Thyroid Dysfunction and Autoimmune Thyroid Diseases Among Atomic Bomb Survivors Exposed in Childhood

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Context: The risk of thyroid cancer increases and persists for decades among individuals exposed to ionizing radiation in childhood, although the long-term effects of childhood exposure to medium to low doses of radiation on thyroid dysfunction and autoimmune thyroid diseases have remained unclear.

Objective: To evaluate radiation dose responses for the prevalence of thyroid dysfunction and autoimmune thyroid disease among atomic bomb survivors exposed in childhood.

Design, Setting, and Participants: Hiroshima and Nagasaki atomic bomb survivors who were younger than 10 years old at exposure underwent thyroid examinations at the Radiation Effects Research Foundation between 2007 and 2011, which was 62 to 66 years after the bombing. Data from 2668 participants (mean age, 68.2 years; 1455 women) with known atomic bomb thyroid radiation doses (mean dose, 0.182 Gy; dose range, 0 to 4.040 Gy) were analyzed.

Main Outcome and Measures: Dose-response relationships between atomic bomb radiation dose and the prevalence of hypothyroidism, hyperthyroidism (Graves’ disease), and positive for antithyroid antibodies.

Results: Prevalences were determined for hypothyroidism (129 cases, 7.8%), hyperthyroidism (32 cases of Graves’ disease, 1.2%), and positive for antithyroid antibodies (573 cases, 21.5%). None of these was associated with thyroid radiation dose. Neither thyroid antibody–positive nor –negative hypothyroidism was associated with thyroid radiation dose. Additional analyses using alternative definitions of hypothyroidism and hyperthyroidism found that radiation dose responses were not significant.

Conclusions: Radiation effects on thyroid dysfunction and autoimmune thyroid diseases were not observed among atomic bomb survivors exposed in childhood, at 62 to 66 years earlier. The cross-sectional design and survival bias were limitations of this study.

Abbreviations: AHS, Adult Health Study; CI, confidence interval; EOR, excess odds ratio; FT4, free thyroxine; LEOR, linear excess odds ratio; RERF, Radiation Effects Research Foundation; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody; TSH, thyroid-stimulating hormone.
Extrinsic radiation exposure of the thyroid to high therapeutic doses (several 10s Gy) is well known to cause hypothyroidism in patients with head-and-neck cancer (1–3), Hodgkin lymphoma (4, 5), or acute lymphoblastic leukemia (6). Internal radiation exposure by radioactive iodine treatment of hyperthyroidism also causes hypothyroidism (typical dose range from 30 to >100 Gy). Furthermore, high-dose radiation exposure to the thyroid has been suggested to induce hyperthyroidism after treatment of Hodgkin lymphoma (4, 5) and acute lymphoblastic leukemia (6), as well as radioactive iodine treatment of nontoxic nodular goiter (7).

In contrast, effects of radiation exposure to medium to low doses (<5 Gy) on thyroid dysfunction and autoimmune thyroid diseases have been inconclusive in studies among people exposed to nuclear weapons testing in the Marshall Islands (8), the Mayak nuclear weapons facility (9), the Hanford nuclear site (10), the Nevada nuclear test site (11), and the Chernobyl nuclear accident (12–16). Inconsistent results might be in part attributable to the differences in methods and diagnostic criteria used for case ascertainment. Moreover, few studies have analyzed radiation dose responses based on estimated thyroid radiation dose. Recent reports of post-Chernobyl studies among Ukrainian and Belarusian children and adolescents have demonstrated significant dose-response relationships for subclinical hypothyroidism based on estimated individual 131I thyroid doses (17, 18).

Studies of thyroid cancer risk among radiation-exposed populations have suggested a higher radiation sensitivity of the thyroid in children than in adults (19–24). Among atomic bomb survivors, whose thyroid radiation doses are estimated to range from 0 to ~4 Gy, the thyroid cancer risk increased sharply with decreasing age at exposure and has persisted for >50 years since exposure (24). Not only the risk of thyroid cancer, but also the risk of benign thyroid nodule increased with younger age at exposure >50 years earlier (25). These results suggest that the thyroid glands of children are radiation sensitive and the influence persists for decades.

