# Thyroid Disease Associated With Exposure to the Nevada Nuclear Weapons Test Site Radiation

## *A Reevaluation Based on Corrected Dosimetry and Examination Data*

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**Background:** A study was begun in 1965 to 1966 to determine whether children exposed to radioactive iodine from nuclear weapons testing at the Nevada Test Site from 1951 through 1962 were at higher risk of thyroid disease. In 1993, we reported that among those examined in 1985 to 1986 (Phase II) there was an association between radiation from the Nevada Test Site and thyroid neoplasms.

**Methods:** We reevaluated the relationship between exposure to Nevada Test Site fallout and thyroid disease using newly corrected dose estimates and disease outcomes from the Phase II study. A prospective cohort of school children 12 to 18 years old living in Utah, Nevada, and Arizona was first examined for thyroid disease in 1965 to 1966 and reexamined in 1985 to 1986. In the Phase II report, 2497 subjects formed the basis for this analysis. Thyroid disease, including thyroid neoplasms and thyroiditis, was expressed as cumulative incidence and risk ratios (RRs) with a dose–response expressed as excess risk ratio (ERR/Gy).

**Results:** The RR between thyroid radiation dose in the highest dose group and thyroid neoplasms increased from 3.4 (in the earlier analysis) to 7.5. The RR for thyroiditis increased from 1.1 to 2.7 with an ERR/Gy of 4.9 (95% confidence interval = 2.0 to 10.0). There were too few malignant thyroid neoplasms to estimate risk.

**Conclusions:** Persons exposed to radioactive iodine as children have an increased risk of thyroid neoplasms and autoimmune thyroiditis up to 30 years after exposure.

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In 1993, we reported an association between thyroid neoplasms and estimates of thyroid radiation dose mainly due to radioactive iodine generated by above-ground testing of nuclear weapons at the Nevada Test Site (NTS).[1] The controversy over the adverse health effects of accidental exposure to radioactive iodine was reopened in 2004 by Davis et al,[2] who reported no statistically significant association between thyroid disease and levels of exposure to radioiodine from those exposed to the U.S. Department of Energy nuclear facility near Hanford, Washington. Although a dose–response for thyroid cancer among children exposed to the releases from the Chernobyl accident has been found,[3] the issue of exposure to radioactive iodine and subsequent thyroid disease remains controversial.[2–5]

We have continued to investigate the association between exposure to radioiodine from weapons testing fallout and the occurrence of adverse health outcomes in our previously studied cohort. In doing so, we identified and corrected a number of errors in the implementation of the dosimetry model used in the previous analyses and updated certain model parameters to reflect the present state of knowledge. This update is designated as Phase IIR (or Phase II *Revised*) to distinguish it from the doses of Phase II reported in Kerber et al[1] and Till et al.[6]

In 1998, we renewed our search for members of the cohort for further follow-up examination. Because of outdated software and computer hardware, we could not retrieve the programming that implemented the dose computation algorithm. In moving to a new computational platform, we discovered multiple errors in the original dosimetry used in our previous report. We corrected these problems and made a few updates to the dosimetry model when necessary. The primary goal was to reproduce the intended model as described in Simon et al.[7] A summary of the corrections and updates is described in this article. A more complete discussion of the corrections and updates in our dosimetry for Phase IIR has been published elsewhere.[8]

We also updated the disease diagnoses based on current understanding of thyroid diagnoses. A panel of 3 clinicians, unaware of each subjects' exposure status, conducted this review of diagnoses. These revised diagnoses and the updated calculations of radiation-absorbed dose to the thyroid glands of individuals resulted in changes in our previously reported association[1] between exposure to radioactive iodine in fallout

and subsequent thyroid disease. Because of the continuing controversy over the health effects of inadvertent, nonmedical exposure of the general public to radioactive iodine, we report these updated findings here.

## METHODS

### Study Population

This study population has been described previously.[1] A cohort of school children in grades 6 through 12 in Washington County, Utah, Graham County, Arizona, and Lincoln County, Nevada, was first identified in 1965 to 1966. The cohort was examined for thyroid disease each year for 5 years beginning in 1965 (Phase I). In 1985 through 1986, efforts were made to find and examine members of the cohort for thyroid disease. A comprehensive, individual dosimetry model was created (Phase II). The original design of this model has been described elsewhere.[7]

A summary description of the cohort studied in Phase II[1] and Phase IIR is shown in Table 1. In reviewing the data used in Kerber et al,[1] we identified 24 subjects who met all the study criteria but who were inappropriately excluded because of clerical errors. Those 24 subjects are included in the Phase IIR analysis.

This study was approved by the University of Utah Institutional Review Board and the U.S. Centers for Disease Control and Prevention Institutional Review Board.

### Dosimetry

In Phase II, the absorbed dose to the thyroid gland (mGy) was estimated for each subject. The uncertainty associated with each individual's dose estimate was represented as a log normal probability distribution of alternative realizations of that person's true dose. A combination of numerical Monte Carlo and analytical methods were used to propagate uncertainty resulting from the estimation of fallout deposition from the mathematical modeling of air, vegetables, and milk contamination from the estimation of inhalation and ingestion of radioiodines (I-131 and I-133) and from the estimation of external exposure that results from fallout deposited on the ground.[6,8] Each subject's log normal dose distribution was summarized as geometric mean and a geometric standard deviation from which an arithmetic mean was obtained to represent that individual's point estimate of dose.

The following is a summary of the corrections and changes made to the dosimetry for Phase IIR.[8]

### Correction of Phase II Problems in the Dosimetry Program Implementation

In 2001, when we reinstated the Phase II computer programs for calculating radiation doses, it was necessary to change the computing platform because computer software and hardware used in 1989 through 1990 had been retired. We discovered that the original dosimetry programs had not correctly accounted for all radioactive iodine ingestion by cows. In addition, the data in a critical file were found to be corrupted for unknown reasons. These problems and the lack of an ongoing quality assurance program led to an underestimation of radioactive iodine dose for many individuals in Phase II, particularly in southwestern Utah where consumption of fresh cows' milk was the most important route of exposure.[9] Those deficiencies have been corrected in the Phase IIR calculations.

