Radiation Dose-Response Relationships for Thyroid Nodules and Autoimmune Thyroid Diseases in Hiroshima and Nagasaki Atomic Bomb Survivors 55-58 Years After Radiation Exposure

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Context Effects of irradiation on thyroid diseases such as thyroid nodules and autoimmune thyroid diseases have not been evaluated among people exposed to radiation more than 50 years in the past.

Objective To evaluate the prevalence of thyroid diseases and their radiation-dose responses in atomic bomb survivors.

Design, Setting, and Participants Survey study comprising 4091 cohort members (mean age, 70 [SD, 9] years; 1352 men and 2739 women) who participated in the thyroid study at the Radiation Effects Research Foundation. Thyroid examinations were conducted between March 2000 and February 2003.

Main Outcome Measures Prevalence of thyroid diseases, including thyroid nodules (malignant and benign) and autoimmune thyroid diseases, and the dose-response relationship of atomic bomb radiation in each thyroid disease.

Results Thyroid diseases were identified in 1833 (44.8%) of the total participants (436 men [32.2% of men] and 1397 women [51.0% of women]) (*P*<.001). In 3185 participants, excluding persons exposed in utero, not in the city at the time of the atomic bombings, or with unknown radiation dose, the prevalence of all solid nodules, malignant tumors, benign nodules, and cysts was 14.6%, 2.2%, 4.9%, and 7.7%, respectively. The prevalence of positive thyroid antibodies, antithyroid antibody–positive hypothyroidism, and Graves disease was 28.2%, 3.2%, and 1.2%, respectively. A significant linear dose-response relationship was observed for the prevalence of all solid nodules, malignant tumors, benign nodules, and cysts (*P*<.001). We estimate that about 28% of all solid nodules, 37% of malignant tumors, 31% of benign nodules, and 25% of cysts are associated with radiation exposure at a mean and median thyroid radiation dose of 0.449 Sv and 0.087 Sv, respectively. No significant dose-response relationship was observed for positive antithyroid antibodies (*P*=.20), antithyroid antibody–positive hypothyroidism (*P*=.92), or Graves disease (*P*=.10).

Conclusions A significant linear radiation dose response for thyroid nodules, including malignant tumors and benign nodules, exists in atomic bomb survivors. However, there is no significant dose response for autoimmune thyroid diseases.

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For editorial comment see p 1060.
thyroid diseases. The Radiation Effects Research Foundation (RERF) biennial health examinations presented clinical information complementary to death and tumor registries data. A detailed description of this program has been published elsewhere. The AHS includes individuals exposed at various doses of radiation: about half were within 2 km of the hypocenter (proximal exposure), a quarter were at distances of more than 3 km (distal exposure), and a quarter were not in the city at the time of the bombings. Individuals exposed in utero were added to the AHS cohort in 1977.

A total of 4552 AHS cohort members visited RERF for biennial health examinations between March 2000 and February 2003, with no knowledge about the thyroid disease study. We asked them to participate in the study at the time of the examinations, and 4091 participants (89.9%; mean age, 70 [SD, 9] years; 1352 men and 2739 women) agreed and completed the thyroid examination. Of that total, 1485 (or 1086, excluding persons exposed in utero, not in the city at the time of the bombings, or with unknown radiation dose) participated in the previous Nagasaki study and this study. Figure 1 shows the breakdown of AHS cohort members into participants and nonparticipants. Table 1 presents the number of cohort members with previously diagnosed thyroid abnormalities in RERF biennial routine health examinations and the distribution of thyroid radiation doses in participants and nonparticipants. Table 2 shows the characteristics of the study participants in Hiroshima and Nagasaki. Table 3 indicates the number of participants classified by thyroid radiation dose and age at exposure. The DS02 was used in estimating the thyroid radiation doses of individual AHS members. This study was reviewed and approved by a RERF institutional ethical committee, the Human Investigation Committee, and written informed consent was obtained from all participants.
Participants visited the RERF Hiroshima and Nagasaki laboratories for clinical examination. A trained nurse used a questionnaire to record information on current and past thyroid disease and thyroid medication. Blood samples were drawn to measure levels of free thyroxine (T₄), thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). All samples were measured at the Nagasaki laboratory; serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory. Levels of free T₄ and TSH were determined with a Lumipulse 1200 analyzer (Fujirebio Inc, Tokyo, Japan) using the immunometric technique based on chemiluminescence. Lyphochek Immunoassay TMJ Control (Bio-Rad Laboratories, Hercules, Calif) was used for quality control at every measurement. Levels of TPOAb and TgAb were measured by enzyme-linked immunosorbent assay (Medical & Biological Laboratories Co Ltd, Nagoya, Japan). When abnormalities of thyroid function were detected (see “Diagnostic Criteria” section), participants were referred to the Hiroshima University Hospital or the Nagasaki University Hospital or the Nagasaki University Hospital, and information on their further examination was obtained.

All participants underwent thyroid ultrasonography (Logiq 500; Yokogawa GE Medical Systems Ltd, Tokyo, Japan [Hiroshima] and Aloka SSD 2000; Aloka Co Ltd, Tokyo, Japan [Nagasaki]) by certified ultrasonographers to detect solid nodules and cysts. All the recorded films were reviewed for diagnosis by radiologists. The ultrasonographers were trained at the outset to ensure uniformity of ultrasound procedures. The films of 140 randomly selected study participants were reviewed by radiologists other than those making the initial diagnoses to ensure diagnostic standardization between Hiroshima and Nagasaki during the examination period; interreviewer agreement was 98.5%.

