Thyroid Neoplasia, Autoimmune Thyroiditis, and Hypothyroidism in Persons Exposed to Iodine 131 From the Hanford Nuclear Site

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The Hanford Nuclear Site in southeastern Washington State (Figure 1) was established in 1943 to produce plutonium for atomic weapons. In 1986, it was revealed that during the initial years of plutonium production at Hanford, large amounts of gaseous and vaporized radionuclides were released into the atmosphere. It was subsequently estimated that about 740000 Ci (2.73 × 10^16 Bq) of iodine 131 (131I) were released to the atmosphere from 1944 through 1957. This disclosure prompted widespread concern among people living near the Hanford Site that such releases may have increased their risk of developing thyroid disease.

Exposure to ionizing radiation from external sources has been linked to increased risk of thyroid neoplasia in studies of childhood exposure to external gamma radiation and of Japanese atomic-bomb survivors. Much less is known about the induction of thyroid disease in humans from 131I exposure. Studies of persons exposed to diagnostic or therapeutic doses of 131I provide no convincing evidence that such exposures increase the risk of thyroid neoplasia. Environmental exposures to 131I at various levels have been linked to: (1) excess thyroid nodularity among Marshall Islands residents exposed to fallout from atmospheric nuclear weapons tests; (2) excess thyroid neoplasia among residents of Utah exposed to fallout from atmospheric nuclear weapons tests; and (3) increased risk of thyroid cancer among residents of the Marshall Islands exposed to atmospheric nuclear weapons tests.

Context
Approximately 740000 Ci (2.73 × 10^16 Bq) of iodine 131 (131I) were released to the atmosphere from the Hanford Nuclear Site in Washington State from 1944 through 1957. The risk of thyroid disease resulting from prolonged environmental 131I exposure is poorly understood.

Objective
The Hanford Thyroid Disease Study (HTDS) was conducted to determine if thyroid disease is increased among persons exposed as children to atmospheric releases of 131I from Hanford.

Design
Retrospective cohort study. Exposure could have occurred from December 1944 through 1957. Follow-up occurred until the time of the HTDS examination (December 1992–September 1997). Participants’ thyroid radiation doses from Hanford’s 131I releases were estimated from interview data regarding residence and dietary histories.

Setting
The cohort included a sample of all births from 1940 through 1946 to mothers with usual residence in 1 of 7 counties in eastern Washington State.

Participants
Of 5199 individuals identified, 4350 were located alive and 3440 were evaluable; ie, had sufficient data for dose estimation and received an HTDS evaluation for thyroid disease, including a thyroid ultrasound, physical examination, and fine needle biopsy if required to evaluate thyroid nodularity.

Main Outcome Measures
Thyroid cancer, benign thyroid nodules, total neoplasia, any thyroid nodules, autoimmune thyroiditis, and hypothyroidism.

Results
There was no evidence of a relationship between Hanford radiation dose and the cumulative incidence of any of the outcomes. These results remained unchanged after taking into account several factors that might confound the relationship between radiation dose and the outcomes of interest.

Conclusion
These results do not support the hypothesis that exposure during infancy and childhood to 131I at the dose levels (median, 97 mGy; mean, 174 mGy) and exposure circumstances experienced by our study participants increases the risk of the forms of thyroid disease evaluated in this study.

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and (3) excess thyroid cancer among persons exposed as children to radiation from the Chernobyl accident.\footnote{15,16} In addition, a relationship between radiation dose and “autoimmune hypothyroidism” has been reported among survivors of the atomic bombing of Nagasaki,\footnote{17} and there is evidence that children exposed to Chernobyl radiation have an increased prevalence of anti-thyroid antibodies not associated with hypothyroidism.\footnote{18} However, the association between radiation exposure and autoimmune thyroiditis is not well established.

Because the risk of thyroid disease resulting from $^{131}$I exposure is poorly understood and because substantial numbers of persons were exposed to $^{131}$I from Hanford, the present study was undertaken to determine whether thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism is increased among persons exposed to atmospheric releases of $^{131}$I from Hanford from 1944 through 1957.

\section*{METHODS}

\subsection*{Study Cohort}

The Hanford Thyroid Disease Study (HTDS) was a retrospective cohort study. Study methods, described in detail elsewhere,\footnote{19} are summarized herein. Since a large region was contaminated and populations living outside that region might have quite different spontaneous thyroid disease risks, which would confound exposure-disease relationships, no attempt was made to identify an unexposed control group. Instead, the study was designed to estimate variation of disease risk over a wide range of doses. Because only preliminary data regarding potential exposures existed when the study was initiated, the cohort was defined on the basis of presumed exposure to Hanford's atmospheric $^{131}$I releases. To maximize the study's statistical power, the cohort included persons with a wide range of doses and focused on persons who were young children at the time of the peak exposures in 1945-1946, since the risk of radiogenic thyroid disease is greater among those exposed in childhood.\footnote{3,12,20-26}

Preliminary estimates of thyroid radiation doses for counties surrounding the Hanford Site\footnote{27} suggested that residents of Benton, Franklin, and Walla Walla counties may have received the highest thyroid doses, while those more removed from the site, particularly to the north and west (Okanagan, Ferry, and Stevens counties), were likely to have been exposed at substantially lower levels. Refined dose estimates indicated that Walla Walla County had somewhat lower doses than originally estimated, while residents of Adams County also received appreciable doses.\footnote{28}

A roster was constructed from Washington State birth certificates of births to mothers with usual place of residence in the 7 counties named herein. Nine geographical areas (geostrata) were defined to distinguish regions of relatively high and low $^{131}$I contamination and predominantly rural areas from predominantly urban areas (TABLE 1). Selection of the cohort was stratified by sex, geostratum, and birth year to include as many individuals from the more heavily exposed areas and time periods as possible. The resulting cohort included 5199 persons born from January 1, 1940, through December 31, 1946.

