Serum TSH, Thyroglobulin, and Thyroidal Disorders in Atomic Bomb Survivors Exposed in Youth: 30-Year Follow-Up Study

Isao Morimoto, Yasuhiko Yoshimoto, Kenshi Sato, Howard B. Hamilton, Sadahisa Kawamoto, Motomori Izumi, and Shigenobu Nagataki

Radiation Effects Research Foundation, Departments of Medicine, Epidemiology and Statistics, and Clinical Laboratories, and the First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

Follow-up examinations to determine the frequency of thyroidal disorders were conducted by the Radiation Effects Research Foundation (RERF) on individuals in Hiroshima and Nagasaki who were less than 20 yr of age at the time of exposure to the atomic bomb. Concentrations of serum thyroid stimulating hormone (TSH), thyroglobulin (TG), and anti-TG antibody 30 yr after exposure were also determined. Nontoxic uninodular goiter was found in 13 cases of the 100+ rad exposed group (n = 477) and in three cases of the nonexposed group (n = 501). The prevalence in the 100+ rad exposed group was significantly higher (chi-squared = 6.584, $p < 0.01$). Thyroid cancer was found in eight exposed cases, all of whom were in the 100+ rad group, and the prevalence was significantly greater (chi-squared = 7.919, $p < 0.01$). Regardless of the presence or absence of thyroidal disorders, serum TSH and TG levels were not statistically different between the 100 rad+ exposed and nonexposed groups. Although hypothyroidism was found in 23 of the total cases, there was no correlation between its development and exposure to ionizing irradiation.

J Nucl Med 28:1115–1122, 1987

The occurrence of radiation-induced thyroid cancer was first noted in animal experiments (*1–5*). The association between irradiation and the occurrence of thyroid cancer in humans, initially reported by Duffy and Fitzgerald (*6*) in 1950, was followed by a number of reports (*7–15*). It has been shown that x-irradiation in childhood, particularly to the head and neck region, results in a high occurrence of thyroid cancer 5–30 yr after exposure (*7–15*). Thyroid cancer has developed following exposure to x-irradiation doses as low as 6.5 rad and as high as 1,000 rad (*9–13*).

Previous studies performed at the Radiation Effects Research Foundation (RERF; formerly the Atomic Bomb Casualty Commission, ABCC) of atomic bomb survivors of Hiroshima and Nagasaki revealed a significantly higher incidence of thyroid cancer and nodular goiter in the 100+ rad exposed group (*16–22*). Conard et al. (*23–26*), in their studies on the residents of the Marshall Islands, who were exposed to radioactive fallout from a hydrogen bomb test, have observed that the incidence of thyroid cancer and nodular goiter were high.

Another radiation-induced abnormality of the thyroid is hypothyroidism. Hypothyroidism was found in the Marshall Island inhabitants who had been exposed to ionizing radiation (*23–26*). Subsequently, subclinical hypothyroidism among the exposed inhabitants was observed at a high frequency by highly sensitive serum thyroid stimulating hormone (TSH) determination, and it was suggested that elevation of serum TSH levels might be involved in the occurrence of nodular goiter (*26–32*). Determinations of serum TSH levels in a limited number of exposed subjects in Hiroshima and Nagasaki were made by Parker et al. (*20*) at ABCC-RERF in 1971. Their study failed to identify a cause-effect relationship between serum TSH levels and the incidence of thyroid nodules in relation to A-bomb exposure. However, serum TSH screening of A-bomb survivors of Hiroshima and Nagasaki is still essential to evaluate a cause–effect relationship between hypothyroidism and A-bomb fallout exposure. It has been re-

Received Apr. 22, 1986; revision accepted Nov. 24, 1986.

For reprints contact: Isao Morimoto, MD, First Department of Internal Medicine, Nagasaki University School of Medicine, Sakamoto-Machi, Nagasaki 852, Japan.

ported that the serum thyroglobulin (TG) level is a metastatic tumor marker for thyroid cancer, especially following thyroidal ablation (*13*, *33–35*).