### Update of Dosimetry Algorithm and Parameter Values

New information has become available since the Phase II program was written in 1988 through 1989. We modified 2 equations and 2 parameter values in our most recent dosimetry model. The soil equation that accounted for ingestion of contaminated soil by dairy cows (as previously used in Phase

**TABLE 1.** Summary of the Cohort Used in the Phase II and Phase IIR Analyses and Reasons for Inclusion Based on 4818 Phase I Subjects

| | Phase II | | Phase IIR | |
|---|---|---|---|---|
| **Inclusion Criteria** | **No.** | **% of Total** | **No.** | **% of Total** |
| Subjects with dosimetry (parent interview) | 3545 | 74 | 3545 | 74 |
| Subjects contacted | 3445 | 72 | 3445 | 72 |
| Subjects examined | 3122 | 65 | 3122 | 65 |
| Subjects with dosimetry and examination | 3043 | 63 | 3043 | 63 |
| Subjects with dosimetry, examination, no race exclusion, no prior radiation therapy, and examination in 3-state area | 2473 | 51 | 2500 | 52 |
| Subjects with dosimetry, examination, no race exclusion, no prior radiation therapy, examination in 3-state area, and dose >0* | 2473 | 51 | 2497 | 52 |
| Subjects with dosimetry, examination, no race exclusion, no prior radiation therapy, examination in 3-state area, dose >0,* and known disease diagnosis* | 2473 | 51 | 2496 | 52 |

*These criteria were not applied in Phase II.

II) was incorrect and resulted in an overestimate of the amount of radioiodines likely consumed. The soil equation was modified as was the depth of soil from which intake occurs. A second equation improperly handled wet and dry weight of vegetables and was modified. We also updated the transfer factor for human breast milk using more recent information published by Simon et al.[10]

## Correcting Misclassification of Individuals Assigned No Dose

Doses assigned included external doses, not all of which were from radioactive iodine. In the mid-1980s, when the cohort members were assigned individual doses (Phase II), there was little information about potential exposures beyond a 200-mile radius from the Test Site. However, in 1997, the U.S. National Cancer Institute (NCI) published estimates of dose resulting from exposure to radioactive iodine for representative persons of various ages and milk consumption habits in all contiguous counties in the continental United States.[11] The NCI also developed a calculator to estimate the dose received from NTS fallout radioiodine by persons living in each county in the United States based on individually input milk consumption habits.[12] This web-based tool is referred to hereafter as the "NCI dose calculator." Of the 3545 individuals with information on milk consumption habits, 135 had been assigned no dose in Phase II because they lived outside of Nevada, Utah, Idaho, Arizona, New Mexico, Colorado, and Wyoming during the period of exposure (1951–1962). Using the NCI dose calculator, we were able to estimate a dose to 130 of those individuals in Phase IIR. An additional 373 individuals who had lived for some of the exposure period outside the 7 states mentioned previously were also assigned doses for those time intervals using the NCI dose calculator.

In an effort to develop an error-free dosimetry program that would handle both the data management aspects of the project as well as the computations, we had 2 programmers simultaneously and independently develop dose-assessment computer programs based on the same suite of algorithms. These programs were written in 2 different software languages, SAS version 9.1.2 (SAS Institute, Cary, NC) and Analytica 3.0 Enterprise (Lumina Decision Systems, Los Gatos, CA). Intermediate computation results of both programs were required to agree for each equation in the dosimetry model and for every individual in the cohort before the programming was considered complete. That procedure identified errors in program operation that otherwise would not have been detected. The errors were corrected before the programmers proceeded to the next programming step.

The changes to individual mean doses in the Phase IIR dosimetry model are summarized in Figures 1 and 2A. The changes to the uncertainty distributions of individual doses between Phase II and Phase IIR are shown in Figure 2B. Overall, the mean dose increased from 110 mGy in Phase II to 120 mGy in Phase IIR (Table 2). This increase was not uniform across geographic areas. In the control population (Graham County), the mean dose increased from 13 mGy to 16 mGy. The dose estimates of those living outside the heavily exposed area (for whom we previously had no or limited exposure information) doubled (mean value, 42–80 mGy). In the more heavily exposed areas (Washington and Lincoln Counties), the mean dose remained the same (220 mGy). For more detail, see Simon et al.[8]

Because the distribution of interindividual variability of individual mean thyroid doses changed, we revised the dose categories so that the proportion of individuals in each of the 4 categories matches the within-category proportions used in the 1993 paper.[1] Specifically, the 4 categories used by Kerber and colleagues, expressed in mGy, were 0–49, 50–249, 250–399, and 400+. The revised dose categories were 0–74.9, 75–215.9, 216–409.9, and 410+ mGy. We also investigated other cut points and obtained similar results.

## Thyroid Disease Diagnoses

We decided that thyroiditis, hypothyroidism, and hyperthyroidism could not be diagnosed unless supported by abnormal laboratory values. Because of these changes, we reviewed the 358 thyroid disease diagnoses that had been made within the cohort since it was first identified in 1965. The review was conducted by a panel of 3 of the authors

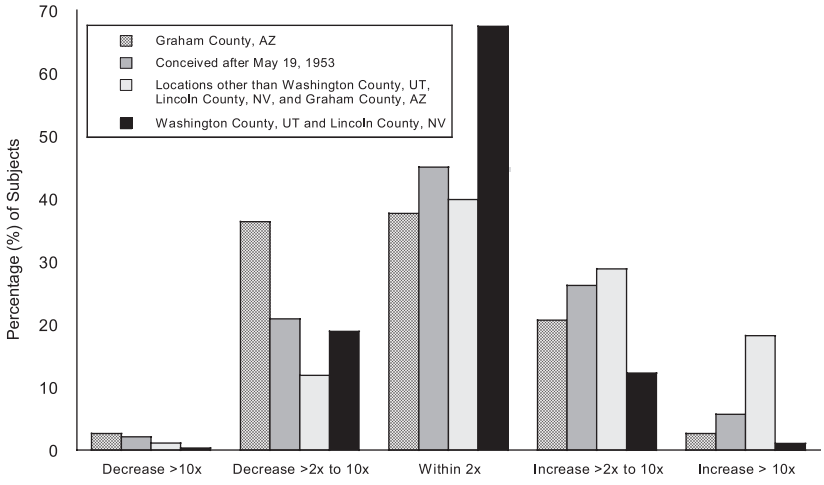


**FIGURE 1.** Distribution of percent of subjects in each study group by ratio of arithmetic mean radiation dose in Phase IIR compared with Phase II.