Participants with solid nodules 1 cm or larger in diameter were referred to the Hiroshima University Hospital or the Nagasaki University Hospital, and ultrasound-guided fine-needle aspiration biopsy was performed after obtaining participant agreement.

Two physicians specializing in thyroid diseases (M.I., T.U.) made final diagnoses of thyroid diseases while unaware of thyroid radiation doses. Because various thyroid diseases such as noncancer thyroid diseases including small nodules, autoimmune thyroiditis, mild thyroid dysfunction, and small thyroid cancers are sometimes asymptomatic, it is difficult to know when newly detected thyroid diseases developed in this screening. We were interested in assessing radiation effects on the thyroid using a cross-sectional study, and therefore patients with new thyroid diagnoses based on this screening and those with prior confirmed diagnoses who had undergone treatment or surgery were treated as prevalent cases. This method is consistent with the methods used in previous studies investigating the association between radiation exposure and thyroid diseases.12,14

Diagnostic Criteria

Thyroid Nodules. Only participants with nodules 1 cm or larger in diameter were classified as having thyroid nodules and evaluated cytologically or histologically. This is because persons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hiroshima</th>
<th>Nagasaki</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at examination, mean (SD) [range], y</td>
<td>71.9 [54-97]</td>
<td>70.8 [54-95]</td>
<td>70.9 [54-97]</td>
</tr>
<tr>
<td>Excluding others*</td>
<td>72.8 [55-97]</td>
<td>70.7 [55-95]</td>
<td>71.8 [55-97]</td>
</tr>
</tbody>
</table>

*Others indicates those exposed in utero, not in the city at the time of the atomic bombings, or with unknown radiation dose according to the Dosimetry System 2002.
with smaller nodules have an excellent prognosis and are generally and practically not considered candidates for biopsy or surgical excision. Those with a prior history of thyroid nodule surgery and histological confirmation were also classified as having thyroid nodules. Solitary and multiple nodules were both classified as thyroid nodules. Thyroid nodules were further classified into solid nodules and cysts. A cystic nodule with a solid component was classified as a solid nodule.

Solid nodules were further evaluated by cytological or histological examination. Cytological examinations were conducted by cytologists, with the nodules classified into the following categories: benign lesion, indeterminate, suspicious for malignancy, and malignant. Cases classified as being suspicious for malignancy (n = 2) were histologically diagnosed as malignancy after surgery. If thyroid surgery was performed, pathological reports stored in RERF medical records were reviewed by thyroid experts. If no pathological report existed in the RERF medical records, reports provided by the Hiroshima and Nagasaki tumor registries and tissue registries were reviewed. Solid nodules were then further classified as malignant tumors, benign nodules, and other. The latter classification consisted of solid-nodule cases whose cytological results were indeterminate or inadequate and cases without cytological or histological examination.

Cancers were reclassified based on the World Health Organization histological classification reported in 1988. Mixed papillary-follicular carcinomas were reclassified as papillary carcinomas. Follicular carcinomas were reclassified as follicular variant papillary carcinomas when the original pathologist indicated the presence of nuclear inclusions. Three participants undergoing surgery had malignant thyroid tumors that could not be classified because we were unable to obtain sufficient histological information. These participants were thus treated as “unknown.”

Positive Antithyroid Antibodies. Participants were classified as positive for antithyroid antibodies if their serum concentration of either TPOAb or TgAb was 10 IU/mL or more.

Hypothyroidism. Participants with a serum TSH level of 4.0 mIU/L or more and a free T4 level lower than 0.71 ng/dL (9.1 pmol/L) were classified as having hypothyroidism. Participants receiving thyroid hormone replacement therapy due to low thyroid hormone levels were also classified as having hypothyroidism, regardless of hormone level at examination. Hypothyroidism was divided into antithyroid antibody–positive and –negative cases. Hypothyroidism after

<p>| Table 3. Numbers of Participants by Thyroid Radiation Dose and Age at Exposure |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Exposure</th>
<th>DS02 Thyroid Radiation Dose, Sv</th>
<th>Dose Unknown (n = 581)</th>
<th>Not in City* (n = 6)</th>
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<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<tr>
<td>0-9 y</td>
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<tr>
<td>Total</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women</td>
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<tr>
<td>10-19 y</td>
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<td>Total</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women</td>
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<tr>
<td>20-29 y</td>
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</tr>
<tr>
<td>Total</td>
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<td></td>
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</tr>
<tr>
<td>Men</td>
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</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 y</td>
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<tr>
<td>Total</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviation: DS02, Dosimetry System 2002.
*Not in the city at the time of the atomic bombings.
ablation with radioiodine therapy, external thyroid radiation therapy, thyroid surgery, or use of antithyroid drugs was not treated as hypothyroidism, and such cases were excluded from the analysis.

**Hyperthyroidism.** Participants with a serum TSH level of less than 0.41 mIU/L and a free T4 level of more than 1.52 ng/dL (19.6 pmol/L), or those with a history of treatment for hyperthyroidism confirmed by medical records, were classified as having hyperthyroidism. Those with thyrotoxicosis due to destructive thyroid changes such as subacute thyroiditis and painless thyroiditis were excluded from this category. Among participants with hyperthyroidism, those testing positive for 1 of the following tests were considered to have Graves disease: TSH receptor antibodies, thyroid-stimulating antibodies, and elevated radionuclide uptake by scintigraphy. Participants with a history of Graves disease and taking antithyroid drugs, or those undergoing surgery or radiation therapy confirmed by medical records, were also classified as having Graves disease. Those with hyperfunctioning nodules or a history of treatment for hyperfunctioning nodules were classified as having toxic nodules.