In the present study, conducted 30 yr after A-bomb exposure, the occurrence of thyroidal disorders among survivors of Hiroshima and Nagasaki who were exposed at a young age was examined by determining levels of serum TSH, TG, and anti-TG antibody in addition to clinical assessment. Although limited in number, the young age group who were exposed to irradiation were specifically chosen because it is well recognized that the thyroid glands of young animals and humans are much more sensitive to the effects of irradiation (*7–15*). The association of radiation exposure with occurrence of thyroid disorders and serum levels of TSH, TG, and anti-TG antibody were evaluated. At the present time a comprehensive 40-yr follow-up study is being conducted among all age groups of A-bomb survivors in the Nagasaki area.

MATERIALS AND METHODS

Subjects

Subjects were selected from the RERF Adult Health Study (AHS) population, in which medical examinations have been conducted on exposed and nonexposed subjects systematically in biennial cycles (*36*). The RERF-AHS is the successor to the ABCC-JNIH (Japanese National Institute of Health) AHS initiated in 1958. The ninth cycle of AHS examinations (1974–1976) was performed on ~9,700 examinees in all age groups. There were ~850 subjects whose ages at the time of A-bomb explosion were less than 20 yr old and exposed to more than 100 rad (100+ rad exposure group) and 800 subjects in the same age group who were not exposed to irradiation (0 rad exposure group). The 978 subjects shown in Table 1, whose blood samples were obtained at the ninth cycle of AHS examinations and preserved in perfect condition (−60°C) and in whom serum TSH and TG levels were determined, are the subjects of the present study. They included 200 male (120 in Hiroshima and 80 in Nagasaki) and 277 female (146 in Hiroshima and 131 in Nagasaki) patients in the 100+ rad exposure group, and 219 male (119 in Hiroshima and 100 in Nagasaki) and 282 female (154 in Hiroshima and 128 in Nagasaki) patients in the nonexposed group.

Estimation of Exposure Dose

The estimated exposure doses of A-bomb fallout radiation presently used at the RERF are based on those developed by collaborating researchers at the Oak Ridge National Laboratory (*37*). Up until the eighth report of the RERF Life Span Study, this dosimetry system was referred to as T65D; however, it was subsequently revised because of the calculated relocation of the hypocenter in Nagasaki. The revised doses, referred to as T65DR (*38*), have been used since the ninth report of the RERF Life Span Study. The T65DR system is presently being reviewed and revised.

Thyroid Palpation

In order to ensure uniformity in thyroid palpation findings, a training period was provided for the examiners of Hiroshima and Nagasaki at the time of the 1971 thyroid study (*21*). It was confirmed that their findings were based on uniform criteria. Thyroid palpation findings were classified on the basis of a modification (*39*, *40*) of the World Health Organization's criteria, which had been reported previously by ABCC-RERF (*19*).

Diagnosis of Thyroid Disorders

The diagnosis of thyroid disorders was made according to the Classification of the American Thyroid Society (*41*) based on the results of the AHS clinical examination, laboratory tests, and pathologic findings through 1976, thyroid findings in the AHS ninth examination cycle, and levels of serum TSH, TG, and anti-TG antibodies in blood samples collected during that cycle. Diagnosis of thyroid cancer, thyroid adenoma, and thyroid cysts were made solely on the basis of histologic findings.

The diagnosis of primary hypothyroidism was established for the following two categories: (a) cases diagnosed by hormone determinations before the ninth cycle, who are presently under thyroid hormone replacement and, (b) cases whose TSH levels were 10 μU/ml or more in the present study. Furthermore, the subjects were divided into two categories (Table 1) as hypothyroidism due to chronic thyroiditis and hypothyroidism of unknown etiology. A diagnosis of chronic thyroiditis was made in the following three groups: (a) cases identified histologically in the past; (b) cases having either anti-Tg or anti-microsomal antibody titers (determined by tanned red cell hemagglutination, TRC) of $>1 \times 10^2$ or anti-Tg antibody titers determined by the precipitation method in this study of 20%; (c) euthyroid cases with large goiters and elevated antibody titers.