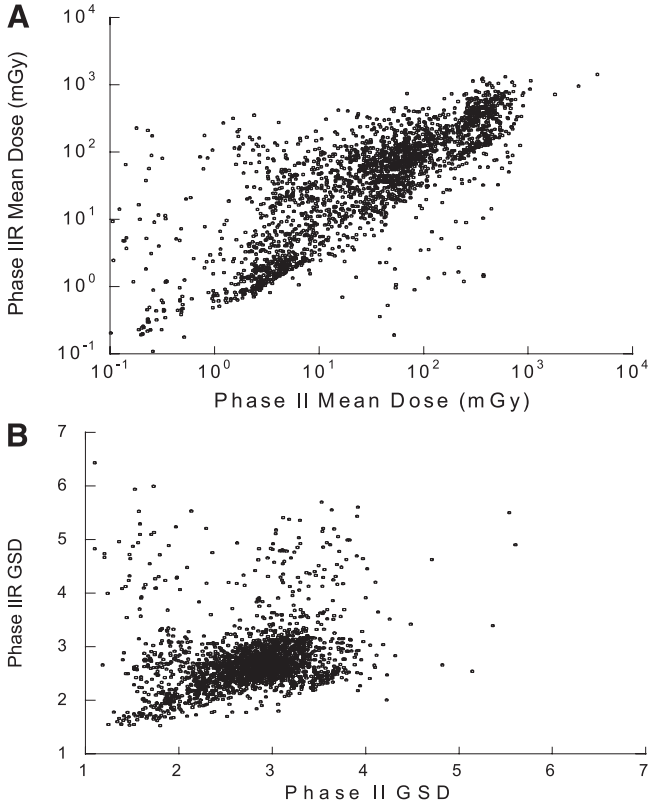


**FIGURE 2.** Comparison of individual dose estimates between Phase IIR and Phase II. (**A**) Arithmetic mean doses (mGy) and (**B**) geometric standard deviations (GSD).

(AWM, GLW, KTH, all senior clinicians, including one thyroidologist). All information about each subject's exposure, including residence history, estimated radiation dose, and previous thyroid disease diagnoses, was removed from the records. Each panel member used a diagnostic algorithm that included physical examination findings, laboratory, imaging, and histologic data to determine the diagnoses (see Table 3 for diagnostic criteria). Each panel member arrived at diagnoses independently; panel members then met to establish consensus diagnosis for each subject.

Thyroid disease diagnoses in 8 of the 9 disease categories changed because of the reevaluation described previously. The changes in disease status were primarily from "disease" to "no disease," including 35 individuals previously diagnosed with simple goiter and 9 with thyroiditis. The difference in the thyroiditis category was largely the result of diagnoses of thyroiditis made in Phase II in the absence of laboratory confirmation. The largest number of new diagnoses in Phase IIR was for hypothyroidism with 5 persons added. Three individuals classified in Phase II with nonneoplastic nodules were changed to the neoplasm category based on histologic evidence. Across the 9 disease categories, 28 individuals diagnosed with a thyroid abnormality in Phase II were reclassified as normal in Phase IIR. Some individuals were diagnosed with multiple thyroid abnormalities, and their reclassification led to changes in more than one disease category.

## Definition of Disease Onset

Two cases of thyroid neoplasia were already present at the time of first examination. These cases were included in the original analysis of the cohort in 1965 through 1966 and were identified as prevalent cases. Further examination of the cohort in 1967 to 1970 identified incident (new) cases of thyroid disease subsequent to the initial assessment. Cases of thyroid disease found by routine medical examination between 1971 and 1984 were identified and date of onset was determined; these cases were verified by review of the relevant medical records and are included as incident cases. Using the approach of the Hanford Thyroid Disease Study,[2] we included the 2 prevalent cases of thyroid neoplasm whose date of onset was unclear and classified them as incident cases in our estimate of cumulative incidence. We calculated cumulative incidence using the incident cases and the 2 prevalent cases identified on the initial screening in 1965.

## Statistical Analysis

As our primary statistical analysis, we assessed the relationship between revised radiation dose estimates, based on each individual's arithmetic mean dose, and the revised diagnoses with sex as a covariate. The Phase II study included state of residence in 1965 and age as covariates.[1] These variables were excluded in the current analysis because they are included in the

**TABLE 2.** Comparison of the Point Estimates of Individual Radiation Doses (mGy) by Various Exposure Categories for the Original (Phase II) and Revised (Phase IIR) Dosimetry

| Study Group | Phase II | | Phase IIR | | Ratio Phase IIR/ Phase II Doses |
|---|---|---|---|---|---|
| | No. | Mean ± SD | No. | Mean ± SD | |
| All locations | 2473 | 110 ± 190 | 2497 | 120 ± 167 | 1.08 ± 0.88 |
| Residence in Graham County (control) on May 19, 1953 | 382 | 13 ± 38.7 | 382 | 16 ± 36.1 | 1.23 ± 0.93 |
| Residence in Lincoln or Washington Counties on May 19, 1953 | 960 | 220 ± 253 | 968 | 220 ± 217 | 1.00 ± 0.86 |
| Residence outside of Graham, Lincoln, and Washington Counties on May 19, 1953 | 594 | 42 ± 90.6 | 607 | 80 ± 90.0 | 1.90 ± 0.99 |
| Subjects conceived after May 19, 1953 | 537 | 27 ± 41.2 | 540 | 39 ± 45.8 | 1.44 ± 1.11 |

SD indicates standard deviation.

**TABLE 3.** Diagnostic Criteria Used by Panel to Review Phase II Records

| |
|---|
| Carcinoma: Any malignant mass that meets the definition of nodule and meets the cytologic or pathologic criteria for diagnosis of papillary carcinoma, follicular carcinoma, medullary carcinoma, anaplastic carcinoma, Hurthle cell carcinoma, or unspecified |
| Benign neoplasm: Any mass that meets the definition of nodule (≥1.0 cm in any direction) and meets the cytologic or pathologic criteria for diagnosis of papillary adenoma, follicular cell adenoma, Hurthle cell adenoma, fetal adenoma, or unspecified |
| Nodule(s): Includes hyperplasia, nodular hyperplasia, adenomatous nodular thyroid, multinodular colloid goiter, colloid adenoma, miscellaneous nodule consistent with Hashimoto thyroiditis, indeterminate pathology, cyst, or nodules palpated but no tissue was obtained; classification of the nodule as to whether it was <1 cm or ≥1 cm was also noted in the review |
| Graves disease: Hyperthyroidism and goiter with or without eye signs, with or without antithyroglobulin or antimicrosomal antibody titers; or, history of treatment of hyperthyroidism for Graves |
| Clinical hyperthyroidism: Treated for hyperthyroidism but no evidence of Graves disease, or signs of hyperthyroidism, no Graves disease and nondetectable TSH (if available) |
| Hyperthyroidism from thyroid nodule(s): Free T4 greater than normal, TSH less than normal, negative antithyroglobulin or antimicrosomal antibody titers, and the presence of thyroid nodule(s) |
| Subclinical hyperthyroidism: Normal Free T4 and T3 and TSH less than normal |
| Autoimmune (Hashimoto) thyroiditis: Antithyroglobulin or antimicrosomal antibody detection above normal limits with or without other abnormalities, or pathology reports Hashimoto thyroiditis |
| Clinical primary hypothyroidism: FTI < 1.15 or a low free T4 and TSH ≥16 μU/mL |
| Subclinical hypothyroidism: FTI between 1.15 and 4.14 or normal free T4 and TSH >5 μU/mL but <16 μU/mL |
| Multinodular goiter: Thyroid >40 g on any one estimate; if no gram weight estimate, reference to at least a 2-fold enlargement; must have at least one palpable or suspect nodule; no evidence of Hashimoto thyroiditis |
| Simple or nontoxic goiter: Thyroid ≥40 g on any one estimate; if no gram weight estimate, reference to at least a 2-fold enlargement; no palpable nodules; no evidence of Hashimoto thyroiditis |

TSH indicates thyroid-stimulating hormone; FTI, free thyroxine index.

dosimetry model and do not confound the risk ratios. However, for comparison purposes, we also ran the Phase IIR model using Phase II covariates.

