

# A Reanalysis of Thyroid Neoplasms in the Israeli Tinea Capitis Study Accounting for Dose Uncertainties

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In the 1940s and 1950s, children in Israel were treated for tinea capitis by irradiation to the scalp to induce epilation. Follow-up studies of these patients and of other radiation-exposed populations show an increased risk of malignant and benign thyroid tumors. Those analyses, however, assume that thyroid dose for individuals is estimated precisely without error. Failure to account for uncertainties in dosimetry may affect standard errors and bias dose–response estimates. For the Israeli tinea capitis study, we discuss sources of uncertainties and adjust dosimetry for uncertainties in the prediction of true dose from X-ray treatment parameters. We also account for missing ages at exposure for patients with multiple X-ray treatments, since only ages at first treatment are known, and for missing data on treatment center, which investigators use to define exposure. Our reanalysis of the dose response for thyroid cancer and benign thyroid tumors indicates that uncertainties in dosimetry have minimal effects on dose–response estimation and for inference on the modifying effects of age at first exposure, time since exposure, and other factors. Since the components of the dose uncertainties we describe are likely to be present in other epidemiological studies of patients treated with radiation, our analysis may provide a model for considering the potential role of these uncertainties. © 2004 by Radiation Research Society

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## INTRODUCTION

Standard methods for analysis of epidemiological data assume that covariates are known without error for all study subjects, even though it is well recognized that assigned dose does not perfectly reflect dose to target tissue. Ignoring misclassified covariates in analysis can bias estimates of dose response, distort the shape of the dose–re-

sponse relationship, and affect inference on the variation of the dose response across other factors (effect modifiers) (1). Adjustment for errors in dosimetry increases dose–response estimates by about 10% in Japanese atomic bomb survivors (2, 3), 50–100% in populations exposed to residential radon (4–8) and 60% in radon-exposed Colorado Plateau uranium miners, where adjustment also reduces the variation of the dose response by dose rate (9). Among nuclear workers, adjustment for dose uncertainties increases standard errors by about 40% but leaves dose–response estimates for leukemia unchanged (10). Failure to account for uncertainties during the design of an epidemiological study can reduce study power (11). Some of these topics were discussed at a conference on adjustments for errors in radiation studies (12).

In the current paper, we consider a study which uses a dosimetry system based on an externally estimated dose-prediction equation. The use of an external prediction equation is widely applicable to radiation studies and to epidemiological studies more generally. For example, dosimetry for individuals exposed to radiation fallout from nuclear weapons tests relies on models of dispersal, deposition, transfer and uptake applied to covariate information from personal interviews (13, 14). In a large cohort study of radiological technologists, dosimetry is based on a regression model using an independent set of film badge measurements and linking those values with radiological procedure, calendar period, type of facility, and other variables. The dose estimation equation is then applied to work patterns of individual radiologists in the study population (15). In an epidemiological case–control study of bladder cancer in three states in New England, one of us (JHL) is involved in developing prediction models for arsenic and other pollutants in drinking water based on the regressions of measurements of pollutants from water samples on geological features, type of aquifer, land use patterns, source of water, and other factors. The regression models will then be used with questionnaire data to estimate exposures of study subjects.

In this paper, we examine uncertainties in an Israeli cohort study of children exposed to radiation in the treatment

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of tinea capitis and the effects of uncertainties on dose-response analyses of malignant and benign thyroid tumors. A link between X irradiation to the head and neck in childhood and increased rates of thyroid cancer and benign thyroid tumors has been reported widely (16–23). A pooled analysis of primary data from seven studies confirms the cancer association (24).

For the Israeli data, Ron *et al.* (19) used results from three independent studies of anthropomorphic phantoms (16, 25, 26) to estimate dose to the thyroid based on age at first irradiation ( $A$ ), filtration of the X-ray machine ( $F$ ), prescribed radiation exposure in roentgens ( $R$ ), and number of treatments. We derive a prediction equation for true dose based on  $V = (A, F, R)$  using data from phantom studies, then apply the prediction equation using  $A, F, R$  and number of treatments from patient records. The presence of missing values for  $A, F$  and  $R$  for approximately 12% of patients adds complexity to the analysis.

While our results may not apply directly to other epidemiological studies that base exposure assessment on an external prediction equation, they may offer insights into effects of exposure uncertainties to the extent that stochastic mechanisms of those uncertainties are similar.

## MATERIALS AND METHODS

### Study Population and Disease Ascertainment

The study population consists of 10,834 children who received X-ray therapy for tinea capitis between 1948–1960 at three main treatment centers in Israel. For each irradiated subject, a general population comparison was selected from the Central Population Registry, matched on sex, age ( $\pm 2$  years), country of birth, and year of immigration ( $\pm 1$  year), resulting in 10,834 nonirradiated subjects from the general population. A second comparison group consists of 5,392 siblings of the irradiated patients, who did not have tinea capitis. Siblings were matched on age ( $\pm 5$  years), country of origin, and year of immigration ( $\pm 1$  year), with preference given to siblings of the same sex as the irradiated patient. All subjects either immigrated to Israel from Africa or Asia or were children of fathers who had immigrated from those regions. The study was reviewed and approved by the institutional review boards at NIH and at the Chaim Sheba Medical Center in Israel.

Follow-up methods differed depending on year and tumor type. For thyroid cancer, follow-up was between 1950–1986. Thyroid cancers incident between 1960–1986 were identified by linking the study roster to the Israel Cancer Registry, which was established in 1960, and confirmed through pathology and medical records. Cancers incident between 1950–1960 were ascertained in a nationwide search of hospital pathology records. Benign thyroid tumors, which are not recorded by the Israel Cancer Registry, were identified through a nationwide search of pathology records and limited to 1950–1980. Among irradiated subjects, 44 thyroid cancers and 55 benign thyroid tumors were ascertained. Among nonirradiated subjects, 16 developed thyroid cancer and 41 developed benign tumors.

