Thyroid Diseases Among Atomic Bomb Survivors in Nagasaki

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Objective.—To elucidate the current thyroid disease status for the Nagasaki Adult Health Study cohort of the Radiation Effects Research Foundation.

Design.—Survey study.

Setting.—Nagasaki, Japan.

Participants.—Cohort members of the Nagasaki Adult Health Study who received biennial health examinations from October 1984 to April 1987 (n=2856). A total of 2587 subjects remained after exclusion of persons exposed in Hiroshima or in utero and those who were not in Nagasaki at the time of the bombing. Thyroid radiation dose by the dosimetry system established in 1986 was available for 1978 of the 2587 subjects.

Main Outcome Measures.—Thyroid diseases were diagnosed using uniform procedures including ultrasonic scanning. The relationship of the prevalence of each thyroid disease with thyroid radiation dose, sex, and age was analyzed using logistic models.

Results.—A significant dose-response relationship was observed for solid nodules, which include cancer, adenoma, adenomatous goiter, and nodules without histological diagnosis, and for antibody-positive spontaneous hypothyroidism (autoimmune hypothyroidism) but not for other diseases. The prevalence of solid nodules showed a monotonic dose-response relationship, yet that of autoimmune hypothyroidism displayed a concave dose-response relationship reaching a maximum (±SE) level of 0.7±0.2 Sv.

Conclusions.—The present study confirmed the results of previous studies by showing a significant increase in solid nodules with dose to the thyroid and demonstrated for the first time a significant increase in autoimmune disease among atomic bomb survivors. A concave dose-response relationship indicates the necessity for further studies on the effects of relatively low doses of radiation on thyroid disease.

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THE EXPLOSION of nuclear weapons or accidents at nuclear power plants can affect the thyroid gland. Patients with radiation-induced thyroid disease can be separated into two groups: those exposed to radiation at the time of detonation or to radioactive fallout (external radiation) and those exposed to radioactive iodine that accumulates within the thyroid (internal radiation).

Patients with radiation-induced thyroid disease can survive for a long time with treatment and often survive even without treatment. Therefore, a survey of subjects with radiation-induced thyroid disease can be conducted using the same protocol to examine all subjects in a certain cohort at the same time. In normal controls, the prevalence of thyroid disease is higher than that of other radiation-induced diseases, which is an advantage for epidemiologic studies. For these reasons, the thyroid is an ideal organ for the investigation of the health effects of the atomic bomb explosions, nuclear tests, and accidents at nuclear power plants.

To investigate the health effects of radiation on the thyroid, it is essential to (1) determine the exact thyroid radiation dose, (2) make a correct diagnosis of thyroid diseases, and (3) analyze the results by the most appropriate statistical method.

The present study was undertaken to determine a useful model for the investigation of radiation-induced thyroid diseases. Using the most recent techniques and knowledge of thyroidology and the most appropriate statistical methods, we surveyed subjects in a carefully followed-up cohort of atomic bomb survivors 40 years after the atomic bomb explosion in Nagasaki, Japan.

The results suggest that in addition to an increased prevalence of thyroid nodules, which confirmed previously published data, the prevalence of antibody-positive spontaneous hypothyroidism (autoimmune thyroiditis) is increased. To our knowledge, this is the first report of a significant increase in the number of atomic bomb survivors with autoimmune disease.

SUBJECTS AND METHODS

Subjects

The subjects in the present study were cohort members of the Nagasaki Adult Health Study (AHS) (started in 1958 with about 6000 atomic bomb survivors in Nagasaki) who visited the Nagasaki Laboratory of the Radiation Effects Research Foundation (RERF) for biennial health examinations from October 1984 to April 1987. A total of 2856 subjects participated in the study, but we excluded two subjects who were exposed in Hiroshima, 79 who were exposed in utero, and 188 who were not in Nagasaki at the time of the bombing. Therefore, the total number of study subjects was 2587 (1001 men and 1586 women). The 2587 subjects were used as study subjects for all studies except the radiation dose-response relationship, in which 1978 subjects (752 men and 1226 women) with Dosimetry System 1986 (DS86) estimates were examined.