The primary measure of effect in this report is the cumulative incidence rate, defined as the number of new cases of thyroid disease among all those screened during the 2 screening examination periods (1965–1970 and 1985–1986) plus those diagnosed with a confirmed medical diagnosis between the 2 screening periods. The cumulative incidence is thus a proportion in which the numerator is all individuals who had thyroid disease after the initial examination in 1965, and the denominator is all those individuals who were screened between 1965 and 1970, excluding those individuals with thyroid disease at the time of their initial screening. The denominator used for Phase II was all those included in the Phase I study who still resided in Utah, Nevada, or Arizona in 1985 through 1986, whose parents (primarily the mother [90%]) completed the interview necessary to assign a dose from radioactive iodine, and who underwent a thyroid examination. (See Table 1 for more information about inclusions and exclusions.) Individuals who had a total thyroidectomy or radiation ablation of the thyroid for a given disease were included in the numerator and denominator of that disease but were excluded from the denominator of other diseases.

Estimates of thyroid dose were divided into 4 dose categories as described previously. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using logistic regression. Tests for trend of increased risk with increasing thyroid-absorbed dose were obtained from the same logistic regression models. Generalized models for binomial odds were used to estimate effects of estimated dose on disease.[15]

In this extension of the conventional logistic model, the logit term for each observation is the sum of a sex-specific intercept term and the logarithm of $(1 + \beta^*\text{estimated dose})$. A likelihood ratio test was used to test the null hypothesis that $\beta$ is equal to zero, indicating no excess risk of disease due to radiation dose. A value of $\beta$ higher than zero is interpretable as increased odds of disease due to radiation exposure. For example, an estimated $\beta = 1.5\ \text{Gy}^{-1}$ indicates that subjects whose thyroid glands were estimated to have received 1 gray (Gy) have odds of disease $(1 + 1.5^*1) = 2.5$ times higher than subjects with negligible exposure. The value of $\beta$ (which may be viewed as a linear slope coefficient for the radiation dose-related risk), together with its likelihood-based 95% CI and $P$ value, was estimated using the GMBO program in the EPICURE biostatistical software package (Hirosoft International Corp., Seattle, WA). The slope estimates obtained from the EPICURE package were originally in $\text{mGy}^{-1}$ and were converted to excess risk ratios per gray (ERR/Gy) by multiplying by 1000.

## RESULTS

### Effects of Changes in Dose Estimations

The change in each of the cohort member's estimated dose was dependent on their location from 1951 through 1962, their age at exposure, their diet, their source of milk, and the amount of milk or garden vegetables consumed. The change in dose estimates between Phase II and Phase IIR is illustrated in Figures 1 and 2. For example, the dose estimate for approximately 68% of study participants living in the more heavily exposed area, Washington County, Utah, and Lincoln County, Nevada, changed by less than a factor of 2. Although the dose estimates for approximately 36% of those living in the control area (Graham County, Arizona) decreased between 2- and 10-fold, the dose estimates for another 20% increased by 2- to 10-fold. The decrease in assigned doses in this county occurred because of the changes to the estimated amount of radioiodines in soil that was ingested by cows. Because of the dry climate in Graham County, Arizona, commercial dairy farmers in the 1950s fed their cows hay year-round. The 20% whose dose increased in Graham County were drinking milk from backyard cows being fed on available pasture.

The larger changes in radiation doses occurred for those who lived outside the 3-county study area during the 1950s.

Approximately 18% of those individuals were reassigned a radiation dose that was more than 10 times higher than their earlier dose. Most of the changes resulting in marked dose increases were due to a residence history that included locations outside of the original 7-state area. In those cases, previously assigned zero doses were replaced with dose estimates obtained from the NCI calculator. The changes to some of the equations and parameters used in the dosimetry model also moved some people from the higher dose to the lower dose categories. Most of those were people who consumed milk from locations where deposition of large particles occurred, which resulted in very low interception of fallout on the surfaces of vegetation.[13]

## Effects of Review of Diagnoses of Thyroid Disease

As previously discussed, the review and reclassification of the clinical evidence for thyroid disease resulted in reassigning disease status for a number of individuals (Table 4).

## Results Taking Into Account the Updated Dosimetry and Diagnoses

Slope estimates, $\beta$ (ERR/Gy), with 95% CIs estimated for the relationship between radiation dose and subsequent thyroid disease are reported in Table 4 (except for benign neoplasms, which is excluded due to failure of the model to converge). Lower-bound estimates were constrained to zero if they were negative. Positive associations that had previously been reported between radioactive iodine and subsequent thyroid disease were stronger in the Phase IIR analysis. Because these estimates included 2 prevalent cases, we also calculated RRs and slope estimates with these cases excluded (data not shown). For carcinomas, the RRs remained the same at 1.7 for both Phase II and Phase IIR with similar slope estimates. In Phase IIR, there was a stronger dose–response for men, but this was based on only a single carcinoma.

For thyroiditis, estimates of the RR were identical for the period prevalence and cumulative estimates and increased at the highest dose category (from 1.1 in Phase II to 2.7 in Phase IIR) with an increase in the slope estimate (ERR/Gy) from 4.2 (lower-bound = 0.00) to 4.9 (95% CI = 2.0 to 10.0).

An additional disease category ("any thyroid disease") encompassed all forms of thyroid disease. For this category, the RRs at the highest dose category increased from 1.4 in Phase II to 2.4 in Phase IIR (Table 5).

We also examined thyroid disease by sex (Table 6). The incidence rate of any thyroid disease among women was approximately 3 times greater than among men, and this difference persisted with increasing radiation dose. There was an increase in the trend from the lowest to the highest dose group and in the slope estimates for neoplasms and for thyroiditis in men and women. For women, neither the test for trend nor the slope estimate for thyroid cancer was statistically significant.