### Radiotherapy

Patients received radiotherapy to five overlapping fields on the scalp to induce epilation (19, 26, 27). Patients wore a cap to locate the fields, with lead shielding covering the face and neck, but were not otherwise immobilized. Beams were superficial X rays, 70–100 kVp, and either unfiltered or filtered with 0.5, 0.6 or 1.0 mm aluminum. All patients were less than 16 years old at treatment.

The usual course of treatment consisted of five sessions over five consecutive days, totaling 375 R ( $9.7 \times 10^{-2}$  C/kg) exposure in air. The prescribed exposure ranged from 350 to 400 R depending on the treatment clinic (16). Nine percent of patients had further infestation and received multiple treatments, with repeat treatments occurring one or more years apart.

### Data Preparation

As in Ron *et al.* (19), we ignore the individual matching and assume that responses of all subjects are independent. Ignoring matching is justified for the population-based comparison group since we adjust for the matching variables. We are not justified in treating siblings as independent. However, since there are only six thyroid cancers and six benign tumors in comparison siblings, none with a treated sibling who developed thyroid disease, it is unlikely that correctly accounting for sibling dependence, which complicates analysis, has an impact on results. Tinea capitis is contagious and may affect family members, resulting in the inclusion of some siblings and cousins in the exposed group. Familial relationships are not recorded, so we must assume that familial effects on the dose response are small.

We apply standard Poisson regression methodology (28), using the Epicure computer program (29). Data are cross-tabulated by sex (two levels), country of origin (three levels: Africa, Asia, Israel), age at first treatment in years (eight levels: 0–1, 2–4, . . . , 14–16), number of treatments (three levels: 0, 1, 2+), follow-up year (five levels: 1950–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1987), attained age in years (eight levels: 0–14, 15–19, . . . , 40–44, 45+) and dose in centigrays (cGy) (six levels: 0, 1–7.4, 7.5–14, 15–22.4, 22.5–29, 30–100). For benign tumors, the latter 2-year categories are merged since follow-up was through 1980. For each cell of the cross-classification, we count person-years at risk and number of events (thyroid cancers or benign tumors) and compute person-year weighted means for continuous variables (attained age, dose, etc.). We compute time since first treatment after the cross-tabulation as attained age minus age at first treatment.

### Model for Risk of Disease

We assume that incidence rate for disease outcome (thyroid cancer or benign tumor) within the  $i$ th cell of the cross-tabulation, denoted  $r_i$ , has the following form:

$$r_i(X, D, \alpha, \beta) = r_0(X, \alpha)(1 + \beta^*D), \quad (1)$$

where  $D$  is total radiation dose to the thyroid,  $X$  is a covariate vector, and  $\alpha$  is a vector of parameters describing the disease incidence rate among nonexposed,  $r_0$ . The parameter  $\beta^*$  represents the dose-response effect. The relative risk in Eq. (1) is linear in dose; however, for technical reasons we re-parameterize  $\beta^*$  as  $\exp(\beta)$ . Effect modification is modeled by adding covariates in the multiplicative factor  $\exp(\beta)$ .

Let  $W$  be a vector of recorded information on each subject, including number of treatments, codes for treatment centers, and age at first treatment. We assume that once covariates ( $X$ ) and true dose ( $D$ ) are known,  $W$  provides no additional information on disease occurrence. The regression calibration approach inserts the expected value of the true dose given  $W$ , denoted  $E(D|W, \theta)$ , where  $\theta$  are parameters relating true dose to  $W$ . Assuming rare disease, the relative risk given the observed data  $X$  and  $W$ , can be written

$$r_i(X, W, \alpha, \beta, \theta) = r_0(X, \alpha) [1 + \beta^*E(D|W, \theta)]. \quad (2)$$

If  $\theta$  and  $E(D|W, \theta)$  are known, then true dose can be calculated for each subject and standard methods used to estimate  $\beta$ . However, it is more typical that  $\theta$  is unknown. Our approach independently estimates  $\theta$ , denoted  $\hat{\theta}$ , inserts  $E(D|W, \hat{\theta})$  in Eq. (2), and proceeds with standard analyses treating  $\hat{\theta}$  as known. While this approach typically works well for estimation, it does not account for the estimation of  $\hat{\theta}$ , and thus some ad hoc adjustment may be needed to characterize accurately the variance of the estimate of  $\beta$ . We previously used a likelihood approach to si-

**TABLE 1**  
**Sources of Uncertainties and Approaches Used in Estimating True Thyroid Dose from Observed Patient Data for the Israeli Tinea Capitis Study**

Sources of uncertainty	Approach
<i>Modeling phantom data and extrapolating to all ages at exposure</i>	
Phantom emulation of an “average” child, embedded dosimeters, general errors in calibration	Ignored, assumed minimal effect
Dose adjustment factor for age at treatment relative to the phantom representation of a 6-year-old child	Assume the physical model is accurate without error
Dose adjustment factor for age at treatment applicable to the study population	Assume relative physical characteristics by age for U.S. children are appropriate for Israeli children
<i>Applying the predication model given age, filtration and beam exposure</i>	
Within-individual variability	Analysis of movement data from Modan (16)
Between-individual uncertainty	Analysis of Lee and Youmans data (25), plus sensitivity analysis
Actual exposure to the skin	Expert opinion, plus sensitivity analysis
<i>Adjusting for missing patient treatment information</i>	
For patients with multiple treatments, unknown ages at second and subsequent treatments	Randomly select age from empirical distribution of ages, conditional on age at first treatment and age <16
For those with multiple treatments at different clinics, unknown order of treatment clinics	Randomly select order of clinics
For clinics with multiple X-ray machines, particular machine used for each patient unknown	Use weighted prescribed exposure and weighted filtration (see text)
Age at treatment rounded to nearest integer	Ignored, assumed minimal effect
Other uncertainty, including variations in machine output, machine on-time, treatment documentation	Ignored, assumed minimal effect

multaneously estimate  $\beta$  and  $\theta$  and their variances (30). The regression calibration and the likelihood approaches results in nearly identical estimates, so we present only the regression calibration results.