Each cohort member was traced, initially using linkages to publicly available records including Washington State death certificates, driver's license records, marriage records, and Vietnam War death records. Persons not located in this manner were sought by searches of telephone directories, reverse directories, directory assistance, Social Security death rosters, and obituaries. For remaining individuals, neighbors, employers, organizations, clubs, the National Death Index, and a professional locating service were used. All procedures and data collection instruments were approved by the Fred

\begin{table}[h]
\centering
\caption{Hanford Nuclear Site and Hanford Environmental Dose Reconstruction Study Area}
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\hline
\textbf{Figure 1.} Hanford Nuclear Site and Hanford Environmental Dose Reconstruction Study Area
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\end{tabular}
\end{table}
Clinical Assessment and Outcomes

Thyroid evaluations were conducted at HTDS clinics throughout Washington State and once in Portland, Ore, from December 1992 through September 1997. After providing written consent, participants were interviewed regarding past radiation exposures, thyroid disease history, lifestyle factors, and general demographic information. Each participant received a thyroid ultrasound examination (Hitachi EUB-310, Japan) by a certified ultrasonographer, which was recorded on videotape for review by a radiologist. Three 10-mL tubes of blood were drawn for thyroid function and autoantibody measurements. Serum was transported within 72 hours to a clinical laboratory in Seattle, Wash.

Participants were examined independently by 2 physicians specializing in thyroid disease. Any disagreement in the physical findings resulted in a joint examination to reach consensus. The physicians reviewed the ultrasound results only after reaching consensus on physical findings. If the ultrasound and physical findings disagreed, another joint physical examination was performed to reach a final consensus. Physicians were blinded to participants’ possible exposure to Hanford radiation (eg, residence, occupation). Four certified sonographers participated in the study. Approximately every 2 months, 2 sonographers independently scanned each of 5 participants to monitor interoperator reliability.

Initially, participants with 1 or more discrete, palpable nodules or discrete dominant nodules in a multinodular gland were offered a fine-needle aspiration (FNA). However, it was soon recognized that the ultrasound examination occasionally identified nonpalpable nodules of appreciable size. Consequently, after 653 (18.9%) of the total number of participants had been examined, FNA was also routinely offered for nonpalpable ultrasound-detected nodules of 1.5 cm or greater, averaged over 3 dimensions. Seven of these 653 had nonpalpable ultrasound nodules that met the 1.5-cm size criterion, and 5 of the 7 underwent FNA biopsy. Four to 8 aspirations were performed per nodule. All slides were reviewed by 1 experienced cytopathologist.

Estimation of Radiation Dose

As described in detail elsewhere,\textsuperscript{39,32} each participant's thyroid radiation dose from Hanford's $^{131}$I releases was estimated using the Hanford Environmental Dose Reconstruction (HEDR) Project's computer program, CIDER,\textsuperscript{33} which estimates prenatal and postnatal thyroid doses received by an individual
while residing inside a 246 × 306-mile study area around the Hanford Site (Figure 1) from December 1944 through 1957. The thyroid doses from Hanford’s $^{131}$I releases were determined in part by the concentrations of that $^{131}$I in media—air, food and milk products, and ground surface—to which people were exposed through immersion and inhalation, ingestion, and proximity, respectively. Time courses of these concentrations at locations throughout the HEDR study area were estimated as part of the HEDR Project.\textsuperscript{33}

Doses for HTDS participants were then estimated by combining these concentration histories with individual characteristics, including sex, and residence and dietary histories, which vary by time, and then converting activity inhaled or ingested, measured in curies, to estimated doses in milligrays using age- and sex-dependent conversion factors. Dietary histories included the quantities and sources of fresh milk, milk products, and selected other foods (vegetables, fruits, and free-range chicken eggs) that the participant consumed. For those born or breastfed after the releases of $^{131}$I began in December 1944, the residence history and a limited dietary history of the participant’s mother were collected to estimate the contributions to the participant’s dose from prenatal exposure or breast milk.

Since the cohort was quite young when $^{131}$I exposures were highest, all participants were asked to identify older persons, preferably their mothers or other close relatives, with direct knowledge of the participants’ infancies and childhoods to provide this information in a computer-assisted telephone interview (CATI). To help minimize possible bias in recall due to awareness of a participant’s thyroid disease status, the CATI was conducted before the participant’s HTDS clinical evaluation. Because the CATI focused on circumstances and events in the distant past, respondents received materials, including a residence history form and memory aid booklet, to prepare for the interview. CIDER provides default

**Box 1. Definitions of Thyroid Disease Outcomes**

**Cancer**
Palpable, discrete mass or nonpalpable, focal ultrasound-detected mass of at least 1.5 cm (averaged across 3 dimensions); histologically confirmed as malignant, original slides reviewed by Hanford Thyroid Disease Study (HTDS) pathologist

**Benign Nodule**
Palpable, discrete mass or nonpalpable, focal ultrasound-detected mass of at least 1.5 cm (averaged across 3 dimensions); histologically or cytologically confirmed as benign by HTDS pathologist\textsuperscript{†}

**Total Neoplasia**
Confirmed cases of thyroid cancer or benign follicular adenoma\textsuperscript{‡}

**Any Nodules**
Thyroid cancer, benign nodule, or nodule suspicious for malignancy\textsuperscript{§}

**Hypothyroidism**
Thyrotropin elevation to higher than the upper limit of the normal range for the assay either in the HTDS clinical evaluation or confirmed in prior medical records

** Permanent Hypothyroidism**
Hypothyroidism excluding euthyroid participants not taking thyroid hormone who had thyrotropin elevations documented in prior medical records

**Autoimmune Thyroiditis**
Any positive result for thyroid peroxidase antibodies (TPOAb) (>2.0 IU/mL) or antimicrosomal antibodies (>25 IU/mL) obtained from clinical evaluation or confirmation of a positive antibody result from medical records in the absence of Graves disease\textsuperscript{||}

**Autoimmune Thyroiditis—Alternative Definitions**
Measurement of TPOAb or thyroglobulin antibodies (TgAb) of greater than 10 IU/mL

Autoimmune thyroiditis with hypothyroidism
Autoimmune thyroiditis with hypothyroidism including only cases with very elevated antibody titers (TPOAb or TgAb in the highest decile of abnormal values [TPOAb ≥774.9 IU/mL; TgAb ≥43 IU/mL])

\textsuperscript{*}Diagnosis was based on HTDS evaluation, prior histological documentation, autoantibodies, or thyrotropin in medical record, or in medical records obtained subsequent to the HTDS clinical evaluation based on HTDS recommendations.