To evaluate long-term effects of radiation on the thyroid in childhood, at a stage considered to be radiation sensitive, we conducted a comprehensive thyroid disease survey of 2668 atomic bomb survivors exposed in childhood at <10 years old. We have previously reported significant risks of cancer (1–3), Hodgkin lymphoma (4, 5), or acute lymphoblastic leukemia (6). Internal radiation exposure by radioactive iodine treatment of hyperthyroidism also causes hypothyroidism (typical dose range from 30 to >100 Gy). Furthermore, high-dose radiation exposure to the thyroid has been suggested to induce hyperthyroidism after treatment of Hodgkin lymphoma (4, 5) and acute lymphoblastic leukemia (6), as well as radioactive iodine treatment of nontoxic nodular goiter (7).

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To evaluate long-term effects of radiation on the thyroid in childhood, at a stage considered to be radiation sensitive, we conducted a comprehensive thyroid disease survey of 2668 atomic bomb survivors exposed in childhood at <10 years old. We have previously reported significant risks of thyroid nodules in this population (26). In the present study, we evaluated radiation dose-response relationships for the prevalence of thyroid dysfunction and autoimmune thyroid disease. Because different diagnostic criteria might contribute to inconsistent results between studies, we tried to use several alternative diagnostic criteria, including those used in post-Chernobyl cohort studies.

Methods

Participants

The Adult Health Study (AHS) is a clinical program established in 1958 by the Radiation Effects Research Foundation (RERF) as a subset of the Life Span Study to examine the late effects of atomic bomb exposure (27, 28). Participants of this study were divided into two groups, the original AHS cohort members and the expanded AHS cohort members (26). Among the original members who were younger than 10 years at exposure, 1639 individuals were invited to the RERF for a health examination during the examination period between 1 October 2007 and 19 October 2011, excluding those who were unable to visit the RERF due to being sick or hospitalized (n = 92), with no knowledge of thyroid examination. Among them, 1141 visited the RERF and were asked to participate in the thyroid study, and 1133 (69.1%) agreed to and completed thyroid examinations. During the same period, 2966 individuals of the Life Span Study cohort, who were younger than 10 years at exposure and lived in or near Hiroshima or Nagasaki, were invited to the RERF for a health examination to increase the number of radiation-exposed subjects who were exposed at young ages in the AHS cohort (26, 29). Among them, 1961 (the expanded AHS cohort members) visited the RERF and were asked to participate in the thyroid study, and 1954 (65.9%) agreed to and completed thyroid examinations. Thus, a total of 3087 AHS cohort members who were younger than 10 years at exposure participated in the study. We excluded 419 participants [367 exposed in utero and 52 with unknown radiation dose according to the dosimetry system 2002 (30), leaving 2668 participants for analysis. The final analysis cohort included 714 original AHS cohort members (including 600 who had been examined in the RERF thyroid study conducted between 2000 and 2003) and 1954 expanded AHS cohort members. Women comprised 1455 (54.5%) of the analysis cohort, and 1748 (65.5%) were exposed in Hiroshima. Thyroid radiation doses ranged from 0 to 4.040 Gy (mean, 0.182 Gy; median, 0.018 Gy). Age at exposure was <10 years, with a mean ± standard deviation of 4.1 ± 2.6 years and a median of 4 years (interquartile range, 2 to 6 years). Age at examination ranged from 62 to 75 years, with a mean of 68.2 ± 2.7 years and a median of 68 years (interquartile range, 66 to 70 years).

This study was reviewed and approved by an RERF institutional ethics committee, the Human Investigation Committee, and written informed consents were obtained from all participants prior to enrolment.