Table 1 shows a breakdown of the subjects classified by thyroid radiation dose in sieverts (1 sievert=100 rem), age (in years) at the time of the bombing (ATB), and sex. The thyroid radiation dose of individual subjects is estimated by DS86.[1] The subjects whose DS86 es-

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Table 1.—Classification of Subjects by Dosimetry System 1986 (DS86) Dose to the Thyroid, Age at the Time of the Bombing (ATB), and Sex

Age ATB, y, and Sex	DS86 Dose to the Thyroid, Sv*							Total
	0	0.01-0.49	0.50-0.99	≥1.0	Unavailable	Unknown	Mean±SE† (range)	
0-9								
M	68	37	22	38	18	8	0.60±0.08 (0-5.85)	**191**
F	74	42	34	31	18	12	0.55±0.07 (0-5.55)	**211**
10-19								
M	169	41	67	62	75	34	0.50±0.04 (0-5.44)	**448**
F	270	73	103	99	158	46	0.46±0.03 (0-4.80)	**749**
20-29								
M	51	17	15	21	40	18	0.57±0.09 (0-5.41)	**162**
F	144	57	65	60	73	20	0.49±0.04 (0-5.47)	**419**
≥30								
M	82	19	16	27	50	6	0.39±0.05 (0-2.07)	**200**
F	77	47	22	28	25	8	0.42±0.05 (0-4.40)	**207**
Total								
M	370	114	120	148	183	66	...	**1001**
F	565	219	224	218	274	86	...	**1586**
Total	**935**	**333**	**344**	**366**	**457**	**152**	...	**2587**
Mean±SD of age (range)								
M	18.9±11.3 (0-52)	16.1±10.6 (0-39)	17.1±9.5 (0-43)	17.3±10.9 (0-52)	21.7±10.1 (1-50)	18.6±9.0 (1-44)	...	...
F	18.8±9.5 (0-48)	20.0±11.1 (0-48)	18.2±9.0 (0-44)	18.4±9.0 (0-40)	18.7±7.4 (0-46)	17.7±7.9 (1-41)	...	...

*Relative biological effectiveness=10. Ellipses indicate not applicable.
†Calculated for subjects with Dosimetry System 1986 dose.

timates were unavailable because of a lack of information concerning shielding conditions, which is necessary for the calculation, were classified as dose unavailable. The tentative 1965 dose (T65D) estimates[1] were available for these subjects. Exposure inside a concrete structure is typical of the dose-unavailable subjects. Many of the dose-unavailable subjects may have received a high dose; among the 457 dose-unavailable subjects in the present study, eight were exposed within 500 m of the hypocenter; 87, within 500 to 999 m; 304, within 1000 to 1499 m; 57, within 1500 to 1999 m; and one, within 2000 to 2499 m. The subjects with neither DS86 nor T65D estimates, because of complicated shielding conditions (eg, exposed under a tree, in a ship or a streetcar), were classified as dose unknown.

Procedure for Diagnosis of Thyroid Diseases

Histories.—All participants were asked for information on family history and individual history of thyroid disease or therapy.

Physical Examination and Ultrasonic Scanning of the Thyroid Gland.—Physicians in the Department of Clinical Studies at RERF performed the physical examinations. A high-resolution ultrasonic scanning technique developed for this study[2] was used to determine the thyroid volume and also to detect structural abnormalities. Since images of each cross section were recorded, several experts could examine the structural abnormalities. Enlargement of thyroid volume (goiter) was defined as a thyroid volume exceeding the following limits:

$\{[1.953-0.366\times\log_{10}(\text{age})]+[0.360 \times (\text{body weight})]\}^3$ for men and

$\{[1.867-0.366\times\log_{10}(\text{age})]+[0.360 \times(\text{body weight})]\}^3$ for women,

where age and body weight are the age in years and the weight in kilograms of a subject at the time of examination. These limits were derived from the data on normal subjects, as described herein.

Determination of the Normal Limit of Thyroid Volume.—A significant correlation between thyroid volume and a set of variates such as age, sex, and body weight has been suggested.[3] Therefore, an adjustment of thyroid volume in accordance with the variates is necessary to define the normal limit of thyroid volume. We selected subjects who satisfied the following conditions: (1) DS86 thyroid dose is less than 0.01 Sv (less than 1 mSv in effect); (2) the levels of thyroxine (T_4), triiodothyronine (T_3), and free T_4 are within normal ranges; (3) the results of antimicrosomal antibody (anti-MA) tests, thyroid function tests, and antithyroglobulin antibody (anti-TgA) tests are all negative; (4) the level of thyrotropin (TSH) is less than 6.0 mU/L; and (5) there is no thyroid disease.

A total of 576 subjects (250 men and 326 women) were selected. The distributions of cube roots of thyroid volume and body weight and the distribution of the base 10 logarithm of the age at the time of examination are closer to normal distributions than those of thyroid volume, body weight, and age. Consequently, we used the following linear model to determine the normal limit of thyroid volume:

$$\text{volume}=\gamma_0+\gamma_1\text{sex}+\gamma_2\text{logage}+\gamma_3\text{weight}+\epsilon,$$

