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

Misa Imaizumi, MD
Toshiro Usa, MD
Tan Tominaga, MD
Kazuo Neriishi, MD
Masazumi Akahoshi, MD
Eiji Nakashima, PhD
Kiyoto Ashizawa, MD
Ayumi Hida, MD
Midori Soda, MD
Saeko Fujiwara, MD
Michiko Yamada, MD
Eri Ejima, MD
Naokata Yokoyama, MD
Masamichi Okubo, MD
Keizo Sugino, MD
Gen Suzuki, MD
Renju Maeda, MD
Shigenobu Nagataki, MD
Katsumi Eguchi, MD

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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THYROID NODULES AND AUTOIMMUNE THYROID DISEASES IN ATOMIC BOMB SURVIVORS

Figure 1. Breakdown of Adult Health Study (AHS) Cohort Members Into Participants and Nonparticipants

![Diagram showing the breakdown of AHS cohort members into participants and nonparticipants.](image)

See Table 1 for previously diagnosed thyroid abnormalities and thyroid radiation doses of participants and nonparticipants. *Most cohort members who were not in the city at the time of the atomic bombings have not been invited to Radiation Effects Research Foundation biennial health examinations since 1975.

than 50 years. Several studies also have reported an association between autoimmune thyroid diseases and radiation exposure, but the results were inconsistent.4,14-20

Many of the studies that examined the association between radiation exposure and thyroid diseases had limitations because they lacked an established large cohort, known thyroid radiation doses, and a sophisticated method with which to diagnose thyroid diseases. The Radiation Effects Research Foundation (RERF, formerly the Atomic Bomb Casualty Commission) established a longitudinal Life Span Study cohort consisting of 120,321 atomic bomb survivors in 195021,22 and its subcohort, the Adult Health Study (AHS), consisting of 19,961 survivors, in 1958. Radiation dose was calculated for each individual by the Dosimetry System 2002 (DS02).23 In the Life Span Study and AHS cohorts, it was shown that a positive radiation dose-response relationship existed in thyroid cancer and thyroid nodules confirmed by tumor registry and autopsy information in Hiroshima and Nagasaki.4,24,25 However, these studies were limited in their ability to diagnose various thyroid diseases, such as benign nodules and autoimmune thyroid diseases.

We previously conducted a comprehensive thyroid disease study among 28,566 Nagasaki AHS cohort members from 1984 to 1987 by using ultrasound examinations and blood tests to evaluate the effects of radiation on thyroid nodules, thyroid autoimmunity, and thyroid function.14 However, this study was conducted only in Nagasaki atomic bomb survivors, not in Hiroshima survivors. Furthermore, screening techniques to diagnose thyroid diseases have advanced remarkably since the last thyroid study. Ultrasound examination has become more sensitive in detecting thyroid nodules. Aspiration biopsy of thyroid nodules has recently been conducted under guidance with ultrasound. The development of a highly sensitive assay for thyroid antibodies and thyroid-stimulating hormone is helpful for more accurate evaluation of thyroid autoimmunity and thyroid function. Therefore, we decided to reevaluate the effects of radiation on thyroid diseases.

In the present study, we conducted a comprehensive thyroid disease survey between 2000 and 2003, using sophisticated methods to diagnose thyroid nodules (malignant and benign) and autoimmune thyroid diseases in both Hiroshima and Nagasaki AHS cohort members, including some participants from the previous Nagasaki study. We investigated radiation dose-response relationships for thyroid diseases.

METHODS

Participants

The AHS is a clinical program established in 1958 by RERF, formerly the Atomic Bomb Casualty Commission, comprising Hiroshima and Nagasaki atomic bomb survivors. The AHS biennial health examinations presented clinical information complementary to death and tumor registries data. A detailed description of this program has been published elsewhere.26,27 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 4,552 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 4,091 participants (89.9%; mean age, 70 [SD, 9] years; 1,352 men and 2,739 women) agreed and completed the thyroid examination. Of that total, 1,485 (or 1086, excluding persons exposed in utero, not in the city at the time of the atomic 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 DS0223 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.
Clinical Examination and Laboratory Methods