### MODELING RADIATION DOSE UNCERTAINTIES

Our approach to adjust for dose uncertainties requires three steps. (1) We develop a prediction equation for true dose  $D$  from  $V = (A, F, R)$  using data from phantom studies, which incorporates estimates of model uncertainties and allows computation of the expected true dose,  $E(D|V)$ . (2) Patient records do not provide  $V = (A, F, R)$  for all treatments and for all subjects. We therefore must adjust for missing patient data. (3) We combine the prediction equation with the observed and imputed covariates for each patient to derive an expected true dose. Table 1 lists the various uncertainties and our approach.

$V = (A, F, R)$  for each exposure is the vector of variables required for the prediction equation, and  $W$  is the vector of covariates actually available for each patient, i.e. age at first exposure, number of treatments, and treatment center. The distinction between  $W$  and  $V$  is important.  $V$  represents variables required by the prediction equation, while  $W$  represents variables actually available for each patient. If patient information is complete, i.e.,  $W = V$ , then the phantom-based prediction equation, along with the uncertainties, allows computation of  $E(D|V)$ . If  $V$  is not known, we must determine the expected true dose given the available data,  $E(D|W)$ , by averaging the prediction equation  $E(D|V)$  over the probability distribution of the required variables given the available data,  $V|W$ .

For patients with multiple treatments, we evaluate each treatment separately and assume that total true dose  $D$  is the sum of  $j = 1, \dots, J$  treatment doses,  $D = \sum_j D_j$ .

Dose uncertainties induce two subtleties that affect the person-years table. Poisson regression requires that cut-points for factors in the person-years table are fixed and not random variables. Thus categorization must use true dose, not estimated dose. While attained age and other factors are assumed known precisely, dose is known only with uncertainty. For the regression calibration, we categorize using expected true dose, i.e.  $E(D|W, \hat{\theta})$ .

A second subtlety in the person-years table is that number of treatments and age at treatment is considered fixed at start of follow-up, although these factors are time-dependent for patients with multiple treatments. Thus precise categories for these factors at each year of follow-up are unknown. We include these factors as fixed variables, although we use an imputed age at treatment in the calculation of true dose. Since only five thyroid cancers and six benign tumors occur among patients with multiple treatments, this simplification should have little impact.

#### *The Prediction Equation for True Dose $D$ from Predictor Variables $V$*

Dosimetry for the tinea capitis study is based on experimental studies that exposed phantoms under treatment conditions (16, 25, 26, 31). Initial studies indicated a thyroid dose of about 0.06 Gy per treatment for a 6-year-old child. However, concerns about the effects of imperfect positioning and patient movement led to additional studies and a

dose adjustment of 1.5 and an estimated dose for a 6-year-old child of about 0.09 Gy (16). We do not know if the true effect on dose of squirming children was captured, but we nonetheless include this adjustment.

For the dose prediction equation, let  $g_1(\cdot)$  be thyroid dose as a function of skin exposure  $R$  and filtration  $F$  for a 6-year-old child,  $A = 6$ , and assume that dose is proportional to exposure for fixed  $F$ . Let  $g_2(\cdot)$  denote the age adjustments for dose relative to a 6-year-old child. For ages 1, . . . , 15, the adjustment factors are 1.70, 1.50, 1.39, 1.25, 1.10, 1.00, 0.90, 0.82, 0.74, 0.66, 0.63, 0.60, 0.59, 0.58 and 0.56, respectively. We assume that  $g_2$  is the same for males and females under age 16 years and accurately reflects the impact of age on dose. The adjustments, which reflect different head and neck sizes, are larger for younger children since their thyroid glands are closer to the radiation source. Although there are some phantom data based on skulls from children of different ages (25), data are insufficient to check the variation of dose with age at treatment (i.e. size of the phantom) empirically, so we assume that these adjustment factors relative to the referent age of the phantom are known. The age adjustment factors were developed for U.S. children, so we must assume that the factors reflect the same relative relationship in the treated Israeli children.

Based on phantom data (16, 25), we assume the following model for  $D$  given  $V = (A, F, R)$ :

$$\begin{aligned} \log(D) &= \log[g_1(R, F) \times g_2(A) \times \text{error}] \\ &= \log(R) + \theta_0 + \theta_1 F^2 + \log(C_A) + \varepsilon_w + \varepsilon_b + \varepsilon_r, \end{aligned}$$

where  $\theta_0$  and  $\theta_1$  are unknown parameters and  $\varepsilon_w$ ,  $\varepsilon_b$  and  $\varepsilon_r$  are random errors representing within-individual, between-individual, and random uncertainties, respectively. We assume that uncertainties are independent and normally distributed, with mean zero and standard deviations  $\sigma_w$ ,  $\sigma_b$  and  $\sigma_r$ , respectively, thus implying that  $D$  is lognormally distributed.