where volume is a thyroid volume (in cubic centimeters), sex assumes a value of 1 for a man and 0 for a woman, logage and weight assume the base 10 logarithm of the attained age (in years) and the body weight (in kilograms) of a subject at the time of examination, respectively, and ϵ is a random variable normally distributed with mean 0 and unknown variance σ^2. We used program 1R of BMDP Statistical Software[4] to fit this model. Since the normal probability plot of the residuals suggested that the four largest values of thyroid volume are outliers, we excluded the subjects with thyroid volume exceeding 30.0 cm^3 and fit this model to the data of the remaining subjects. The parameter estimates (±SE) are as follows: $\gamma_0=1.494$, $\gamma_1=0.086$ (0.021), $\gamma_2=-0.366$ (0.133), $\gamma_3=0.360$ (0.050), and $\sigma=0.227$. We define the normal limit of thyroid volume as the point at which the normalized residual ϵ/σ exceeds the 95th standard normal percentile, eg, $z_{0.95}$. By substituting these estimates for the parameters in this model and letting $z_{0.95}$ be 1.645, we obtain the normal limit given in the text (Fig 1).

Tests for Thyroid Function and Anti-TgA.—A blood sample was taken from each participant to assay the following substances: TSH, T_4, free T_4, T_3, thyroglobulin (Tg), anti-MA, and anti-TgA. The normal ranges of TSH, T_4, free T_4, T_3, and Tg were determined from the instructions of the respective commercial kits, and the antithyroid antibody was deemed positive if either anti-MA or anti-TgA was positive in more than 100 times dilution.

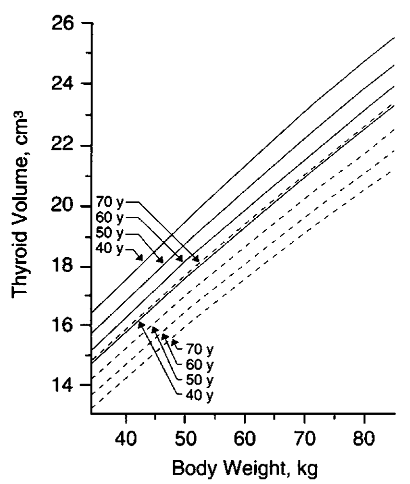

Fig 1.—Age- and sex-specific upper normal limits of thyroid volume. Solid line indicates men; dotted line, women.

Confirmation of Diagnosis of Thyroid Diseases.—Subjects with any physical or laboratory abnormalities were referred, if they so desired, to the First Department of Internal Medicine, Nagasaki University School of Medicine, for further evaluation. Approximately 600 of the 2856 subjects were examined at Nagasaki University. Only a few subjects who did not visit the university received final diagnosis at RERF by thyroid experts from the university.

Diagnostic Criteria

Uniform diagnostic criteria that can be applied to all subjects are essential. The following are the criteria used in the present study.

Thyroid Nodule.—Patients with either a history of thyroid nodules or nodules found by ultrasonic scanning (more than 5 mm in diameter) were considered to have thyroid nodules, and nodules were classified as either solid or cystic. Solid nodules were further classified by the results of histological examination either in the past or at the time of this study as (1) cancers, (2) adenomas, (3) adenomatous goiters, or (4) nodules without histological diagnosis. Cystic nodules without any solid components were defined as cysts, while cystic nodules with some solid components were designated as solid nodules without histological diagnosis.

Hypothyroidism.—Subjects with a serum TSH level of 10 mU/L or more and a free T_4 level lower than 10 pmol/L (0.78 ng/dL) were considered to have hypothyroidism. Patients receiving T_4 replacement therapy for whom less-than-normal thyroid hormone levels had been confirmed in the past were also given a diagnosis of hypothyroidism, regardless of hormone levels at the time of examination. Subjects with an elevated level of TSH but normal free T_4 were designated as having subclinical hypothyroidism. Both hypothyroidism and subclinical hypothyroidism were classified into two categories: postablative and spontaneous. Hypothyroidism after thyroid surgery or ablation with radioiodine was defined as postablative hypothyroidism, and hypothyroidism without any history of an ablated thyroid was defined as spontaneous hypothyroidism, which was further subclassified into autoantibody-positive and autoantibody-negative groups.

Hyperthyroidism.—The diagnosis of hyperthyroidism was made on the basis of clinical signs and symptoms of thyrotoxicosis and a free T_4 level of 32 pmol/L (2.5 ng/dL) or more with suppressed serum TSH levels. Patients with a history of thyrotoxicosis and elevated serum thyroid hormone levels were included in this category.

Diffuse Nontoxic Goiter.—A diagnosis of diffuse nontoxic goiter was established when none of the previously mentioned thyroid diseases was present, but the thyroid volume exceeded the limits described in "Procedure for Diagnosis of Thyroid Disease." Diffuse nontoxic goiter was classified into antibody-positive and antibody-negative groups.

Hashimoto's disease or autoimmune thyroiditis was not included in the classification of thyroid disease in the present study because the definition of the disease differs among experts,[5] except for the histological findings, which were difficult to obtain from all subjects in the present study. However, we used the criterion of autoimmune hypothyroidism, in which patients have increased serum TSH levels with or without decreased serum thyroid hormone levels (clinical or subclinical hypothyroidism) and positive thyroid autoantibodies, because there is much less disagreement regarding this criterion.

