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SERUM TSH, THYROGLOBULIN, AND THYROID DISORDERS IN ATOMIC BOMB SURVIVORS EXPOSED IN YOUTH: A STUDY 30 YEARS AFTER EXPOSURE

若年被爆者の血清TSH, サイログロブリン, 甲状腺疾患: 原爆被爆30年後の調査

ISAO MORIMOTO, M.D. 森本勲夫
YASUHIKO YOSHIMOTO, D.H.Sc. 吉本泰彦
KENSHI SATO, M.D. 佐藤賢士
HOWARD B. HAMILTON, M.D.
SADAHISA KAWAMOTO, M.D. 河本定久
MOTOMORI IZUMI, M.D. 和泉元衛
SHIGENOBU NAGATAKI, M.D. 長瀧重信

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若年被爆者の血清TSH，サイログロブリン，甲状腺疾患：原爆被爆30年後の調査

ISAO MORIMOTO, M.D. (森本勲夫)[1]; YASUHIKO YOSHIMOTO, D.H.Sc. (吉本泰彦)[2];
KENSHI SATO, M.D. (佐藤賢士)[1]; HOWARD B. HAMILTON, M.D.[3];
SADAHISA KAWAMOTO, M.D. (河本定久)[1]; MOTOMORI IZUMI, M.D. (和泉元衛)[4];
SHIGENOBU NAGATAKI, M.D. (長瀧重信)[4]

RERF Departments of Medicine[1], Epidemiology & Statistics[2], and Clinical Laboratories[3]; First Department of Internal Medicine, Nagasaki University School of Medicine[4]

放影研臨床部[1]，疫学統計部[2]，及び臨床検査部[3]；長崎大学第一内科学教室[4]

SUMMARY

A study of individuals in Hiroshima and Nagasaki who were under 20 years of age at the time of atomic bomb exposure and who had been exposed to 100+ rad was conducted to determine the frequency of thyroid disorders as well as the levels of serum thyroid stimulating hormone (TSH), antithyroglobulin antibody, and thyroglobulin (TG), 30 years after exposure. Thyroid disorders were detected in 56 of the 477 subjects of the 100+ rad exposed group and in 39 of the 501 subjects of the 0 rad exposed group, the prevalence being significantly higher in the former group (χ^2 =3.872, P=0.049). This increased prevalence of thyroid disorders in the 100+ rad exposed group was due to the increased occurrence of thyroid cancer and nontoxic uninodular goiter. Thyroid cancer was found in eight exposed individuals, all of whom belonged to the 100+ rad group; statistically, the prevalence was significantly higher (χ^2 =7.919, P=0.005). Nontoxic uninodular goiter was observed in 13 cases of the 100+ rad exposed group and 3 cases of the 0 rad exposed group, the prevalence in the 100+ rad exposed group being significantly higher (χ^2 =6.584, P=0.010). In these cases no increase of serum TSH or TG levels was observed. Mean serum TSH levels in individuals without thyroid disorders were 1.64 ± 1.89 μU/ml (n=421) in the 100+ rad exposed group and 1.54 ± 1.86 μU/ml (n=462) in the 0 rad exposed

要　約

広島，長崎両市で被爆時年齢が20歳未満で100 rad以上の線量に被曝した者について，被爆30年後の甲状腺疾患の頻度，血清中の甲状腺刺激ホルモン(TSH)，抗サイログロブリン抗体，サイログロブリンについて検索した．甲状腺疾患は100 rad 以上被曝群477名中56例，0 rad 被曝群501名中39例にみられ，その有病率は100 rad 以上被曝群で有意(χ^2 = 3.872, p= 0.049)に高い．なおこの上昇は，甲状腺癌と非中毒性甲状腺単結節の発生上昇に基づくものである．甲状腺癌は8例認められ，すべて100 rad 以上被曝群で，その有病率は統計的に有意に高い(χ^2 = 7.919, p= 0.005)．非中毒性甲状腺単結節は100 rad 以上被曝群で13例，0 rad 被曝群で3例で，100 rad 以上被曝群が有意に高い(χ^2 = 6.584, p= 0.010)．これら疾患において，血清TSHとサイログロブリン値の上昇はみられなかった．甲状腺疾患を有しない者の血清 TSH の平均値は100 rad 以上被曝群で1.64± 1.89 μU/ml (n= 421)，0 rad 被曝群で1.54±1.86 μU/ml (n= 462)，血清サイログロブリンの平均値は100 rad 以上被曝群で13.49± 13.88 ng/ml (n= 421)，　0 rad 被曝群で14.76±

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group. Mean serum TG levels were 13.49 ± 13.88 ng/ml (n=421) in the 100+ rad exposed group and 14.76 ± 15.69 ng/ml (n=462) in the 0 rad exposed group. Thus, these differences between the two groups were not significant. Also, no significant differences were observed between the 100+ rad and 0 rad exposed groups in the mean serum TSH and TG levels of the subjects who had thyroid diseases but had not been treated for the diseases, and the subjects who had no thyroid diseases. A significant positive correlation between serum TSH and TG levels was observed in the 100+ rad exposed group, the 0 rad exposed group, and the two groups combined.

INTRODUCTION

The occurrence of radiation-induced thyroid cancer was first indicated through animal experiments.[1-5] The association between irradiation and the occurrence of thyroid cancer in man was first reported by Duffy and Fitzgerald[6] in 1950, and later in a number of other reports.[7-15] It has been shown that X-irradiation in childhood, particularly to the cervical region, results in a high occurrence of thyroid cancer 5 to 30 years after exposure.[7-15] Thyroid cancer has developed following X-irradiation with doses as small as 6.5 rad as well as with doses over 1,000 rad.[9-13]

Studies made at RERF on A-bomb survivors of Hiroshima and Nagasaki revealed a significantly higher occurrence 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 the radioactive fallout from the hydrogen bomb, have observed that the incidences of thyroid cancer and nodular goiter were high.

Another radiation-induced abnormality of the thyroid is hypothyroidism. Such hypothyroidism was noted in patients treated for hyperthyroidism[27-31] with large doses of ^{131}I and in the Marshallese exposed to ionizing radiation.[23-26] Recently, subclinical hypothyroidism among exposed Marshallese was observed at a high frequency by highly sensitive TSH determination, and it was suggested that elevation of serum TSH level might be involved in the occurrence of nodular goiter.[26,32]

Determination of serum TSH levels of A-bomb survivors in Hiroshima and Nagasaki was made by

15.69 ng/ml (n＝462) で，両群間に差はなかった．また甲状腺疾患を有し，しかし何ら甲状腺疾患に対する治療を受けてない症例と，甲状腺疾患を有しない対象者の血清 TSH 及びサイログロブリンの平均値は，100 rad 以上被曝群と 0 rad 被曝群の間で有意に異ならなかった．一方，血清 TSH とサイログロブリン値の間には 100 rad 以上被曝群，0 rad 被曝群，及び両群を合わせた場合にも有意の正の相関があった．

緒　言

放射線による甲状腺癌の発生は，まず動物実験で明らかとなった．[1-5] ヒトにおける放射線被曝と甲状腺癌発生の関係は，1950 年に Duffy 及び Fitzgerald[6] の報告以来，数多くの報告がなされた．[7-15] 特に頸部への若年時の X 線被曝により甲状腺癌が高頻度に発生することが被曝後 5 ～ 30 年の間にみられている．[7-15] 放射線被曝による甲状腺癌の発生は，1,000 rad 以上の大量被曝から 6.5 rad の少量の X 線照射でも認められている．[9-13]

放影研における広島，長崎の原爆被爆者に対する調査で甲状腺癌，甲状腺結節の発生が 100 rad 以上被曝群で有意に高かった．[16-22] マーシャル諸島での水爆放射性降下物に被曝した住民にも，高頻度に甲状腺癌や甲状腺結節が発生することが Conard ら[23-26] によって明らかにされている．

放射線の与えるその他の異常としては，甲状腺機能低下症がある．すなわち，甲状腺機能亢進症の治療目的で ^{131}I の大量投与により発生する甲状腺機能低下症[27-31] 及び電離放射線に被曝したマーシャル諸島の住民における甲状腺機能低下症である．[23-26] 最近，高感度の TSH 測定により，臨床症状のない甲状腺機能低下症がマーシャル諸島の被曝者に高頻度にみられ，更に血清 TSH 値の上昇が甲状腺結節の発生に関与することが示唆された．[26,32]

ABCC による広島，長崎の原爆被爆者に対する血清

Parker et al[20] at ABCC in 1971. This determination failed to identify a cause-effect relation between serum TSH level and prevalence of goiter. However, no studies have been conducted on the occurrence of hypothyroidism in relation to A-bomb exposure. Serum TSH screening of A-bomb survivors of Hiroshima and Nagasaki is essential.

Recently it has been reported that serum TG level is a tumor marker for thyroid cancer.[13,33-35] In the study reported here, conducted 30 years after A-bomb exposure, the occurrence of thyroid 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 antibodies in addition to clinical assessment. The association of radiation exposure with occurrence of thyroid disorders and the levels of serum determinations was examined. Hopefully, the results of the present study will be taken over by a study to be conducted 40 years after A-bomb exposure.