\textsuperscript{†}Includes cytological result with moderate to abundant colloid but few, inadequate, or no cellularity (colloid-only nodules). Additional analyses were performed with colloid-only nodules excluded from the benign nodules.

\textsuperscript{‡}This outcome was developed to compare HTDS results with the thyroid neoplasms outcome in the Utah study.\textsuperscript{14}

\textsuperscript{§}The outcome of “suspicious for malignancy” includes cytological suspicion for either malignancy or follicular neoplasm. Individuals with this outcome were recommended for consideration of surgery. However, 16 of these participants chose not to have surgery. None of these individuals had fine-needle aspiration results that were suspicious for cancer. Their fine-needle aspiration results showed either intermediate or high probability of follicular neoplasm; none was suspicious for papillary cancer. Although these most likely represented benign thyroid nodules, the risk of thyroid cancer in such cases has been reported to be approximately 10% to 30%.\textsuperscript{20-31}

\textsuperscript{||}Thyroglobulin antibodies were subsequently measured on frozen serum samples (unpublished data, Carol Spencer, MD, University of Southern California, April-May 1998) at the end of the clinical evaluation phase, and positive antibodies were defined as TgAb level greater than 1.0 IU/mL.
information regarding dietary factors, based on estimated typical diets during those years, for use when some or all of a participant’s dietary history is unknown.

For participants without CATI respondents, the clinical interview included a residence history and limited questions about sources of dairy products that were used in conjunction with CIDER default dietary data for dose estimation. CIDER characterizes dosimetric uncertainty by calculating 100 estimates of dose for each individual based on randomly generated values of the uncertain parameters that influence the release, environmental and food chain transport and uptake of $^{131}$I. Each participant’s 100 dose estimates were approximately log-normally distributed with geometric standard deviations ranging from 1.56 to 5.42 (mean, 2.18). The median of these 100 estimates is referred to as the participant’s estimated dose in this article. CIDER only estimates doses of in-area participants; i.e., those who resided within the HEDR study area for at least some time from December 1944 through 1957. Participants who never resided within the study area during this period were designated as out-of-area participants and excluded from the primary dose-response analyses.

Statistical Considerations

Because accurate dates were not available for many diagnoses made before this study, cumulative incidence of each disease outcome was estimated by the proportion of participants diagnosed as having the disease before or as a result of the HTDS examination. The primary analyses of the relationship between risk of disease and thyroid dose from Hanford’s $^{131}$I releases were based on sex-stratified linear dose-response models for the in-area participants with individual estimates of thyroid dose. Sex-stratified logistic and linear-quadratic models were also examined to explore possible nonlinearity of the dose response. The parameters of these models, i.e., the sex-specific background rates and the coefficient(s) in the radiation effect term(s), were estimated by the method of maximum likelihood. The likelihood ratio test was used to test the significance of the dose response. Since the alternative hypothesis of primary interest was that risk increased with dose, statistical significance was represented by 1-sided P values.

Ninety-five percent confidence intervals (CIs) (but not P values) were adjusted for the simultaneous estimation of sex-specific background rates and the dose coefficient(s) using the Bonferroni technique. Confidence intervals for the linear dose-response model were calculated under the constraint that cumulative incidence must be between 0% and 100% for all observed doses, which could be violated, for example, for outcomes with low background rates and modest or negative dose responses. In some instances, 95% CIs could not be estimated precisely because of this constraint, and upper (lower) bounds for lower (upper) confidence limits were reported or, if the estimate was too close to its constrained minimum, no confidence limit was reported. For comparison with results of other studies, the excess relative risk (ERR) for the sex-stratified linear model was calculated as the average of the 2 ratios of the estimated slope to the estimated sex-specific background rates.

Confounding and effect modification were examined by allowing the intercepts and/or dose coefficients of the logistic model to vary as functions of sex, age at first exposure to Hanford’s $^{131}$I releases (including prenatal exposure as early as gestational age of 90 days), age at HTDS examination, smoking history, medical and occupational radiation exposures, or exposure to radiiodine from the Nevada Test Site (NTS). For the latter analyses, each participant’s NTS dose was estimated as the total of doses from all 57 atmospheric weapons tests at the NTS between 1951 and 1957, using data released by the National Cancer Institute. The calculation accounted for the participant’s county of residence and age on the date of each test. Additional analyses examined whether the estimated dose response differed according to the source of dosimetry data (e.g., CATI of a person with knowledge of participant’s infancy and childhood vs in-person interview of participant).

Since the HTDS investigated not only thyroid neoplasia, autoimmune disease, and hypothyroidism but all thyroid diseases, the required number of participants was derived from statistical power calculations for 3 exemplary outcomes with a range of background rates that would encompass all of the outcomes under investigation: low (female, 0.7%; male, 0.3%), intermediate (female, 5%; male, 2%), and high (40% for both sexes). As described in detail elsewhere,19 power was projected using participation rates and estimated dose data observed in a pilot phase of the HTDS. These projections suggested a predicted enrollment of 3277 participants with dose mean and variance of 152 mGy and 38619 mGy$^2$, respectively. The statistical power actually achieved by the study is discussed further herein and elsewhere.22

RESULTS

A total of 5199 individuals (2559 women and 2640 men) were selected for the study cohort. More than 60% were born between 1943 and 1945. A total of 4877 (93.8%) were located; 4350 (83.7%) were living and 527 (10.1%) were deceased. Only 322 (6.2%) remained unlocated at the end of the study. The proportion of located cohort members did not vary substantially according to sex, year of birth, or geostatum. Although living cohort members resided in 49 states and several countries outside of the United States, more than half lived in Washington State and approximately 80% lived in the western part of the United States.

A total of 3564 individuals (84% of those contacted by phone) agreed to participate. Of those located alive, 634 (14.6%) refused to participate. Forty-eight refusals (8%) were due to illness or impairment, although only 1 person cited prior thyroid disease (can-
cer) as the reason for refusal. Willingness to participate did not differ appreciably by sex, year of birth, or geostratum.

A total of 3447 individuals attended an HTDS clinic (66% of the 5199 selected for study) and underwent an in-person interview and thyroid physical examination. All but 1 received an ultrasound examination. Of the 272 participants for whom an FNA biopsy was recommended, 259 (95.2%) underwent the procedure. Seven persons were not evaluable because of incomplete study data. The proportion of evaluable participants did not differ appreciably by sex, year of birth, or geostratum.