Dosimetry

The following quotation from the preface of the previously mentioned literature[1] will facilitate an understanding of the difference between the two dosimetry systems (annotation in brackets).

> This system [T65D] was formulated on the basis of data obtained at A-bomb tests in Nevada, the BREN experiment, and large-scale shielding experiments. The T65D estimates have been in use at ABCC [Atomic Bomb Casualty Commission] and RERF in Hiroshima and Nagasaki since 1965. However, criticism was raised regarding the computation system; consequently, dosimetry reassessment groups were established in 1981 in the United States and Japan.... Thanks to the dedicated efforts of these groups, a new dosimetry system called Dosimetry System 1986 [DS86] was developed. Whereas T65D was based on experimental data, the new dosimetry system was based on the establishment of an appropriate model and on computation by the Monte Carlo method. To verify the validity of this model, various experimental data and results of new measurements as well as those made in the past in Hiroshima and Nagasaki were employed. The DS86 dose estimates which have been developed are regarded as the best possible that can be made in view of the present scientific state of the art.

The organ dose to the thyroid determined by DS86 was used and the relative biological effectiveness of neutrons relative to γ rays was set at 10.

Each atomic bomb survivor may have received both external and internal radiation, and the external radiation could be either from the explosion or from fallout. However, no information is available on internal radiation due to radioactive fallout.

The only data currently available on radioactive fallout are the levels of radioactive cesium and plutonium in soil. Most of the radioactive materials fell in the east of the city because of the wind after the explosion.[6] Areas with increased levels of radioactive materials are similar to those affected by "black rain" after the explosion. No significant increase in radioactive cesium or plutonium was found in other areas. The residents in the fallout areas were not included in this study. Therefore, the thyroid dose in the present study is mostly due to external radiation from the explosion of the atomic bomb, which is expressed as DS86 organ dose to the thyroid.

The residents in the highest radioactive-fallout area were not exposed to direct external radiation because of hills lying between the hypocenter and this area, and the health effects of radioactive fallout in this area have been described previously.[7]

Statistical Analysis

The prevalence of each thyroid disease was analyzed using linear logistic models[8] with sex, age ATB, and DS86 organ dose to the thyroid as covariates. A quadratic term of dose was included to examine the linearity in the dose response along with the terms regarding the interactions between the covariate factors of sex, age ATB, and dose. We restricted the models in the class to make them hierarchical[8] in the sense that an interaction term is included in the model only if the corresponding main factors are all included in the model. The most appropriate model was selected for each thyroid disease by means of deviance[9]: when a model with the interaction of dose with sex was selected, the most appropriate model was selected separately for men and women in the subclass of the models of the similar form.

Once the most appropriate model was selected for each thyroid disease, significance tests of parameters in the model were conducted using likelihood ratio statistics. The program LR of BMDP Statistical Software[4] was used for the calculations.

RESULTS

Diagnosis

Among the 2587 study subjects, thyroid diseases including subclinical hypothyroidism were diagnosed in 447 (17.3%), consisting of 112 men (11.2%) and 335 women (21.1%). Table 2 gives a breakdown of the subjects classified by sex and dose. Two or more diagnoses were given to 17 subjects: eight with postablative hypothyroidism and thyroid cancer; three with postablative hypothyroidism and hyperthyroidism; one with subclinical hypothyroidism and a cystic lesion; two with nodules without histological diagnosis and cystic lesions; one with spontaneous hypothyroidism, a nodule without histological diagnosis, and a cystic lesion; one with subclinical hypothyroidism, a nodule without histological diagnosis, and a cystic lesion; and one with a thyroid adenoma, a nodule without histological diagnosis, and a cyst.

A total of 260 of the 447 subjects did not report a history of thyroid disease. One of these subjects received a diagnosis of adenoma; 28, a diagnosis of nodule without histological diagnosis; 85, a diagnosis of cystic lesion; 124, a diagnosis of diffuse goiter (31 antibody positive and 93 antibody negative); nine, a diagnosis of spontaneous hypothyroidism (two antibody positive and seven antibody negative); 14, a diagnosis of subclinical hypothyroidism (seven antibody positive and seven antibody negative); and one, a diagnosis of hyperthyroidism. Two of these 260 subjects received two diagnoses: one with a nodule without histological diagnosis and a cystic lesion and the other with subclinical hypothyroidism and a cystic lesion.

The following are diagnosis-specific descriptions.

Nodular Lesion.—Nodular lesions were found in 39 men and 151 women. All of the subjects were nonthyrotoxic and were classified as having a nontoxic nodular lesion. In 42 of these subjects, lesions had been surgically removed and histological diagnoses were available. However, in the remaining 148 subjects, no histological confirmation was available.