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 TM (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, 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; interrviewer 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 1. Participants and Nonparticipants With Previously Diagnosed Thyroid Abnormalities and Distribution of Thyroid Radiation Doses*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n = 4091)</th>
<th>Nonparticipants (n = 461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously diagnosed thyroid abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular thyroid disease</td>
<td>516 (12.6)</td>
<td>23 (5.0)</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>71 (1.7)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Nonnodular thyroid disease</td>
<td>672 (16.4)</td>
<td>69 (15.0)</td>
</tr>
<tr>
<td>Thyroid radiation dose, Sv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.005</td>
<td>1370 (33.5)</td>
<td>159 (34.5)</td>
</tr>
<tr>
<td>0.005–0.499</td>
<td>821 (20.1)</td>
<td>74 (16.1)</td>
</tr>
<tr>
<td>0.500–0.999</td>
<td>476 (11.6)</td>
<td>42 (9.1)</td>
</tr>
<tr>
<td>≥1.000</td>
<td>518 (12.7)</td>
<td>64 (13.9)</td>
</tr>
<tr>
<td>Others†</td>
<td>906 (22.1)</td>
<td>122 (26.5)</td>
</tr>
</tbody>
</table>

*The previous diagnosis of each cohort member was classified according to International Classification of Diseases, Ninth Revision codes. “Nodular thyroid disease” consists of nontoxic and toxic nodular goiter (codes 241, 242.1–4), cyst of thyroid (242.2), malignant neoplasm of thyroid gland (193), and benign neoplasm of thyroid gland (228). “Nodular thyroid disease” consists of goiter (246), thyrotoxicosis (242.0, 242.9), hypothyroidism (243, 244), and thyroiditis (245).

†Those exposed in utero, not in the city at the time of the atomic bombings, or with unknown radiation dose according to Dosimetry System 2002.

### Table 2. Characteristics of Study Participants in Hiroshima and Nagasaki

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hiroshima</th>
<th>Nagasaki</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>2468</td>
<td>1623</td>
<td>4091</td>
</tr>
<tr>
<td>Excluding others*</td>
<td>2008</td>
<td>1177</td>
<td>3185</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total men</td>
<td>756</td>
<td>596</td>
<td>1352</td>
</tr>
<tr>
<td>Excluding others*</td>
<td>598</td>
<td>425</td>
<td>1023</td>
</tr>
<tr>
<td>Total women</td>
<td>1712</td>
<td>1027</td>
<td>2739</td>
</tr>
<tr>
<td>Excluding others*</td>
<td>1410</td>
<td>752</td>
<td>2162</td>
</tr>
<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>Total cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding others*</td>
<td>72 (8)</td>
<td>70 (7)</td>
<td>71 (8)</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 Dosimetry System 2002.
with smaller nodules have an excellent prognosis and are generally 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

### Table 3. Numbers of Participants by Thyroid Radiation Dose and Age at Exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>DS02 Thyroid Radiation Dose, Sv (n = 4091)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>(1551)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>532 (34.3)</td>
</tr>
<tr>
<td>Women</td>
<td>1019 (65.7)</td>
</tr>
<tr>
<td>In utero</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>181 (11.7)</td>
</tr>
<tr>
<td>Men</td>
<td>88 (16.5)</td>
</tr>
<tr>
<td>Women</td>
<td>93 (9.1)</td>
</tr>
<tr>
<td>At 0-9 y</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>293 (19.9)</td>
</tr>
<tr>
<td>Men</td>
<td>120 (22.6)</td>
</tr>
<tr>
<td>Women</td>
<td>173 (17.0)</td>
</tr>
<tr>
<td>At 10-19 y</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>709 (45.7)</td>
</tr>
<tr>
<td>Men</td>
<td>252 (47.4)</td>
</tr>
<tr>
<td>Women</td>
<td>457 (44.8)</td>
</tr>
<tr>
<td>At 20-29 y</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>308 (19.9)</td>
</tr>
<tr>
<td>Men</td>
<td>53 (10.0)</td>
</tr>
<tr>
<td>Women</td>
<td>255 (25.0)</td>
</tr>
<tr>
<td>At ≥30 y</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60 (3.9)</td>
</tr>
<tr>
<td>Men</td>
<td>19 (3.6)</td>
</tr>
<tr>
<td>Women</td>
<td>41 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviation: DS02, Dosimetry System 2002.
*Not in the city at the time of the atomic bombings.
ablation with radiiodine therapy, external thyroid radiation therapy, thyro
doid surgery, or use of antithyroid
drugs was not treated as hypothyroid-
ism, 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 hyperthyroid-
ism confirmed by medical records, were
classified as having hyperthyroidism.
Those with thyrotoxicosis due to de-
structive thyroid changes such as sub-
acute thyroiditis and painless thyroid-
itis were excluded from this category.
Among participants with hyperthyroid-
ism, those testing positive for 1 of the
following tests were considered to have
Graves disease: TSH receptor antibod-
ies, thyroid-stimulating antibodies, and
elevated radionuclide uptake by scin-
tigraphy. Participants with a history of
Graves disease and taking antithyroid
medication confirmed by medical records,
were also classified as having
Graves disease. Those with hyper-
functioning nodules or a history of
treatment for hyperfunctioning nod-
ules were classified as having toxic nod-
ules.