**Autoimmune Thyroid Disease.** Participants testing positive for antithyroid antibodies or Graves disease were defined as having autoimmune thyroid disease. Antithyroid antibody–positive hypothyroidism was classified as a subclass of positive for antithyroid antibodies.

**Statistical Analysis**

In the analysis of radiation dose response, a total of 3185 participants were analyzed, excluding 906 exposed in utero, not in the city at the time of the atomic bombings, or with unknown radiation dose according to the DS02. Because radiation effects on the thyroid may be affected by the developmental stage of the thyroid glands of persons exposed in utero, such persons were excluded from the analyses of radiation dose response. As shown in Table 3, the dose distribution of the participants is highly skewed, with the majority in the low-dose range.

To calculate the odds of prevalence \( p \) of a thyroid disease dependent on city, sex, age at exposure, and radiation dose, we assumed the following full model:

\[
\frac{p}{1-p} = BGM \times (1 + EM \times \beta \times d),
\]

where \( BGM \) is a log-linear background model in terms of city, sex, age at exposure, and their second-order interactions, and \( EM \) is a log-linear effect modification part in terms of the main effects of city, sex, and age at exposure. The radiation dose \( d \) is the DS02 thyroid-equivalent dose in Sv, with an assigned relative biological effectiveness for neutrons of 10, which is the sum of the \( \gamma \) thyroid dose and 10 times the neutron thyroid dose. The \( \gamma \) and neutron thyroid doses were adjusted for 35% dose error and truncated at 4 Gy.33,34 This adjustment reduced risk estimation bias. The neutron component is very minor in atomic bomb radiation. The age at exposure is included in the model as (age at exposure – 10)/10. In the above model, the excess odds ratio (EOR) is linear in terms of radiation dose, which we call a linear EOR model. The EOR, or excess relative risk when the prevalence is small, can be written as \( EM \beta \) per Sv. The GMBO program in Epicure version 2 was used to obtain maximum likelihood estimates of the parameters.34 In the fitting, only the linear term in dose was included in the model, because the model did not converge when both linear and quadratic terms for radiation dose were included, and we believed the radiation dose response should be monotonic.

The Akaike Information Criterion (AIC) model selection criterion35,36 is defined as deviance of the fit plus 2 times the number of parameters used in the fit. Using the minimum AIC model selection criterion procedure, the best model was selected for each thyroid disease under the condition that if an interaction term is included in the model, the main effects are included as well. Model selection was carried out separately for the BGM part and the EM part. Model selection for the BGM part was made in fitting all the submodels, and the model attaining the minimum AIC value was selected. Note that for most of the thyroid diseases, the above linear EOR model fits equally well as or better than the usual linear logistic model when using the AIC criterion.

As is well known, by the first-order Taylor approximation, we can linearize prevalence \( p \) in terms of radiation dose parameter and, after some approximation, apply the large-sample asymptotic normal theory37 for the maximum likelihood estimator of the dose-response parameter, which results in the statistical power calculation that is used for normal distribution. In this cohort, when a 2-tailed 5% significance test is performed with a power of 95%, the detectable EOR per Sv is less than 0.8 in absolute value for thyroid nodules and autoimmune thyroid diseases. Given the data set, because of the large dose-response parameter, statistical powers of the tests are almost 100% for all nodules despite relatively few cases, while the powers are less than 60% for autoimmune thyroid diseases including Graves disease, due to relatively small dose-response parameters.

When we construct confidence intervals (CIs) by dose group or by age at exposure group, the dose category cutpoints are defined as 0.005, 0.3, 1.0, and 2.0 Sv, with persons exposed to doses from 0 Sv to 0.005 Sv serving as a reference group. Age at exposure category cutpoints are defined as 10 and 20 years. For persons receiving known doses, the mean age at exposure was 15.4 years and the mean age at examination was 71.3 years, a difference of about 56 years. All CIs are constructed using likelihood ratio statistics and all tests are 2-sided, based on \( \chi^2 \) likelihood ratio statistics.

We first analyzed each thyroid disease using the older Dosimetry System 86 (DS86),30 then reanalyzed the diseases using the newer DS02. Since...
there were only 2 significance tests in terms of radiation dose effect per disease, the problem of multiple comparisons on the dose effect for each disease was of little consequence. We found that, for diseases except malignant tumors, the linear EOR dose response fit well. However, there is a chance possibility that, for a specific disease among many diseases with linear dose responses, the dose response may become nonlinear, as was seen in the dose response for malignant tumors. The major interest in the dose-response analyses is whether prevalence increases significantly with radiation dose, and the shape of the dose responses is of secondary interest, though it may include important biological implications. Therefore, for all thyroid diseases, we presented the results using linear EOR models, which are easily interpreted, and additionally described the results of nonlinear analysis, especially for malignant tumors. The GMBO program in Epicure version 2 was used for all analyses.

### RESULTS

Table 4 shows the prevalence of thyroid diseases in all study participants. Among 4091 participants, thyroid diseases were diagnosed in 1833 (44.8%) (436 men [32.2% of men] and 1397 women [51.0% of women]). The prevalence of thyroid diseases was significantly higher in women than in men (goodness of fit $\chi^2$: $P<.001$). The following are diagnosis-specific descriptions.

