Hiroshima and Nagasaki were exposed to both y and neutron radiation. Dosimetric studies were undertaken soon after the bombings and have been modified and refined since then. For this study, the latest version of the RERF dose estimation system (DS86) was used to compute individual organ-specific doses based on exposure and shielding histories attenuated by distance, materials and tissue *(42, 43).* Weighted organ doses were computed as the γ-ray dose plus 10 times the neutron dose and are expressed in sieverts. In the recent RERF analysis of thyroid cancer incidence, people who were exposed to a thyroid dose of less than 0.01 Sv were considered the comparison population and were referred to as nonexposed *(25).* We have used the same terminology in this paper.

It is estimated that, by 1980, about 20% of the surviving members of the study cohort no longer resided in Hiroshima or Nagasaki. To account for emigration, cases were restricted to residents in Hiroshima and Nagasaki at the time of diagnosis and statistical procedures were used to adjust the person-years of observation *(15, 44).*

2. *Rochester Infants Irradiated for Enlarged Thymus Gland*

In the early 1950s, a study of persons who were given X-ray treatment as infants for an enlarged thymus was initiated. The current study includes 2,856 persons treated between 1926 and 1957 and all 5,053 nonexposed available siblings *(16, 36, 45).* All patients were irradiated before the age of 1 year and 90% were treated before they were 6 months old. Follow-up of this cohort began in the 1950s. Information regarding incidence of benign and malignant tumors, as well as information on potential risk factors, has been obtained through periodic mail surveys. At the end of the last survey in 1987, 86% had responded to the questionnaire, 4% were deceased, and 10% were not located or did not respond. The study subjects have been followed for an average of 35 years. Over this period, 42 thyroid cancers were ascertained. Tumor information was verified through medical or pathology records, and pathology slides were reviewed for most thyroid tumors.

Information about radiation treatment was obtained from the radiation records and interviews with physicians providing the radiotherapy. Patients were treated at 10 medical institutions and radiologists' private offices in Rochester, NY, using X-ray machines with beams ranging from 75 kVp without added filtration to 250 kVp with 1 mm of Al filtration. Radiation exposure ranged from 30 to 1,200 R air dose. Field sizes ranged from 3 x 5 cm (14% of patients) to 10 x 10 cm (14% of patients), but the largest group of patients (27%) were treated with a 4 x 5-cm field. The source-to-skin distance ranged from 30-50 cm. Patients received between 1 and 11 treatments, with the majority treated once or twice. The total period of treatment was less than 1 week for approximately 80% of the patients, and only about 3% received treatment over more than 2 months. Individual thyroid doses were estimated for 91% of the exposed subjects by irradiating a radiological phantom of an infant using representative treatment parameters and calculating the thyroid dose based on whether the thyroid was inside or outside the primary beam, the beam quality and the source-to-skin distance *(46).* For 239 persons, information was not adequate to allow dose estimation. Since four of these were thyroid cancer cases, our analysis is based on 38 thyroid cancers. Thyroid doses ranged from 0.03 to 11 Gy and the distribution was highly skewed. Although the mean was 1.36 Gy, the median was only 0.3 Gy.

3. *Israeli Children Irradiated for Tinea Capitis*

The study population is comprised of 10,834 persons who received X-ray therapy for tinea capitis between 1948 and 1960, 10,834 tinea-free, nonirradiated matched (on gender, age, country of origin and year of immigration) comparison subjects selected from the general population, and 5,392 tinea-free, nonirradiated siblings *(17, 47).* All irradiated patients were treated before age 16, Study subjects either immigrated to Israel from Africa or Asia or were children of fathers who had immigrated from the same regions. Thyroid cancers occurring between 1960-1986 were ascertained by computer linkage of the study subject roster with the Israel Cancer Registry and were subsequently validated individually. Tumor diagnoses were verified by obtaining pathology, medical or surgical records. As part of an early study, original pathology slides of tumors diagnosed before 1978 were reviewed. Hospital pathology records in all Israeli hospitals were screened to identify thyroid cancers diagnosed between 1950-1960 (before the Cancer Registry was established). A total of 60 thyroid cancers were identified in the study population.

The Adamson-Kienbock radiotherapy technique (a five-field treatment of the scalp, with lead shielding on the face and neck) was followed closely at four treatment centers in Israel, using X-ray machines with beams of 70-100 kVp, 0.5 mm Al filter and 1.0 Al half-value layer. A course of therapy consisted of five fractionated exposures, each exposure delivered on consecutive days. Typically the exposure in air was about 375 R (range 350 to 425) to each of the five scalp fields. Most patients received only one course of therapy, but about 9% of the patients received multiple treatments, with at least 1 year between treatments. The mean thyroid dose was originally estimated to be 0.06 Gy *(39),* but when slight patient movement was taken into account, the dose estimates increased by 50%. The mean dose was 0.09 Gy (range 0.05 to 0.5 Gy) but varied with age. Individual doses were estimated based on measurements made on an

anthropomorphic phantom, age at time of treatment and the prescribed medical center-specific exposure technique, taking patient movement into account *(17).*

4. *Children Irradiated for Benign Head and Neck Conditions at Michael Reese Hospital (MRH)*

Between 1939 and 1962, over 5,000 patients received head and neck radiation therapy for benign conditions (80% for enlarged tonsils and adenoids) at MRH in Chicago *(19, 50-52).* A follow-up and screening program was initiated in 1974. The study population was recently redefined to include the 4,296 subjects who were treated with conventional (200 kVp) radiotherapy to the head and neck area before the age of 16 years *(19).* Information concerning benign and malignant thyroid neoplasms has been obtained, by either questionnaire or clinical examination, for 3,042 persons. Self-reported information on thyroid disease was validated by obtaining medical records.