Clinical examination and laboratory methods

We used the same examination and laboratory methods applied in our previous study (25). Participants visited the Hiroshima and Nagasaki laboratories for biennial clinical examinations. A trained nurse recorded information such as current and past thyroid disease and thyroid medication using a questionnaire. A blood sample was drawn to measure levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory to measure all antibody (TgAb). Serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory for biennial clinical examinations. A trained nurse recorded information such as current and past thyroid disease and thyroid medication using a questionnaire. A blood sample was drawn to measure levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory to measure all antibody (TgAb). Serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory for biennial clinical examinations. A trained nurse recorded information such as current and past thyroid disease and thyroid medication using a questionnaire. A blood sample was drawn to measure levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Serum samples obtained in Hiroshima were frozen and sent to the Nagasaki laboratory to measure all
Hercules, CA) was used for quality control at every measurement. Levels of TPOAb and TgAb were measured by enzyme-linked immunosorbent assay (Medical and Biological Laboratories, Nagoya, Japan).

**Diagnostic criteria**

Definitions of thyroid dysfunction and autoimmune thyroid diseases are shown in Table 1. Diagnoses of disease outcomes were made based on laboratory results, RERF medical records, and medical information obtained from clinics or hospitals. Primary outcomes were hypothyroidism, hyperthyroidism, positive for antithyroid antibodies as markers of autoimmune thyroiditis, and Graves’ disease. Hypothyroidism was further divided into antithyroid antibody–positive and –negative hypothyroidism. Reference ranges for FT4 and TSH were 0.71 to 1.52 ng/dL (9.1 to 19.6 pmol/L) and 0.41 to 3.9 mIU/L, respectively. Participants were classified as positive for antithyroid antibodies if the serum concentration of either TPOAb or TgAb was $\geq$10 IU/mL. All diagnoses of thyroid diseases were made by investigators blinded to thyroid radiation doses.

**Statistical analysis**

We used the same statistical method used in the previous publications to analyze dose responses for thyroid diseases (25, 26). For a thyroid disease prevalence $p$ depending on city, sex, age at exposure, and radiation dose, the linear excess odds ratio (LEOR) model (25, 31) for dose was assumed as $p(1 - p) = BGM(1 + \beta \times d \times EM)$, where the background model (BGM), which is thought of as an odds for the 0 Gy group, is assumed as a log linear in terms of city (0 for Hiroshima, 1 for Nagasaki), sex (0 for male, 1 for female), age at exposure (age at exposure in years, $s$), and second-order interactions, and the log-linear effect modifier (EM term) consists of the main effects of city, sex, and age at exposure. Radiation dose $d$ is the dosimetry system 2002 weighted total thyroid dose (Gy) with an assigned relative biological effectiveness for neutrons of 10, as the sum of the $\gamma$ and 10-fold the neutron thyroid doses. These thyroid doses were truncated at 4 Gy, adjusted for 35% dose measurement error (32, 33), to reduce radiation risk estimation bias (25, 26). Parameter $\beta$ is a linear dose-response parameter interpreted as the excess odds ratio (EOR) per gray at the covariate value of EM term = 1 corresponding to Hiroshima males at 5 years of age at exposure. The LEOR model with no dose effect modifier ($EM = 1$ fixed) was used for the test of dose response at first, and we then checked the dose effect modifiers when the main dose effect was significant. For the individual binary data of a thyroid disease, the GMBO binary regression program in the Epicure software (31) for the LEOR model was used to obtain maximum-likelihood estimates of parameters. We made a complete data analysis due to the small number of missing data (52 subjects with dose unknown), representing $\sim$2% of the complete data set ($n = 2668$).