#### Thyroid Nodules

The prevalence of thyroid nodules is shown in Table 4. Malignant tumors were identified in 87 participants (2.1% of total) and benign nodules in 207 (5.1% of total). Table 5 lists histological and cytological classification of malignant tumors and benign nodules. One hundred fifteen participants had undergone thyroid surgery before this study; 71 with malignant tumors, 43 with benign nodules, and 1 with a cyst. Most of the malignant tumors (77 of 87) were papillary carcinoma. No cases of anaplastic or medullary carcinomas were detected among the participants with known histological types. All of the participants with thyroid nodules were nonthyrotoxic, except 2 with postsurgical toxic adenoma.

#### Autoimmune Thyroid Disease, Hypothyroidism, and Hyperthyroidism

As shown in Table 4, antithyroid antibodies (TPOAb or TgAb) were detected in 1127 participants (27.5% of total). The serum concentration of TPOAb and TgAb ranged from less than 3 to 9131 IU/mL and from less than 4 to 326 000 IU/mL.

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**Table 4. Prevalence of Thyroid Diseases in All Participants**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid diseases</td>
<td></td>
<td>1833 (44.8)</td>
</tr>
<tr>
<td>Thyroid nodule*</td>
<td>166 (12.3)</td>
<td>845 (20.7)</td>
</tr>
<tr>
<td>Solid nodule‡</td>
<td>108 (8.0)</td>
<td>589 (14.4)</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>11 (0.8)</td>
<td>87 (2.1)</td>
</tr>
<tr>
<td>Benign nodule</td>
<td>41 (3.0)</td>
<td>207 (5.1)</td>
</tr>
<tr>
<td>Other‡</td>
<td>59 (4.4)</td>
<td>321 (7.8)</td>
</tr>
<tr>
<td>Cyst</td>
<td>64 (4.7)</td>
<td>324 (7.9)</td>
</tr>
<tr>
<td>Positive for antithyroid antibodies§</td>
<td>285 (21.1)</td>
<td>1127 (27.5)</td>
</tr>
<tr>
<td>TPOAb</td>
<td>151 (11.2)</td>
<td>543 (13.3)</td>
</tr>
<tr>
<td>TgAb</td>
<td>224 (16.6)</td>
<td>966 (23.6)</td>
</tr>
<tr>
<td>Hypothyroidism*</td>
<td>54 (4.0)</td>
<td>230 (5.6)</td>
</tr>
<tr>
<td>Antithyroid antibodies-positive</td>
<td>28 (2.1)</td>
<td>124 (3.0)</td>
</tr>
<tr>
<td>Antithyroid antibodies-negative</td>
<td>26 (1.9)</td>
<td>106 (2.6)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>9 (0.7)</td>
<td>62 (1.5)</td>
</tr>
<tr>
<td>Graves disease</td>
<td>6 (0.4)</td>
<td>51 (1.2)</td>
</tr>
<tr>
<td>Toxic nodule</td>
<td>0</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Unknown†</td>
<td>3 (0.2)</td>
<td>9 (0.2)</td>
</tr>
</tbody>
</table>

*Abbreviations: TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody.

**Table 5. Histological and Cytological Results of Malignant Thyroid Tumor and Benign Thyroid Nodule**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Operated, No.</th>
<th>Detected in This Study, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumor*</td>
<td>87</td>
<td>17</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>77</td>
<td>16</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unknown†</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Benign nodule‡</td>
<td>207</td>
<td>171</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Adenomatous goiter</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Cytological benign nodule§</td>
<td>168</td>
<td>168</td>
</tr>
</tbody>
</table>

*One participant had both papillary carcinoma with surgery and newly diagnosed follicular carcinoma.

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respectively. Both TPOAb and TgAb were detected in 382 participants (9% of total) (90 men [7% of men] and 292 women [11% of women]).

Hypothyroidism was detected in 230 participants (5.6% of total) (Table 4), of whom 127 already were receiving thyroid hormone replacement therapy. Among them, antithyroid antibody--positive hypothyroidism was detected in 124 (3.0% of total).

Hyperthyroidism was detected in 62 participants (1.5% of total) (Table 4). Among them, Graves disease was diagnosed in 51 (1.2% of total). Four cases of Graves disease were newly detected, and 47 were already diagnosed before this study, including 9 who had undergone thyroid surgery, 3 who had received iodine 131 therapy, and 2 who had received external radiation therapy. Two were postsurgical patients with toxic adenoma. We were unable to obtain further information for 9 participants with hyperthyroidism.

**Radiation Dose Responses**

TABLE 6 shows the numbers of participants with thyroid diseases, classified by thyroid radiation dose. Mean and median thyroid radiation doses were 0.499 Sv and 0.087 Sv, respectively. FIGURE 2 shows dose-response relationships for thyroid diseases, and TABLE 7 summarizes the EORs per Sv and their 95% CIs. The prevalence of all solid nodules, malignant tumors, benign nodules, other solid nodules, and cysts was significantly associated with thyroid radiation dose ($P<.001$). We estimate that about 130 (28%) of all solid nodules, 26 (37%) of malignant tumors, 49 (31%) of benign nodules, 64 (25%) of other solid nodules, and 61 (25%) of cysts were associated with radiation exposure.