Past diagnoses of thyroid disease were reported by 694 participants (or their CATI respondents), resulting in requests for 1259 sets of medical records. Of these, 795 (63%) were obtained; at least 1 record was retrieved for 494 (71%) participants. Pathology or cytology slides were requested for 52 of the 649 and received for 42 (81%). Medical records documenting further diagnostic studies recommended as a result of the HTDS examination were requested for 35 individuals (72 separate requests; 71 were received). Thirty-three of these individuals also had requests for slides; all were received.

A CATI sufficiently complete for dose estimation was available for 2123 (62%) of the 3440 evaluable participants. This percentage did not vary appreciably by sex or geostratum but was somewhat smaller among those born in the earliest years. The most common reason for failure to conduct a CATI was inability to identify a knowledgeable respondent.

The median age at HTDS examination was 51 years (range, 45-57 years) among the 3440 evaluable participants (1747 women and 1693 men). Doses estimated for the 3191 in-area participants ranged from 0.0029 to 2823 mGy (median, 97 mGy; mean, 174 mGy; SD, 224 mGy). Twenty-four and 7 had doses higher than 1000 and 2000 mGy, respectively. Estimated doses did not differ appreciably between women and men but tended to be lower among those born in 1946 or to mothers with usual residence in Okanogan, Ferry, or Stevens counties.

### Neoplasia

Twelve women (0.7%) and 7 men (0.4%) had diagnoses of thyroid cancer based on HTDS (12 cases) or prior histological evidence (7 cases). One additional participant had a prior diagnosis of thyroid cancer for which no histological confirmation was available in the medical records obtained. Five of the 19 histologically confirmed cases and the 1 without histological confirmation were among the 249 out-of-area participants. Benign thyroid nodule was diagnosed from HTDS or prior histological or cytological evidence in 170 women (9.7%) and 79 men (4.7%), including 14 out-of-area participants. TABLE 2 lists the histological classification of the 19 cases of thyroid cancer and the cytological or histological classification of the 249 cases of benign nodule.

Cumulative incidence of thyroid cancer, benign nodule, total neoplasia, and any nodule is shown by sex and thyroid dose category in Figure 2. TABLE 2 summarizes the radiation dose-response analyses. Among the 3191 in-area participants, the cumulative incidence of thyroid cancer did not increase significantly with increasing dose (P = .25), with an estimated slope of 0.2%/Gy, and a 95% CI ranging from less than −0.1%/Gy to 1.7%/Gy. (A slope of 0.2%/Gy indicates an additive increase of 0.2 percentage points for each increase of 1 Gy [eg, from 0.3% at 0 Gy to 0.5% at 1 Gy], not a multiplicative change.) Based on the estimated background rates for the sex-stratified linear model, this slope corresponds to ERRs at 1 Gy of 0.3 and 1.0 for women and men, respectively, or about 0.7 overall.

There was no evidence that the cumulative incidence of benign thyroid nodule increased with increasing dose (P = .68), with an estimated slope of −0.8%/Gy (95% CI, −2.2%/Gy to 4.1%/Gy). In the primary analysis, thyroid nodules with abundant colloid but insufficient follicular cells (colloid-only nodules) were classified as benign thyroid nodules, even though such a cytological result is technically nondiagnostic. This decision was made in part because of the biopsy technique in the HTDS (up to 8 aspirations per nodule), resulting in intensive sampling of each nodule. Consequently, it was thought that a sample with abundant colloid but few follicular cells was likely representative of the cytology within the nodule rather than an inadequate sample. Eighteen participants (12 women and 6 men) had diagnoses of benign nodule...
EXPOSURE TO 131I AND THYROID DISEASE

based solely on colloid-only nodules. There was no marked change in the dose-response results when colloid-only nodules were excluded.20

The outcome of “total neoplasia” included 19 cases of thyroid cancer and 14 cases of benign adenoma. Based on the in-area participants (28 cases), the cumulative incidence of total neoplasia did not increase significantly with estimated dose (P = .42), with an estimated slope of 0.1%/Gy (95% CI, −0.3%/Gy to 2.2%/Gy) and corresponding ERR of about 0.1/Gy.

“Any nodule” was defined as the presence of 1 or more of the following diagnoses by HTDS or prior confirmation: thyroid cancer, benign thyroid nodule, or nodule “suspicious for malignancy.” The last group consisted almost entirely of cases classified as sus-

Figure 2. Cumulative Incidence of Thyroid Neoplasia Outcomes by Sex and Estimated Dose Category

Table 3. Cumulative Incidence and Dose-Response Results for Thyroid Neoplasia

<table>
<thead>
<tr>
<th>Thyroid Radiation Dose, mGy</th>
<th>Women</th>
<th>Benign Thyroid Nodule</th>
<th>Total Neoplasia</th>
<th>Any Thyroid Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Participants</td>
<td>Cases</td>
<td>No.</td>
<td>%</td>
<td>Cases</td>
</tr>
<tr>
<td>0-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-49</td>
<td>2</td>
<td>1</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>50-99</td>
<td>3</td>
<td>3</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>100-199</td>
<td>1</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>200-399</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>400-3000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall Cumulative Incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>12/1747</td>
<td>0.7</td>
<td>7/1693</td>
<td>0.4</td>
</tr>
<tr>
<td>Benign nodule‡</td>
<td>170/1747</td>
<td>9.7</td>
<td>79/1693</td>
<td>4.7</td>
</tr>
<tr>
<td>Total neoplasia</td>
<td>20/1747</td>
<td>1.1</td>
<td>13/1693</td>
<td>0.8</td>
</tr>
<tr>
<td>Any nodule§</td>
<td>193/1747</td>
<td>11.0</td>
<td>88/1693</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*The 95% confidence intervals (CIs) were adjusted by the Bonferroni technique for simultaneous estimation of slope and sex-specific background rates.
†One-tailed P value by test for positive dose response.
‡For 19 cases (7.6%), the diagnosis was based only on a cytological result of moderate to abundant colloid but few, inadequate, or no cellularity (ie, colloid-only nodules; see Box 1). Exclusion of these 18 cases did not affect the dose-response results.
§Exclusion of 13 participants whose palpable nodules were not confirmed by ultrasound did not affect this finding.