For the best model selection in terms of prediction, we used the Akaike information criterion model selection criterion with the minimum Akaike information criterion model selection procedure (34, 35). In the present analysis, the LEOR model did not provide worse fit to the data compared with the usual linear-logistic model in the Akaike information criterion, except for hypothyroidism and hyperthyroidism by Chernobyl criteria. The 95% confidence intervals (CIs) and two-sided $p$ values of the significance tests were based on the likelihood ratio statistics. Dose category-specific odds ratios with 95% CIs are reported by dose groups defined as $<0.005$ Gy, 0.005 to 0.499 Gy, 0.5 to 0.999 Gy, 1.0 to 1.999 Gy, and $\geq2.0$ Gy, with persons exposed to $<0.005$ Gy serving as a reference group.

**Results**

**Primary outcomes of thyroid dysfunction and autoimmune thyroid diseases**

Case numbers and prevalences of primary outcomes by thyroid radiation dose categories in men and women are shown in Table 2. Prevalences of all categories in women were about double those in men.

Among 129 hypothyroid cases, 37 were diagnosed by abnormal thyroid function test (high TSH and low FT4 levels) at the examinations, and 92 were being prescribed thyroid hormone replacement therapy due to spontaneous hypothyroidism irrespective of thyroid function at the examinations. All 32 cases of hyperthyroidism were diagnosed as Graves’ disease by having history of treatment of Graves’ disease | surgery ($n = 2$), radiiodine

<table>
<thead>
<tr>
<th>Table 1. Definitions of Primary Outcomes</th>
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<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Antithyroid antibody–positive hypothyroidism</td>
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<tr>
<td>Antithyroid antibody–negative hypothyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Graves’ disease</td>
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<tr>
<td>Positive for antithyroid antibodies</td>
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*“Thyroid treatment” indicates thyroid ablation with radiiodine therapy, external thyroid radiation, thyroid surgery, or use of antithyroid drugs.
therapy (n = 5), and/or use of antithyroid drugs (n = 29); no cases of toxic adenoma or toxic multinodular goiter were detected. Among Graves’ disease cases, 11 were using antithyroid drugs and five had abnormal thyroid function tests (low TSH and high FT4 levels) at the time of examinations. Four other participants had low TSH and high FT4 levels at the time of examination and were referred to clinics and ultimately diagnosed as painless thyroiditis because their thyroid dysfunctions were transient. Positive TPOAb and TgAb prevalences were 11.9% (9.3% in men and 14.0% in women) and 17.8% (12.1% in men and 22.6% in women), respectively.

In the analyses of radiation dose responses for thyroid diseases, no significant dose responses were observed for hypothyroidism, hyperthyroidism (Graves’ disease), positive for antithyroid antibodies, or antithyroid antibody–positive or –negative hypothyroidism (Table 3; Fig. 1). Radiation dose responses were separately analyzed among subgroups with positive for TPOAb and positive for TgAb, but no significant responses were observed (EOR/Gy = −0.20, P = 0.09 and EOR/Gy = −0.14, P = 0.16, respectively; data not shown in Table 3).

Alternative definitions of outcomes
We further conducted additional analyses using alternative definitions of hypothyroidism and hyperthyroidism. Five alternative definitions of hypothyroidism were considered: (1) hypothyroidism alternative definition including past history of thyroid hormone replacement therapy for hypothyroidism (n = 158, 5.9%); (2) hypothyroidism including subclinical hypothyroidism (n = 386, 14.5%); (3) hypothyroidism diagnosed by the same criteria used for post-Chernobyl cohorts (17, 18) (n = 246 out of 2200 subjects excluding those with a self-reported history of any thyroid disease or thyroid hormone intake, 11.2%); (4) antithyroid antibody–positive hypothyroidism including subclinical hypothyroidism (n = 114, 4.3%); and (5) antithyroid antibody–negative hypothyroidism including subclinical hypothyroidism (n = 272, 10.2%). All disease categories had higher prevalences in women than in men; for example, the prevalence of hypothyroidism including subclinical hypothyroidism was 12.4% in men and 16.2% in women. In the radiation dose-response analyses using either alternative definition, prevalence of hypothyroidism was not significantly associated with thyroid radiation dose (P ≥ 0.14).