The interaction of age at exposure with dose was significant for the prevalence of all solid nodules ($P<.001$) (Figure 3), benign nodules ($P=.002$) (Figure 3), and other solid nodules ($P=.002$), showing that the dose effects were significantly higher in those exposed when young. It was not, however, statistically significant for the prevalence of malignant tumors ($P=.10$) (Figure 3). There was no interaction of age at exposure with dose in the prevalence of cysts ($P=.49$). We performed further analyses in fitting age at exposure, grouping age at exposure variables into 0 through 9 years, 10 through 19 years, and 20 years or older. The EORs per Sv of all solid nodules in the participants with age at exposure of 0 through 9 years, 10 through 19 years, and 20 years or older were 3.83 (95% CI, 2.27 to 6.21; $P<.001$), 1.10 (95% CI, 0.65 to 1.71; $P<.001$), and 0.42 (95% CI, 0.03 to 1.01; $P=.03$), respectively. The EORs for malignant tumors in the participants with age at exposure of 0 through 9 years, 10 through 19 years, and 20 years or older were 3.46 (95% CI, 0.92 to 10.51; $P<.001$), 1.49 (95% CI, 0.37 to 3.74; $P=.002$), and 0.25 (95% CI, −0.28 to 1.96; $P=.57$), and those for benign nodule were 2.89 (95% CI, 1.32 to 5.77; $P<.001$), 0.83 (95% CI, 0.28 to 1.70; $P=.001$), and 0.25 (95% CI, −0.20 to 1.21; $P=.38$), respectively. Radiation dose responses in ages at exposure of older than 30 years could not be evaluated because most cohort members had died before this study was conducted, 55 to 58 years after radiation exposure.

There was no interaction of sex with dose in the prevalence of all solid nodules ($P=.46$), malignant tumors ($P=.83$), benign nodules ($P=.38$), other solid nodules ($P=.52$), and cysts ($P=.92$). There was no interaction of city with dose in the prevalence of all solid nodules ($P=.69$), malignant tumors ($P=.91$), benign nodules ($P=.73$), other solid nodules ($P=.57$), and cysts ($P=.47$). For malignant tumors, there was a model with better fit in terms of AIC than the linear EOR model given in the “Statistical Analysis” section, and that was a nonlinear model that replaced dose in the linear EOR model with the square root of the dose. With this model, EOR at 1 Sv at 10 years of age at exposure was 3.96 (95% CI, 1.31 to 12.86; $P<.001$), with significant effect modification by age at exposure ($P=.04$) and 36 cases (52%) associated with radiation exposure. The EOR per 1 Sv for malignant tumor with age at exposure of 0 through 9 years, 10 through 19 years, and 20 years or older were 6.61 (95% CI, 1.78 to 22.94; $P<.001$), 2.58 (95% CI, 0.77 to 6.69; $P<.001$), and 0.43 (95% CI, −0.44 to 2.80; $P=.47$), respectively.

The prevalence of positive antithyroid antibodies was not associated with thyroid radiation dose ($P=.20$) (Table 7 and Figure 2). The separate analyses for TPOAb and TgAb showed that neither prevalence of TPOAb-positive nor TgAb-positive was associated with dose ($P=.91$ and $P=.52$, respectively) (Table 7). The serum concentrations of TPOAb and TgAb also showed no significant association with dose (EOR per Sv, 0.02 [$P=.36$] and −0.02 [$P=.41$], respectively). Neither antithyroid antibody--positive nor--negative hypothyroidism was associated with dose ($P=.92$ and $P=.31$, respectively) (Table 7 and Figure 2). Furthermore, the younger population (age at exposure of 0–9 years, $n=709$) was separately analyzed because testing positive for antithyroid antibodies is strongly affected by increasing age. The prevalence of positive antithyroid antibodies and antithyroid antibody--positive hypothyroidism was not associated with dose in the younger population (EOR per Sv, −0.17 [$P=.11$] and −0.09 [$P=.72$], respectively).

We also analyzed antibody-positive hypothyroidism by the linear quadratic logistic model, the same model used in the previous Nagasaki study. No significant convex dose response was observed by the linear quadratic dose-response model ($P=.86$), but the interaction of city (Hiroshima or Nagasaki) with dose was suggestive ($P=.09$). Separate analyses of participants in Hiroshima and Nagasaki showed no significant dose responses for either city ($P=.45$ for Hiroshima, $P=.17$ for Nagasaki). On the other hand, an association between the prevalence of Graves disease and radiation dose was suggested but did not reach the level of statistical significance ($P=.10$).
Table 6. Number of Participants with Thyroid Diseases by Thyroid Radiation Dose