The treatment records for the newly defined cohort were abstracted in detail to permit estimations of thyroid doses for each individual. The majority of these patients were treated with right and left lateral fields (6 x 8 cm or 8 x 10 cm, 10 x 10 cm) directed to the posterior pharynx using orthovoltage X rays (0.5 mm Cu plus 0.5 mm Al filter, 1.2 mm Cu half-value layer and a skin-to-source distance of 50 cm). A course of therapy consisted of three treatments given at weekly intervals for a total of 375 R to each field. Approximately 12% of the study cohort received more than one treatment course. Individual organ doses were estimated based on an anthropomorphic phantom, age at exposure and treatment parameters for the patients with sufficiently described treatment parameters *(19).*

Among the 2,634 subjects with adequate follow-up and estimated dose information, 309 thyroid cancers were ascertained. Thyroid doses ranged from 0.01 to 5.8 Gy with a mean of 0.59 Gy. Because of uncertainty in field orientation for the 70% of the patients having rectangular treatment fields, three estimates of thyroid dose were computed for each patient (maximum, minimum and average of the maximum and minimum estimates). This analysis is based on the average dose. Risk estimates for all subjects were statistically similar to estimates based on patients treated with square fields.

5. *Children Irradiated for Lymphoid Hyperplasia at Children's Hospital Medical Center (CHMC)*

Between 1938-1969, several thousand patients under age 18 years were treated for lymphoid hyperplasia (97% for enlarged tonsils or adenoids) at CHMC in Boston *(18),* The study population consists of 1,590 irradiated patients and 1,499 patients treated with surgery only. Of these subjects, 2,671 (86%) were successfully traced as either alive (83%) or deceased (3%). Data about thyroid cancer and benign thyroid tumors were obtained through a mail questionnaire. Of the living subjects, 90% of the exposed and 86% of the nonexposed subjects completed the questionnaire. A clinical examination was offered to those subjects. Examinations were completed on 59% of the exposed and 52% of the nonexposed eligible subjects. This analysis is restricted to thyroid cancers identified only through the questionnaire since too few persons participated in the examination phase of the study. No thyroid cancers were reported by the nonexposed patients, but 11 were identified among the exposed questionnaire respondents. Dose estimates were available for 10 thyroid cancer patients. Attempts were made to validate information on thyroid disease obtained from the questionnaire. Radiation records were abstracted for information needed to estimate individual organ doses. Typically both the left and right side of the nasopharyngeal region were irradiated on one day and then irradiated again a week later. The average cumulative air dose was 800 R. Treatment fields were generally smaller in Boston (5 x 7 cm, 6 x 7 cm or 6 x 8 cm) than in Chicago. Thyroid doses were estimated for subjects based on measurements made on an anthropomorphic phantom, age at treatment and treatment records. The mean estimated thyroid dose was 0.24 Gy (range 0.03-55).

6. *Childhood Cancer Survivors*

In a Late Effects Study Group (LESG) cohort study of 9,170 childhood cancer patients who had survived 2 or more years, 23 subsequent thyroid cancers developed *(53),* Detailed treatment data were obtained for these 23 cases and a stratified random sample of 89 controls who did not develop a second cancer *(21).* Controls were matched on histology of first tumor, duration of follow-up, age at time of diagnosis of the first cancer, gender and race. The LESG pathologists confirmed the diagnosis of all first and subsequent cancers. Patients were treated with a wide variety of radiotherapy and chemotherapy for many different types of cancers at 13 participating centers of LESG.

The majority of patients were treated with orthovoltage radiation, although toward the end of the study megavoltage radiation was also used. Individual doses were estimated based on an anthropomorphic phantom and treatment conditions, adjusted for age at exposure, height, weight, body surface area and estimated thyroid gland size. Patients received a mean thyroid radiation dose of 12.5 (range 1–76) Gy. Because few patients received no or low thyroid doses, the referent category for the dose–response analysis was <2 Gy. One case and seven controls were omitted because of insufficient dose information. This left 22 cases and 82 controls to be included in the present analysis.

7. *Cervical Cancer Patients*

The 43 women who developed thyroid cancer at least 5 years after their diagnosis of cervical cancer were identified from a cohort of 150,000 cervical cancer patients treated in

14 countries (20, 54, 55). Eighty-one controls were matched individually to the cases by clinic, age at cervical cancer diagnosis and length of survival. Eighty-four percent of the thyroid cancers were confirmed histologically. The 126 cases and controls were diagnosed with cervical cancer between 1920 and 1971 and their mean age at diagnosis was 53 years. Follow-up for occurrence of thyroid cancer was through 1984.

Patients were commonly treated with various combinations of intracavity radium and external-beam X rays (orthovoltage or megavoltage). Measurements were made in an Alderson phantom of a typical adult woman, and organ doses were estimated based on simulated usual therapy conditions *(56).* The mean thyroid dose was 0.11 Gy and ranged from 0.01 to 0.24 Gy. The referent category was <0.05 Gy because there were no nonexposed cases and only three nonexposed controls.

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