Cases with normal thyroid function tests who had neither anti-TG nor anti-microsomal antibodies in whom one thyroid nodule was palpable were defined as nontoxic uninodular goiter and those in whom two or more nodules were palpable, as nontoxic multinodular goiter. Goitrous euthyroid subjects who had no anti-TG or anti-microsomal antibody were defined as having nontoxic diffuse goiters.

All cases of hyperthyroidism in this study had been diagnosed previously and treated with iodine-131 (^{131}I) therapy or subtotal thyroidectomy before this study commenced.

Serum TSH, TG, and Anti-TG Antibody Level Measurements

Serum samples were preserved at −60°C for 3–5 yr prior to analysis. All analyses were performed at the same time in the same laboratory. Serum TSH was measured by radioimmunoassay (RIA) using a TSH RIA kit (*42*) and serum TG and anti-TG antibody were measured by the RIA method reported previously by Izumi (*43*).

Statistical Analysis

The group was divided into 0 rad exposure and 100+ rad exposure groups. Variables adjusted by stratification were age at time of bomb (0–9, 10–19), sex, and city. The relationship between radiation exposure and the prevalence rates of thyroid diseases was examined using the Mantel-Haenszel method. Thus, degrees of freedom of all the chi-squared statistics were 1, and the relative risk was the weighed mean of estimated stratification ratio. Similarly, the Mantel-Haenszel method (*44*) was also used for a comparison between variables other

TABLE 1
Number of Subjects and Type of Thyroid Disorders by City, Sex, and Exposure Groups

	City combined						Hiroshima						Nagasaki					
	0 rad			>100 rad			0 rad			>100 rad			0 rad			>100 rad		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Number of subjects	501	219	282	477	200	277	273	119	154	266	120	146	228	100	128	211	80	131
Thyroid cancer	0	0	0	8	0	8	0	0	0	2	0	2	0	0	0	6	0	6
Nontoxic uninodular goiter	3	1	2	13	4	9	2	1	1	4	1	3	1	0	1	9	3	6
Nontoxic multinodular goiter	3	1	2	4	0	4	2	1	1	1	0	1	1	0	1	3	0	3
Hypothyroid, unknown etiology	9	3	6	7	1	6	6	3	3	4	0	4	3	0	3	3	1	2
Hypothyroid, chronic thyroiditis	5	0	5	2	0	2	3	0	3	1	0	1	2	0	2	1	0	1
Euthyroid, chronic thyroiditis	8	0	8	8	1	7	1	0	1	4	1	3	7	0	7	4	0	4
Nontoxic diffuse goiter	8	2	6	12	0	12	4	1	3	11	0	11	4	1	3	1	0	1
Hyperthyroidism	2	1	1	1	0	1	2	1	1	1	0	1	0	0	0	0	0	0
Thyroid cyst	0	0	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0
Thyroid adenoma	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
All thyroid disorders	39	9	30	56	6	50	21	8	13	29	2	27	18	1	17	27	4	23

than radiation exposure (e.g., sex) and prevalence rates of thyroidal disorders. In this case, radiation exposure was also adjusted by stratification. To compare the means of TSH and TG levels and examine the significance of correlation coefficients (Ho: r = 0), t-statistics were used. Also, regression analyses with dummy variables were used in order to review simultaneous effects of city, sex, age at exposure, and radiation exposure on TSH and TG levels. These results are not presented.

RESULTS

All Thyroid Disorders

Among the 978 subjects in this study, 95 cases of thyroid abnormalities were detected (Table 1). The 95 subjects consisted of 56 in the 100+ rad exposure group and 39 in the nonexposed group. The overall relative risk of thyroid disorders in the 100+ rad exposure group compared with the nonexposed group was high with a nominal significance ($\chi^2 = 3.872$, $p < 0.05$) in the former, and the high prevalence of thyroid disorders was observed in female, but not in male patients (Table 2). However, this is attributable to the statistically high relative risk of the females with thyroid cancer and nontoxic uninodular goiter in the 100+ exposure group.