Table 2.—Classification of Subjects With Thyroid Disease by Sex and Dosimetry System 1986 (DS86) Thyroid Dose

	DS86 Thyroid Dose, Sv*					
Diagnosis and Sex	**<0.01**	**0.01-0.99**	**≥1.0**	**Unavailable**	**Unknown**	**Total**
Solid nodule						
M	4	4	1	6	0	**15**
F	12	19	22	20	2	**75**
Cancer						
M	0	1	0	2	0	**3**
F	1	6	3	8	0	**18**
Adenoma						
M	0	0	0	1	0	**1**
F	3	4	4	4	0	**15**
Adenomatous goiter						
M	0	0	0	0	0	**0**
F	1	1	1	0	0	**3**
Without histological diagnosis						
M	4	3	1	4	0	**12**
F	7	8	14	8	2	**39**
Cyst						
M	5	3	8	8	1	**25**
F	27	23	11	15	4	**80**
Subclinical hypothyroidism (clinical hypothyroidism)						
M	7 (5)	4 (2)	5 (2)	4 (3)	0	**20 (12)**
F	12 (9)	25 (18)	6 (5)	13 (10)	2 (2)	**58 (44)**
Spontaneous						
M	19 (11)	7 (5)	4 (2)	5 (2)	3 (2)	**0**
F	10 (7)	20 (13)	4 (3)	10 (7)	2 (2)	**46 (32)**
Antibody positive						
M	3 (2)	2 (1)	3 (1)	2 (1)	0	**10 (5)**
F	5 (3)	12 (10)	2 (1)	7 (6)	2 (2)	**28 (22)**
Antibody negative						
M	4 (3)	2 (1)	2 (1)	1 (1)	0	**9 (6)**
F	5 (4)	8 (3)	2 (2)	3 (1)	0	**18 (10)**
Postablative						
M	0	0	0	1	0	**1**
F	2	5	2	3	0	**12**
Hyperthyroidism						
M	1	0	0	0	0	**1**
F	4	9	3	0	0	**16**
Diffuse goiter						
Antibody positive						
M	1	2	1	5	0	**9**
F	23	12	8	8	2	**53**
Antibody negative						
M	13	12	7	9	3	**44**
F	30	16	7	12	5	**70**
No. of study subjects						
M	370	234	148	183	66	1001
F	565	443	218	274	86	1586

*Relative biological effectiveness=10.

Solid Nodule.—There were 21 subjects with thyroid cancer, all of whom had undergone operations before inclusion in this study. Thyroid adenomas were found in 16 subjects. Except for three subjects who were diagnosed at operation, all had been diagnosed before inclusion in this study. Adenomatous goiters were detected in three subjects, all of whom had undergone operations before inclusion in this study. Nodules without histological diagnosis were diagnosed in 51 subjects. Of the 51 subjects, 14 had received a diagnosis of nontoxic nodular goiter and two of these 14 had undergone operations for thyroid nodules before inclusion in this study, but the histological diagnoses could not be confirmed. Solid nodules were detected in the other 49 subjects by ultrasonic scanning. Of these 49 subjects, 19 (39%) underwent aspiration biopsies: 12 were class I, one was class II, and two were class III, according to the results of cytological examinations. The specimens of the remaining four subjects, however, were inadequate for diagnosis.

Cyst.—Cysts were found in 105 subjects. All except two subjects, who had undergone an operation for the disease, were detected by ultrasonic scanning.

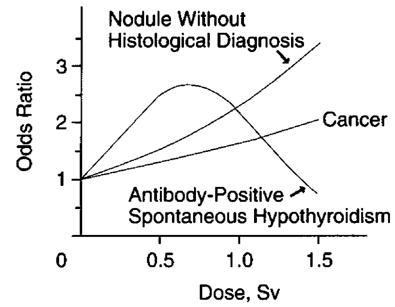

Fig 2.—Odds ratios of the prevalence of nodule without histological diagnosis (women only), cancer, and antibody-positive spontaneous hypothyroidism where the prevalence is adjusted for sex and age at the time of bombing (cancer) and for age at the time of bombing (antibody-positive spontaneous hypothyroidism).

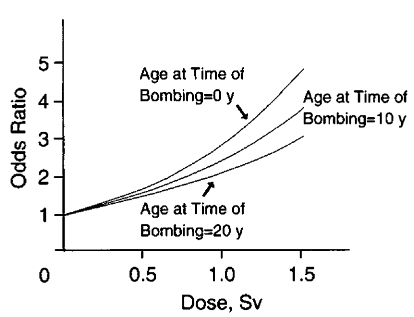

Fig 3.—Odds ratios of the prevalence of solid nodule in women exposed at 0, 10, and 20 years of age.