OOA indicates out of area.

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picious for follicular neoplasm. A total of 281 (8.2%) participants were included in this outcome (193 women [11%] and 88 men [5.2%]). Among the in-area participants (261 cases), there was no evidence that cumulative incidence of any nodule increased with increasing dose ($P = .65$), with an estimated slope of $-0.7\%/\text{Gy}$ (95% CI, $-2.3\%/\text{Gy}$ to $4.3\%/\text{Gy}$).

Additional analyses were conducted (Box 2) to assess the impact of (1) using alternative definitions of disease outcome; (2) using alternative dose-response models or characterizations of exposure to Hanford’s $^{131}\text{I}$ releases; (3) including or excluding participants who might have exceptionally strong influence on the estimated dose-response; and (4) accounting for potential modifying or confounding factors. Conclusions from the primary analyses were not altered by these additional analyses. In particular, analyses that did not rely on estimated doses found no evidence that exposure to Hanford’s $^{131}\text{I}$ releases increased risk of thyroid neoplasia. For example, rates of thyroid neoplasia were not significantly higher among participants born to mothers residing in the 4 counties near Hanford, compared with the less contaminated Okanogan, Ferry, and Stevens counties. Analyses of confounding and effect modification were not performed for thyroid cancer or total neoplasia, since there were only 14 and 28 cases of each, respectively, among the 3191 in-area participants. However, there was no statistically significant evidence of confounding or effect modification for either benign nodule.

**Box 2. Additional Analyses**

**Alternative Definitions of Thyroid Neoplasia Outcomes**

**Benign Nodule**
- Add 38 cases with Hanford Thyroid Disease Study (HTDS) or prior clinical diagnosis only (287 total)$^*$
- Add 10 cases based solely on participant report (297 total)$^{†}$
- Exclude 74 cases associated with autoimmune thyroiditis, Graves disease, or hypothyroidism due to toxic nodular goiter or solitary toxic nodule (175 total)

**Any Nodule**
- Add 39 cases with HTDS or prior clinical diagnosis only (320 total)$^*$
- Add 10 cases based solely on participant report (330 total)$^{†}$

**Additional Analyses for All Outcomes**

**Alternative Dose-Response Functions and Characterizations of Exposure**
- Logistic rather than linear dose response
- Linear-quadratic rather than linear dose response
- Estimate dose using default (ie, estimated average) dietary data for all participants, not just those without individual dietary data from computer-assisted telephone interview (CATI)
- Comparisons of disease rates by geostratum (heterogeneity among all 9 geostrata and among Okanogan/Ferry/Stevens geostrata vs all others; see Table 1)

**Participants Who Might Have Exceptional Influence on Dose Response**
- Include 249 out-of-area participants (total 3440 participants)$‡$
- Exclude 349 participants with doses of greater than 400 mGy (2842 total participants)
- Exclude 24 participants with doses of greater than 1000 mGy (3167 total participants)

**Confounding and Dose Effect Modification**
- Adjust for the effects of each of 7 potential confounding factors§
- Analyses for dose effect modification by each of 7 factors§

$^*$Clinical diagnosis was based on HTDS or prior physical examination for which cytological or histological data were not available.
$^{†}$Participant reports were cases with no nodule or neoplasia on HTDS evaluation but with in-person or CATI report of a diagnosis that could not be confirmed by prior medical records.
$‡$Out-of-area participants who lived in Washington, Oregon, Idaho, Montana, British Columbia, or Alberta at any time from December 1944 through 1957 were assigned a maximum dose (range, 8-51 mGy) that could have been received had they lived at a location on the boundary of the Hanford Environmental Dose Reconstruction domain corresponding to 1 of 4 subregions closest to their residence. Those who never lived within this 4-state/2-province region in this time period were assigned a dose of 0 mGy. One analysis assigned out-of-area participants with the outcome their associated dose, while those without the outcome were assigned a dose of 0. In a second analysis, the reverse was done.
§The 7 factors are sex, age at first exposure to Hanford’s $^{131}\text{I}$ releases (including prenatal exposure as early as gestational age of 90 days), age at HTDS examination, smoking history, medical and occupational radiation exposures, estimated thyroid dose from Nevada Test Site fallout, and source of dosimetry data (ie, CATI of mother or other respondent with knowledge of participant’s infancy and childhood vs in-person interview of participant).
or any nodule. In particular, there was no significant difference between the dose responses of women and men (P = .45 for benign nodule and P = .62 for any nodule) or between those with doses estimated from CATI vs in-person interview (P = .73 and P = .91, respectively).

**Autoimmune Thyroiditis**
Cumulative incidence of autoimmune thyroiditis is shown by sex and thyroid dose category in Figure 3. Table 4 shows the cumulative incidence and dose-response results for various definitions of autoimmune thyroiditis. For the primary definition of autoimmune thyroiditis (ie, positive TPOAb or antimicrosomal antibodies by HTDS examination [623 cases] or with antibody results documented in medical records [2 cases]), the overall cumulative incidence was 18.2% (23.1% in women and 13.1% in men). Among the 3191 in-area participants, the cumulative incidence decreased slightly with increasing dose, with an estimated slope of −2.6%/Gy (95% CI, −5.7%/Gy to 4.4%/Gy; P = .82).

Two alternative definitions of autoimmune thyroiditis were considered: (1) positive result for thyroglobulin antibodies (TgAb) alone and (2) positive TPOAb/antimicrosomal antibodies and/or positive TgAb results. The cumulative incidence of autoimmune thyroiditis was 14.7% if based on TgAb result alone and 22.6% if based on positive TPOAb/antimicrosomal antibodies and/or positive TgAb results. With use of either of these alternative definitions, the cumulative incidence of autoimmune thyroiditis did not increase significantly with increasing dose (Table 4).

For comparison with the results of Pacini et al., we also examined autoimmune thyroiditis based on criteria of TPOAb and TgAb measurements of greater than 10 IU/mL each. Again, there was no evidence that the risk of autoimmune thyroiditis, as defined by these diagnostic criteria, increased with increasing dose (Table 4).