Autoimmune Thyroid Disease. Par-
ticipants testing positive for antithy-
roid antibodies or Graves disease were
defined as having autoimmune thy-
roid disease. Antithyroid antibody–
positive hypothyroidism was classi-
fied 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 DS02.23 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 distribu-
tion 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:

\[
p / (1 - p) = BGM \cdot (1 + EM \cdot \beta \cdot d),
\]

where BGM is a log-linear back-
ground model in terms of city, sex, age
at exposure, and their second-order in-
teractions, and EM is a log-linear effect
modification part in terms of the main
effects of city, sex, and age at expo-
sure. The radiation dose d is the DS02
thyroid-equivalent dose in Sv, with an
assigned relative biological effective-
ness for neutrons of 10, which is
the sum of the γ thyroid dose and 10 times
the neutron thyroid dose. The γ and
neutron thyroid doses were adjusted for
35% dose error and truncated at 4
Gy.32,33 This adjustment reduced risk es-
timation bias. The neutron compo-
nent is very minor in atomic bomb ra-
diation. 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 radia-
tion 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 pro-
gram 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 qua-
dratic terms for radiation dose were in-
cluded, 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 thy-
roid 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 linear-
ize 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 calcula-
tion that is used for normal distribu-
tion. 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 autoim-
mune 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 autoim-
mune thyroid diseases including
Graves disease, due to relatively small
dose-response parameters.

When we construct confidence in-
tervals (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 cat-
egory 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 exami-
nation was 71.3 years, a difference of
about 56 years. All CIs are con-
structed using likelihood ratio statis-
tics and all tests are 2-sided, based on
\( \chi^2 \) likelihood ratio statistics.

We first analyzed each thyroid dis-
ease using the older Dosimetry Sys-
tem 86 (DS86),38 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 GMBP program in Epicure version 2 was used for all analyses.

Table 4. Prevalence of Thyroid Diseases in All Participants

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Men (n = 1352)</th>
<th>Women (n = 2739)</th>
<th>Total (N = 4091)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid diseases</td>
<td>436 (32.2)</td>
<td>1397 (51.0)</td>
<td>1833 (44.8)</td>
</tr>
<tr>
<td>Thyroid nodule*</td>
<td>166 (12.3)</td>
<td>679 (24.8)</td>
<td>845 (20.7)</td>
</tr>
<tr>
<td>Solid nodule†</td>
<td>108 (8.0)</td>
<td>481 (17.6)</td>
<td>589 (14.4)</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>11 (0.8)</td>
<td>76 (2.8)</td>
<td>87 (2.1)</td>
</tr>
<tr>
<td>Benign nodule</td>
<td>41 (3.0)</td>
<td>166 (6.1)</td>
<td>207 (5.1)</td>
</tr>
<tr>
<td>Other‡</td>
<td>59 (4.4)</td>
<td>262 (9.6)</td>
<td>321 (7.8)</td>
</tr>
<tr>
<td>Cyst</td>
<td>64 (4.7)</td>
<td>260 (9.5)</td>
<td>324 (7.9)</td>
</tr>
<tr>
<td>Positive for antithyroid antibodies§</td>
<td>285 (21.1)</td>
<td>842 (30.7)</td>
<td>1127 (27.5)</td>
</tr>
<tr>
<td>TPOAb</td>
<td>151 (11.2)</td>
<td>392 (14.3)</td>
<td>543 (13.3)</td>
</tr>
<tr>
<td>TgAb</td>
<td>224 (16.6)</td>
<td>742 (27.1)</td>
<td>966 (23.6)</td>
</tr>
<tr>
<td>Hypothyroidism†</td>
<td>54 (4.0)</td>
<td>176 (6.4)</td>
<td>230 (5.6)</td>
</tr>
<tr>
<td>Antithyroid antibodies-+</td>
<td>28 (2.1)</td>
<td>96 (3.5)</td>
<td>124 (3.0)</td>
</tr>
<tr>
<td>Antithyroid antibodies-−</td>
<td>26 (1.9)</td>
<td>80 (2.9)</td>
<td>106 (2.6)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>9 (0.7)</td>
<td>53 (1.9)</td>
<td>62 (1.5)</td>
</tr>
<tr>
<td>Graves disease</td>
<td>6 (0.4)</td>
<td>45 (1.6)</td>
<td>51 (1.2)</td>
</tr>
<tr>
<td>Toxic nodule</td>
<td>0</td>
<td>2 (0.1)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Unknown¶</td>
<td>3 (0.2)</td>
<td>6 (0.2)</td>
<td>9 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody.
*Sixty-eight participants had both solid nodules and cysts.
†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).
§Positive for either TPOAb or TgAb.
§Positive for antithyroid antibodies.