The within-individual random uncertainty  $\varepsilon_w$  reflects the different thyroid doses if a child were irradiated twice under the same prescribed conditions, due to movement during treatment and differences in positioning the body for treatment. The between-individual random uncertainty  $\varepsilon_b$  reflects the different thyroid doses for different children of identical ages under ideal machine conditions, due to differences in head size and shape. The uncertainty  $\varepsilon_r$  reflects additional random uncertainty. Phantom data are not sufficient to jointly estimate  $\theta_0$  and  $\theta_1$ , their variances, and  $\sigma_w$ ,  $\sigma_b$  and  $\sigma_r$ . We therefore estimate these parameters using various data sources. We estimate  $\sigma_w = 0.17$ , based on 13 degrees of freedom, from the data of Modan, in which a phantom was repeatedly repositioned and reirradiated. An estimate of  $\sigma_b$  from a study of three phantoms (25) is  $\sigma_b = 0.49$ , based on two degrees of freedom. There are no data for estimating  $\sigma_r$ . A study of a single X-ray machine found that the actual skin exposure might differ from the prescribed amount by 15% or more (26). The physicist

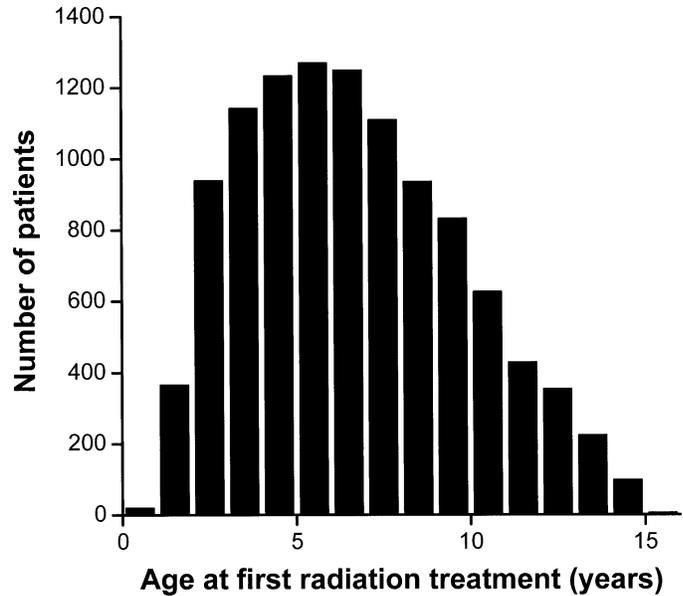


FIG. 1. Histogram of age at first irradiation for exposed subjects from the Israeli tinea capitis study.

among us (MS) believes that 25% is a better estimate. The values of these estimates are assessed by a sensitivity analysis.

With  $\tilde{\theta}_0 = -3.9$  and  $\tilde{\theta}_1 = 0.5$  estimated from the data of Modan, the mean of a lognormal distribution is

$$\begin{aligned} E[D|V = (A, R, F)] \\ = C_A R \exp\left(-3.9 + 0.5F^2 + \frac{\sigma_w^2 + \sigma_b^2 + \sigma_r^2}{2}\right). \end{aligned} \quad (3)$$

For example, for a 6-year-old ( $C_A = 1.0$ ), with  $R = 375$ ,  $F = 0.5$  filtration,  $\hat{\sigma}_w = 0.17$ ,  $\hat{\sigma}_b = 0.49$ , and  $\hat{\sigma}_r = 0.25$ , the expected true dose is  $375 \times \exp(-3.9 + 0.5 \times 0.25 + 0.17) = 10.2$  cGy.

#### Modeling Dose Predictor Variables $V$ from Available Patient Data $W$

This step is necessary because patient data are not complete for all subjects. When data are missing or indeterminate, we link data for  $W$  for each subject [age at first treatment, treatment clinic(s), year of first treatment, and number of treatments] to clinic-specific information (types of X-ray machines, filtration, standard treatment protocols, and machine settings) to determine the required variables  $V = (A, F, R)$  for the dose prediction model. For example, we know only age at first treatment for those with multiple treatments and therefore impute values for ages of second and later irradiations. Figure 1 shows a histogram of ages at first irradiation. For those with multiple treatments, we impute an age at subsequent treatment by randomly selecting an age from the histogram, conditional on age at prior treatment plus 1 year, the minimum time between treatments, and treatment under age 16.

Dose to the thyroid depends on the prescribed exposure

**TABLE 2**  
**Information on X-Ray Machines Used at the Treatment Centers and Approach to the Estimation of Filtration and Exposure**

Location	Percentage of all treatments	Machine	Prescribed		Nominal		Imputed value for location	
			Filtration	Exposure	Filtration	Exposure	Filtration	Exposure
Center 1	72%	1	0.5	400	0.5	400	0.5 w prob 0.75	400 w prob 0.25
		2	0.5	384	0.5	384	0.6 w prob 0.25	384 w prob 0.25
		3	0.5	383	0.5	383		383 w prob 0.25
		4	0.6	NA <sup>a</sup>	0.6	U[350,425]		U[350,425] w prob 0.25
Center 2	11%	1	0.0	350	0.0	350	nominal value	nominal value
		2	0.0	350				
Center 3	13%	1	0.5	425	0.5	425	nominal value	nominal value
		2	0.5	425				
		3	0.5	425				
Unknown	1.6%		1.0	350–400	NA	U[350,425]	1.0	nominal value
Abroad	1.9%		NA	NA	NA	U[350,425]	0.0, w prob 0.10 0.5, w prob 0.85 1.0, w prob 0.05	nominal value
Other	0.8%		NA	NA	NA	U[350,425]	0.0, w prob 0.10 0.5, w prob 0.85 1.0, w prob 0.05	

<sup>a</sup> Not available.