**TABLE 4.** Changes in Thyroid Disease Diagnoses Based on Review by Panel of Experts

| Diagnosis | No. in Phase II | No. in Phase IIR | Change |
|---|---|---|---|
| Nonneoplastic nodules | 36 | 32 | −4 |
| Neoplasms | 20 | 22 | +2 |
| Benign neoplasms | 12 | 15 | +3 |
| Cancer | 8 | 8 | 0 |
| Hyperthyroidism | 10 | 12 | +2 |
| Thyroiditis | 132 | 123 | −9 |
| Hypothyroidism | 37 | 42 | +5 |
| Simple goiter | 70 | 35 | −35 |
| Miscellaneous and unspecified nodules | 33 | 39 | +6 |
| Total | 358 | 328 | −30 |

## Uncertainties in Dosimetry and Their Effect on Risk Ratios

Measurement errors can be random or systematic. The most common random types are the Berkson uncertainties and individual-specific classic uncertainties.[14] Mallick et al[15] describe a model for random uncertainties in dosimetry that is a mixture of Berkson and classic uncertainties, and in section 2 of their article, they discuss why such a mixture is reasonable.

The analysis reported in Table 5 is based on the arithmetic mean dose and is equivalent to a regression calibration analysis (Carroll et al,[14] chapter 4) when all uncertainty is assumed to be of Berkson type (Mallick et al[15]). Thus, our analysis is appropriate for a specific type of uncertainty in the dosimetry, namely Berkson uncertainties. Statistical hypothesis testing using the arithmetic mean dose is an appropriate procedure (Carroll et al,[14] chapter 10).

More complex models for dose uncertainty would incorporate a mixture of Berkson and classic random uncertainties along with systematic biases. Depending on how they are apportioned, the numeric effects can vary considerably. The literature, however, is clear that when there are no systematic biases, an analysis assuming only Berkson-type error is the most conservative (ie, it is more likely to understate rather than overstate the true risk and the true level of uncertainty). For example, Mallick et al[15] address the question of the effect of uncertainties in dosimetry when the uncertainties are a mixture of Berkson and classic types. They show that allowing for classic uncertainties has 4 consequences: it increases the estimated excess risk ratio per gray with the increase becoming more substantial as more of the uncertainty is apportioned to the classic type of uncertainty; it increases the upper end of the 95% CI; it increases the length of the 95% CIs; and the CIs are generally shifted upward from the Berkson-only analysis. These 4 trends are observed in our data as well. For example, if 50% of the uncertainty is of classic type and 50% is of Berkson type, then using regression calibration through equation number 6 of Mallick et al,[15] the point estimate for thyroiditis changes from 4.2 to 7.2, and the 95% CI changes from 1.4–9.6 to 2.9–14.9. Mallick et al[15] describe a similar phenomenon. For example, in their Table 1 in which our Phase II data for neoplasms are analyzed, the slope using the arithmetic mean