MATERIALS AND METHODS

Subjects. Subjects of the present study are A-bomb survivors in Hiroshima and Nagasaki who were under 20 at the time of the bomb (ATB). The subjects included 477 individuals who received an estimated A-bomb dose of 100+ rad and 501 individuals in the 0 rad exposed group (Table 1).

These subjects were selected from the RERF Adult Health Study (AHS) population. In the AHS, medical examinations have been conducted systematically on approximately 20,000 subjects in biennial cycles since 1958. The sampling method and composition of the AHS population are described elesewhere.[36] From approximately 9,700 AHS examinees of cycle 9 (1974-76), for those aged under 20 ATB, about 850 survivors exposed to an estimated dose (T65D)[37] of 100+ rad and about 800 exposed to 0 rad were initially randomly selected and matched by age, sex, and city. The subjects of the present study consist of 978 individuals from the initial group, whose blood samples were obtained and preserved in a perfect condition (−60°C) at AHS examination cycle 9 and whose serum TSH and TG levels were determined (Table 1).

TSHの測定は，1971年 Parker ら[20] により行われた．その結果，血清 TSH 値と甲状腺腫の間に因果関係を突き止めることはできなかった．しかし，原爆被爆と甲状腺機能低下症の発生に関する検討は現在までなされず，広島，長崎の原爆被爆者に対する血清 TSH のスクリーニングが必要である．

最近，血清サイログロブリン値が甲状腺癌の腫瘍マーカーになることが言われている．[13,33-35] この研究は，被爆30年後の広島，長崎の若年被爆者における甲状腺疾患の発生について検討することを目的にし，臨床的な検査のほか，血清 TSH，サイログロブリン，抗サイログロブリン抗体を測定して，放射線被曝と甲状腺疾患の発生及びそれらの血清レベルの測定値との関係を調べたものである．なお，本研究の結果は被爆40年後の調査に引き継がれることを期待する．

材料及び方法

対象者． 本研究の対象者は，被爆時年齢20歳未満で，推定線量100 rad 以上の原爆放射線を受けた被曝群477名と，0 rad 被曝群501名の広島，長崎の原爆被爆者からなる（表1）．

これら対象者は放影研の成人健康調査集団から選ばれた．この成人健康調査は1958年から2年を一周期として系統的に検診しているもので，その対象者は約2万である．成人健康調査集団の抽出方法及び構成については，ほかに詳述されている．[36] 今回の研究の対象者は，当初，成人健康調査第9診察周期（1974−76年）の受診者約9,700人から，被爆時年齢20歳未満で，推定線量（T65D）[37] 100 rad 以上の放射線を受けた広島，長崎の原爆被爆者合計約850名と，この被爆群と年齢・性・都市の構成がほぼ一致する0 rad 被曝群約800名が無作為に抽出された．このうち，第9周期成人健康調査時に採血し血液サンプルが完全な状態で保存され（−60℃），かつ血清 TSH，サイログロブリンが共に測定できた者978名を本研究の対象者とした（表1）．

TABLE 1 NUMBER OF SUBJECTS AND TYPE OF THYROID DISORDERS BY CITY, SEX, AND EXPOSURE GROUPS

表 1　対象者数及び甲状腺疾患の種類；都市，性，及び被曝群別

	Cities 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

These subjects include 200 males (120 in Hiroshima and 80 in Nagasaki) and 277 females (146 in Hiroshima and 131 in Nagasaki) in the 100+rad exposed group, and 219 males (119 in Hiroshima and 100 in Nagasaki) and 282 females (154 in Hiroshima and 128 in Nagasaki) in the 0 rad exposed group. There were 128 subjects who were aged 0-9 ATB and 349 who were aged 10-19 ATB in the 100+rad exposed group. With regard to the 0 rad exposed group, 139 subjects were aged 0-9 ATB and 362 were aged 10-19 ATB (Table 2).

調査対象者の構成は，100 rad 以上被曝群では男性200名（広島120，長崎80），女性277名（広島146，長崎131），0 rad 被曝群では男性219名（広島119，長崎100），女性282名（広島154，長崎128）である．被爆時年齢別では，100 rad 以上被曝群では0－9歳128名，10－19歳349名，0 rad 被曝群では0－9歳139名，10－19歳362名であった（表2）．

TABLE 2 PREVALENCE OF ALL THYROID DISORDERS BY SEX, AGE ATB*, AND EXPOSURE GROUPS

表2 全甲状腺疾患の有病率；性，原爆時年齢及び被曝群別

Sex		Age ATB (0-19)		Age ATB (0-9)		Age ATB (10-19)	
		0 rad	100+ rad	0 rad	100+ rad	0 rad	100+ rad
Total	N	501	477	139	128	362	349
	Obs	39	56	9	21	30	35
	Exp	47.97	47.03	14.93	15.07	33.04	31.96
	RR**	1.000	1.537	1.000	2.615	1.000	1.233
	χ^2***	3.872 (P=0.049)		5.487 (P=0.019)		0.643 (P=0.423)	
Male	N	219	200	70	57	149	143
	Obs	9	6	4	2	5	4
	Exp	7.78	7.22	3.21	2.79	4.58	4.42
	RR	1.000	0.718	1.000	0.564	1.000	0.830
	χ^2	0.410 (P=0.522)		0.442 (P=0.506)		0.082 (P=0.775)	
Female	N	282	277	69	71	213	206
	Obs	30	50	5	19	25	31
	Exp	40.19	39.81	11.73	12.27	28.46	27.54
	RR	1.000	1.823	1.000	4.631	1.000	1.329
	χ^2	6.046 (P=0.014)		9.064 (P=0.003)		0.984 (P=0.321)	

* At the time of the bomb.
原爆時.

** Mantel-Haenszel summary relative risk estimate.
Mantel-Haenszel summary の相対危険度推定.

*** Mantel-Haenszel test statistics for stratified analysis (df=1).
Mantel-Haenszel 検定統計量の層化解析（自由度1）.

The managers of blood sample storage and the persons in charge of serum TSH and TG determinations were kept uninformed of the A-bomb radiation dose received by the survivors and presence or absence of thyroid diseases. This is believed to preclude introduction of any biases in the analysis of the relationship between A-bomb radiation exposure and prevalence of thyroid diseases, even if preserved blood samples are unavailable or the subjects are lost due to unsuccessful serum TSH and TG determinations.

Estimation of Exposure Dose. The estimated exposure doses of A-bomb radiation presently used at RERF are based on those developed by the collaborating researchers at the Oak Ridge National Laboratory.[37] They were estimated with consideration given to the shielding conditions of A-bomb survivors, and others on the basis of theoretical air doses of gamma rays and neutrons. Up to the 8th Report of the RERF Life Span Study (LSS), this dosimetry system was abbreviated as T65D, but T65D was slightly revised because of the relocation of the hypocenter in Nagasaki, and the revised doses, abbreviated as T65DR,[38] have been used since the 9th Report of the RERF LSS. In the present study, the total of gamma ray and neutron doses by T65DR was used. The T65DR system at present is being revised. As the purpose of the present study is to compare the prevalence of thyroid diseases and thyroid functions between those heavily exposed to A-bomb radiation and those exposed to 0 rad, errors in the estimated doses will not introduce any substantial errors in the results of the present study.

Thyroid Palpation. In order to insure uniformity in thyroid palpation findings between Hiroshima and Nagasaki, a training period was provided for the examiners of both cities at the time of the 1971 thyroid study,[21] and it was confirmed that their findings were based upon a uniform criterion. Thereafter, thyroid palpation was conducted by the same examiners, and in order to assure accuracy, abnormal thyroid palpation findings were recorded only after consulting with the physicians responsible for the AHS examination. These findings were classified on the basis of a modification[39,40] of the World Health Organization's criteria which had previously been reported by ABCC.[19] The physicians responsible for AHS examination

血液サンプルの保存管理者や，血清 TSH 及びサイログロブリン測定担当者には原爆被爆者が受けた原爆放射線量及び甲状腺疾患の有無は知らされていない．このことから，血液サンプルの保存の有無あるいは血清 TSH 及びサイログロブリン測定の失敗から生じた対象者の欠落が，原爆放射線被曝と甲状腺疾患有病率との関連を分析する上で偏りを生じることはないと考えられる．

線量推定． 放影研で使用している原爆放射線の推定被曝線量は，Oak Ridge 研究所の共同研究者によって開発されたものが基礎になっている．[37] これは，ガンマ線と中性子線別の理論的な空気線量を基本として，原爆被爆者の遮蔽状態などが考慮されている．放影研の寿命調査第８報までは，この線量測定法は T65D と略称されていた．しかし，放影研の寿命調査第９報から，長崎の爆心地の変更により T65D が若干改訂され，T65DR[38] と略称される推定線量が使用されるようになり現在に至っている．本研究ではこの T65DR のガンマ線と中性子線の合計線量を使用した．この T65DR 線量測定法も再検討されている．本研究の目的自体が，原爆放射線の高線量被曝群と 0 rad 被曝群の甲状腺疾患の有病率，甲状腺機能の比較にあるので，推定線量の相違は，本研究の結果に本質的な誤りを生じるものではない．

甲状腺の触診． 広島と長崎の甲状腺触診所見の同一性を期するため，1971 年の甲状腺の研究[21] に際して両地区の担当者に対し訓練期間が設けられた．その結果，それぞれの担当者の所見が一定基準に基づいていることが確認された．以後引き続き，同じ担当者により甲状腺触診が行われており，甲状腺異常所見は，正確を期するため成人健康調査の担当医と協議の上でのみ記録された．これらの触診所見は ABCC が以前に報告した[19] 世界保健機構の基準を修正した方法[39,40] で分類した．成人健康調査の担当医並びに甲状腺の触診担当者は，被検者

and the examiners in charge of thyroid palpation were uninformed whether the subjects belonged to the 100+rad exposed group or the 0rad exposed group.