Among these subjects, 35 (33%) underwent aspiration biopsies, among whom 32 were class I and one was class II, according to the results of the cytological examinations. The specimens of the two remaining subjects were inadequate for examination.

Hypothyroidism.—Postablative hypothyroidism was diagnosed in 13 subjects: eight due to thyroid cancer, one due to thyroid adenoma, two due to chronic thyroiditis, and two due to Graves' disease. All had received treatment for hypothyroidism. Spontaneous hypothyroidism was diagnosed in 43 subjects, 27 of whom were antibody positive and 16 of whom were antibody negative. Goiters were found in 12 of the 27 subjects with antibody and in three of the 16 subjects without antibody. Among the 43 subjects with spontaneous hypothyroidism, 10 had not received any treatment previously. Twenty-two subjects (eight men and 14 women) were found to be subclinically hypothyroid.

Hyperthyroidism. — Hyperthyroidism had already been diagnosed in 16 subjects, all of whom suffered from Graves' disease and had been treated for the disease. Seventy-one other subjects showed a high level of T_3 (≥3.1 nmol/L) or free T_4 (≥32 pmol/L [≥2.5 ng/dL]). In six subjects, the increase was due to T_4 treatment: four for thyroid cancer and adenoma and two for hypothyroidism. Forty of the remaining 65 were referred to the First Department of Internal Medicine, Nagasaki University School of Medicine, for further examinations. Thirty-nine of these 40 subjects were euthyroid, including one with a high level of T_4-binding globulin due to estrogen administration for prostatic carcinoma. One subject was found to be suffering from hyperthyroidism. Twenty-five subjects showing high levels of thyroid hormones refused to have further blood testing. The results of these subjects' early blood tests were carefully reviewed by thyroid experts at the university and RERF; it was found that these subjects had no clinical signs or symptoms of thyrotoxicosis and that their serum TSH levels at the first test were not suppressed. Elevation of free T_4 and/or T_3 was marginal, and none of the subjects showed abnormalities in thyroid ultrasonic scanning. Therefore, a diagnosis of euthyroidism was made in all of the 25 subjects without further examinations.

Diffuse Goiter.—Diffuse goiters were found in 176 subjects with 62 in the antibody-positive group and 114 in the antibody-negative group. Aspiration biopsy was performed in 75 subjects, but the specimens from 14 of them were inadequate for cytological examination. Lymphocytic infiltration was recognized in nine of the remaining 61 subjects.

Dose-Response Relationship

The prevalence of thyroid diseases was significantly (P<.05) higher in women than in men except for adenomatous goiter, antibody-negative diffuse goiter, and spontaneous hypothyroidism (both antibody positive and antibody negative). A significant interaction of sex with dose was indicated in the prevalence of solid nodules and nodules without histological diagnosis, and thus we reanalyzed the data separately in men and women for the two diagnoses.

The diagnoses showing an association between prevalence and dose were solid nodule (women only), cancer, adenoma, nodule without histological diagnosis (women only), and antibody-positive spontaneous hypothyroidism. A significant (P<.01) and monotonic dose-response relationship was noted in the prevalence of all these diseases except cancer and antibody-positive spontaneous hypothyroidism. In cancer, a monotonic dose-response relationship was suggested but was not significant (P=.09), which may be due to the existence of the dose-unavailable and dose-unknown subjects, as discussed later. The interaction of age ATB with dose was significant (P<.05) in the prevalence of adenoma, indicating that the effects of dose to the thyroid were significantly higher in those exposed at a younger age. The prevalence of solid nodules in women also indicated an interaction of age ATB with dose but was not significant. A significant (P<.05) linear-quadratic and concave dose-response relationship was noted in the prevalence of antibody-positive spontaneous hypothyroidism. The dose to the thyroid (±SE) giving the maximum prevalence of antibody-positive spontaneous hypothyroidism was estimated to be 0.7±0.2 Sv.

Figure 2 shows the odds ratio (OR) of the prevalence adjusted for sex and/or age ATB as a function of the dose to the thyroid for nodules without histological diagnosis (women only), cancer, and antibody-positive spontaneous hypothyroidism. The ORs of the prevalence of solid nodule in women is shown in Fig 3 for selected ages ATB.