**Hypothyroidism**
Cumulative incidence of hypothyroidism is shown by sex and thyroid dose category in Figure 3. As shown in Table 4, the cumulative incidence of hypothyroidism was 7.8% (11.7% in women and 3.7% in men). The estimated dose response was slightly negative (−0.6%/Gy; 95% CI, <−1.6%/Gy to

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**Figure 3.** Cumulative Incidence of Autoimmune Disorders by Sex and Estimated Dose Category

![Graphs showing cumulative incidence of Hashimoto Thyroiditis, Hypothyroidism, and Autoimmune Thyroiditis by sex and thyroid radiation dose category.](https://www.jama.com)

OOA indicates out of area.

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**Autoimmune Thyroiditis With Hypothyroidism**

Because counting participants with low antibody titers among cases of autoimmune thyroiditis might mask a radiation effect, we performed analyses including as cases only those with autoimmune thyroiditis associated with hypothyroidism (Table 4 and Figure 3). Furthermore, since antibody results in the study by Nagataki et al17 of Nagasaki atomic-bomb survivors were classified as positive only after a 1:100 dilution, we created a comparable outcome for “autoimmune hypothyroidism” with antibody level in the highest decile of the positive results for the cohort and associated with hypothyroidism. The cumulative incidence of autoimmune thyroiditis with any hypothyroidism was 5.1% (7.7% for women and 2.4% for men), with permanent hypothyroidism was 4.7% (7.0% for women and 2.3% for men), for highest decile of TPOAb measurement with hypothyroidism was 1.3% (2.0% for women and 0.6% for men), and for highest decile of TgAb measurement with hypothyroidism was 0.8% (1.2% for women and 0.4% for men). There was no evidence that the cumulative incidence of any of these outcomes increased with increasing dose (Table 4).

To more closely simulate the analysis of Nagataki et al, analyses of highest-decile TPOAb and TgAb measurements with hypothyroidism were repeated af-

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**Table 4. Cumulative Incidence and Dose-Response Results for Autoimmune Thyroiditis, Hypothyroidism, and Autoimmune Thyroiditis With Hypothyroidism**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
<th>No. With</th>
<th>Estimated Slope (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Cumulative Incidence</td>
<td>Cases/Total</td>
<td>%</td>
<td>Cases/Total</td>
<td>%</td>
<td>Cases/Total</td>
<td>%</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>403/1747</td>
<td>23.1</td>
<td>222/1693</td>
<td>13.1</td>
<td>625/3440</td>
<td>18.2</td>
</tr>
<tr>
<td>Positive TgAb result§</td>
<td>327/1747</td>
<td>18.7</td>
<td>180/1693</td>
<td>10.6</td>
<td>507/3440</td>
<td>14.7</td>
</tr>
<tr>
<td>Positive result for TPOAb§, antimicrosomal antibodies‡, and/or TgAb§</td>
<td>500/1747</td>
<td>28.6</td>
<td>279/1693</td>
<td>16.5</td>
<td>779/3440</td>
<td>22.6</td>
</tr>
<tr>
<td>Alternative definitions of outcome</td>
<td>TgAb &gt; 10 IU/mL§</td>
<td>187/900</td>
<td>20.8</td>
<td>83/817</td>
<td>10.2</td>
<td>270/1717</td>
</tr>
<tr>
<td>TPOAb &gt; 10 IU/mL§</td>
<td>88/1732</td>
<td>5.1</td>
<td>39/1687</td>
<td>2.3</td>
<td>127/3419</td>
<td>3.7</td>
</tr>
<tr>
<td>TPOAb‡ or TgAb‡</td>
<td>239/939</td>
<td>25.5</td>
<td>103/829</td>
<td>12.4</td>
<td>342/1768</td>
<td>19.3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hypothyroidism based on HTDS evaluation or medical record with documentation</td>
<td>204/1747</td>
<td>11.7</td>
<td>63/1693</td>
<td>3.7</td>
<td>267/3440</td>
</tr>
<tr>
<td>Permanent hypothyroidism</td>
<td>196/1747</td>
<td>11.2</td>
<td>61/1693</td>
<td>3.6</td>
<td>257/3440</td>
<td>7.5</td>
</tr>
<tr>
<td>Autoimmune thyroiditis with hypothyroidism</td>
<td>135/1747</td>
<td>7.7</td>
<td>40/1693</td>
<td>2.4</td>
<td>175/3440</td>
<td>5.1</td>
</tr>
<tr>
<td>Autoimmune thyroiditis with permanent hypothyroidism</td>
<td>122/1747</td>
<td>7.0</td>
<td>39/1693</td>
<td>2.3</td>
<td>161/3440</td>
<td>4.7</td>
</tr>
<tr>
<td>Alternative definitions of outcome</td>
<td>Highest decile of TPOAb with hypothyroidism</td>
<td>18/900</td>
<td>2.0</td>
<td>5/817</td>
<td>0.6</td>
<td>23/1717</td>
</tr>
<tr>
<td>Highest decile of TgAb with hypothyroidism</td>
<td>20/1732</td>
<td>1.2</td>
<td>7/1687</td>
<td>0.4</td>
<td>27/3419</td>
<td>0.8</td>
</tr>
<tr>
<td>Highest decile of TPOAb with hypothyroidism, excluding those exposed in utero</td>
<td>11/577</td>
<td>1.9</td>
<td>3/572</td>
<td>0.5</td>
<td>14/1149</td>
<td>1.2</td>
</tr>
<tr>
<td>Highest decile of TgAb with hypothyroidism, excluding those exposed in utero</td>
<td>10/1067</td>
<td>0.9</td>
<td>4/1079</td>
<td>0.4</td>
<td>14/2146</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HTDS, Hanford Thyroid Disease Study; NE, confidence limit was not estimated due to its close proximity to the point estimate; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

*The 95% CIs were adjusted by the Bonferroni technique for simultaneous estimation of slope and sex-specific background rates.
†One-tailed P value by test for positive dose response.
‡By HTDS examination or medical record confirmation.
§By HTDS examination only.
||Alternative definitions of outcome were created for comparisons with other published data.
ter excluding participants whose estimated in utero doses from Hanford’s 131I releases were greater than 0. No change in the dose-response results was observed (Table 4).