**TABLE 5.** Association of Radiation Dose (mGy) With Thyroid Disease Adjusted for Sex for Phase II and Phase IIR*

| | Phase II† | | | Phase IIR† | | |
|---|---|---|---|---|---|---|
| **Disease Category†** | **Dose (mGy)** | **No. Cases/ No. at Risk** | **Rate/1000** | **Adjusted RR (95% CI)** | **Dose (mGy)** | **No. Cases/ No. at Risk** | **Rate/1000** | **Adjusted RR (95% CI)** |
| Nodules | 0–49‡ | 29/1418 | 20.5 | 1.0 | >0–74‡ | 21/1435 | 14.6 | 1.0 |
| | 50–249 | 12/646 | 18.6 | 0.9 (0.4–2.1) | 75–215 | 13/651 | 20.0 | 1.4 (0.7–2.9) |
| | 250–399 | 8/240 | 33.3 | 1.9 (0.5–6.1) | 216–409 | 7/242 | 28.9 | 2.2 (0.9–5.1) |
| | 400+ | 7/169 | 41.4 | 2.3 (0.6–8.0) | 410+ | 8/164 | 48.8 | 4.0 (1.7–9.3) |
| | | $\beta$ (lower bound) = 1.2 (0.0), $P$ = 0.16 | | | | $P$ for trend = 0.00240<br>$\beta$ (95% CI) = 4.65 (1.1–12.3), $P$ = 0.002 | | |
| Nonneoplastic nodules | 0–49‡ | 16/1418 | 11.3 | 1.0 | >0–74‡ | 15/1434 | 10.5 | 1.0 |
| | 50–249 | 8/646 | 12.4 | 0.9 (0.3–2.6) | 75–215 | 10/651 | 15.4 | 1.5 (0.7–3.5) |
| | 250–399 | 2/240 | 8.3 | 0.8 (0.1–6.6) | 216–409 | 4/241 | 16.6 | 1.7 (0.6–5.2) |
| | 400+ | 2/169 | 11.8 | 1.1 (0.1–7.9) | 410+ | 3/165 | 18.2 | 2.0 (0.6–7.1) |
| | | $\beta$ (lower bound) = 2.2 (0.0), $P$ = 0.40 | | | | $P$ for trend = 0.231<br>$\beta$ (95% CI) = 1.82 (0.0–8.3), $P$ = 0.213 | | |
| Neoplasms | 0–49‡ | 7/1418 | 4.9 | 1.0 | >0–74‡ | 7/1435 | 4.9 | 1.0 |
| | 50–249 | 3/646 | 4.6 | 0.8 (0.1–6.3) | 75–215 | 4/651 | 6.1 | 1.3 (0.4–4.5) |
| | 250–399 | 5/240 | 20.8 | 2.8 (0.4–22.9) | 216–409 | 4/242 | 16.5 | 3.7 (1.1–12.8) |
| | 400+ | 4/169 | 23.7 | 3.4 (0.5–26.9) | 410+ | 5/164 | 30.5 | 7.5 (2.3–24.3) |
| | | $\beta$ (lower bound) = 7.0 (0.7), $P$ = 0.019 | | | | $P$ for trend = 0.000071<br>$\beta$ (95% CI) = 13.02 (2.7–68.7), $P$ = 0.00061 | | |
| Benign neoplasms | 0–49‡ | 2/1418 | 1.4 | NA | >0–74‡ | 3/1434 | 2.1 | 1.0 |
| | 50–249 | 3/646 | 4.6 | NA | 75–215 | 3/650 | 4.6 | 2.3 (0.5–11.5) |
| | 250–399 | 3/240 | 12.5 | NA | 216–409 | 3/241 | 12.4 | 6.5 (1.3–32.3) |
| | 400+ | 3/169 | 18.0 | NA | 410+ | 4/164 | 24.4 | 13.8 (3.0–62.8) |
| | | | | | | $P$ for trend = 0.000117<br>$\beta$ (95% CI)§ | | |
| Cancers | 0–49‡ | 5/1418 | 3.5 | 1.0 | >0–74‡ | 5/1435 | 3.5 | 1.0 |
| | 50–249 | 0/646 | 0.0 | 0.0 | 75–215 | 1/651 | 1.5 | 0.5 (0.05–4.0) |
| | 250–399 | 2/240 | 8.3 | 3.8 (0.2–110.7) | 216–409 | 1/242 | 4.1 | 1.3 (0.2–11.2) |
| | 400+ | 1/169 | 5.9 | 1.7 (0.1–138.8) | 410+ | 1/165 | 6.1 | 2.1 (0.2–18.2) |
| | | $\beta$ (lower bound) = 7.9 (0.0), $P$ = 0.096 | | | | $P$ for trend = 0.763<br>$\beta$ (95% CI) = 0.8 (0.0–14.9), $P$ = 0.739 | | |
| Thyroiditis | 0–49‡ | 70/1414 | 49.5 | 1.0 | >0–74‡ | 54/1433 | 37.7 | 1.0 |
| | 50–249 | 34/646 | 52.6 | 0.8 (0.5–1.3) | 75–215 | 37/651 | 56.8 | 1.6 (1.1–2.5) |
| | 250–399 | 16/240 | 66.7 | 1.0 (0.4–2.2) | 216–409 | 15/242 | 62.0 | 1.9 (1.0–3.4) |
| | 400+ | 11/169 | 65.1 | 1.1 (0.5–2.7) | 410+ | 17/165 | 103.0 | 5.6 (3.5–9.2) |
| | | $\beta$ (lower bound) = 4.2 (0.0), $P$ = 0.29 | | | | $P$ for trend = 0.0001254<br>$\beta$ (95% CI) = 4.9 (2.0–10.0), $P$ = 0.00000841 | | |
| Thyroiditis with hypothyroidism | 0–49‡ | 23/1414 | 16.2 | 1.0 | >0–74‡ | 17/1433 | 11.9 | 1.0 |
| | 50–249 | 12/646 | 18.6 | 0.8 (0.4–2.0) | 75–215 | 11/651 | 16.9 | 1.5 (0.7–3.3) |
| | 250–399 | 4/240 | 16.7 | 0.7 (0.1–2.9) | 216–409 | 2/241 | 8.3 | 0.8 (0.2–3.4) |
| | 400+ | 1/169 | 5.9 | 0.3 (0.0–2.2) | 410+ | 5/165 | 30.3 | 3.3 (1.2–9.1) |
| | | $\beta$ (lower bound) = 0.000 (0.0), $P$ = 0.73 | | | | $P$ for trend = 0.180<br>$\beta$ (95% CI) = 2.89 (0.0–11.7), $P$ = 0.086 | | |
| Any thyroid disease | 0–49‡ | 135/1418 | 95.2 | 1.0 | >0–74‡ | 107/1436 | 74.5 | 1.0 |
| | 50–249 | 74/646 | 114.6 | 1.0 (0.7–1.5) | 75–215 | 66/652 | 101.2 | 1.5 (1.1–2.1) |
| | 250–399 | 31/240 | 129.2 | 1.2 (0.6–2.1) | 216–409 | 24/243 | 98.8 | 1.5 (0.9–2.4) |
| | 400+ | 22/169 | 130.2 | 1.4 (1.7–2.6) | 410+ | 23/164 | 140.2 | 2.4 (1.5–5.5) |
| | | $\beta$ (lower bound) = 7.9 (0.0), $P$ = 0.098 | | | | $P$ for trend = 0.00125<br>$\beta$ (95% CI) = 2.37 (0.9–4.6), $P$ = 0.0003 | | |

*All $\beta$ are slope estimates and are given in ERR/Gy.

†Nonneoplastic nodules plus neoplasms equals nodules except in Phase II in which nodules included miscellaneous and unspecified nodules. These have been removed from Phase IIR categories. Benign neoplasms plus cancers total to neoplasms unless a subject had more than one subcategory disease.

‡Reference category.

§Point estimate and 95% CI not identified due to lack of model convergence for estimating these values.

NA indicates data not available.