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Operated, No.</th>
<th>Detected in This Study, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumor*</td>
<td>87</td>
<td>71</td>
<td>17</td>
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<tr>
<td>Papillary carcinoma</td>
<td>77</td>
<td>61</td>
<td>16</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
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</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unknown†</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Benign nodule†</td>
<td>207</td>
<td>43</td>
<td>171</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>36</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Adenomatous goiter</td>
<td>10</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Cytological benign nodule.§</td>
<td>168</td>
<td>NA</td>
<td>168</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*One participant had both papillary carcinoma with surgery and newly diagnosed follicular carcinoma.
†Histology of 3 malignant tumors was unknown because there was insufficient histological information.
‡Seven participants had 2 kinds of benign nodule among follicular adenoma, adenomatous goiter, and cytological benign nodule.
§Indicates nonoperated nodule diagnosed as benign by cytological examination.

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

Hyothyroidism 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 hyothyroidism 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 0.449 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 tumor 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 = .37), 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, 0.17 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>Overall</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
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<td><strong>DS02 Thyroid Radiation Dose, Sv</strong></td>
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<tr>
<td>&lt;0.005 (n = 1370)</td>
<td>444</td>
<td>926</td>
<td>235</td>
<td>586</td>
<td>138</td>
<td>338</td>
<td>206</td>
</tr>
<tr>
<td>0.005-0.499 (n = 821)</td>
<td>24</td>
<td>24</td>
<td>5.4</td>
<td>5.4</td>
<td>13.5</td>
<td>13.5</td>
<td>19.4</td>
</tr>
<tr>
<td>0.500-0.999 (n = 476)</td>
<td>115</td>
<td>42</td>
<td>12.4</td>
<td>12.4</td>
<td>89</td>
<td>89</td>
<td>18.5</td>
</tr>
<tr>
<td>≥1.000 (n = 518)</td>
<td>0.005-0.499 (n = 821)</td>
<td>24</td>
<td>42</td>
<td>5.4</td>
<td>12.4</td>
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<td>Women</td>
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</table>

**Abbreviations:** DS02, Dosimetry System 2002; TgAb, antithyrogblobulin 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, 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, but this issue has rarely been studied in atomic bomb survivors. 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

<p>| Table 7. Estimates of Thyroid Diseases Prevalence as Excess Odds Ratios (EORs)* |
|---------------------------------|------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
<th>EOR per Sv</th>
<th>95% CI</th>
<th>P Value</th>
<th></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>
<td></td>
<td></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>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
<tr>
<td>Other§</td>
<td>258 (8.1)</td>
<td>1.67 (0.93 to 2.83)‡</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyst</td>
<td>244 (7.7)</td>
<td>0.89 (0.48 to 1.47)</td>
<td>&lt;.001</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive TPOAb</td>
<td>427 (13.4)</td>
<td>0.01 (−0.12 to 0.19)</td>
<td>.91</td>
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<td></td>
</tr>
<tr>
<td>Positive TgAb</td>
<td>761 (23.9)</td>
<td>−0.04 (−0.13 to 0.05)</td>
<td>.52</td>
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<td></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>
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<td></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>
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<td></td>
</tr>
<tr>
<td>Graves disease</td>
<td>38 (1.2)</td>
<td>0.49 (−0.06 to 1.69)</td>
<td>.10</td>
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<td></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.
Figure 3. Trend for Age at Exposure in Radiation Dose Response for Thyroid Diseases