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, pathological findings through 1976, thyroid findings in the AHS examination cycle 9, and the levels of serum TSH, TG, and anti-TG antibodies in blood samples collected during that cycle.

Diagnosis of thyroid cancer, thyroid adenoma, and thyroid cyst was made solely on the basis of pathological findings.

The diagnosis of primary hypothyroidism was established for cases of the following two categories: 1) cases diagnosed as such by hormone determination before cycle 9 who are presently under thyroid drug treatment and, 2) cases whose TSH levels were 10μU/ml or more by the determinations made in the present study. Further, cases of this disease satisfying the following definition of chronic thyroiditis are shown in Table 1 as hypothyroidism due to chronic thyroiditis and the rest as hypothyroidism of unknown cause.

Diagnosis of chronic thyroiditis was made for the following three groups: 1) cases pathologically identified as such in the past; 2) cases of hypothyroidism presenting either anti-TG or anti-microsomal antibody titers (determined by tanned red cell hemagglutination)[42] greater than 1×10^2 or anti-TG antibody titers (determined by the precipitation method in this study) greater than 20%; and 3) euthyroid cases with large goiters and elevation of foregoing antibody titers.

Cases of clinically normal thyroid function presenting neither anti-TG antibodies 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. Cases of thyroid cancer, thyroid adenoma, and thyroid cyst were excluded from these diagnostic groups.

が100 rad 以上被曝群か0 rad 被曝群かは全く知らされていなかった.

甲状腺疾患の診断. 甲状腺疾患の診断は，1976年までの成人健康調査の定期診察結果，検査成績，病理学的所見と成人健康調査第9周期の甲状腺所見，及びそのとき採血した血清中のTSH，サイログロブリン，抗サイログロブリン抗体価などを基にして，米国甲状腺学会の分類[41]に従って行った.

甲状腺癌，甲状腺腺腫，甲状腺嚢腫の診断は病理学的所見によるものに限った.

原発性甲状腺機能低下症の診断は次の二つのカテゴリーに属するものに行った. 1) 第9周期以前のホルモン測定によってその診断がなされ，現在ホルモン補充療法が行われている症例. 2) 今回のTSH測定で，その値が10μU/ml以上を示した症例である. なお，本症で次の慢性甲状腺炎の定義をみたす症例は，慢性甲状腺炎による甲状腺機能低下症とし，残りは原因不明の甲状腺機能低下症として表1に示した.

慢性甲状腺炎の診断は次の3群になされた. 1) 過去に病理学的に確認された症例，2) 甲状腺機能低下症で抗サイログロブリン及び抗マイクロゾーム抗体価(タンニン酸処理感作赤血球凝集反応[42])のどちらかが1×10^2以上，あるいは今回の検索で抗サイログロブリン抗体(沈澱法)が20%以上を呈した症例，3) 甲状腺機能は正常であるが甲状腺腫は肥大し上記抗体価が上昇している症例である.

甲状腺機能は正常で，抗サイログロブリン抗体，抗マイクロゾーム抗体を認めない症例で甲状腺結節が1個触知するものを非中毒性甲状腺単結節，2個以上触知するものを非中毒性甲状腺多結節と定義した. なお，甲状腺癌，甲状腺腺腫，甲状腺嚢腫は本診断群から除外した.

Cases of clinically normal thyroid function with absence of anti-TG antibodies and antimicrosomal antibodies were defined as nontoxic diffuse goiter cases if the thyroid was readily palpable, measuring 7 cm or more in transverse diameter and protruding at the time of swallowing, or if the thyroid was, at least unilaterally, definitely hypertrophic and readily palpable, even if the transverse diameter was less than 7 cm. Generally speaking, this was when hypertrophy was so remarkable that the goiter was macroscopically observable.

非中毒性瀰漫性甲状腺腫は，臨床上甲状腺機能正常，抗サイログロブリンと抗マイクロゾーム抗体陰性の症例で，甲状腺の横径が7 cm以上で容易に触れ，嚥下の際隆起するもの，又は横径が7 cm以下でも少なくとも片側の甲状腺にはっきりした肥大があって容易に触れることができ，一般に甲状腺腫が肉眼的に観察可能であるものに定義した．

All the hyperthyroid cases considered in this study were cases which had been diagnosed as such and given ^{131}I therapy or surgical therapy before this study was commenced, and whose thyroid function was either normal or decreased.

甲状腺機能亢進症はすべて今回の診断決定以前に診断され，この研究開始前に^{131}I治療若しくは外科的治療を受けて，現在甲状腺機能は正常か低下している症例である．

Measurement of Serum TSH, TG, and Anti-TG Antibody Levels. Serum samples had been preserved at −60°C for three to five years prior to analysis. All analyses were performed at the same time in the same laboratory. Serum TSH was measured by the radioimmunoassay (RIA) method[43] using a TSH kit manufactured by Eiken Co., Ltd., Japan (double antibody method) and serum TG was measured by the RIA method reported previously by Izumi and Larsen.[44] For the measurement of anti-TG antibodies, ^{125}I-labeled TG was applied to serum, the ^{125}I-labeled TG bound with antibodies was then precipitated along with a second group of antibodies (from antihuman gammaglobulin rabbit serum), and the binding rate of the applied ^{125}I-labeled TG was determined.[44] Binding rates up to 10% were considered nonspecific. When the binding rate exceeded 10%, the serum was considered to have TG autoantibodies, and consequently TG in the blood was not measured.

血清TSH，サイログロブリン，抗サイログロブリン抗体の測定． 測定に使用した血清は−60℃で3～5年間保存されており，下記の測定は同一の研究室で同時に行われた．血清TSHの測定は栄研TSHキット(二抗体法)によるラジオイムノアッセイ(RIA)法[43]で，血清サイログロブリンは和泉とLarsen[44]が既に報告したRIA法で行った．抗サイログロブリン抗体は血清に^{125}I標識サイログロブリンを添加し，抗体を結合した^{125}I標識サイログロブリンを更に第2抗体(抗ヒトガンマグロブリン家兎血清)で沈澱させ，添加した^{125}I標識サイログロブリンに対する結合率で求めた．[44] この結合率は10%までは非特異的結合と考えられ，一方，10%以上を示した血清はサイログロブリン自己抗体があると考えるため，血清サイログロブリンは測定しなかった．

Statistical Analysis. The relation between radiation exposure and the prevalence rates of thyroid diseases was examined using the Mantel-Haenszel method. The sample was divided into two exposure groups (0 rad and 100+ rad). Variables adjusted by stratification were age ATB (0-9, 10-19), sex, and city. Thus, degrees of freedom of all the χ^2 statistics were 1, and the relative risk was the weighted mean of stratum-specific odds ratio. Similarly, the Mantel-Haenszel method[45] was also used for the comparison between variables other than radiation exposure (e.g., sex) and prevalence

統計学的分析． 放射線被曝と甲状腺疾患の有病率との関連比較にはMantel-Haenszelの方法を用いた．対象群は0 rad被曝群と100 rad以上被曝群の2群である．層化によって補正した変数は，被爆時年齢(0－9，10－19)，性，都市である．したがって，得られたχ^2統計量はすべて自由度1で，相対危険度は層別見込比の加重平均である．また放射線被曝以外の変数(例えば性)と甲状腺疾患の有病率との関連比較にも同様にMantel-Haenszelの方法[45]を

rates of thyroid diseases. 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 (H_0: r=0), t statistics were used. Also, regression analyses with dummy variables were used in order to review simultaneous effects of city, sex, age ATB, and radiation exposure on TSH and TG levels. Results obtained from transformation values of square roots are shown because, compared with raw determinations and logarithmic transformation values of both TSH and TG levels, transformation values of square roots were considered to lead to error variation which is closer to that of the normal distribution.

RESULTS

All Thyroid Disorders

Among the 978 subjects, 95 cases of thyroid abnormalities were detected, which were classified according to the diagnostic criteria used in this study (Table 1). The cause of hypothyroidism in seven cases was evidently chronic thyroiditis. These 95 subjects consisted of 39 in the 0 rad exposed group and 56 in the 100+ rad exposed group. The relative risk of thyroid disorders in the 100+ rad exposed group compared with the 0 rad exposed group was 1.537 (χ^2=3.872, P=0.049) and tended to be higher in the former (Table 2). This is attributable to the statistically high relative risk of 4.631 (χ^2=9.064, P=0.003) of the females in the 100+ rad exposed group who were aged 0-9 ATB. With regard to these females the relative risk of thyroid diseases other than thyroid cancer (15 cases in the 100+ rad exposed group and 5 cases in the 0 rad exposed group) was high, being 3.385 (χ^2=5.329, P=0.021).