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>DS02 Thyroid Radiation Dose, Sv</th>
<th>No. (%)</th>
<th>Exposure</th>
<th>Exposed</th>
<th>Not in City*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.005 (n = 1370)</td>
<td>0.005-0.499 (n = 821)</td>
<td>0.500-0.999 (n = 476)</td>
<td>≥1.000 (n = 518)</td>
<td>Unknown (n = 572)</td>
<td>(N = 4091)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>444</td>
<td>235</td>
<td>138</td>
<td>206</td>
<td>166</td>
<td>162</td>
</tr>
<tr>
<td>Women</td>
<td>926</td>
<td>586</td>
<td>338</td>
<td>312</td>
<td>406</td>
<td>166</td>
</tr>
<tr>
<td>Solid nodule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>24 (5.4)</td>
<td>13 (5.5)</td>
<td>13 (9.4)</td>
<td>40 (19.4)</td>
<td>12 (7.2)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Women</td>
<td>115 (12.4)</td>
<td>61 (18.0)</td>
<td>89 (28.5)</td>
<td>75 (18.5)</td>
<td>29 (17.5)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>15 (1.1)</td>
<td>2 (0.5)</td>
<td>1 (0.7)</td>
<td>5 (2.4)</td>
<td>1 (0.6)</td>
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</tr>
<tr>
<td>Women</td>
<td>13 (1.4)</td>
<td>19 (3.2)</td>
<td>11 (3.3)</td>
<td>17 (5.4)</td>
<td>11 (2.7)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Benign nodule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10 (2.3)</td>
<td>4 (1.7)</td>
<td>4 (2.9)</td>
<td>16 (7.8)</td>
<td>7 (4.2)</td>
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<tr>
<td>Women</td>
<td>42 (4.5)</td>
<td>28 (4.8)</td>
<td>20 (5.9)</td>
<td>32 (10.3)</td>
<td>32 (7.9)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Other†</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>12 (2.7)</td>
<td>7 (3.0)</td>
<td>8 (5.8)</td>
<td>21 (10.2)</td>
<td>5 (3.0)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Women</td>
<td>65 (7.0)</td>
<td>65 (11.1)</td>
<td>34 (10.1)</td>
<td>46 (14.7)</td>
<td>37 (9.1)</td>
<td>14 (8.4)</td>
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<tr>
<td>Cyst</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>12 (2.7)</td>
<td>10 (4.3)</td>
<td>4 (2.9)</td>
<td>18 (8.7)</td>
<td>13 (7.8)</td>
<td>6 (3.7)</td>
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<tr>
<td>Women</td>
<td>67 (7.2)</td>
<td>48 (8.2)</td>
<td>38 (11.2)</td>
<td>47 (15.1)</td>
<td>45 (11.1)</td>
<td>12 (7.2)</td>
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<tr>
<td>Positive for antithyroid antibodies‡</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>97 (21.8)</td>
<td>52 (22.1)</td>
<td>34 (24.6)</td>
<td>43 (20.9)</td>
<td>35 (21.1)</td>
<td>24 (14.8)</td>
</tr>
<tr>
<td>Women</td>
<td>290 (31.3)</td>
<td>185 (31.6)</td>
<td>119 (35.2)</td>
<td>78 (25.0)</td>
<td>109 (26.8)</td>
<td>60 (36.1)</td>
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<tr>
<td>Positive for TPOAb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>52 (11.7)</td>
<td>25 (10.6)</td>
<td>22 (15.9)</td>
<td>21 (10.2)</td>
<td>22 (13.3)</td>
<td>9 (5.6)</td>
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<tr>
<td>Women</td>
<td>119 (12.9)</td>
<td>95 (16.2)</td>
<td>47 (13.9)</td>
<td>46 (14.7)</td>
<td>51 (12.6)</td>
<td>33 (19.9)</td>
</tr>
<tr>
<td>Positive for TgAb</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>73 (16.4)</td>
<td>42 (17.9)</td>
<td>25 (18.1)</td>
<td>35 (17.0)</td>
<td>25 (15.1)</td>
<td>24 (14.8)</td>
</tr>
<tr>
<td>Women</td>
<td>252 (27.2)</td>
<td>162 (27.6)</td>
<td>105 (31.1)</td>
<td>67 (21.5)</td>
<td>99 (24.4)</td>
<td>56 (33.7)</td>
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<td>Antithyroid antibodies–positive hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>9 (2.0)</td>
<td>9 (3.8)</td>
<td>3 (2.2)</td>
<td>1 (0.5)</td>
<td>3 (1.8)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Women</td>
<td>9 (2.0)</td>
<td>25 (4.3)</td>
<td>13 (3.8)</td>
<td>13 (4.2)</td>
<td>10 (2.5)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Antithyroid antibodies–negative hypothyroidism</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7 (1.6)</td>
<td>6 (2.6)</td>
<td>0</td>
<td>3 (1.5)</td>
<td>7 (4.2)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Women</td>
<td>29 (3.1)</td>
<td>14 (2.4)</td>
<td>9 (2.7)</td>
<td>13 (4.2)</td>
<td>12 (3.0)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Graves disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2 (0.5)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>2 (1.0)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Women</td>
<td>9 (1.0)</td>
<td>12 (2.0)</td>
<td>3 (0.9)</td>
<td>9 (2.9)</td>
<td>4 (1.0)</td>
<td>8 (4.8)</td>
</tr>
</tbody>
</table>

Abbreviations: DS02, Dosimetry System 2002; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody.

*Not in the city at the time of the atomic bombings.
†Participants with solid nodules whose cytological results were indeterminate (n = 13) or inadequate (n = 18), or those without cytological or histological examination results (n = 290). Indicates positive for either TPOAb or TgAb.
This is the first comprehensive thyroid disease screening study for both Hiroshima and Nagasaki atomic bomb survivors. We evaluated radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases among atomic bomb survivors using survivors whose estimated doses were below 0.005 Sv as a reference group, but we did not compare disease prevalence between atomic bomb survivors and unexposed control individuals who were not in Hiroshima or Nagasaki at the time of the bombings to avoid possible bias due to socioeconomic status and genetic background.