The curves display the trend for age at exposure in excess odds ratio per Sv based on the best-fitting model. The points are excess odds ratios per Sv in each age at exposure category with 95% confidence intervals, plotted at the mean age for each age category. The age at exposure shown on the plot represents 0 through 9, 10 through 19, and ≥20 years. *P values are calculated by likelihood ratio test.

*Indicates detectable limit.

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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. However, the early suggestions that specific rearrangements of the ret proto-oncogene may be a marker for radiation exposure have not been substantiated.

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. 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, through medical irradiation, and in atomic bombings. 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 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 but not in others, women were at greater risk for radiation-induced thyroid diseases than were men.

Reports of 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. Eheman et al 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%). 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. 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. Most previous epidemiologic studies of atomic bomb survivors have not supported the association between radiation exposure and thyroid autoimmunity. However, the study conducted in Nagasaki AHS members...
from 1984 through 1987 demonstrated a convex dose-response relation-
ship in antithyroid antibody–positive hypothyroidism, with maximum prev-
alence at a dose of 0.7 Sv, based on the DS86.54 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 differ-
et diagnostic techniques used for measuring levels of thyroid antibodies and TSH, and (3) change of dose dis-
tribution of the cohort members over time because mortality and cancer risks are partially dependent on radia-
tion dose.55 Furthermore, we made diagnoses on the basis of serum test results at a single point in both stud-
ies, 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 re-
ported that Graves disease was in-
duced by radioiodine therapy for func-
tional or nonfunctional thyroid nodules,54-58 but individuals with such nodules in those studies were irradi-
ated using much higher doses than the exposures in participants in our study. An epidemiologic study evaluating chil-
dren 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.59 Future epidemiologic stud-
ies on irradiated persons, animal stud-
ies, and molecular-biological studies are necessary to more accurately investi-
gate 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 dis-
ases might have tended to agree to par-
ticipate, possibly creating a motiva-
tion bias in this study. Participants in this study had more nodular thyroid diseases diagnosed before this study than did nonparticipants, while no differ-
ence in prevalence of previously di-
agnosed nonnodular thyroid diseases was observed (Table 1). However, because the participation rate was very high (89.9%), we believe that a pos-
sible bias due to motivation does not affect the overall conclusion.

Second, a survival bias exists in this study. Median life expectancy de-
creases with increasing radiation dose at rate of about 1.3 years per Gy,60 sug-
uggesting 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 structured. Fur-
thermore, not only mortality but also cancer risks partially depend on radia-
tion 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 nod-
ules persisted after exposure because the present cross-sectional study was conducted 55 to 58 years after the atomic bombings. In the study of child-
hood radiation treatment, it was demon-
strated that increased risk for thy-
roid cancer continued for as long as 40 years after exposure.3,47 Furthermore, in atomic bomb survivors, a radiation-
related excess cancer rate was still ob-
served, based on cancer deaths from 1988 through 1997.53 Thus, the ef-
effects of radiation on thyroid nodules may exist long after radiation expo-
sure in atomic bomb survivors.

CONCLUSION

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

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Study concept and design: Imaizumi, USA, Tomimaga, Neriishi, Akahoshi, Nakashima, Ashizawa, Fujiwara, Yamada, Yokoyama, Suzuki, Maeda, Nagataki, Eguchi.

Analysis and interpretation of data: Imaizumi, USA, Tomimaga, Neriishi, Akahoshi, Nakashima, Ashizawa, Hida, Soda, Fujiwara, Yamada, Ejima, Yokoyama, Okubo, Suzuki, Maeda.

Drafting of the manuscript: Imaizumi.

Critical revision of the manuscript for important in-

Statistical analysis: Nakashima.

Study supervision: Akahoshi, Maeda, Nagataki, Eguchi.

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