Four alternative definitions of hyperthyroidism were considered: (1) thyrotoxicosis including destructive thyroiditis (n=36, 1.3%); (2) hyperthyroidism alternative definition excluding remission cases for those who previously received treatment of hyperthyroidism (n = 15, 0.6%); (3) hyperthyroidism including subclinical hyperthyroidism (n = 46, 1.7%); and (4) hyperthyroidism diagnosed by the same criteria used for post-Chernobyl cohorts (18, 36) (n = 14 out of 2200 subjects, 0.6%). Prevalences of all disease categories were higher in women than in men; for example, prevalence of hyperthyroidism including subclinical hyperthyroidism was

### Table 2. Case Numbers and Prevalences of Primary Outcomes by Thyroid Radiation Dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thyroid Radiation Dose (Gy), n (%)</th>
<th>Total (n = 2668)</th>
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<tbody>
<tr>
<td>Overall</td>
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<td>Men</td>
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<td>Women</td>
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<tr>
<td>Hypothyroidialism</td>
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<td>Men</td>
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<td>Women</td>
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<tr>
<td>Antithyroid antibody–positive hypothyroidism</td>
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<td>Men</td>
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<tr>
<td>Women</td>
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<tr>
<td>Antithyroid antibody–negative hypothyroidism</td>
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<td>Men</td>
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<tr>
<td>Women</td>
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<td></td>
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<tr>
<td>Hyperthyroidism (Graves’ disease)</td>
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<td>Men</td>
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<td>Women</td>
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<td>Positive for antithyroid antibodies</td>
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<td>Men</td>
<td></td>
<td></td>
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<tr>
<td>Women</td>
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1.0% in men and 2.3% in women. Again, using either of these alternative definitions, the prevalence of hyperthyroidism was not significantly associated with thyroid radiation dose ($P_{\geq 0.29}$).

**Discussion**

The present study focuses on thyroid dysfunction and thyroid autoimmunity among Hiroshima and Nagasaki atomic bomb survivors exposed in childhood who were considered sensitive to radiation. Because different diagnostic criteria might have contributed in part to inconsistent results of thyroid dysfunction and thyroid autoimmunity between studies of radiation-exposed populations, we evaluated radiation dose responses with individual thyroid doses for various outcome definitions used by several alternative diagnostic criteria. No significant associations for any outcomes with thyroid doses were observed in this study.

Cross-sectional studies relating to thyroid function and antithyroid antibodies have been conducted since the 1970s for atomic bomb survivors. Until the early 1980s, individual organ radiation doses were not available. Therefore, tentative dose estimates (37) were used and inconsistent results were observed in differences between control and exposed groups in rates of hypothyroidism (38–40). In studies after the late 1980s analyzing radiation dose responses using estimated individual thyroid dose (30, 41), no association between thyroid dose and prevalences of positive for antithyroid antibodies (25, 42, 43), hypothyroidism (25, 42), hyperthyroidism (42), or Graves’ disease (25) were observed. Although a significant convex dose response was observed for thyroid antibody–positive hypothyroidism among Nagasaki atomic bomb survivors in the study of 1980s (42), this finding was not confirmed among Hiroshima and Nagasaki atomic bomb survivors in the study of 2000s (25). However, these studies could not focus on the effects of radiation exposure in childhood because of the relatively small number of participants exposed in childhood (25, 42, 43) [maximum number was 710 in Imaizumi et al. (25)]. The results of the present study focusing on survivors exposed in childhood (n = 2668) are almost in line with those from previous studies of all-exposure aged survivors, indicating no dose responses for thyroid dysfunction or autoimmunity.