It is well documented that the incidence and prevalence of thyroid cancer increase with radiation exposure,1-4,10,11 and our study results were consistent with those of previous reports.1-4 In this study, therefore, we conducted ultrasound-guided fine-needle aspiration biopsy for thyroid nodules and evaluated a dose-response relationship for benign thyroid nodules. Our results clearly demonstrated that prevalence of benign nodules also increased with radiation dose. However, there remained 321 participants with solid nodules classified as “other” (ie, neither benign nor malignant). We believe this does not affect the overall conclusion that prevalence of both benign or malignant nodules increased with radiation dose, because a positive dose-response relationship in solid nodules

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
<th>EOR per Sv (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid nodule</td>
<td>464 (14.6)</td>
<td>2.01 (1.33 to 2.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>70 (2.2)</td>
<td>1.95 (0.67 to 4.92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Benign nodule</td>
<td>156 (4.9)</td>
<td>1.53 (0.76 to 2.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other§</td>
<td>258 (8.1)</td>
<td>1.67 (0.93 to 2.83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cyst</td>
<td>244 (7.7)</td>
<td>0.89 (0.48 to 1.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive antithyroid antibodies</td>
<td>898 (28.2)</td>
<td>-0.07 (-0.16 to 0.04)</td>
<td>.20</td>
</tr>
<tr>
<td>Positive TPOAb</td>
<td>427 (13.4)</td>
<td>0.01 (-0.12 to 0.19)</td>
<td>.91</td>
</tr>
<tr>
<td>Positive TgAb</td>
<td>761 (23.9)</td>
<td>-0.04 (-0.13 to 0.09)</td>
<td>.52</td>
</tr>
<tr>
<td>Antithyroid antibodies–positive hypothyroidism</td>
<td>102 (3.2)</td>
<td>0.01 (-0.20 to 0.40)</td>
<td>.92</td>
</tr>
<tr>
<td>Antithyroid antibodies–negative hypothyroidism</td>
<td>81 (2.5)</td>
<td>0.17 (-0.12 to 0.67)</td>
<td>.31</td>
</tr>
<tr>
<td>Graves disease</td>
<td>38 (1.2)</td>
<td>0.49 (-0.06 to 1.69)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody.
*Estimates are adjusted by age at exposure, sex, and city.
†Excluding 906 exposed in utero, not in the city at the time of the atomic bombings, or with unknown radiation dose according to the Dosimetry System 2002.
‡EOR based on a model at age 10 years at time of exposure.
§Participants with solid nodules whose cytological results were indeterminate (n = 9) or inadequate (n = 13), or those without cytological or histological examination results (n = 236).
¶Indicates positive for either TPOAb or TgAb.

The straight line displays the odds ratio from the best-fitting linear excess odds ratio model at age 10 years at exposure. The points are dose category-specific odds ratios with 95% confidence intervals, plotted at the mean radiation dose of the study population within each dose category. The dose categories shown on the plots represent <0.005 Sv, 0.005-0.499 Sv, 0.500-0.999 Sv, 1.000-1.999 Sv, and ≥2.000 Sv. P values are calculated by likelihood ratio test.

**COMMENT**

This is the first comprehensive thyroid disease screening study for both Hiroshima and Nagasaki atomic bomb survivors. We evaluated radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases among atomic bomb survivors using survivors whose estimated doses were below 0.005 Sv as a reference group, but we did not compare disease prevalence between atomic bomb survivors and unexposed control individuals who were not in Hiroshima or Nagasaki at the time of the bombings to avoid possible bias due to socioeconomic status and genetic background.

It is well documented that the incidence and prevalence of thyroid cancer increase with radiation exposure,1-4,10,11 and our study results were consistent with those of previous reports. There also have been several studies on the association between benign thyroid nodules and thyroid radiation dose,3,6,8 but this issue has rarely been studied in atomic bomb survivors.4 In this study, therefore, we conducted ultrasound-guided fine-needle aspiration biopsy for thyroid nodules and evaluated a dose-response relationship for benign thyroid nodules. Our results clearly demonstrated that prevalence of benign nodules also increased with radiation dose. However, there remained 321 participants with solid nodules classified as “other” (ie, neither benign nor malignant). We believe this does not affect the overall conclusion that prevalence of both benign or malignant nodules increased with radiation dose, because a positive dose-response relationship in solid nodules.
of the “other” category was also observed. Radiation is known to induce DNA strand breaks, but the molecular mechanisms of radiation-induced thyroid tumor are not fully understood. Recent studies suggest that rearrangements of the ret proto-oncogene are associated with post-Chernobyl thyroid cancer.\(^4\) However, the early suggestions that specific rearrangements of the ret proto-oncogene may be a marker for radiation exposure have not been substantiated.\(^4\)

A significant dose-response relationship for cysts also existed in this study. Thyroid cysts usually represent degenerative change and previous hemorrhage within nodules or adenomas.\(^5\) This is likely the reason that prevalence of cysts showed the same dose-response relationship as prevalence of solid nodules.

The present study showed that individuals who were exposed when young were at higher risk of solid thyroid nodules. On the other hand, for the prevalence of malignant tumors, interaction of age at exposure with dose was not statistically significant. However, participants with age at exposure of younger than 20 years did show significant dose-response relationships, while those with age at exposure of 20 years or older showed no significant dose response. This observation indicates that a positive dose response in malignant tumors was mainly due to a positive dose response in the participants exposed at younger ages. This result is consistent with previous studies of children exposed to radiation in the Chernobyl disaster,\(^1\) through medical irradiation,\(^2\) and in atomic bombings.\(^3\) The reason why radiation causes increased prevalence of solid thyroid nodules with exposure at younger ages is unknown. The fact that not only solid thyroid nodules but also other solid cancers in various organs are observed more frequently in participants exposed at younger ages\(^4\) indicates that organs in children may be more sensitive to radiation than adult organs, probably due to higher rates of cell proliferation. We observed that the prevalence of thyroid diseases was higher in women than in men but did not observe a greater radiation risk in women compared with men on a relative scale. In several reports,\(^5\) women were at greater risk for radiation-induced thyroid diseases than were men.