The additional analyses described in Box 2 did not modify the aforementioned findings regarding autoimmune thyroiditis or hypothyroidism.19

COMMENT

No statistically significant association was found between estimated thyroid radiation dose from Hanford and cumulative incidence of thyroid cancer, benign thyroid nodule, total neoplasia, any nodule, autoimmune thyroiditis, hypothyroidism, or autoimmune thyroiditis with hypothyroidism. In evaluating these results, it is important to keep the following in mind. First, thyroid doses were almost exclusively from 131I. Such exposure circumstances may result in lower risk because of the relatively long half-life of 131I and corresponding low dose rate and the heterogeneous distribution of dose within the thyroid gland. Second, most exposures occurred over months to many years, resulting in protracted, low dose rates. Third, estimated thyroid doses were relatively low (median, 97 mGy; mean, 174 mGy) compared with other environmental and medical exposures that have been studied. Finally, most participants were very young and, presumably, at greater risk of radiogenic thyroid disease at the times of their highest exposures; follow-up occurred after about 50 years, almost certainly an adequate duration for development of radiogenic outcomes.

Comparison With Findings in Other Populations Exposed to Radiation

Thyroid Neoplasia. Several cohorts exposed in childhood to external gamma radiation and x-rays have demonstrated a dose-response relationship with risk of benign thyroid adenoma and thyroid cancer.35-46 Similarly, studies of Japanese atomic-bomb survivors, who were exposed primarily to whole-body external gamma irradiation, show a significant radiation dose-response relationship for thyroid cancer.50-47 Analysis of the primary data from 7 published studies of persons exposed to external radiation demonstrated a linear dose response for thyroid cancer in individuals exposed before age 15 years.46 These studies have generally reported radiation effects with ERRs of about 5/Gy to 10/Gy for thyroid cancer, much larger than the ERR of 0.7/Gy observed in this study.

More relevant to the Hanford circumstances are studies of exposure to radioactive iodine. Early studies of persons receiving therapeutic 131I for hyperthyroidism found no convincing evidence that thyroid cancer was increased,14 but most of the participants were adults with existing thyroid disease at the time of treatment, had short follow-up, and were treated with very high radiation doses (generally 20000-100000 mGy). Results7 from a follow-up of 1 of these studies1 suggest an increased risk of death from thyroid cancer, and similar results were reported from a study of 7400 patients treated with radiiodine from 1950 to 1991 in England.8 However, the numbers of excess deaths were small, and the authors suspected that underlying thyroid disease at the time of 131I treatment might have contributed to these results. Studies of persons exposed through diagnostic procedures (doses of generally 500-1000 mGy) have reported small increases in thyroid cancer risk,6,9,10 but there is a lack of consistency in the findings and the small increases are likely due to the underlying thyroid condition. Recently, an increased risk of thyroid cancer was reported in Swedish patients receiving diagnostic 131I, but the increase was confined to those with prior exposure to x-rays and the study included few individuals younger than 20 years at exposure. The authors concluded that the increased risk was not due to 131I exposure.50

Little information is available regarding the effects of environmental exposure to radioactive iodine. Although initial studies found that thyroid disease incidence was not increased in Utah schoolchildren exposed to fallout from atmospheric nuclear testing at the NTS,51-52 a follow-up study of this cohort reported an excess risk of thyroid neoplasms that was associated with radiiodine exposure, with an ERR of about 7/Gy.54 Although positive dose-response trends were noted for total nodules (ERR, 1.2/Gy) and thyroid cancer (ERR, 7.9/Gy) when analyzed separately, they were not statistically significant. The study was limited by small numbers of exposed individuals and a low incidence of thyroid neoplasms and by the fact that the examiners were not blinded to exposure.

The explanation for the differing results between the Utah study (ERR, 7/Gy and 7.9/Gy for total neoplasia and cancer) and the HTDS (ERR, 0.1 and 0.7, respectively) is not clear. The outcome of total neoplasia was defined identically in the 2 studies. One possibility is the different exposure circumstances. The Hanford thyroid dose was almost entirely from 131I, whereas in Utah there was greater contribution from other radioiodines and external radiation.14,53 Exposures in Utah were also more concentrated and episodic than at Hanford, resulting in doses likely being delivered at substantially higher dose rates, although total dose among 3545 Utah study participants (mean, 98 mGy) was similar to HTDS doses.

An increase in benign and malignant thyroid nodules has been shown in residents of the Marshall Islands exposed to nuclear fallout from atmospheric weapons testing.12,13 In contrast with Hanford, thyroid doses were primarily due to short-lived radioiodines (131I, 132I, and 133I) and external gamma radiation and due to a much lesser extent to 131I.35,35 Marked increases in childhood thyroid cancer have been reported in children who were exposed to radiation from the Chernobyl accident.16 These reports are from ecologic studies that do not relate individual exposure or dose to disease outcome. Only 2 recent studies report a significant dose-response relationship between Chernobyl radiation and thyroid cancer, one based on individual thyroid dose estimates56 and the other based on individual doses to chil-

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Children inferred from village cesium 137 (\(^{137}\text{Cs}\)) measurements.57 However, in contrast with protracted, low-dose \(^{131}\text{I}\) exposures at Hanford, the characteristics of the Chernobyl exposure were more similar to the Utah situation.

**Autoimmune Thyroiditis.** There is little information regarding the association between radiation exposure and autoimmune thyroid disease in humans.58 Nagataki et al17 reported an association between radiation dose from the Nagasaki atomic bomb and autoimmune hypothyroidism, which was defined by both elevated thyroid-stimulating and positive antiaminosmal antibodies or TgAb after a 100-fold dilution. Using a similar definition for autoimmune hypothyroidism, the HTDS did not find a dose-response relationship. The mean and maximum estimated thyroid doses in 1978 atomic-bomb survivors were about 490 and 5850 mSv, respectively, compared with 174 and 2823 mGy for the HTDS cohort. The explanation for the difference in results is uncertain; however, the exposure conditions were quite different than those at Hanford, as the irradiation at Nagasaki was an acute external exposure of primarily gamma rays.

Other studies of external gamma radiation and x-ray exposure have not uniformly shown an increase in autoimmune thyroiditis.59-61 No evidence of a dose-response effect on thyroid autoantibodies or incidence of autoimmune thyroid disease has been found in atomic-bomb survivors,56 and Akiyama advised caution in predicting that an elevation in thyroid autoantibodies leads to thyroid dysfunction. Similarly, Yoshimoto et al60 found no autopsy evidence of thyroiditis in atomic bomb survivors from Hiroshima, and Kaplan et al61 found no significant increase in thyroiditis in tuberculosis patients receiving fluoroscopic x-ray exposure.