Thyroid Cancer

Thyroid cancer was detected in eight cases, all of whom were female in the 100+ rad exposure group. Thus, the overall relative risk (RR) of the 100+ rad exposure group adjusted for city and age at exposure could not be calculated (RR = ∞), but the chi-squared value was 7.919 ($p < 0.01$) and the prevalence rate was significantly increased (Table 2). There was no significant difference in the 0–9 yr old group (four cases) compared with the 10–19 yr old group (four cases) who were exposed to 100+ rad. Of the eight cases, six had been reported in 1971 and two new cases were added during the present study. The pathologic diagnosis was papillary adenocarcinoma in seven cases and follicular adenocarcinoma in one case.

Nontoxic Uninodular Goiter

Nontoxic uninodular goiter was found in three cases of the nonexposed group and in 13 of the 100+ rad exposure group. The overall relative risk of the 100+ rad exposure group adjusted for city, sex, and age at exposure was 4.539 ($\chi^2 = 6.584$, $p < 0.01$), compared with the nonexposed group (Table 2). Thus, the prevalence rate was significantly increased, and this is atributable to the high prevalence rate in females. Neither thyroid scintiscans nor biopsies were performed on these patients.

Nontoxic Multinodular Goiter

Nontoxic multinodular goiter was detected in three cases in the nonexposed group and in four cases in the 100+ rad exposure group (Table 1). Pathologic diagnosis was made in three of the seven cases and all three had adenomatous goiters. There was no significant difference in prevalence between the nonexposed and 100+ rad exposure groups.

TABLE 2
Prevalence of All Thyroidal Disorders, Nontoxic Uninodular Goiter, and Thyroid Cancer

		Total		Male		Female	
	n:	0 rad	>100 rad	0 rad	>100 rad	>0 rad	>100 rad
		501	477	219	200	282	277
All thyroid disorders	Obs	39	56	9	6	30	50
	Exp	4.97	47.03	7.78	7.22	40.19	39.81
	RR	1.000	1.573	1.000	0.718	1.000	1.823
	χ^2	3.872 (p < 0.05)		0.410 (N.S.)		6.046 (p < 0.02)	
Thyroid cancer	Obs	0	8	0	0	0	8
	Exp	3.95	4.05	0	0	3.95	4.05
	RR	—		—	—	—	
	χ^2	7.99 (p < 0.01)		—		7.919 (p < 0.01)	
Nontoxic uninodular goiter	Obs	3	13	1	4	2	9
	Exp	8.07	7.93	2.63	2.37	5.44	4.56
	RR	1.000	4.539	1.000	4.434	1.000	4.590
	χ^2	6.584 (p < 0.01)		2.163 (N.S.)		4.423 (p < 0.05)	

N, number; Obs, observed; Exp, expected; RR, Mantel–Haenzel summary relative risk estimate; χ^2, Mantel–Haenzel test statistics for stratified analysis (*df* = 1); N.S., not significant difference (p < 0.05).

Primary Hypothyroidism and Chronic Thyroiditis

Twenty-three cases of hypothyroidism were found, seven of which had chronic thyroiditis. Nine of 16 subjects with hypothyroidism of unknown etiology were in the nonexposed group, so there did not appear to be any significant correlation between irradiation exposure and development of hypothyroidism.

Other Thyroid Disorders

Other thyroid disorders were observed, such as nontoxic diffuse goiter, hyperthyroidism, and cysts (Table 1); however, their prevalence when comparing exposure with irradiation and nonexposure, was not significantly different.