Thyroid Cancer

Thyroid cancer was detected in eight individuals, all of whom were females belonging to the 100+ rad exposed group. Thus, the relative risk of the 100+ rad exposed group could not be calculated (RR=∞), but the χ^2 value was 7.919 (P=0.005) and the prevalence rate was significantly high (Table 3). Of the eight cases, two were survivors in Hiroshima and six were survivors in Nagasaki, and the prevalence in Nagasaki tended to be higher, but there was no statistically significant difference. Furthermore, four of the eight cases were in the 0-9 age ATB group and the remaining four cases were

用いた．この場合には放射線被曝も層化によって補正した．TSH，サイログロブリンの平均値の比較，相関係数の有意性（帰無仮説$\gamma=0$）の検討にはt統計量を用いた．また，TSH，サイログロブリン値に対する都市，性，被爆時年齢，放射線被曝の同時的な影響を検討するために，二値変数（dummy variable）による回帰分析を用いた．この場合，TSH，サイログロブリンとも，生の測定値と対数変換値を比較したとき，平方根による変換値の方が誤差変動が正規分布に近いと考えられたので，平方根の変換値による結果を示した．

結　果

全甲状腺疾患

対象者978名中95例に甲状腺異常が見られ，本調査の診断基準に従って分類した結果を表1に示した．これらのうち，原因が明らかに慢性甲状腺炎で甲状腺機能低下を示した7例が観察された．95例の内訳は0 rad 被曝群39例，100 rad 以上被曝群56例で，甲状腺疾患有病率の100 rad 以上被曝群の0 rad 被曝群に対する相対危険度は1.537（$\chi^2=3.872$, p=0.049）で，100 rad 以上被曝群が高い傾向を示す（表2）．これは，100 rad 以上被曝群の被爆時年齢0－9歳の女性の相対危険度が4.631（$\chi^2=9.064$, p=0.003）と統計的に高いことに起因している．これらの女性では，甲状腺癌を除く甲状腺疾患（100 rad 以上被曝群15例，0 rad 被曝群5例）に限った場合も，相対危険度が3.385（$\chi^2=5.329$, p=0.021）と高い．

甲状腺癌

甲状腺癌は8例に認められ，全例が女性で，しかも100 rad 以上被曝群であった．したがって100 rad 以上被曝群の相対危険度は計算できない（RR=∞）が，χ^2 値は7.919（p=0.005）であり，有病率が有意に高いことを示している（表3）．8例中2例は広島，6例は長崎の原爆被爆者で，有病率は長崎に高い傾向があるが，統計的有意差ではない．更に，8例中4例は被爆時年齢0－9歳で，残り4例は被爆時年齢10－19歳であり，被爆時年齢0－9歳の

in the 10-19 age ATB group. The prevalence of the former tended to be higher, but there was no statistically significant difference.

有病率が高い傾向にあるが，統計的に有意な差ではない．

TABLE 3 PREVALENCE OF THYROID CANCER BY SEX, AGE ATB*, AND EXPOSURE GROUPS

表 3　甲状腺癌の有病率；性，原爆時年齢及び被曝群別

Sex		Age ATB (0-19)		Age ATB (0-9)		Age ATB (10-19)	
		0 rad	100+ rad	0 rad	100+ rad	0 rad	100+ rad
Total	N	501	477	139	128	362	349
	Obs	0	8	0	4	0	4
	Exp	3.95	4.05	1.93	2.07	2.02	1.98
	RR**	-	-	-	-	-	-
	χ^2***	7.919 (P=0.005)		3.804 (P=0.051)		4.118 (P=0.042)	
Male	N	219	200	70	57	149	143
	Obs	0	0	0	0	0	0
	Exp	0.00	0.00	0.00	0.00	0.00	0.00
	RR	-	-	-	-	-	-
	χ^2	-		-		-	
Female	N	282	277	69	71	213	206
	Obs	0	8	0	4	0	4
	Exp	3.95	4.05	1.93	2.07	2.02	1.98
	RR	-	-	-	-	-	-
	χ^2	7.919 (P=0.005)		3.804 (P=0.051)		4.118 (P=0.042)	

See Table 2 footnotes. 表 2 の脚注を参照.

Of the eight cases, six cases had already been reported in 1971 and two new cases were added during the period between the previous study and this study. The pathological diagnosis was papillary adenocarcinoma in seven cases and follicular adenocarcinoma in one case.

8 例中 6 例は1971年に既に報告された症例であるが，前回の調査から今回の調査までの間に新たに 2 例の甲状腺癌が発生した．病理学的診断は 7 例が乳頭状腺癌，1 例が濾胞状腺癌であった．

Nontoxic Uninodular Goiter

Nontoxic uninodular goiter was found in 3 cases of the 0 rad exposed group and 13 of the 100+ rad exposed group. The relative risk of the 100+ rad exposed group vs the 0 rad exposed group was 4.539 (χ^2=6.584, P=0.010), and its prevalence rate was significantly high. This is attributable to the fact that the rates of both males and females of the 10-19 age ATB group were higher in the 100+ rad exposed group than in the 0 rad exposed group (Table 4).

非中毒性甲状腺単結節

非中毒性甲状腺単結節は 0 rad 被曝群に 3 例，100 rad 以上被曝群に13例が観察された．本疾患の有病率は，100 rad 以上被曝群の 0 rad 被曝群に対する相対危険度が 4.539 (χ^2 = 6.584, p= 0.010) と，有意に高かった．これは，男性，女性を通じて被爆時年齢 10—19歳で，100 rad 以上被曝群が 0 rad 被曝群に比べて高い傾向にあることに起因している（表 4）．

TABLE 4 PREVALENCE OF NONTOXIC UNINODULAR GOITER BY SEX, AGE ATB*, AND EXPOSURE GROUPS

表 4　非中毒性甲状腺単結節の有病率；性，原爆時年齢及び被曝群別

Sex		Age ATB (0-19)		Age ATB (0-9)		Age ATB (10-19)	
		0 rad	100+ rad	0 rad	100+ rad	0 rad	100+ rad
Total	N	501	477	139	128	362	349
	Obs	3	13	2	4	1	9
	Exp	8.07	7.93	2.90	3.10	5.17	4.83
	RR**	1.000	4.539	1.000	1.938	1.000	9.802
	χ^2***	6.584 (P=0.010)		0.561 (P=0.454)		7.066 (P=0.008)	
Male	N	219	200	70	57	149	143
	Obs	1	4	1	1	0	3
	Exp	2.63	2.37	1.02	0.98	1.61	1.39
	RR	1.000	4.434	1.000	1.037	-	-
	χ^2	2.163 (P=0.141)		0.001 (P=0.975)		3.535 (P=0.060)	
Female	N	282	277	69	71	213	206
	Obs	2	9	1	3	1	6
	Exp	5.44	5.56	1.88	2.12	3.56	3.44
	RR	1.000	4.590	1.000	2.818	1.000	6.405
	χ^2	4.423 (P=0.035)		0.818 (P=0.366)		3.794 (P=0.051)	

See Table 2 footnotes. 表 2 の脚注を参照.

Nontoxic Multinodular Goiter

Three cases of nontoxic multinodular goiter were detected in the 0 rad exposed group and four cases in the 100+ rad exposed group (Table 1). Pathological diagnosis was made for three of the seven cases and all three were adenomatous goiter. There was no significant difference in prevalence between the 0 rad and 100+ rad exposed groups.

Primary Hypothyroidism and Chronic Thyroiditis

A total of 23 cases of primary hypothyroidism (14 in the 0 rad exposed group and 9 in the 100+ rad exposed group) were observed, but no significant difference in occurrence between the 100+ rad exposed group and the 0 rad exposed group could be demonstrated. As for its cause, it was assumed to be chronic thyroiditis in 7 cases, but the cause could not be confirmed for the remaining 16 cases. No relationship could be observed between A-bomb exposure and occurrence of hypothyroidism by cause (Table 1).

非中毒性甲状腺多結節

非中毒性甲状腺多結節は 0 rad 被曝群に 3 例，100 rad 以上被曝群に 4 例が観察された（表 1）．7 例中 3 例で病理学的診断がなされ，3 例すべてが腺腫様甲状腺腫であった．0 rad 被曝群と 100 rad 以上被曝群の間で有病率の有意な差はみられない．

原発性甲状腺機能低下症，慢性甲状腺炎

原発性甲状腺機能低下症は計23例（0 rad 被曝群 14 例，100 rad 以上被曝群 9 例）が認められたが，この頻度には 0 rad 被曝群と 100 rad 以上被曝群の間で有意な差はなかった．このうち 7 例はその原因が慢性甲状腺炎と考えられ，残り16例はその原因は断定できなかった．原因別による甲状腺機能低下症の発生と放射線被曝との間に何ら関係はみられなかった（表 1）．

A total of 23 cases of chronic thyroiditis (13 cases in the 0 rad exposed group and 10 cases in the 100+ rad exposed group) were seen with no significant difference in occurrence between the two groups. Of the 23 cases, there were 7 cases of hypothyroidism (5 cases in the 0 rad exposed group and 2 cases in the 100+ rad exposed group) and 16 cases with normal thyroid function (8 cases in the 0 rad exposed group and 8 cases in the 100+ rad exposed group) with no significant difference between the 0 rad and 100+ rad exposed groups in either category (Table 1).