Reports on effects of radiation on autoimmune thyroid diseases have been inconsistent because of methodological differences, including sample selection differences and the wide variety of diagnostic techniques and criteria used in such studies.\(^6\) Eheman et al\(^1\) pointed out that some studies had limitations due to small numbers of participants, absence of thyroid radiation dose information, or uncertain diagnostic methods. Therefore, we diagnosed autoimmune thyroid diseases using sophisticated laboratory methods and clear diagnostic criteria in a large cohort with known radiation doses. In this study, spontaneous overt hypothyroidism was detected in 5.6% of the total participants, which is a higher prevalence compared with reports in Japan and other countries (0.1%-2.0%).\(^6\) The rate of positive thyroid antibodies in all participants was 27.5% and that in those with hypothyroidism was 54%, which are similar to the rates of previous reports in elderly individuals.\(^7\) However, comparisons of disease prevalence between the present study and other published data of unexposed individuals may be biased due to differences in study participants or protocols.

In the dose-response analysis, we did not observe significant radiation dose responses in participants testing positive for antithyroid antibodies and in those with antithyroid antibody–positive hypothyroidism. This is consistent with the results of a recent publication evaluating people exposed as young children to iodine 131 from the Hanford Nuclear Site.\(^8\) Most previous epidemiologic studies of atomic bomb survivors have not supported the association between radiation exposure and thyroid autoimmunity.\(^9\) However, the study conducted in Nagasaki AHS members
from 1984 through 1987 demonstrated a convex dose-response relationship in antithyroid antibody–positive hypothyroidism, with maximum prevalence at a dose of 0.7 Sv, based on the DS86. On the other hand, the analyses of the present study using the DS02 and DS86 showed no significant dose response (EOR per Sv, 0.01 [P = .92] and 0.03 [P = .81], respectively). This discrepancy may result from (1) the present study’s increased study population, which includes both Hiroshima and Nagasaki atomic bomb survivors, (2) the different diagnostic techniques used for measuring levels of thyroid antibodies and TSH, and (3) change of dose distribution of the cohort members over time because mortality and cancer risks are partially dependent on radiation dose. Furthermore, we made diagnoses on the basis of serum test results at a single point in both studies, but the results of serum tests sometimes vary over time.

A dose response for Graves disease was suggested in the present study (P = .10). Several studies have reported that Graves disease was induced by radiiodine therapy for functional or nonfunctional thyroid nodules but individuals with such nodules in those studies were irradiated using much higher doses than the exposures in participants in our study. An epidemiologic study evaluating children exposed to iodine 131 from the Hanford Nuclear Site (median dose, 97 mGy; mean dose, 174 mGy) showed no evidence for an increased risk of Graves disease. Future epidemiologic studies on irradiated persons, animal studies, and molecular-biological studies are necessary to more accurately investigate the possible association between radiation and thyroid autoimmunity, particularly time-dependent effects of radiation exposure and mechanisms of disease.

**Study Limitations**

First, persons with nodular thyroid diseases might have tended to agree to participate, possibly creating a motivation bias in this study. Participants in this study had more nodular thyroid diseases diagnosed before this study than did nonparticipants, while no difference in prevalence of previously diagnosed nonnodular thyroid diseases was observed (Table 1). However, because the participation rate was very high (89.9%), we believe that a possible bias due to motivation does not affect the overall conclusion.

Second, a survival bias exists in this study. Median life expectancy decreases with increasing radiation dose at rate of about 1.3 years per Gy, suggesting that the proportion of atomic bomb survivors exposed to high-dose radiation in the present study is smaller than the original proportion in 1958, when the cohort was constructed. Furthermore, not only mortality but also cancer risks partially depend on radiation dose. Patients with severe thyroid cancer may not have been included in this study due to their possible death before this study period. Therefore, we realize that a survival bias exists in the present population, especially in the atomic bomb survivors exposed to high-dose radiation.

Third, we were not able to clarify the earlier effects of radiation and how long the effects of radiation on thyroid nodules persisted after exposure because the present cross-sectional study was conducted 55 to 58 years after the atomic bombings. In the study of childhood radiation treatment, it was demonstrated that increased risk for thyroid cancer continued for as long as 40 years after exposure. Furthermore, in atomic bomb survivors, a radiation-related excess cancer rate was still observed, based on cancer deaths from 1988 through 1997. Thus, the effects of radiation on thyroid nodules may exist long after radiation exposure in atomic bomb survivors.

**CONCLUSION**

The present study revealed that, 55 to 58 years after radiation exposure, a significant linear dose-response relationship existed in the prevalence of not only malignant thyroid tumors but also benign thyroid nodules and that the relationship was significantly higher in those exposed at younger ages. On the other hand, autoimmune thyroid diseases were not found to be significantly associated with radiation exposure in this study. Careful examination of the thyroid is still important long after radiation exposure, especially for people exposed at younger ages.

**REFERENCES**

THYROID NODULES AND AUTOIMMUNE THYROID DISEASES IN ATOMIC BOMB SURVIVORS