Previous studies of thyroid dysfunction and thyroid autoimmunity in radiation-exposed populations have been thoroughly reviewed by Eheman et al. (44) and Ron and Brenner (45). A few studies have been conducted for studying medium to low dose responses based on estimated individual thyroid dose for hypothyroidism with adequate sample sizes. In the Hanford thyroid disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases (%) (n = 2668)</th>
<th>EOR/Gy (95% CI)</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>129 (4.8)</td>
<td>0.05 (−0.23, 0.62)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Antithyroid antibody–positive hypothyroidism</td>
<td>57 (2.1)</td>
<td>−0.03 (ND, 0.81)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Antithyroid antibody–negative hypothyroidism</td>
<td>72 (2.7)</td>
<td>0.16 (−0.26, 1.11)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Hyperthyroidism (Graves’ disease)$^a$</td>
<td>32 (1.2)</td>
<td>0.23 (ND, 1.87)</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Positive for antithyroid antibodies</td>
<td>573 (21.5)</td>
<td>−0.15 (−0.27, 0.05)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

EOR/Gy (95% CI) indicates EOR per gray (95% CI) for individuals 5 years old at exposure based on the selected best model.

Abbreviation: ND, not determined.

$^a$All hyperthyroidism cases were diagnosed with Graves’ disease.

**Figure 1.** Dose-response for thyroid dysfunction and autoimmune thyroid diseases. The straight line displays the odds ratio from the best fitting linear excess odds ratio model for age 5 years old at exposure. Points represent dose category–specific odds ratios with 95% CIs. Dose categories shown on the plots represent <0.005 Gy, 0.005 to 0.499 Gy, 0.5 to 0.999 Gy, 1.0 to 1.999 Gy, and $\geq$2.0 Gy.
study, no significant dose responses for hypothyroidism were seen despite the use of various outcome definitions (10). In post-Chernobyl studies among children and adolescents who were exposed to radiation doses between low and high, significant associations between subclinical hypothyroidism as defined by TSH levels and thyroid doses (0 to 40.8 Gy in the Ukrainian cohort; 0.001 to 26.64 Gy in the Belarusian cohort) were observed (17, 18). However, these significant associations disappeared in analyses limited to the subjects with lower dose ranges (<3 Gy in the Ukrainian cohort and <5 Gy in the Belarusian cohort). These findings are in agreement with the present result showing no significant dose response at <4 Gy for hypothyroidism diagnosed using the same criteria.

Inconsistent results have been observed regarding associations between positive for antithyroid antibodies and medium- to low-dose radiation exposure (10, 11, 18, 46). Alternatively, in studies of autoimmune hypothyroidism (or thyroid antibody–positive hypothyroidism), no significant radiation risk was observed in the Nevada test site cohort (11), Hanford thyroid disease study (10), and Chernobyl cohort studies (17, 18, 46, 47), irrespective of the results of radiation risks for antithyroid antibodies. Present reports do not support positive radiation effects on clinically relevant hypothyroidism caused by thyroid autoimmunity. An association between antithyroid antibody–negative hypothyroidism and radiation dose was not assessed in other radiation-exposed populations (10, 11, 17, 18, 46, 47). In the present study, no significant association was observed, suggesting that exposed radiation doses (<4 Gy) might not be high to induce hypothyroidism. Reported exposed radiation doses to induce hypothyroidism are several 10s Gy (1–6). In Japan, it is suggested that excessive iodine intake from seaweeds may be associated with antithyroid antibody–negative hypothyroidism (48, 49).

The data concerning the risk of hyperthyroidism from radiation exposure at medium to low thyroid doses are limited even in all exposure aged subjects (18, 36, 50). So far, no significant radiation effects have been observed in any studies, the same as in the present study. Careful diagnoses are needed for hyperthyroidism, as a heterogeneous disease category including autoimmune disease (Graves’ disease), functional tumors (toxic nodules) and others, and destructive thyroiditis representing transient thyrotoxicosis (decreased TSH level) is sometimes misdiagnosed as hyperthyroidism. In Japan, most cases of hyperthyroidism are Graves’ disease, whereas up to 60% of hyperthyroidism cases involve toxic nodules in iodine-deficient areas (51). In the present study, we carefully diagnosed Graves’ disease as shown in Table 1 and demonstrated no dose response. Because data in this field are very sparse, more studies of other radiation-exposed cohorts with clear diagnoses are necessary.