Other Thyroid Disorders

Nontoxic diffuse goiter was observed in 8 cases in the 0 rad exposed group and 12 cases in the 100+ rad exposed group, but there was no difference in prevalence between the two groups (Table 1). Three cases which showed hyperthyroidism and are presently being treated, showed normal or decreased thyroid function. Thyroid cyst was observed in one case.

Serum TSH levels

Table 5 shows the means and standard deviations of serum TSH levels of 462 cases of the 0 rad exposed group and 421 cases of the 100+ rad exposed group, excluding the above-mentioned 95 cases with thyroid disorders. The reason these thyroid disorder cases were excluded from this analysis was that some of them (thyroid cancer, hypothyroidism, hyperthyroidism, thyroid adenoma, and thyroid cyst) had undergone treatment for thyroid disorders and their serum TSH levels might have been changed artificially. In both the 100+ rad and 0 rad exposed groups, the serum TSH levels were distributed with a right tail and did not show a normal distribution. However, because of the large number of samples, the test of difference in means which is based on t statistics (Table 5) is only slightly affected by this distribution. In fact, this does not contradict the results obtained by the under-mentioned variable transformation in further consideration of normality of the distribution (Table 6). It is also important to show measurement values without transformation. The serum TSH levels were 1.54 ± 1.86 μU/ml (n=462) in the 0 rad exposed group and 1.64 ± 1.89 μU/ml (n=421) in the 100+ rad exposed group with no significant difference observed between the two groups. Also, study was made on the difference by sex in the 0 rad and 100+ rad exposed groups,

慢性甲状腺炎は23例（0 rad 被曝群13例，100 rad 以上被曝群10例）で両群の間にその発生頻度の有意な差はなかった．なお，23例中甲状腺機能低下例が7例（0 rad 被曝群5例，100 rad 以上被曝群2例），甲状腺機能正常例が16例（0 rad 被曝群8例，100 rad 以上被曝群8例）で，共に0 rad 被曝群と100 rad 以上被曝群の間に有意な差はなかった（表1）．

その他の甲状腺疾患

非中毒性瀰漫性甲状腺腫は0 rad 被曝群8例，100 rad 以上被曝群12例にみられたが，両群で有病率の差はみられない（表1）．甲状腺機能亢進症は3例であったが，現在治療中で，その甲状腺機能は正常ないし低下していた．甲状腺嚢腫は，1例認められた．

血清 TSH 値

上記甲状腺疾患95例を除く0 rad 被曝群462名と100 rad 以上被曝群421名の血清 TSH 値の平均と標準偏差を表5に示した．甲状腺疾患を有する例を本解析から除外した理由は，これら症例の一部（甲状腺癌，甲状腺機能低下症，甲状腺機能亢進症，甲状腺腺腫，甲状腺嚢腫）は甲状腺疾患に対する各種の治療が行われており，それらの血清 TSH 値は人工的に変動していると考えられたためである．血清 TSH 値の分布は，100 rad 以上被曝群，0 rad 被曝群共に右方に尾を引く分布で正規分布を示さない．しかし標本数がかなり大きいので，表5に示したt統計量に基づく平均値の差の検定に与えるこの分布の影響は小さい．実際，後述する変数変換で分布の正規性を更に考慮して得た結果と相反するものではない（表6）．測定値を加工しないで示すことも重要であろう．血清 TSH 値は0 rad 被曝群 1.54±1.86 μU/ml（n＝462），100 rad 以上被曝群 1.64±1.89 μU/ml（n＝421）で両群の間に有意な差はみられなかった．また，0 rad 被曝群あるいは100 rad 以上被曝群の各群内で性差を検討すると，両被曝群内で共に男性より女性で血清 TSH 値が有意に

TABLE 5 SERUM TSH LEVELS (μU/ml) IN SUBJECTS WITHOUT THYROID DISORDERS BY CITY, SEX, AND EXPOSURE GROUPS

表5 甲状腺疾患を有しない者の血清 TSH 値(μU/ml); 都市, 性及び被曝群別

City			Total		Male		Female	
			0 rad	100+ rad	0 rad	100+ rad	0 rad	100+ rad
Total		No.	462	421	210	194	252	227
		Mean	1.54	1.64	1.11	1.44	1.90	1.82
		SD	1.86	1.89	1.67	1.76	1.94	1.98
	0 rad vs 100+	t test	0.807		1.888		0.429	
		P-value	0.420		0.060 Sug		0.668	
Hiroshima		No.	252	237	111	118	141	119
		Mean	1.50	1.48	1.13	1.38	1.79	1.58
		SD	1.87	1.82	1.78	1.75	1.90	1.89
	0 rad vs 100+	t test	0.121		1.068		0.900	
		P-value	0.904		0.286		0.369	
Nagasaki		No.	210	184	99	76	111	108
		Mean	1.59	1.85	1.09	1.52	2.03	2.09
		SD	1.86	1.96	1.55	1.77	2.00	2.05
	0 rad vs 100+	t test	1.368		1.700		0.198	
		P-value	0.172		0.091 Sug		0.843	

TABLE 6 REGRESSION ANALYSIS WITH DUMMY VARIABLES FOR SUBJECTS WITHOUT THYROID DISORDERS

表6 甲状腺疾患を有しない者の二値変数による回帰分析

Variables			$\sqrt{\text{Serum TSH}}$			$\sqrt{\text{Thyroglobulin}}$		
			β	SE (β)	t (P-value)	β	SE (β)	t (P-value)
Interception			0.815			3.354		
City	X=1	Hiroshima	−0.081	0.053	−1.539 (P=0.124)	−0.408	0.110	−3.714 (P<0.001)
	X=0	Nagasaki						
Sex	X=1	Female	0.262	0.052	5.013 (P<0.001)	0.513	0.110	4.684 (P<0.001)
	X=0	Male						
Age ATB*	X=1	0-9	0.063	0.059	1.075 (P=0.283)	0.045	0.124	0.368 (P=0.713)
	X=0	10-19						
T65DR	X=1	100+ rad	0.062	0.052	1.199 (P=0.231)	−0.120	0.109	−1.100 (P=0.272)
	X=0	0 rad						

	SS	df	MS	F	SS	df	MS	F
Regression	18.496	4	4.624	7.748	100.352	4	25.088	9.581
Residual	523.993	878	0.597	(P<0.001)	2299.177	878	2.619	(P<0.001)
R^2**	0.034				0.042			

*At the time of the bomb. 原爆時. **Coefficient of determination. 決定係数

and serum TSH levels in both exposure groups were observed to be significantly higher in females than in males (0 rad exposed group: n=462, t=4.599, P<0.001; the 100+ rad exposed group: n=421, t=2.095, P=0.037). Similarly, difference by city was not significant in the 0 rad exposed group but was significant in the 100+ rad exposed group (0 rad exposed group: n=462, t=−0.512, P=0.609; the 100+ rad exposed group: n=421, t=−2.016, P=0.044). To examine simultaneously the effects of city, sex, age ATB, and A-bomb radiation exposure on serum TSH, results of regression analyses using dummy variables are shown in Table 6. These were obtained by square root transformation of serum TSH levels, and when the measurement value was zero, 0.01 μU/ml (the minimum value excluding 0) was used. In this case also, it is shown that the serum TSH level is significantly higher in females than in males. No effects of city, sex, and age ATB on the serum TSH levels are observed.

The serum TSH levels in the subjects with nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter who had not received any treatment for thyroid were 0.37 ± 0.64 μU/ml (n=3), 2.90 ± 0.54 μU/ml (n=3), and 1.97 ± 2.67 μU/ml (n=8), respectively, in the 0 rad exposed group and 0.92 ± 1.37 μU/ml (n=13), 1.58 ± 1.65 μU/ml (n=4), and 2.03 ± 1.94 μU/ml (n=12), respectively, in the 100+ rad exposed group, indicating no significant difference between the two groups. The serum TSH levels for these three thyroid disorders combined were 1.83 ± 2.17 μU/ml (n=14) in the 0 rad exposed groups and 1.47 ± 1.69 μU/ml (n=29) in the 100+ rad exposed group and no significant difference was observed between the two groups. Further, the serum TSH levels of the subjects without thyroid disorders and those with the three thyroid disorders previously mentioned were 1.55 ± 1.87 μU/ml (n=476) in the 0 rad exposed group and 1.63 ± 1.87 μU/ml (n=450) in the 100+ rad exposed group, and no significant difference was observed between the two groups. On the other hand, when the 0 rad exposed group and the 100+ rad exposed group were combined, the serum TSH level of cases with the above-mentioned three thyroid disorders was 1.58 ± 1.84 μU/ml (n=43), which was not significantly different from 1.59 ± 1.87 μU/ml (n=883), the serum TSH value of subjects without thyroid disorders.