**TABLE 6.** Association of Radiation Dose (mGy) With Thyroid Disease Rates by Sex for Phase IIR*

| | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|
| **Disease Category†** | **Dose (mGy)** | **No. Cases/ No. at Risk** | **Rate/1000** | **RR (95% CI)** | **No. Cases/ No. at Risk** | **Rate/1000** | **RR (95% CI)** |
| Nodules | >0–74‡ | 4/664 | 6.0 | 1.0 | 17/771 | 22.0 | 1.0 |
| | 75–215 | 3/327 | 9.2 | 1.5 (0.3–6.9) | 10/324 | 30.9 | 1.4 (0.6–3.1) |
| | 216–409 | 1/126 | 7.9 | 1.3 (0.1–11.9) | 6/116 | 51.7 | 2.4 (0.9–6.3) |
| | 410+ | 3/95 | 31.6 | 5.4 (1.2–24.4) | 5/69 | 72.5 | 3.5 (1.2–9.7) |
| | | $P$ for trend = 0.0095 | | | $P$ for trend = 0.0055 | | |
| | | $\beta$ (95% CI) = 7.4 (0.4–55.8), $P$ = 0.026 | | | $\beta$ (95% CI) = 3.8 (0.3–12.3), $P$ = 0.027 | | |
| Nonneoplastic nodules | >0–74‡ | 4/664 | 6.0 | 1.0 | 11/770 | 14.3 | 1.0 |
| | 75–215 | 2/327 | 6.1 | 1.0 (0.2–5.6) | 8/324 | 24.7 | 1.7 (0.7–4.4) |
| | 216–409 | 0/126 | 0 | — | 4/115 | 34.8 | 2.5 (0.8–7.9) |
| | 410+ | 1/96 | 10.4 | 1.7 (0.2–15.7) | 2/69 | 30.0 | 2.1 (0.4–9.5) |
| | | $P$ for trend = 0.9989 | | | $P$ for trend = 0.0961 | | |
| | | $\beta$ (95% CI) = 0.5 (0.0–12.8), $P$ = 0.81 | | | $\beta$ (95% CI) = 2.76 (0.0–13.1), $P$ = 0.17 | | |
| Neoplasms | >0–74‡ | 0/664 | 0 | NC | 7/771 | 9.1 | 1.0 |
| | 75–215 | 1/327 | 3.1 | NC | 3/324 | 9.3 | 1.0 (0.3–4.0) |
| | 216–409 | 1/126 | 7.9 | NC | 3/116 | 25.9 | 2.9 (0.7–11.4) |
| | 410+ | 2/95 | 21.1 | NC | 3/69 | 43.5 | 5.0 (1.3–19.6) |
| | | $P$ for trend <0.0001 | | | $P$ for trend = 0.0122 | | |
| | | $\beta$ (95% CI) = 525.0 (5.6–‖), $P$ = 0.001 | | | $\beta$ (95% CI) = 6.4 (0.1–35.9), $P$ = 0.043 | | |
| Benign neoplasms | >0–74‡ | 0/664 | 0 | NC | 3/770 | 3.9 | 1.0 |
| | 75–215 | 1/327 | 3.1 | NC | 2/323 | 6.2 | 1.6 (0.3–9.6) |
| | 216–409 | 1/126 | 7.9 | NC | 2/115 | 17.4 | 4.5 (0.7–27.4) |
| | 410+ | 1/95 | 10.5 | NC | 3/69 | 43.5 | 11.6 (2.3–58.7) |
| | | $P$ for trend = 0.0011 | | | $P$ for trend = 0.0009 | | |
| | | $\beta$ (95% CI),§ $P$ = 0.009 | | | $\beta$ (95% CI),§ $P$ = 0.0029 | | |
| Cancers | >0–74‡ | 0/664 | 0 | NC | 5/771 | 6.5 | 1.0 |
| | 75–215 | 0/327 | 0 | NC | 1/324 | 3.1 | 0.5 (0.06–4.1) |
| | 216–409 | 0/126 | 0 | NC | 1/116 | 8.6 | 1.3 (0.2–11.5) |
| | 410+ | 1/96 | 10.4 | NC | 0/69 | 0 | — |
| | | $P$ for trend = 0.0152 | | | $P$ for trend=0.6069 | | |
| | | $\beta$ (95% CI) = 400.0 (0.0–‖), $P$ = 0.096 | | | $\beta$ (95% CI) = –0.88 (‖–‖), $P$ = 0.50 | | |
| Thyroiditis | >0–74‡ | 7/663 | 10.6 | 1.0 | 47/770 | 61.0 | 1.0 |
| | 75–215 | 4/327 | 12.2 | 1.2 (0.3–4.0) | 33/324 | 101.9 | 1.7 (1.1–2.8) |
| | 216–409 | 4/127 | 31.5 | 3.0 (0.9–10.6) | 11/115 | 95.7 | 1.6 (0.8–3.2) |
| | 410+ | 5/96 | 52.1 | 5.1 (1.6–16.6) | 12/69 | 173.9 | 3.2 (1.6–6.4) |
| | | $P$ for trend = 0.0024 | | | $P$ for trend = 0.0004 | | |
| | | $\beta$ (95% CI) = 8.2 (1.1–48.2), $P$ = 0.006 | | | $\beta$ (95% CI) = 4.24 (1.4–9.6), $P$ = 0.0004 | | |
| Thyroiditis with hypothyroidism | >0–74‡ | 1/663 | 1.5 | 1.0 | 16/770 | 20.8 | 1.0 |
| | 75–215 | 0/327 | 0 | — | 11/324 | 34.0 | 1.7 (0.8–3.6) |
| | 216–409 | 1/126 | 7.9 | 5.3 (0.3–85.2) | 1/115 | 8.7 | 0.4 (0.05–3.1) |
| | 410+ | 1/96 | 10.4 | 7.0 (0.4–112.3) | 4/69 | 58.0 | 2.9 (0.9–8.9) |
| | | $P$ for trend = 0.0799 | | | $P$ for trend = 0.2176 | | |
| | | $\beta$ (95% CI) = 56.6 (0.0–‖), $P$ = 0.12 | | | $\beta$ (95% CI) = 2.09 (0.0–10.0), $P$ = 0.19 | | |
| Any thyroid disease | >0–74‡ | 22/664 | 33.1 | 1.0 | 85/772 | 110.1 | 1.0 |
| | 75–215 | 13/327 | 39.8 | 1.2 (0.6–2.4) | 53/325 | 163.1 | 1.6 (1.1–2.3) |
| | 216–409 | 7/127 | 55.1 | 1.7 (0.7–4.1) | 17/116 | 146.6 | 1.4 (0.8–2.4) |
| | 410+ | 6/95 | 63.2 | 2.0 (0.8–5.0) | 17/69 | 246.4 | 2.6 (1.5–4.8) |
| | | $P$ for trend = 0.0455 | | | $P$ for trend = 0.0008 | | |
| | | $\beta$ (95% CI) = 2.11 (0.0–7.0), $P$ = 0.064 | | | $\beta$ (95% CI) = 2.48 (0.7–5.3), $P$ = 0.0018 | | |

*All $\beta$ are slope estimates and are given in ERR/Gy.

†Nonneoplastic nodules plus neoplasms equals nodules except in Phase II in which nodules included miscellaneous and unspecified nodules. These have been removed from Phase IIR categories. Benign neoplasms plus cancers total to neoplasms unless a subject had more than one subcategory disease.

‡Reference category.

§Point estimate and 95% CI not identified due to lack of model convergence for estimating these values.

‖Coefficients for a linear dose response could not be obtained from the GMBO model.

NC indicates that no RR could be calculated because no disease was observed in the baseline dose category.

and a Berkson-only analysis was estimated as 7.9 with a 95% CI (3.8 to 11.8), whereas with a mixture of Berkson and classic uncertainties, the slope estimate was 13.2 with a 95% CI (5.0 to 23.1).

## DISCUSSION

After correcting dosimetry algorithms, updating disease classification, and correcting database errors in the exposure assessment and disease diagnosis, we found that the association between estimates of radiation dose to the thyroid due to fallout from NTS and subsequent thyroid neoplasms among those exposed as young children was stronger for several forms of thyroid disease (neoplasms and thyroiditis). An association between thyroiditis and estimated thyroid dose also emerged. Removing misclassification of exposure or disease from a study population will allow a true exposure–disease relationship to emerge that may not have been previously present or strengthen a previously detected association.[16] The correction of errors and updating of the dosimetry algorithm were done before the examination of the exposure–disease relationship.