at a specified distance and beam filtration, which were known for most X-ray machines at the various centers (Table 2). However, the precise machine used on a particular patient was not recorded. For some patients the treatment center was abroad or unknown. For those with multiple treatments, the sequence of the treatment centers was not known. Table 2 shows the imputation approaches we use. For example, in treatment centers 2 and 3, machines had common filtrations and nominal exposures, although at different values. In treatment center 1, there were four machines, with filtrations (0.5, 0.5, 0.5, 0.6) and nominal exposures (400, 384, 383, NA), where NA denoted not available. For treatment center 1, we assume that the filtration was 0.5 with probability 0.75 and 0.6 with probability 0.25. For nominal exposures, we assume that the distribution was 400, 384, 383 and distributed uniformly between 350 and 425, reflecting the range of nominal exposures recorded in the various centers, each with probability 0.25. For those with an unknown treatment center, we assume that filtration was 1.0, and nominal exposure was distributed uniformly between 350 and 425. For those irradiated abroad, we assume that nominal exposure was distributed uniformly between 350 and 425, and assume filtration values (0.0, 0.5, 1.0) with probabilities (0.10, 0.85, 0.05), a distribution in keeping with the observed filtrations.

Among 27,060 children, 5,451 (20.1%) and 15,799 (58.4%) immigrated themselves or had a father who had immigrated from Asia or Africa, respectively. The remaining 5,810 (21.5%) children were born in Israel but had a father who immigrated from Asia or Africa. Ninety-three percent of Asian children and 79% of African children had no listed month of birth, and we assume that birth occurred on June 15. Nearly all children of Israeli birth had a listed

birth month. Dates of cohort entry were known, but uncertainty in birth month meant that ages at first treatment for patients and ages at entry for comparison subjects were accurate only to the nearest integer. Birth month for those with a complete birth date was distributed uniformly throughout the year, suggesting no systematic bias from this age rounding.

Finally, we assume that all other sources of random uncertainty, such as fluctuations in machine power output, machine on-time, treatment records, etc., were minimal.

#### Combining the Dose Prediction Model and Patient Data

The final step is to compute the expected true dose from the available patient data and the prediction equation. For a patient with  $J$  treatments, the expected dose is

$$E(D|W, \hat{\theta}) = \sum_{j=1}^J \int E(D_j|V_j, \hat{\theta})f(V_j|W_j) dV_j, \quad (4)$$

where  $E(D_j|V_j, \hat{\theta})$  is dose from the prediction equation, and the determination of required data from available data,  $V_j|W_j$ , is described above. A Monte Carlo approach is used to evaluate Eq. (4) by taking  $K = 100$  random samples of  $V_j = (A_j, F_j, R_j)$  from the distribution of  $V_j|W_j$  to get the approximation,

$$E(D|W, \hat{\theta}) \approx K^{-1} \sum_{k=1}^K \sum_{j=1}^J C_{jA} R_j \times \exp\left(-3.9 + 0.5F_j^2 + \frac{\sigma_w^2 + \sigma_b^2 + \sigma_r^2}{2}\right)$$

where values for  $\hat{\sigma}_w^2$ ,  $\hat{\sigma}_b^2$  and  $\hat{\sigma}_r^2$  replace  $\sigma_w^2$ ,  $\sigma_b^2$  and  $\sigma_r^2$ .

**TABLE 3**  
**Distribution of Subjects, Mean Doses, and**  
**Incidence Rate for Thyroid Cancer and Benign**  
**Tumor (Events per Person-Year of Follow-up) by**  
**Number of Courses of Treatment**

No. of courses	No. of subjects <sup>a</sup>	Mean dose		Rate ( $\times 10,000$ person-years)			
		Original	Model	Cancer	Benign	Adenoma	Nodule
0	16,226	0.0	0.0	0.32	1.05	0.43	0.63
1	9,814	8.4	9.9	1.32	2.05	1.05	1.00
2	904	17.5	18.6	1.79	2.21	0.44	1.77
3	110	26.0	26.4	0.0 <sup>b</sup>	3.64	0.0 <sup>b</sup>	3.64
4	6	27.5	28.7	0.0 <sup>b</sup>	0.0 <sup>b</sup>	0.0 <sup>b</sup>	0.0 <sup>b</sup>

Note. Doses in cGy based on original doses or the expected true dose based on the modeling of dosimetry errors.

<sup>a</sup> Includes 44 thyroid cancers and 55 benign tumors (26 adenomas and 29 nodules) among exposed, and 16 thyroid cancers and 41 benign tumors (17 adenomas and 24 nodules) among nonexposed.

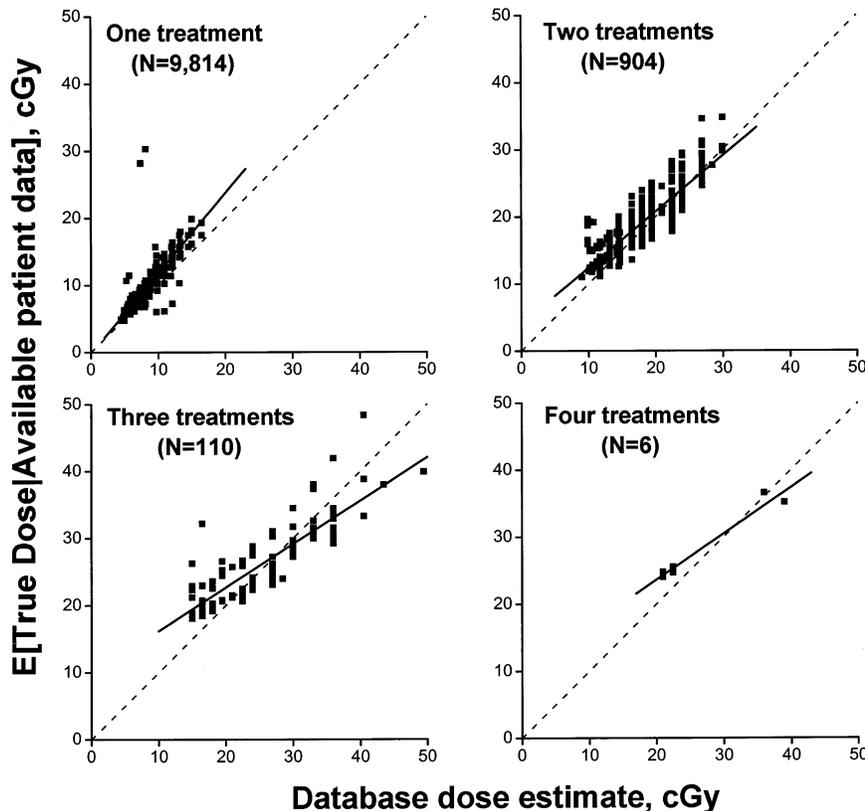
<sup>b</sup> No observed events.