高値を示した（0 rad 被曝群：n＝462，t＝4.599，p＜0.001；100 rad 以上被曝群：n＝421，t＝2.095，p＝0.037）．同様に都市別でみると，0 rad 被曝群では差はないが，100 rad 以上被曝群では有意である（0 rad 被曝群：n＝462，t＝−0.512，p＝0.609；100 rad 以上被曝群：n＝421，t＝−2.016，p＝0.044）．血清 TSH に対する都市，性，被爆時年齢，原爆放射線被曝の影響を同時に検討するために，二値変数による回帰分析の結果を表6に示した．ここでは血清 TSH 値の平方根変換によるもので，測定値が0の場合，0.01μU/ml（0を除いた最小値）とした．この場合でも，血清 TSH 値は男性より女性で有意に高いことを示している．血清 TSH 値における都市，性，被爆時年齢の影響は観察されない．

甲状腺の治療を全く受けていない非中毒性甲状腺単結節，非中毒性甲状腺多結節及び非中毒性瀰漫性甲状腺腫の血清 TSH 値は，0 rad 被曝群で各々0.37±0.64μU/ml（n＝3），2.90±0.54μU/ml（n＝3），1.97±2.67μU/ml（n＝8），100 rad 以上被曝群で各々0.92±1.37μU/ml（n＝13），1.58±1.65μU/ml（n＝4），2.03±1.94μU/ml（n＝12）で両群間に有意な差はみられない．この三つの甲状腺疾患を合わせた血清 TSH 値は，0 rad 被曝群1.83±2.17μU/ml（n＝14），100 rad 以上被曝群1.47±1.69μU/ml（n＝29）で両群間に有意な差はみられない．更に，甲状腺疾患を有しない対象者と上記三つの甲状腺疾患を合わせた血清 TSH 値は0 rad 被曝群1.55±1.87μU/ml（n＝476），100 rad 以上被曝群1.63±1.87μU/ml（n＝450）で両群間に有意な差はない．なお，上記三つの甲状腺疾患を有する症例の血清 TSH 値は0 rad 被曝群，100 rad 以上被曝群合わせて1.58±1.84μU/ml（n＝43）で，甲状腺疾患を有しない0 rad 被曝群，100 rad 以上被曝群合わせた血清 TSH 値1.59±1.87μU/ml（n＝883）と有意な差はない．

Serum TG Levels

Table 7 shows the mean and standard deviation of 462 subjects in the 0 rad exposed group and 421 subjects in the 100+ rad exposed group who had no thyroid disorders. As in the case of serum TSH levels, the TG levels were distributed with a right tail and did not show a normal distribution. However, as in the case of serum TSH, because of the large number of samples, the test of difference in means based on t statistics is affected by this distribution only slightly. Serum TG levels were 14.76 ± 15.69 ng/ml (n=462) in the 0 rad exposed group and 13.49 ± 13.88 ng/ml (n=421) in the 100+ rad exposed group with no significant difference observed between the two groups. Serum TG level in the 0 rad exposed group was significantly higher in females than in males (n=462, t=4.409, P<0.001), and the 100+ rad exposed group showed a similar tendency (n=421, t=1.859, P=0.064). By city, the level was significantly higher in Nagasaki than in Hiroshima (the 0 rad exposed group: n=462, t=−2.705, P=0.007; the 100+ rad exposed group: n=421, t=−2.278, P=0.023). To examine simultaneously the

血清サイログロブリン値

甲状腺疾患を有しない0 rad 被曝群462名と100 rad 以上被曝群421名の血清サイログロブリン値の平均と標準偏差を表7に示した．血清サイログロブリン値の分布も，血清TSH値と同様に右方に尾を引く分布で正規分布を示さない．しかし，血清TSHの場合と同様に標本数がかなり大きいので，t統計量に基づく平均値の差の検定に与えるこの分布の影響は小さい．血清サイログロブリン値は，0 rad 被曝群14.76±15.69 ng/ml (n＝462)，100 rad 以上被曝群13.49±13.88 ng/ml (n＝421) で両群間に有意な差はみられない．血清サイログロブリン値は0 rad 被曝群内で女性は男性より有意に高く (n＝462, t＝4.409, p＜0.001)，100 rad 以上被曝群内でも同様の傾向にある (n＝421, t＝1.859, p＝0.064)．また，同様に都市別に比較すると，広島より長崎で有意に高い値を示した (0 rad 被曝群: n＝462, t＝−2.705, p＝0.007; 100 rad 以上被曝群:

TABLE 7 SERUM THYROGLOBULIN LEVELS (ng/ml) IN SUBJECTS WITHOUT THYROID DISORDERS BY CITY, SEX, AND EXPOSURE GROUPS

表7　甲状腺疾患を有しない者の血清サイログロブリン値 (ng/ml)；都市，性及び被曝群別

City			Total		Male		Female	
			0 rad	100+ rad	0 rad	100+ rad	0 rad	100+ rad
Total		No.	462	421	210	194	252	227
		Mean	14.76	13.49	11.30	12.13	17.64	14.65
		SD	15.69	13.88	10.55	11.58	18.47	15.50
	0 rad vs 100+	t test	1.270		0.755		1.910	
		P-value	0.204		0.451		0.057	Sug
Hiroshima		No.	252	237	111	118	141	119
		Mean	12.97	12.14	9.61	11.28	15.61	12.99
		SD	13.13	11.86	8.70	11.19	15.28	12.49
	0 rad vs 100+	t test	0.733		1.250		1.495	
		P-value	0.464		0.212		0.136	
Nagasaki		No.	210	184	99	76	111	108
		Mean	16.91	15.23	13.19	13.46	20.22	16.47
		SD	18.10	15.97	12.06	12.13	21.67	18.14
	0 rad vs 100+	t test	0.971		0.144		1.386	
		P-value	0.332		0.885		0.167	

effects of city, sex, age ATB, and A-bomb radiation exposure on serum TG levels, results of regression analyses using dummy variables are shown in Table 6. These were obtained by square root transformation of serum TG levels, and when the measurement value was zero, 0.2 ng/ml (the minimum value excluding 0) was used. In this case also, it is shown that the serum TG level is significantly higher in Nagasaki than in Hiroshima, and in females than in males. No effects of age ATB and A-bomb radiation were observed.

As in the case of serum TSH levels, the serum TG levels in the subjects with three thyroid disorders who had not received any treatment for thyroid were examined. The serum TG levels of nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter were 5.50 ± 4.89 ng/ml (n=3), 22.08 ± 17.27 ng/ml (n=3), and 26.70 ± 25.59 ng/ml (n=8), respectively, in the 0 rad exposed group and 29.33 ± 31.29 ng/ml (n=13), 26.41 ± 26.37 ng/ml (n=4), and 22.62 ± 14.20 ng/ml (n=12), respectively, in the 100+ rad exposed group with no significant difference between the two groups. Though the number of samples was small, the serum TG levels of nontoxic uninodular goiter tended to be higher in the 100+ rad exposed group than in the 0 rad exposed group. When the above-mentioned three thyroid disorders were combined, the serum TG levels were 21.17 ± 21.86 ng/ml (n=14) in the 0 rad exposed group and 26.15 ± 24.15 ng/ml (n=29) in the 100+ rad exposed group with no significant difference observed between the two groups. Also, when the subjects without thyroid disorders and subjects with the three thyroid disorders who had not received treatment for thyroid disorder were combined, the serum TG levels were 14.95 ± 15.91 ng/ml (n=476) in the 0 rad exposed group and 14.30 ± 15.04 ng/ml (n=450) in the 100+ rad exposed group with no significant difference observed between the two groups.

On the other hand, when the 0 rad and 100+ rad exposed groups were combined, the serum TG level of cases with the three thyroid disorders was 24.53 ± 23.29 ng/ml (n=43), which was significantly higher than 14.15 ± 14.86 ng/ml (n=883) of the subjects without thyroid disorders (t=−4.332, P<0.001). Among the subjects without thyroid disorders, a total of 16 cases, i.e., 10 cases in the 0 rad exposed group and

n＝421，t＝－2.278，p＝0.023）．血清サイログロブリン値に対する都市，性，被爆時年齢，原爆放射線被曝の影響を同時に検討するために，二値変数による回帰分析の結果を表6に示した．ここでは血清サイログロブリン値の平方根変換によるもので，測定値が0の場合，0.2ng/ml（0を除いた最小値）とした．この場合でも，血清サイログロブリン値は，広島より長崎，男性より女性で有意に高いことを示している．被爆時年齢，原爆放射線による影響は観察されない．