The present study clearly suggested no significant radiation dose responses for thyroid dysfunctions or autoimmune thyroid diseases. Careful attention is necessary when we try to simply compare prevalences in the present study to those in other studies conducted in a general population, because prevalences of thyroid dysfunctions and autoimmune thyroid diseases are largely affected by backgrounds of subjects such as age, sex, race (52), and diagnostic method and criteria. Kasagi et al. (53) reported prevalences of thyroid dysfunction detected by a general health checkup system in Japan according to age and sex categories. The prevalences in the study were similar to those in the present study; increased TSH (hypothyroidism including subclinical hypothyroidism), decreased TSH (hyperthyroidism including subclinical hyperthyroidism), positive for TgAb, and positive for TPOAb were detected in 21.1%, 2.6%, 30.7%, and 14.9% among women at age >60 years in the Kasagi et al. study and in 16.2%, 2.3%, 22.6%, and 14.0% among women at age 62 to 75 years in the present study, respectively, although diagnostic criteria were not exactly the same in these studies.

Strengths of the present study were the precise diagnoses of thyroid diseases, as well as the use of estimated individual thyroid radiation doses. We used not only TSH, but also FT4 measurements for the diagnosis of thyroid dysfunction, because 30% to 50% of subclinical hypothyroidism diagnosed by increased TSH alone is known to be transient (54, 55). Furthermore, we considered not only levels of thyroid function test, but also thyroid medication for diagnoses of thyroid diseases, which could avoid missing cases. Although some hypo-thyroid cases under thyroid hormone replacement therapy might have had subclinical hypothyroidism before therapy, a possible bias would be limited because mild subclinical hypothyroid patients with <10 mIU/L of TSH levels are usually untreated in clinical practice (56) and a dose response for hypothyroidism including subclinical hypothyroidism was not significant.

Key limitations of this study were the cross-sectional design and the survival bias. We could not examine time-dependent changes in radiation effects. The risk of cancer mortality reportedly increases with radiation dose for most major sites (57), and median life expectancy decreases with increasing radiation dose, suggesting that a survival bias was most likely present in the cohort of this study, particularly among subjects exposed to high-dose radiation (58). The results might therefore have been affected by radiation-associated early deaths. However, considering significant associations between thyroid cancer and nodules and radiation dose in the same cohort member.
examined >60 years after radiation exposure (26), the present results suggested that radiation effects on thyroid dysfunction and autoimmune thyroid diseases are, at least, less than those on thyroid cancer and nodules. We should also consider that a bias from differences between the original cohort members and the newly expanded members might exist such as in a motivation to participate and a past history of thyroid examinations. We were unable to conduct analyses considering the influences of concomitant diseases or pharmacotherapies that might have affected thyroid function. However, we carefully conducted case asertnments of primary outcomes using medical information from other clinics and hospitals and excluding the subclinical thyroid dysfunction caused by those factors.

Conclusion
The present study, conducted 62 to 66 years after the atomic bombings, showed that radiation effects on thyroid dysfunction and autoimmunity were not apparent among atomic bomb survivors exposed in childhood, who were considered to be radiation sensitive. Considering previous studies, we suppose that radiation exposure <4 Gy may not increase the risks of thyroid dysfunction or autoimmune thyroid diseases among atomic bomb survivors beyond several decades after radiation exposure. However, we are aware of the fact that further studies are necessary before such speculation can be generalized to other radiation-exposed populations. Although relationships between radiation exposure and thyroid dysfunction and autoimmunity have been fairly weak in studies, including the present investigation, careful interpretations are needed because limited data from cross-sectional studies are available. Longitudinal studies are needed for better understanding in this field.

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