**RESULTS**

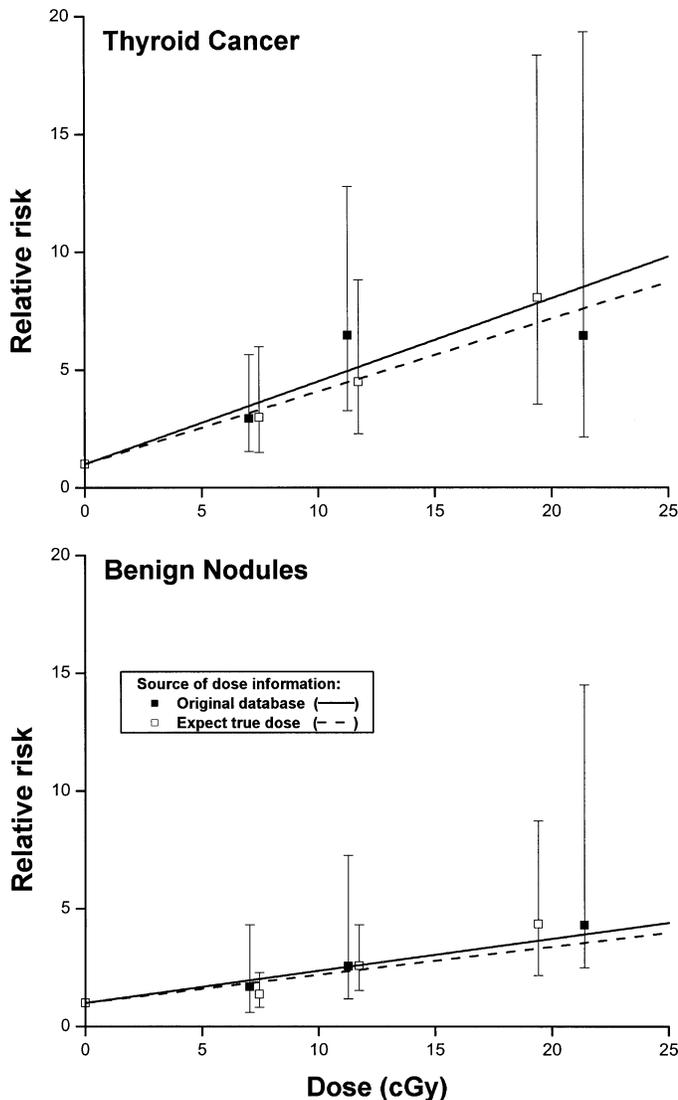
Expected true doses are generally larger than original doses. Person-year weighted means for original doses and expected true doses were 9.4 and 10.8 cGy, respectively, for treated patients, 10.1 and 11.6 for thyroid cancer cases, and 10.2 and 11.5 cGy for benign tumor cases. A total of

1,020 of 10,832 irradiated patients (9.4%), including 5 of 44 thyroid cancer cases (11.4%) and 6 of 55 benign tumors (10.9%), had more than one treatment (Table 3). Mean expected doses are higher than mean original doses for each category of number of treatments. Figure 2 shows expected true doses and original doses, the 45-degree line, and the linear least-squares regression line. For one treatment, expected dose is generally higher than original dose, primarily due to the mean of the lognormal distribution being higher than the median. Slopes of the fitted lines for patients with multiple treatments are less than one (Fig. 2), indicating that higher original doses correspond to progressively lower true doses. This pattern is due to the age adjustment for multiple exposures and to failure of the original doses to account for ages at second or later treatment.

Table 4 shows numbers of exposed cases and estimated ERRs per centigray using original doses or expected true doses, and the relative impact of effect modifiers. Since original doses are generally less than expected true doses, the ERR/cGy for thyroid cancer estimated using expected true doses (0.31 with 95% CI 0.14–0.64) is 12% smaller than the estimate using original doses (0.35 with 95% CI 0.16–0.73) (Fig. 3). Differences in the ERR/cGy using unadjusted and adjusted doses are small, and the use of expected dose does not significantly improve model fit compared to observed dose ( $P = 0.73$ ). Similar results occur for benign tumors.



**FIG. 2.** Scatter plots of estimated true doses and original doses, 45-degree line, and the fitted linear least-squares line by number of radiation treatments.



**FIG. 3.** Relative risk for thyroid cancer and benign thyroid tumors by thyroid dose using the original dose or the error-adjusted expected true dose given the original dose. Individual relative risk estimates located at the category-specific, person-year weighted mean dose. Fitted dose response based on a linear relative risk model.

Tests of homogeneity of the ERR/cGy by sex are non-significant, although the results suggest different sex effects in the dose response for thyroid cancer and benign tumors (Table 4). The dose response for males relative to females is about 0.2 using either dose estimate but about 2.0 for benign tumors. The differences by sex for thyroid cancer and benign nodules, however, are not statistically significant (for example,  $P = 0.15$  using expected true dose).