Davis et al[2] have suggested that our Phase II study findings might be explained by examiner bias. Some types of thyroid disease in their early stages are detectable only by screening examination. The basis of their argument was that those performing the screening examinations knew the exposure level of each study subject and performed a more thorough thyroid examination on those subjects with higher exposure. The issue of potential examiner bias has been explored in a more detailed report from our earlier study.[17] That report concluded that examiner bias could not account for the association between NTS radiation and subsequent thyroid disease for the following reasons. Although the most heavily exposed area in this study was Washington County, Utah, the classification of heavy exposure to radioactive iodine in this area during this period (May 19–31, 1953) required the consumption of milk from backyard cows rather than commercial dairies. Such detailed information was not available to those conducting the examinations; in fact, the significance of consumption of milk from backyard cows (or goats) was recognized only after the screening examinations were completed in 1985 through 1986.

Additionally, 813 (35%) of the residents of Washington County, Utah, had left the county after the 1965 through 1970 screening examinations and were living in other locations within the 3-state area of Utah, Nevada, and New Mexico. In 1985 through 1986, the screening examiners were not aware of the person's residential history during the years 1951 through 1958. Furthermore, the positive association between exposure to NTS fallout and thyroid disease was concentrated among subjects exposed to shot HARRY that occurred on May 19, 1953, and not among those born after the test or who moved into the area after the test. Again, the history of an individual's exposure to fallout from shot HARRY was not known to the examiners. Based on our previously published analysis regarding potential examiner bias, we believe this bias is not an explanation for the association we found.

We have addressed other factors that could cause selection and information bias in the Phase II study.[1] Because the same population formed the basis for the Phase IIR study, the same conclusions of low likelihood of positive associations due to these biases apply.

An association between exposure and thyroid carcinoma was not detected with only 8 subjects having been diagnosed with carcinoma. However, benign thyroid neoplasms are strongly associated with the development of subsequent thyroid neoplasms with odds ratios reported as high as 10-fold.[18] The screening of our cohort for thyroid disease with benign nodules having been removed along with part or all of the thyroid gland may have reduced the subsequent occurrence of thyroid carcinoma among those at highest risk in this cohort.

Whether exposure to radioactive iodine results in an excess of thyroid diseases or dysfunctions has been controversial for many years. Some studies of persons receiving radioactive iodine for diagnostic tests have reported no increase in the risk of later neoplasms.[19,20] Those studies have been limited in their generalizability because many of the individuals already had some form of thyroid disease and because the use of radioiodine was limited mostly to adolescents and adults with few being exposed under the age of 10. Studies of those exposed to radioactive iodine released by the Chernobyl accident found increased risk for thyroid carcinoma in those exposed as children.[3,5,21,22]

Thyroiditis is the most common form of thyroid disease in the United States and is thought to be mediated through an autoimmune mechanism.[23] The association between radioactive iodine and subsequent thyroiditis has been suggested by reports of individuals treated for various forms of thyroid disease with iodine-131.[24–26] The findings from those studies were also confounded by the fact that subjects already had suspected or diagnosed thyroid disease when exposed to I-131.

Among the population exposed to radioactive iodine from the Chernobyl reactor accident, the subgroup exposed before age 5 and who had the highest estimated radiation doses, also had higher levels of thyroid antibodies (a precursor of thyroiditis) among those exposed before age 5 to higher calculated radiation doses.[27] Davis et al[2] found no association between radiation exposure and thyroiditis. Weiss et al[28] found a 2-fold increase in surgery for thyroiditis among young adults in Utah after the end of above-ground nuclear testing compared with young adults before the onset of testing. They were not able to adjust for a number of factors, including changing diagnostic standards or in- and outmigration nor could they link the increase with actual radiation exposures. An association between external radiation and subsequent thyroiditis was first reported by Ito in 1987 in the Japanese atomic bomb survivors.[29] A recent study from the Japanese atomic bomb survivors reported a 2-fold excess for all forms of thyroid nodes, including benign and malignant neoplasms, but no association with autoimmune thyroid disease.[30] These authors were not able to confirm their earlier finding of an association between radiation exposure and thyroiditis.[31]

In our study, the dosimetry algorithm includes external radiation, although its contribution to the total radiation dose to the thyroid gland was only approximately 4.5% in the highest dose category I-133 contributed approximately 17% in the highest dose category with I-131 contributing the remaining 78.5%. In the lowest dose category in which exposure due to inhalation and ingestion of radioactive iodine was much less, the contribution of external irradiation to the total thyroid dose, expressed as a proportion, was substantially greater.

The only other study in the United States on accidental exposure of radioactive iodine and subsequent thyroid disease was that on citizens living near the Hanford nuclear facility, conducted by Davis et al.[2] They reported an absence of association between exposure to radioiodine and any type of thyroid disease. The Hanford Thyroid Disease Study used methods similar to those we used to identify thyroid disease, but the dosimetry they used to assign a radiation dose to each individual was not based on exposure rate or ground contamination measurements after the releases. Their estimates of air concentrations and depositions at each location where subjects lived were developed many years later and based on model calculations of the emission rate of I-131 and historical meteorologic data. Davis et al[2] have proposed that the differences observed between our study and theirs might be explained by higher dose rates and the mixture of radionuclides associated with exposure to weapons fallout. We do not believe this explanation is plausible. The discrepancy between the 2 sets of findings is likely due, in part, to the other study's dependence on mathematical models to estimate individual exposures to radioiodines. We believe that the uncertainties in the dosimetry used in that study are substantially greater than those in our dosimetry model and are larger and more complex than estimated by the authors of that report. Large and complex uncertainties in dose reconstruction will contribute to nondifferential dose misclassifications that, in turn, will affect the statistical power of the study and the estimation of measures of effect, including the slope and confidence intervals of the dose–response relationship.[14,15]

Both U.S. studies involved exposure at low-dose rates in which total dose accumulated over a period of several weeks to many months. Moreover, both studies involve I-131 as the primary contributor to the total dose.

The BEIR VII Committee of the National Academy of Sciences does not presently consider, there to be substantial differences in risk per unit dose for doses delivered at various low dose rates.[32] However, investigations of the effects of exposure to radioactive iodine from the Chernobyl accident are also identifying evidence of positive associations between exposure and the subsequent development of thyroid disease.[3,5,26,32] The findings from the Chernobyl studies, coupled with our Phase II and Phase IIR findings, indicate that exposure to radioactive iodine is associated with increased incidence of thyroid disease.

Our previously reported association between exposure to NTS-created radioactive iodine and subsequent thyroid neoplasms was substantially strengthened by removing important sources of misclassification of exposure and disease that were undetected in earlier analyses. A previously undetected relationship between thyroiditis and exposure to radioactive iodine has emerged. This is the first report of such a relationship in a U.S. population; hence, we believe that this cohort represents a unique opportunity to provide further assessment of a range of exposures and disease end points among U.S. citizens. Further follow up of this cohort may increase our understanding of the long-term health consequences of exposure to radioactive iodine regardless of its origin in reactors, accidents, or nuclear detonations.

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