血清TSH値と同様，甲状腺に対する治療を全く受けていない三つの甲状腺疾患について血清サイログロブリン値を検討してみた．非中毒性甲状腺単結節，非中毒性甲状腺多結節及び非中毒性瀰漫性甲状腺腫の症例における血清サイログロブリン値は，0 rad 被曝群で各々5.50±4.89 ng/ml（n＝3），22.08±17.27 ng/ml（n＝3），26.70±25.59 ng/ml（n＝8），100 rad 以上被曝群で各々29.33±31.29 ng/ml（n＝13），26.41±26.37 ng/ml（n＝4），22.62±14.20 ng/ml（n＝12）で両群間に有意な差はみられない．標本数は少ないが，非中毒性甲状腺単結節は100 rad 以上被曝群が0 rad 被曝群に比べて血清サイログロブリン値が高い傾向にある．上記の三つの甲状腺疾患を合わせた場合，血清サイログロブリン値は0 rad 被曝群21.17±21.86ng/ml（n＝14），100 rad 以上被曝群26.15±24.15ng/ml（n＝29）で両群間に有意な差はみられない．また，甲状腺疾患を有しない対象者と甲状腺疾患に対する治療を全く受けていない三つの甲状腺疾患を合わせた血清サイログロブリン値は0 rad 被曝群14.95±15.91 ng/ml（n＝476），100 rad以上被曝群14.30±15.04 ng/ml（n＝450）で両群間に有意な差はない．

なお，三つの甲状腺疾患を有する症例の血清サイログロブリン値は，0 rad 被曝群，100 rad 以上被曝群合わせて24.53±23.29ng/ml（n＝43）で，甲状腺疾患を有しない0 rad 被曝群，100 rad 以上被曝群合わせた14.15±14.86ng/ml（n＝883）に比べて有意に高い（t＝－4.332，p＜0.001）．甲状腺疾患を有しない対象者中，血清サイログロブリン値が上昇

6 cases in the 100+rad exposed group, showed an increase in serum TG levels (61.00～148.50 ng/ml). For the following four years after determination, no clinically evident thyroid disorders have been observed in these cases.

Correlation Between Serum TSH and TG Levels

Table 8 shows correlation coefficients of serum TSH and TG levels in 883 subjects without thyroid disorders. Both in the 0 rad and 100+rad exposed groups, a positive correlation was observed. This is attributable to the high correlation coefficients in both males and females in Nagasaki. Especially, in Nagasaki, the 0 rad exposed group (n=210, $\hat{r}_1$=0.546) showed a significantly higher correlation than the 100+rad exposed group (n=184, $\hat{r}_2$=0.265; test by Z transformation, Z=3.353, P<0.001 for H_0: $r_1=r_2$). When subjects with nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter who had not received any treatment were combined, the correlation coefficient of serum TSH and TG levels was r=0.255 (t=1.689, P=0.098), and when the subjects with these three thyroid disorders and the subjects without thyroid disorders were combined (n=926), the coefficient was r=0.280 (t=8.862, P<0.001).

DISCUSSION

The ABCC-RERF AHS disclosed that the occurrence of thyroid nodule was significantly higher among exposed subjects in 1958-59, 15 years after the A-bomb.[16,17] By 1971, subsequent studies had shown that the occurrence of thyroid cancer in the group that had been exposed in Hiroshima and Nagasaki was significantly high.[18-22] Several studies[6-15] have reported that the thyroids of young persons are more sensitive to the effects of radiation than are those of older persons.

The subjects of this study were limited to those whose ages ATB were less than 20. Study was made on serum TSH, serum TG, and the prevalence of all the cases of thyroid disorders which had developed by 1975-76, 30 years after the A-bomb exposure. Comparison with the strictly selected 0 rad exposed group revealed significantly high occurrence of thyroid disorders in the 100+rad exposed group. This significant increase in the prevalence of thyroid disorders is attributable to the high occurrence of thyroid cancer and nontoxic uninodular goiter in the 100+rad exposed group.

(61.00～148.50 ng/ml) していた症例が0 rad 被曝群10例，100 rad 以上被曝群6例，計16例に観察された．これら症例は測定後4年間で特に臨床上明らかな甲状腺疾患はみられていない．

血清 TSH とサイログロブリン値の相関

甲状腺疾患を有しない883名の対象者における血清 TSH，サイログロブリン値の相関係数を表8に示した．0 rad 被曝群，100 rad 以上被曝群共に正の相関関係がみられた．これは，長崎で男女を通じて，高い相関係数が観察されたことに起因している．特に，長崎では0 rad 被曝群 (n＝210, $\hat{r}_1$＝0.546) が100 rad 以上被曝群 (n＝184, $\hat{r}_2$＝0.265) より有意に高い相関関係を示していた (z 変換による検定，z＝3.353, p＜0.001; 帰無仮説は $r_1=r_2$)．治療を受けていない非中毒性甲状腺単結節，非中毒性甲状腺多結節及び非中毒性瀰漫性甲状腺腫の三つの甲状腺疾患合計における血清 TSH とサイログロブリン値の相関係数は r＝0.255 (t＝1.689, p＝0.098)，この三つの甲状腺疾患症例と甲状腺疾患を有しない者を合わせた対象者 (n＝926) では r＝0.280 (t＝8.862, p＜0.001) であった．

考　察

ABCC-RERF の成人健康調査は，原爆被爆後15年の1958－59年に甲状腺結節を有する症例が原爆被爆者に有意に高いことを見いだした．[16,17] その後，1971年までの調査で広島，長崎の原爆放射線被曝群に甲状腺癌の発生が有意に高かった．[18-22] 若年者の甲状腺は，高齢者の甲状腺に比べて放射線被曝の影響を受けやすいことが過去の研究[6-15]で報告されている．

今回の調査は，被爆時年齢20歳未満の若年者を対象とした．被爆30年後の1975－76年までに発生したすべての甲状腺疾患を対象にその頻度及び血清 TSH，サイログロブリンについて検討した．厳格に規定された0 rad 被曝群と比較すると，100 rad 以上被曝群で甲状腺疾患の発生頻度が有意に高かった．この甲状腺疾患有病率の有意の上昇は，100 rad 以上被曝群における甲状腺癌及び非中毒性甲状腺単結節の症例の高発生に基づくものである．

TABLE 8 CORRELATION COEFFICIENTS OF SERUM TSH AND TG LEVELS IN SUBJECTS WITHOUT THYROID DISORDERS

表8 甲状腺疾患を有しない者の血清 TSH とサイログロブリン値の相関係数

City	Sex		Total	0 rad	100+ rad
Total	Total	r	0.287	0.328	0.242
		t test	8.895	7.439	5.108
		p-value	<0.001***	<0.001***	<0.001***
		No.	883	462	421
	Male	r	0.240	0.216	0.258
		t test	4.957	3.188	3.704
		p-value	<0.001***	0.002**	<0.001***
		No.	404	210	194
	Female	r	0.288	0.339	0.223
		t test	6.566	5.697	3.435
		p-value	<0.001***	<0.001***	0.001***
		No.	479	252	227
Hiroshima	Total	r	0.140	0.088	0.202
		t test	3.111	1.400	3.157
		p-value	0.002**	0.163	0.002**
		No.	489	252	237
	Male	r	0.107	−0.119	0.267
		t test	1.623	1.254	2.989
		p-value	0.106	0.213	0.003**
		No.	229	111	118
	Female	r	0.135	0.123	0.142
		t test	2.182	1.465	1.550
		p-value	0.030*	0.145	0.124
		No.	260	141	119
Nagasaki	Total	r	0.413	0.546	0.265
		t test	8.989	9.390	3.712
		p-value	<0.001***	<0.001***	<0.001***
		No.	394	210	184
	Male	r	0.401	0.548	0.240
		t test	5.763	6.460	2.126
		p-value	<0.001***	<0.001***	0.037*
		No.	175	99	76
	Female	r	0.399	0.521	0.265
		t test	6.417	6.381	2.824
		p-value	<0.001***	<0.001***	0.006**
		No.	219	111	108

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 this study were all in the 100+rad exposed group, demonstrating a significantly higher prevalence than in the 0 rad exposed group. Kugimoto et al[46] have made a report on the frequency of thyroid cancer in Japanese based on a population in Nagano Prefecture. Among the 30,359 residents, 40 cases of thyroid cancer were observed, the frequency being 1.3 cases/1,000. The frequency of thyroid cancer increases with age. In the same Nagano Prefectural study, when the onset age was limited to approximately 30-50 years as in the present study, the frequency of thyroid cancer was 2.0 cases/1,000, the frequency among females being 2.8 cases/1,000. The prevalence of thyroid cancer in our study population, which is smaller than that in Nagano, was 8 among 477 persons of the 100+rad exposed group, that is, 16.8 cases/1,000. Thus, the prevalence of thyroid cancer is much higher in survivors than in the population in Nagano. The occurrence of thyroid cancer as a late radiation effect has been observed even 35 years after exposure.[12,14,15] The estimated radiation doses of the eight subjects with thyroid cancer were all 100 rad or more, which is considered sufficient to induce thyroid cancer.