Serum TSH Levels

Table 3 shows the means and standard deviations (s.d.) of serum TSH levels of 462 cases of the 0 rad exposure group and 421 cases of the 100+ rad exposure group, excluding the 95 cases with various thyroid disorders. The serum TSH level was 1.5 ± 1.9 μU/ml (mean ± s.d.) in 462 nonexposed subjects and 1.6 ± 1.9 μU/ml in 421 100+ rad exposure subjects. No significant difference was observed between the two groups. Serum TSH levels in both nonexposed and exposed groups were significantly higher in females than in males ($p < 0.001$ and $p < 0.05$, respectively). However, the serum TSH levels in any of the subjects with three thyroid disorders (nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter) who were not being treated with exogenous hormone replacement were not significantly different between the nonexposed and exposed groups. Regression analyses using dummy variables also showed that serum TSH level is significantly higher in females than in males in their respective two groups. No effects of city, sex, and age at exposure on the serum thyroid cancer levels are observed.

TABLE 3
Serum TSH and TG Levels in Exposed and Nonexposed Subjects without Thyroid Disorders

		Total		Male		Female	
		0 rad	>100 rad	0 rad	>100 rad	0 rad	>100 rad
	n	462	421	210	194	252	227
TSH (μU/ml)	Mean	1.5	1.6	1.1	1.4	1.9	1.8
	s.d.	1.9	1.9	1.7	1.8	1.9	2.0
	t-test*	N.S.		N.S.		N.S.	
TG (ng/ml)	Mean	14.8	13.5	11.3	12.1	17.6	14.7
	s.d.	15.7	13.9	10.6	11.6	18.5	15.5
	t-test	N.S.		N.S.		N.S.	

* 0 rad versus 100 rad exposure.

Serum TG Levels

Table 3 shows the mean and standard deviation of 462 subjects in the 0 rad exposure group and 421 subjects in the 100+ rad exposure group who had no thyroid disorders. Again, there was no significant difference observed among the nonexposed or exposed group. Serum TG levels were also higher among women than men ($p < 0.001$ in nonexposed and not significant in exposed), similar to what was observed in serum TSH. Although results are not shown, the serum TG levels were significantly higher in Nagasaki than in Hiroshima ($p < 0.01$ in nonexposed, $p < 0.05$ in exposed). The serum TG levels in subjects with three thyroid disorders (nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter) who had not received treatment for thyroid were 24.5 ± 23.3 ng/ml (n = 43), which was significantly higher ($p < 0.001$) than that of the subject without thyroid disorders (14.2 ± 14.9, n = 883). Regression analyses also showed that the serum TG level is significantly higher in Nagasaki than in Hiroshima, and higher in females than in males.

DISCUSSION

The ABCC-RERF Adult Health Study disclosed that the occurrence of thyroid nodules was significantly higher among exposed subjects in 1958–1959, 15 years after the A-bomb (*16, 17*). By 1971, subsequent studies showed that the incidence of thyroid cancer in the group that had been exposed in Hiroshima and Nagasaki was significantly increased (*18–22*). The present study was limited to those subjects who were <20 yr old at the time of the A-bomb. Several studies (*6–15*) have reported that the thyroid glands of young persons are more sensitive to the effects of radiation than are those of older persons. The study was made on the incidence, serum TSH, and TG levels in all cases of thyroid disorders that occurred in 1975–1976, 30 yr after exposure to the A-bomb. Comparisons with strictly selected, nonexposed individuals revealed a high incidence of thyroid disorders in the 100+ rad exposure group with a nominal significance. The increased prevalence of thyroid disorders, however, is attributable to the significant high incidence of thyroid cancer and nontoxic uninodular goiter in the 100+ rad exposure group.