Medical uses of external-beam radiation have also been implicated in the induction of autoimmune thyroid disease. Neck irradiation for treating Hodgkin disease increased the risk of subsequent Graves disease by 7- to 20-fold,54 and external-beam irradiation for benign diseases of the head and neck has been shown to increase the prevalence of elevated microsomal and thyroglobulin hemagglutination tests.59 Radiation doses in these studies were quite high, however, with maximum doses to the cervical neck nodes of 4400 mGy and an average of 4510 mGy in the 2 studies, respectively.

Hypothyroidism is a well-documented consequence of high-dose radionuclide therapy for hyperthyroidism and has been reported in Marshall Islanders receiving the highest doses from radioactive fallout.65 The absence of a dose response for hyperthyroidism in the HTDS is not surprising, since radioiodine doses used to treat hyperthyroidism are 20- to 200-fold higher than those received at Hanford.

Several ecologic studies have reported an increase in thyroid autoantibodies in children exposed to Chernobyl fallout. Pacini et al64 reported an age- and sex-adjusted odds ratio of 6.89 (95% CI, 3.17-14.99) for thyroid antibody positivity (TPOAb or TgAb >10 IU/mL) in children in the Gomel region of Belarus exposed at younger than 12 years of age compared with children from the less contaminated Vitebsk region. No thyroid dysfunction or thyrotrpin difference was found between the exposed and unexposed groups, although the authors note a short follow-up period. Similar results were reported by Vermiglio et al65 for severely iodine-deficient children living in a contaminated area of Russia. The authors suggested that a combination of late radiation effects and iodine insufficiency might determine the development of autoimmune phenomena.65 Furthermore, no association was found between body or soil \(^{137}\text{Cs}\) concentrations and thyroid autoantibodies in the 114870 children examined by the Chernobyl Saskawa Health and Medical Cooperation Project.

If a relationship truly exists between radiation exposure and autoimmune thyroiditis with or without hypothyroidism, it is of interest to speculate about its clinical significance. Several studies have shown that the presence of circulating thyroid autoantibodies significantly increases the risk of thyrotropin elevation in subsequent years.57-60 A key question is whether antithyroid antibody positivity indicates an increased risk of thyroid dysfunction such as occurs in chronic autoimmune thyroiditis. Tomer70 has questioned whether certain thyroid autoantibodies are disease-defining, pathologic antibodies or alternatively, nonpathologic antibodies generated in response to tissue damage. This is an important public health issue since in the former case the risk of thyroid dysfunction would predictably increase over time, whereas an inflammatory reaction to prior radiation injury might not progress to overt hypothyroidism. Although the HTDS cannot answer this question, the current study not only found no evidence of a dose-related increase in thyroid dysfunction from Hanford \(^{131}\text{I}\) releases but also showed no dose effect for thyroid antibody positivity alone or in combination with hypothyroidism.

**Consideration of Features of Study Design**

In interpreting the absence of radiation effects reported here, several features of the study design have been considered and are described more fully elsewhere.19 In summary, there is no indication that participation, attending a clinic, or data collection differed appreciably according to a person's sex, geostatrum, date of birth, or current residence in ways that might bias the estimated dose-response relationships. First, in an effort to minimize the possibility that the interview data used to estimate thyroid doses might be influenced by knowledge of thyroid disease status, the questionnaires (both CATI and in-person) were administered before the clinical examination. Second, death certificates for 504 of the 543 deceased members of the cohort were obtained. Cause of death and underlying conditions were abstracted and coded according to the *International Classification of Diseases, Ninth Revision*.71 There is no indication of a substantial loss due to mortality in ways...
that are likely related to both exposure and the development of the thyroid disease outcomes reported here. Third, given the comprehensive clinical evaluation and the long follow-up period since exposure, it is unlikely that many cases of the outcomes under study were undetected. In addition, several measures were taken to ensure that physicians, sonographers, and the cytopathologist were not aware of a participant’s possible level of exposure. Fourth, alternative means of classifying exposure did not change the results, providing some reassurance that the absence of a dose response was not due to misclassification of exposure introduced by difficulties in recall from the distant past or by relying solely on estimates using the CIDER dosimetry system. Nevertheless, there was considerable uncertainty associated with the individual dose estimates. Consequences of this uncertainty are considered in more detail elsewhere.18,32

Finally, the study had sufficient statistical power to detect dose-response effects of magnitudes that have been reported from other studies. Power was estimated for analyses of sex-stratified linear models based on the 3191 participants with estimated thyroid dose for exemplary outcomes assumed to have low (female, 0.7%; male, 0.3%), intermediate (female, 5%; male, 2%), or high (both 40%) background rates. With the number of participants and estimated dose distribution actually observed, the study had sufficient statistical power (>85%) to detect radiation effects with slopes of 2.5%/Gy, 5%/Gy, and 13%/Gy for outcomes with low, intermediate, or high background rates, respectively. With the exemplary background rates mentioned herein, these slopes correspond to relative risks (average of women and men) of 2.0, 1.3, and 1.06 at the mean estimated dose of 174 mGy. The study’s power is discussed in detail elsewhere.19,32

CONCLUSIONS
The HTDS found no evidence that exposure to 131I from Hanford atmospheric emissions between 1944 and 1957 was associated with an increased cumulative incidence of thyroid cancer, benign thyroid nodules, hypothyroidism, or autoimmune thyroiditis. These results remained the same when alternative methods of characterizing exposure were used, and after taking into account factors that might confound or modify the relationships between radiation dose and disease outcomes. There is no evidence of bias in selection of the cohort, loss to follow-up, or enrollment or participation. The study had sufficient statistical power to detect dose-response effects of magnitudes that have been reported elsewhere. Given the important differences in radiation exposure circumstances between those at Hanford and other populations studied in relation to radiation-induced thyroid disease, particularly the relatively low doses and protracted nature of the exposure, the findings of the current study are consistent with other published findings.

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REFERENCES
EXPOSURE TO 131I AND THYROID DISEASE