一方，Conard ら[23-26]によるマーシャル諸島の住民調査でも，水爆放射性降下物に被曝した者に甲状腺癌が高頻度に発生している．今回の対象例中，甲状腺癌の8例はすべて100 rad 以上被曝群であり0 rad 被曝群より有意に高い有病率であった．日本人における甲状腺癌の発生頻度に関する報告は Kugimoto ら[46]の長野県の住民調査がある．30,359名の住民中，甲状腺癌の発生は40例で，その発生頻度は1,000人当たり1.3例であった．また，甲状腺癌の頻度は加齢とともに増加する．本研究と同様に発病年齢を約30—50歳に限った場合の長野県の同調査では，甲状腺癌の発生頻度は1,000人当たり2.0例で，このうち女性の発生頻度は1,000人当たり2.8例であった．我々の調査は長野県の調査よりも小グループであるが，甲状腺癌の発生は477名の100rad 以上被曝群中8例，すなわち1,000人当たり16.8例と100 rad 以上被曝群の甲状腺癌の発生は長野県の住民に比べて非常に高い比率である．放射線の後障害としての甲状腺癌発生は，被爆35年後でも認められている．[12,14,15] 今回の8例の甲状腺癌発生者の被曝線量は100rad 以上であり，甲状腺癌を誘発するには十分な量と考えられる．

In this study, the pathological diagnosis of thyroid cancer among survivors exposed in youth was predominantly papillary adenocarcinoma, as in the previous results of the ABCC study by Parker et al.[21] Furthermore, the thyroid cancer in the exposed residents of the Marshall Islands was, in each case, papillary adenocarcinoma.[23-26] Generally, thyroid cancer not induced by radiation is predominantly papillary adenocarcinoma,[46,47] which is also highly prevalent among thyroid cancer as a late effect of radiation.[12,14] Serum TSH and TG levels in these eight thyroid cancer cases were normal.

今回の若年被爆者の甲状腺癌の病理学的診断は，過去の Parker ら[21]による ABCC の調査結果と同様で，乳頭状腺癌が多く見られた．更に，マーシャル諸島の被爆者の甲状腺癌はすべて乳頭状腺癌であった．[23-26] 一般的に放射線後障害によらない甲状腺癌は乳頭状腺癌が多いが，[46,47] 放射線後障害としての甲状腺癌も乳頭状腺癌の発生が高率である．[12,14] これら甲状腺癌の8例の血清 TSH 及びサイログロブリン値は正常であった．

Also in this study, nontoxic uninodular goiter was observed at a significantly high frequency among the 100+rad exposed group. In the ABCC study[17,21] in 1959 and in the study of residents of the Marshall Islands by Conard et al,[25,26] thyroid nodule was observed also at a significantly high frequency among the

非中毒性甲状腺単結節は今回の調査でも100 rad 以上被曝群に有意に高い頻度でみられた．甲状腺結節は1959年の ABCC 調査，[17,21] 及び Conard ら[25,26]によるマーシャル諸島の住民調査で本症例が被曝群に多数みられた．Kugimoto ら[46]の長野県の調査では

exposed group. In the study of residents in Nagano Prefecture by Kugimoto et al,[46] 353 (1.1%) nontoxic thyroid nodule cases were observed among approximately 30,000 individuals. The prevalence for those who were about 30-50 years old at onset as were our study subjects, was 1.3% (males 0.8% and females 1.7%). Frequency of nontoxic uninodular goiter in the 0 rad exposed group in Hiroshima and Nagasaki was 0.6%, half as high as that in Nagano. Among the 100+ rad exposed group, on the other hand, the frequency was 3.0% for all the survivors, 2.7% for males and 3.2% for females, each being twice as high as that in Nagano.

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] However, in the present study of those exposed at young ages in Hiroshima and Nagasaki, no relation could be observed between occurrence of thyroid nodule and serum TSH or TG level. As Schneider et al[13] and Yamashita et al[48] have reported that serum TG level cannot be regarded as a tumor marker for small thyroid cancers, it cannot be determined by serum TG whether these thyroid nodule cases are cancerous or not. In a previous report by ABCC,[21] cancer was detected in 8 cases among 19 nontoxic uninodular goiter cases studied histopathologically. Pathological studies of exposed Marshallese disclosed benign goiter in 38 cases and cancer in 7 cases.[26] There is a strong possibility of thyroid cancer being included in the nontoxic uninodular goiter cases that were frequently observed in the 100+ rad exposed group in Hiroshima and Nagasaki. Thus, a careful follow-up is necessary.

No specific relation was observed between the development of chronic thyroiditis or primary hypothyroidism and radiation exposure. In 7 of the 23 cases of primary hypothyroidism, the cause of the disease was chronic thyroiditis. The cause of the disease in the remaining 16 cases is unknown, but primary hypothyroidism is not considered to be induced by radiation exposure because there is no significant difference in occurrence between the 100+ rad and 0 rad exposed groups.

There was no significant difference between the 100+ rad and 0 rad exposed groups in prevalence

非中毒性甲状腺結節症は約3万人の対象者中353例(1.1%)に認められた．本研究と同様に発病年齢が約30－50歳である全対象者では1.3%(男性0.8%，女性1.7%)で発生している．広島，長崎の0 rad被曝群の非中毒性甲状腺単結節の発生頻度は0.6%で長野県の1/2であった．一方，100 rad以上被曝群ではこの発生頻度は全被爆者では3.0%，男性では2.7%，女性では3.2%と長野県のそれぞれの頻度の2倍の値を示した．

Conardら[26]によりマーシャル諸島の被曝者で甲状腺結節発生とTSH値上昇の関係が初めて報告された．しかしながら今回の広島，長崎の若年被爆者の調査では，甲状腺結節の発生と血清TSHあるいはサイログロブリン値の間に何ら関係を見いだすことはできなかった．更に，Schneiderら，[13] 山下ら[48]は，血清サイログロブリン値は小さな甲状腺癌の腫瘍マーカーになり得ないと報告しており，これら甲状腺結節症例に癌が発生しているかどうかは血清サイログロブリンで判定できない．ABCCの過去の報告[21]では病理学的検索を行った非中毒性甲状腺単結節患者19例中8例に甲状腺癌が発見された．一方，マーシャル諸島の被曝者の甲状腺結節の病理学的所見は38例が良性で7例が癌であった.[26] したがって，今回高頻度にみられた広島，長崎の原爆被爆者の非中毒性甲状腺単結節症例に甲状腺癌が含まれている可能性も大きく，今後注意深い観察が必要である．

慢性甲状腺炎あるいは原発性甲状腺機能低下症の発生は，特に放射線被曝と関係はなかった．原発性甲状腺機能低下症の23例中7例はその原因が慢性甲状腺炎であった．残りの16例はその病因が不明であるが，100 rad以上被曝群と0 rad被曝群間の発生頻度に有意な差がないことにより，放射線被曝による原発性甲状腺機能低下症の発生は考えられない．

非中毒性瀰漫性甲状腺腫の発生は，過去のABCCの

of nontoxic diffuse goiter, which is consistent with the previous report by ABCC.[20] Serum TSH level was little related to thyroid swelling, which is consistent with the previous result.[20] On the other hand, serum TG levels were high in the group in which the three thyroid disorders of nontoxic uninodular goiter, nontoxic multinodular goiter, and nontoxic diffuse goiter were combined. This might indicate a relationship between the occurrence of these thyroid disorders and release of TG into the blood from the thyroid. However, discussion on the relationship between occurrence and A-bomb exposure cannot be made under present circumstances, and further review will be necessary.

Serum TSH and TG levels were measured in the 100+rad exposed persons without thyroid diseases to determine if there were any disorders in thyroid cells, but no significant difference was shown in comparison with those in the 0 rad exposed group. Serum TSH and TG levels were not specifically affected by A-bomb exposure, but were higher in females than in males. The serum TG levels of both 100+rad and 0 rad exposed groups were higher in Nagasaki than in Hiroshima, and were closely correlated with serum TSH levels. The reason for this difference in serum TG levels between Hiroshima and Nagasaki is unclear. Higher TSH levels in females as compared to males have been reported previously.[20] The fact that TSH and TG levels showed a positive correlation in these subjects may be consistent with the finding in previous reports[49,50] that TG levels are elevated by TSH.

報告[20]同様，100 rad 以上被曝群と 0 rad 被曝群間に有意な差はなかった．また血清 TSH 値も甲状腺肥大とあまり関係がなく，過去の結果[20]と同じであった．一方，血清サイログロブリン値は非中毒性甲状腺単結節，非中毒性甲状腺多結節，非中毒性瀰漫性甲状腺腫の3疾患を合わせた群で高かった．このことは，これら甲状腺異常の発生と甲状腺から血清へのサイログロブリンの流出との間に何か因果関係があるかもしれない．しかし，症例発生と放射線被曝との因果関係については現状では何も論ずることはできず，今後の検討が必要である．

甲状腺疾患を有しない100 rad 以上被曝者で，何らかの甲状腺細胞の障害を検索する目的で血清 TSH 及びサイログロブリン値を測定したが，特に 0 rad 被曝群と比べてそれらは有意な差を示さなかった．一方，血清 TSH 及びサイログロブリン値は，特に放射線被曝により影響を受けなかったが，男性より女性においてそれらの値は高かった．血清サイログロブリン値は，長崎の100 rad 以上被曝群，0 rad 被曝群とも，広島のそれより高く，この値は血清 TSH 値と密接な相関関係にあった．この広島と長崎の血清サイログロブリン値の差の理由は明らかでない．男性よりも女性における TSH 値上昇は既に報告されている．[20] TSH とサイログロブリン値がこれら対象群で正の相関を示したことは，TSH によるサイログロブリン値の上昇という過去の報告[49,50]と一致する所見かもしれない．

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