COMMENT

The present study was preceded by several clinical thyroid studies in the AHS cohort. The report by Hollingsworth et al[10] dealt extensively with various thyroid diseases in 5553 AHS subjects from Hiroshima between July 1958 and November 1959. In this study, palpable abnormalities were noted in 146 subjects (2%), including 12 with thyroid cancer. Functional abnormalities were found in 17 subjects, 16 with hyperthyroidism and one with hypothyroidism. In addition, a diagnosis of chronic thyroiditis was made in five subjects after histological review of the biopsy specimens. Subsequent thyroid studies in the AHS cohort were aimed at the identification of subjects with thyroid cancer. Socolow et al[11] further expanded the study to include 15 369 AHS subjects (10 780 in Hiroshima and 4589 in Nagasaki) examined between July 1958 and July 1961, and Wood et al[12] conducted a similar study during the fourth cycle of the AHS biennial examinations. Parker et al[13] reported a total of 74 thyroid cancer cases after 6⅔ cycles of AHS examinations (40 clinical cases and 34 silent cases found only at autopsy). All of these cases were analyzed using the then available T65D. The study by Parker et al confirmed the previous reports of an association between radiation exposure and thyroid cancer, that is, that thyroid cancer was significantly more prevalent in subjects exposed to 0.5 Gy or more of radiation and was most pronounced in women whose age ATB was younger than 20 years.

In the present study, we found various thyroid diseases in 447 (17.3%) of the 2587 subjects studied in Nagasaki. This number is substantially more than the 168 (3.0%) of 5553 subjects studied in Hiroshima some 30 years ago.[10] This increase, which is seen in each diagnostic category, is due primarily to the adoption of various diagnostic procedures that were not then available. However, it also reflects the natural increase in various thyroid diseases accompanying the advancing age of the survivors. The use of the ultrasonic scanning technique in the present study made it possible to estimate thyroid volume more accurately than the evaluation by palpation in the past. Past use of palpation was subjective in nature and relied on the consensus of physical findings by a group of examiners. The accuracy of ultrasonic scanning has been demonstrated by Yokoyama et al,[2] Rasmussen and Hjorth,[14] and Hegedüs et al,[3] who compared the ultrasonically determined volumes with the volumes of the same glands removed surgically, including the surgeon's estimate of the amount that had been left behind. The high prevalence of thyroid cysts (105 of 2587 or 4%) observed in the present study is probably due to the use of high-resolution ultrasonic scanning, which readily reveals cystic lesions that cannot be differentiated from solid nodules by palpation alone.

Neither thyroid dose (P=.09) nor age ATB (P=.05) showed a significant association with the prevalence of thyroid cancer in the current investigation. However, this lack of significant association is probably due to two factors: (1) the exclusion of dose-unavailable or dose-unknown subjects and (2) cancers still without histological confirmation that were designated as nodules without histological diagnosis. In the present study, there were 457 dose-unavailable subjects (17.7%) who were all exposed within 2.5 km of the hypocenter. Notably, 399 (87.7%) of the 457 dose-unavailable subjects were exposed within 1.5 km of the hypocenter and are expected to have received a high dose, and among the 21 cancer subjects (three men and 18 women), 10 subjects (two men and eight women) were dose unavailable. Since the T65D estimates were available for all dose-unavailable subjects, we conducted the same analyses using the T65D estimates of kerma (kinetic energy released in material) dose as those conducted in the present study. Except for cancer, the results concerning the significance of variables in the models were similar to those based on DS86 estimates. For the prevalence of cancer, significant associations with age ATB (P<.05) and dose (P<.01) were demonstrated. The data from the present study, therefore, are consistent with the results of the previous studies reporting an increased frequency of thyroid cancer in people who had received radiation therapy[15-20] and among atomic bomb survivors.[11-13,21] A significant interaction of sex with dose to the thyroid was observed in the prevalence of nodular lesions, solid nodules, and nodules without histological diagnosis. Furthermore, the interaction of age ATB with dose to the thyroid was significant with respect to adenomas. The present data are consistent with the previous results[13,22] indicating a high susceptibility to radiation-related thyroid tumorigenesis among young people, especially young women.

The prevalence of autoimmune thyroiditis, including autoimmune hypothyroidism, increases with each passing decade. However, the statistical analyses based on linear logistic models describing the prevalence of each thyroid disease as a function of sex, age ATB, and organ dose to the thyroid indicated a concave dose-response curve attaining the maximum at about 0.7 Sv for the prevalence of antibody-positive spontaneous hypothyroidism. Since no association was observed between dose to the thyroid and the prevalence of postablative hypothyroidism or antibody-negative spontaneous hypothyroidism, the relationship observed with antibody-positive spontaneous hypothyroidism conceivably stemmed from an underlying autoimmune thyroid disorder such as chronic thyroiditis. There are studies that seem to support this conjecture. Spitalnik and Strauss[23] reported a high prevalence of chronic thyroiditis among people who had received radiation therapy to the head and neck region. Tamura et al[24] stated that the frequency of radiation-associated hypothyroidism in patients treated for malignant lymphoma decreased significantly when radiation therapy was accompanied by chemotherapy with immunosuppressive agents. Kaplan et al[25] investigated the frequency of thyroid diseases in 91 women who about 40 years earlier (while younger than 30 years) had suffered from pulmonary tuberculosis and had undergone repeated fluoroscopic examinations (with average exposures of 0.11 to 1.12 Gy) for therapeutic pneumothorax. From the comparison of these women with 72 women treated for tuberculosis by other modalities without fluoroscopic examination, Kaplan et al suggested that low-dose radiation exposure to the thyroid gland may be a risk factor for the subsequent development of autoimmune thyroid disease. Finally, Kotani et al[26] demonstrated a high incidence of chronic thyroiditis in rats exposed to external radiation.