Data on sex, number of treatments, time and age-related factors are assumed known with a high degree of accuracy. The relative impact of those factors and the  $P$  values for tests of homogeneity are unaffected by uncertainty in dosimetry (Table 4). Effects of radiation exposure on thyroid cancer risk are highest in patients exposed under the age of 5, remain elevated 25 years and more after initial irra-

diation, and are smaller in patients with multiple treatments, although tests of homogeneity are not statistically significant.

## DISCUSSION

Our analysis characterizes uncertainties in thyroid dosimetry for childhood irradiation for the treatment of tinea capitis and extends the analysis in Schafer *et al.* (30). The current paper demonstrates the use of an external prediction equation in conjunction with adjustment through regression calibration and presents a more complete analysis of thyroid cancer, as well as an analysis of benign thyroid tumors. Dosimetric uncertainties are due to a variety of factors, including uncertainty in the model for true dose based on studies of phantoms, random differences in sizes of children of a given age, and random movements by children during treatment. Additional uncertainties arise from missing data for ages at subsequent exposure for those with multiple treatments and for treatment center. Results are reassuring that within the limitations of our understanding uncertainties in dosimetry have minimal impact on estimates of ERR/cGy and on statistical inference on the role of age at treatment, time since exposure, and other effect modifiers for both thyroid cancer and benign thyroid tumors. The relationship between original doses and our predicted doses varies by categories of number of treatments and highlights the importance of the adjustment for age at treatment in the dosimetry for patients with multiple treatments.

While our assessment includes most major sources of uncertainty, we do not explicitly account for all uncertainties. In the prediction equation, we assume that measurement error associated with the conduct of the phantom studies is minimal, including instrument calibration and evaluation of embedded dosimeters, that the adjustment factors for physical differences in ages at treatment relative to the referent 6-year-old child are correct, and that age adjustment factors apply equally to females and males and to Israeli children of diverse ethnic backgrounds.

External dose-prediction equations are widely applicable and in the simplest setting are very intuitive. For subjects  $i = 1, \dots, n$ , suppose there is a linear relationship between disease response  $Y_i$  and true dose  $D_i$ , denoted  $E(Y_i|D_i) = \beta_0 + \beta_1 D_i$ . However, the primary data set yields  $Y_i$  and only a vector of surrogate variables  $V_i$ , which may be viewed as  $D_i$  recorded with uncertainty or more generally a vector of variables that characterize  $D_i$ . (Our analysis was further complicated by some patients with missing values for  $V_i$ .) An independent set of data consisting of  $D_j$  and  $V_j$  for  $j = 1, \dots, m$  exists, with  $D_j$  and  $V_j$  defined by the relationship  $E(D_j|V_j) = \theta_0 + \theta_1 V_j$ . (This relationship was loglinear in our data.) A sensible approach estimates  $\theta_0$  and  $\theta_1$  from the secondary data, then uses those estimates to predict a value for  $D_i$  for each subject in the primary data, i.e.  $E(D_i|V_i)$ . The  $Y_i$ 's and the predicted variables  $E(D_i|V_i)$  are then used to estimate the risk parameters  $\beta_0$  and  $\beta_1$ . The

**TABLE 4**  
**Excess Relative Risk<sup>a</sup> (ERR) per cGy for Thyroid Cancer and Benign Tumors (Adenomas and Nodules) and 95% Confidence Intervals (CI), Overall and by Categories of Other Factors**

Factor	Cancer			Benign		
	Original	Model	N <sup>b</sup>	Original	Model	N
Overall ERR/cGy (95% CI)	<b>0.351</b> (0.16, 0.73)	<b>0.308</b> (0.14, 0.64)	44	<b>0.136</b> (0.06, 0.26)	<b>0.119</b> (0.05, 0.23)	55
Sex						
Female	<b>0.456</b>	<b>0.400</b>	37	<b>0.118</b>	<b>0.098</b>	45
Male	0.234	0.245	7	1.883	1.927	10
P <sup>c</sup>	0.17	0.18		0.46	0.49	
Attained age						
<20	2.570	2.518	13	0.197	0.226	3
20–29	<b>0.236</b>	<b>0.210</b>	17	<b>0.206</b>	<b>0.179</b>	39
≥30	1.569	1.569	14	0.095	0.109	3
P	0.60	0.61		0.18	0.19	
Years since first exposure						
<15	0.628	0.620	14	—	—	7
15–19	<b>0.507</b>	<b>0.444</b>	11	<b>0.107</b>	<b>0.094</b>	17
20–24	0.775	0.777	10	2.412	2.425	29
≥25	0.514	0.527	9	0.262	0.298	2
P	0.81	0.81		0.02	0.02	
Age at first exposure						
<5	<b>0.505</b>	<b>0.446</b>	21	<b>0.247</b>	<b>0.216</b>	20
5–9	0.412	0.419	14	0.352	0.363	21
≥10	0.566	0.546	9	0.115	0.108	14
P	0.17	0.17		0.05	0.05	
No. of treatments						
1	<b>0.394</b>	<b>0.337</b>	39	<b>0.152</b>	<b>0.129</b>	49
≥2	0.581	0.637	5	0.691	0.725	6
P	0.32	0.42		0.54	0.61	

Notes. Doses from original values or expected true dose based on model of uncertainties. Bold font denotes ERR/cGy for the base level category and standard font denotes the proportional effect of the dose response relative to the base level category.

<sup>a</sup> Parameter estimates adjusted for attained age, sex and ethnicity.