In the study of the residents of the Marshall Islands conducted by Conard et al. (*23–26*), thyroid cancer occurred at a high frequency among those exposed to the radioactive fallout from the hydrogen bomb. The eight cases of thyroid cancer found in our study were all in the 100+ rad exposure group. Kugimoto et al. (*45*) reported on the frequency of thyroid cancer among ~30,000 residents of the Nagano region of Japan. The frequency of thyroid cancer among the same age residents as in the present study was 2/1,000 cases, the frequency among females being 2.8/1,000 cases. The prevalence of thyroid cancer in our study population, which was much smaller than that in Nagano, was eight of 477 persons of the 100+ rad exposure group (16.8/1,000 cases). Thus, the prevalence of thyroid cancer is much higher among exposed survivors than in the population in Nagano. The occurrence of thyroid cancer as a late radiation effect has been observed even 35 yr after exposure (*12*, *14*, *15*). The estimated radiation doses of the eight subjects with thyroid cancer were all 100+ rad, which is considered sufficient to induce thyroid cancer. In the present study, the pathologic diagnosis of thyroid cancer among survivors exposed in youth was predominantly papillary adenocarcinoma, as in the previous results of the ABCC-RERF study by Parker et al. (*21*). Furthermore, all thyroid cancers in the exposed residents of the Marshall Islands were papillary adenocarcinoma (*23–26*).

Nontoxic uninodular goiter was also observed with significantly high frequency among the 100+ rad exposure group. In the ABCC-RERF study in 1959 (*17*, *21*) and study of the residents of the Marshall Islands by Conard et al. (*25*, *26*), thyroid nodules were found with significantly high frequency among the 100+ rad exposure group. In the study of residents in Nagano Prefecture by Kugimoto et al. (*45*), the frequency of thyroid nodule in the subjects of Nagano Prefecture who were 30–50 yr old at age of onset as were our study subjects, was 1.3%; the frequency in males being 0.8% and in females 1.7%. The frequency of nontoxic uninodular goiter in the nonexposed groups in Hiroshima and Nagasaki was 0.6%, however, among the 100+ rad exposure group, the frequency was 3.0%, 2.7% for males and 3.2% for females. A relation between occurrence of thyroid nodule and increased TSH level in exposed Marshall Islands subjects was reported for the first time by Conard et al. (*26*). In the present study, however, among those exposed at a young age in Hiroshima and Nagasaki, no correlation was observed between the occurrence of thyroid nodule and serum TSH levels. In a previous report by ABCC-RERF (*21*), cancer was detected in eight of 19 nontoxic uninodular goiter cases studied histopathologically. Pathologic studies of thyroid nodule in the exposed Marshallese disclosed benign goiter in 38 cases and cancer in seven cases (*26*). There is a strong possibility of thyroid cancer in the nontoxic uninodular goiter cases frequently observed in the 100+ rad exposure group in Hiroshima and Nagasaki. Thus, it is believed that careful follow-up is necessary.

No specific relationship was observed between the development of chronic thyroiditis or primary hypothyroidism and radiation exposure. There was no significant difference between the 100+ rad exposure and 0 rad exposure groups in prevalence of nontoxic diffuse goiter, which is consistent with the previous report by ABCC-RERF (*20*). Serum TSH level was not much related to goiter, which is consistent with the previous result (*20*). Although some subjects with uninodular goiter had low levels of serum TSH and thyroid scans were not performed for evaluation of autonomous nodule, the subjects have remained clinically euthyroid for the following 4 yr. On the other hand, serum TG levels were high in the subjects with thyroid disorders who were not being treated with exogenous hormone replacement. This might indicate a relationship between the incidence of the abovementioned thyroid disorders and release of TG into blood from the thyroid. However, serum TSH and TG levels were not affected by A-bomb exposure, but were higher in females than in males as previously described by ABCC-RERF (*20*). The serum TG levels of both 100+ rad and 0 rad exposure groups were higher in Nagasaki than in Hiroshima. The reason for this difference in serum TG levels between the two cities is unclear.

In the studies of thyroid disease 30 yr after the exposure to the A-bomb, we conclude that thyroid disorders were increased among those exposed to the A-bomb with a nominal significance because of a greater significant increase of thyroid cancer and nontoxic uninodular goiter. However, no increased incidence of hypothyroidism was observed in the exposed group. Respective serum levels of TSH and TG were not different between the exposed and the nonexposed group. A comprehensive, 40-yr follow-up study is being performed in the Nagasaki area.

ACKNOWLEDGMENTS

The authors thank Prof. L.F. Kumagai (University California, Davis) for correcting the English text, and the staffs in RERF for their assistance.

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