A high prevalence of hypothyroidism after radiation therapy that included the thyroid in its field for patients with malignant lymphoma[24,27-29] and other malignant diseases[30,31] has been documented, but the radiation doses in these subjects were usually in the range of 35 to 50 Gy and sometimes as high as 70 Gy. On the other hand, little data are available for persons exposed to low or moderate doses of radiation. Hollingsworth et al[10] found only one case (a 47-year-old nonexposed woman) of idiopathic hypothyroidism among the 5553 AHS subjects examined in Hiroshima during 1958 and 1959. Pincus et al[32] found that none of 105 subjects who underwent thymic irradiation 18 to 34 years previously was hypothyroid in a follow-up examination, which included determination of protein-bound iodine and 24-hour thyroidal radioiodine uptake and scan. However, these reports were based on clinical evaluations, since TSH assays were not yet available. Refetoff et al,[33] in a similar study of 100 consecutive patients with a history of radiation therapy for benign conditions in the head and neck areas, found serum TSH to be normal in all the patients, six of whom were already receiving thyroid hormone replacement. In at least two of these six patients, a possible history of preexisting hypothyroidism was obtained. In a 1971 to 1972 study using the then newly introduced serum TSH radioimmunoassay method, Parker et al[34] found elevated TSH levels in 25 of 1563 AHS subjects (601 men and 962 women) whose age ATB was younger than 20 years, including one possible and four definite cases of hypothyroidism (one man and four women). Subsequently, Morimoto et al[35] reported 23 cases (four men and 19 women) of hypothyroidism (including subclinical) among 978 AHS subjects whose age ATB was younger than 20 years. Morimoto et al[35] compared two groups, that is, 477 subjects (266 in Hiroshima and 211 in Nagasaki) with an estimated T65D kerma dose of 1 Gy or more and 501 (273 in Hiroshima and 228 in Nagasaki) with an estimated dose of 0 Gy and excluded subjects with known thyroid disease, while Parker et al[34] did not. No significant effects of radiation exposure were observed in either study. The present study included 1599 subjects (639 men and 960 women) whose age ATB was younger than 20 years. Among these subjects, 32 were found to be subclinically hypothyroid, and four men and 21 women were found to qualify for the diagnosis of spontaneous hypothyroidism.

Hypothyroidism was noted within 10 years in the children exposed in the Marshall Islands accident,[36] while in the atomic bomb survivors a significant appearance of autoimmune hypothyroidism was noted for the first time 40 years after the explosion of the atomic bomb. The reasons for the difference in the incidence of hypothyroidism between the two groups are not clear. However, there exist several differences in the two groups with regard to radiation exposure and type of hypothyroidism. In Marshall Islanders, the thyroid radiation dose was mainly due to internal radiation (radioactive iodine), and the estimated thyroid doses are higher than those in hypothyroid subjects among atomic bomb survivors, whose radiation dose was due to direct external radiation from the atomic bomb. Many cases of hypothyroidism in Marshall Islanders are not the autoimmune type, but in atomic bomb survivors a significant increase was found only in autoimmune hypothyroidism and not in the other types of hypothyroidism.

Reviewing the history of the 51 subjects with nodules without histological diagnosis, we found 31 subjects (eight men and 23 women) with no past record of thyroid abnormalities. Some of these "new cases" may have had nodules not detected by palpation because of their small size. Notably, five of these women had been exposed to 1.5 Sv or more, and one woman with goiter was found to have thyroid cancer 2 years after receiving a diagnosis of a cystic lesion during the program. These facts suggest that radiation tumorigenesis is present even more than 40 years after atomic bomb exposure.

The present study has shown for the first time an increase in prevalence of autoimmune hypothyroidism among atomic bomb survivors. The dose-response curve is concave, reaching a maximum of about 0.7 Sv, and thus indicates the necessity for further studies on relatively low-dose radiation effects on thyroid disease.

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Conversion From Système International (SI) Unit to Traditional Unit (Modified From *The SI Manual in Health Care*)

System	Component	SI Reference Interval*	SI Unit†	Conversion Factor (Divide by)	Traditional Reference Interval*	Traditional Unit
Serum	Thyrotropin (thyroid-stimulating hormone [TSH])	2-11	mU/L	1.00	2-11	μU/mL
	Triiodothyronine (T_3)	1.2-3.4	nmol/L	0.01536	75-220	ng/dL

*This reference value is not intended to be definitive since each laboratory determines its own values. It is provided for illustration only.