<sup>b</sup> Number of exposed cases. There were 16 (cancer), 42 (benign tumor), 17 (adenoma), and 25 (nodule) unexposed cases.

<sup>c</sup> P denotes value for test of homogeneity of dose–response relationship.

<sup>d</sup> Denotes that model did not converge to a finite estimate.

use of the expected value of true dose  $D$  given the observed data  $V$  in the risk analysis is called regression calibration (1).

If the prediction equation is precisely true without uncertainty and if predictor variables are known for all subjects in the primary data, then standard statistical methods apply, since the equation produces true doses. More typically, the prediction includes uncertainty. One source of uncertainty arises from the estimation of the parameters in the prediction equation. The prediction is thus an “estimate” of true dose. In the statistical literature, this type of uncertainty is often called “classical error”, which tends to reduce effects and create curvilinearity. With a prediction equation, this uncertainty represents a “shared error” common to all subjects (32). A second source of uncertainty results from the random deviation of the (log) dose prediction for each subject from the (log) true dose. This latter uncertainty is called (multiplicative) “Berkson error”. For rare diseases and relative risks which are approximately

linear in dose, Berkson error tends to increase variance while inducing minimal bias. Technical details of analyses with external prediction equations are given in Schafer *et al.* (30).

The prediction equation is applied to patient data accounting for missing data on treatment clinic, the exact X-ray machine used if more than one, nominal exposure, and ages at subsequent treatments for those with multiple treatments. The imputation of these missing data are presumably unbiased for the true covariate data, and so only increase variability. The extent to which we do not correctly account for the random process generating the missing data or ignore systematic influences is unknown; however, any residual random or systematic errors are likely small.

We find parameter estimates, standard errors and inferences essentially unchanged, after accounting for uncertainty. The results in Table 4 are based on random errors in Eq. (4) of  $(\sigma_w, \sigma_b, \sigma_r) = (0.17, 0.49, 0.15)$  but are similar when standard errors for the uncertainties are specified as

**TABLE 4**  
**Extended**

Adenoma			Nodule		
Original	Model	N	Original	Model	N
<b>0.138</b> (0.02, 0.37)	<b>0.124</b> (0.02, 0.32)	26	<b>0.135</b> (0.04, 0.30)	<b>0.115</b> (0.03, 0.26)	29
<b>0.126</b> 1.553 0.75	<b>0.114</b> 1.475 0.79	22 4	<b>0.114</b> 2.105 0.49	<b>0.097</b> 2.062 0.50	23 6
— <sup>d</sup>	—	2	—	—	1
<b>0.207</b> — 0.04	<b>0.185</b> — 0.04	19 5	<b>0.208</b> 0.291 0.09	<b>0.178</b> 0.303 0.09	20 8
0.872	0.873	5	—	—	2
<b>0.155</b> 1.405 — 0.29	<b>0.136</b> 1.423 — 0.29	9 12 0	<b>0.096</b> 3.305 1.495 0.02	<b>0.083</b> 3.325 1.551 0.02	8 17 2
<b>0.156</b> 0.709 1.087 0.89	<b>0.139</b> 0.728 1.037 0.91	7 10 9	<b>0.346</b> 0.246 — 0.002	<b>0.303</b> 0.252 — 0.001	13 11 5
<b>0.200</b> 0.039 0.08	<b>0.171</b> 0.033 0.10	25 1	<b>0.118</b> 1.465 0.59	<b>0.100</b> 1.558 0.54	24 5

(0.17, 0.25, 0.25) or (0.5, 0.5, 0.5). These parameters specify Berkson error from the uncertainty in expected true dose for the prediction equation. Even extreme values appear not to influence the estimates of dose response or effect modification. The error model, Eq. (3), includes two parameters ( $\theta_0$  and  $\theta_1$ ), which define the relationship between added filtration and dose and are estimated from phantom studies. This uncertainty results in classical error. Results suggest that this classical error is small relative to random prediction error from phantom studies.

The confidence intervals in Table 4 are similar using original doses or expected true doses because the regression calibration does not account for the variability arising from measurement error. The full likelihood approach, which does account for measurement errors, results in slightly larger standard errors (30). Those results suggest that upper and lower confidence limits should be multiplied and divided by a factor of about 1.06, respectively.

Although patterns of effect modification of the dose response for thyroid cancer by categories of sex, attained age, time since exposure, age at first exposure, and number of treatments are statistically consistent with homogeneity, the direction of the dose–response variations is similar to the patterns found in a pooled analysis of seven studies (24).

In particular, the pooled analysis indicates an increased risk with younger ages at exposure, a pattern suggested in the current analysis. It may be argued that the age-at-exposure variation is due at least in part to the age adjustment that is applied in the dosimetry, with the increased risk at younger ages due to adjustment parameters which are too small. While we cannot entirely rule this out, the age adjustment factors for children under age 5 years would need to be nearly doubled to account entirely for the greater radiation effect at the youngest ages at exposure. The age adjustment factors were established independently of the tinea capitis study and were based on physical characteristics of children. In addition, similar patterns of risk with age at exposure are observed consistently in studies of thyroid disease and childhood radiation exposure (24). Thus it seems unlikely that the age-at-exposure effects are entirely the result of the age adjustment.

In summary, our analysis of thyroid cancer and benign thyroid tumors in the Israeli tinea capitis study, accounting for a variety of dosimetric uncertainties, indicates that these uncertainties have relatively little influence on the estimated dose response and on inference regarding potential effect modifiers. The similarity of the unadjusted and the adjusted results in the Israeli data is the result of the linearity of

relative risk in dose and the predominance of Berkson-type error. Since the components of the dose uncertainties we describe are likely to be present in other epidemiological studies of patients treated with radiation, our analysis may provide a model for considering the potential role of these uncertainties.

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