行政院國家科學委員會專題研究計畫成果報告

低劑量輻射效應及流行病學研究-低劑量輻射與甲狀腺疾病之關係

Low Dose Radiation Effect and Epidemiological Study – The Relationship Between Low Dose Radiation and Thyroid Diseases

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一、中文摘要

為瞭解居住於輻射屋居民之輻射暴露劑量是否與甲狀腺疾病有關，我們為 1349 位居住於輻射污染建築之居民做身體檢查，測定血中三碘甲狀腺素、甲狀腺素、甲促素和抗甲狀腺微粒體抗體，及做甲狀腺超音波檢查。若有結節，則做超音波導引下細針吸引細胞學檢查。然後將這些人按年齡 (≤15 歲和 >15 歲) 分成兩組, 每組再按照輻射劑量分成五組 (<5 mSv, ≥5-10 mSv, >10-100 mSv, >100-1000 mSv, 和 >1000 mSv)。以 unconditional logistic regression 計算 odds ratio，分析輻射暴露劑量與甲狀腺疾病盛行率之關係，再用 logistic regression model 計算 level of significance of regression coefficient, 探討輻射暴露劑量增加與甲狀腺疾病盛行率增加之趨勢的 P 值。結果顯示單純性甲狀腺腫之盛行率與輻射暴露劑量有關，無甲狀腺腫之自體免疫性甲狀腺炎在大於 15 歲組與輻射暴露劑量有關。甲狀腺功能異常在 15 歲及 15 歲以下組與輻射暴露劑量有關。結節性甲狀腺腫、甲狀腺囊腫、甲狀腺癌、橋本氏甲狀腺炎、甲狀腺微粒體抗體陽性等，與輻射暴露劑量無關。雖然輻射污染建築之輻射暴露劑量不若原子彈爆炸或核能電廠意外事故之輻射劑量那麼高，但仍會影響甲狀腺。主要的變化為甲狀腺瀰漫性增生，而非甲狀腺癌。

關鍵詞：輻射、甲狀腺、甲狀腺瀰漫性增生

Abstract

Background Many people in Taiwan have been living in buildings constructed with ^{60}Co-contaminated reinforcing steel bars. The aim of the present study was to elucidate the effect of chronic low-dose, low-dose-rate γ-radiation on the thyroid gland of residents living in such buildings.

Methods Physical examination of the thyroid, determination of thyroid function and anti-thyroid microsomal antibody, and thyroid ultrasonography were performed in 1349 residents living in the irradiated buildings. Ultrasound-guided aspiration cytology was done if a thyroid nodule was found. Then the persons were stratified by age into two groups (equal or < 15 years and >15 years). Each group was further stratified by radiation-exposed dose into five groups Then odds ratio (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression to examine the association between the radiation-exposed dose and the prevalence of thyroid diseases.

Findings The prevalence of simple goiter (euthyroid, diffuse hyperplasia of the thyroid, and without thyroid antibody in the serum) was related to the radiation-exposed dose. The prevalence of autoimmune thyroiditis without goiter was related to the radiation-exposed dose only in the group of age more than 15 years. The prevalence of abnormal thyroid function was related to the radiation-exposed dose only in the group of age less than 15 years. There was no relationship between the prevalence of nodular goiter, thyroid cyst, thyroid cancer, Hashimoto's

thyroiditis, presence of anti-thyroid microsomal antibody and the radiation-exposed dose.

Interpretation These findings suggest that chronic low-dose and low-dose-rate γ-radiation have effect on the thyroid gland of human beings. Diffuse hyperplasia is the major change.

Keywords: Radiation, Thyroid, Diffuse Thyroid Hyperplasia

Introduction

Reinforcing steel bars, commonly referred to as rebar, are an integral part of the concrete beams and columns, which form a part of the floors, ceilings and walls of modern buildings. Buildings constructed with radioactivity-contaminated rebars were first found in Taipei in July, 1992.[1,2] The source of the radioactive material was ^{60}Co, suspected to have been inadvertently discarded with scrap metal that had been melted during a steel-making process. By the end of 1996, 103 buildings with a total of 1026 housing units were identified by Atomic Energy Council of Taiwan as being contaminated with radioactive rebars at different levels.[1] All these buildings were constructed during the period of 1982 to 1984. [1-5] Many families have been exposed to excessive γ-radiation for 1-11 years, mostly around 10 years, on the basis of time spent indoors.[1,2,3] The background radioactivity (0.5-132.0 μSv/h) in the apartments of Ming-shan Villa, measured in 1994, is several to more than 1000 times that in most Taiwanese buildings (0.08-0.1 μSv/h). [6]

An epidemiological study of the health effects of exposure of these residents to the radiation was started at the end of 1993, with the support of the Department of Health in Taiwan. In an early report, cytogenetic damage was found in residents of irradiated buildings.[6] The aim of the present study was to elucidate the effect of chronic low-dose, low-dose-rate γ-radiation on the thyroid gland of residents living in ^{60}Co-contaminated rebar buildings

Methods

Physical examination of the thyroid, determination of serum triiodothyronine, thyroxine, thyrotrophin and anti-thyroid microsomal antibody, and thyroid ultrasonography were performed in 1349 residents living in the irradiated buildings. Serum triiodothyronine, thyroxine and thyrotrophin were determined by radioimmunoassay. Anti-thyroid microsomal antibody was checked by the particle agglutination method. If a thyroid nodule was found, ultrasound-guided aspiration cytology[7] was done to determine the nature of the thyroid nodule. If malignancy was diagnosed or suspected by aspiration cytology, the patient was referred to operation and confirmed by pathology.

In the process of evaluation of radiation dose equivalent received by residents of ^{60}Co-contaminated rebar buildings, three methods have been adopted, namely, area γ-ray survey, measurement by necklace-type thermoluminescent dosimeter and analyses of chromosomal aberrations of peripheral lymphocytes.[8-10] The radiation dose equivalent used for correlation with prevalence of thyroid disease in the present study is by area γ-ray survey. [8] The details of the method were described in the report by Chen et al. [8]

Then the persons were stratified by age into two groups (≤ 15 years and > 15 years). Each group was further stratified by radiation-exposed dose into five groups (< 5 mSv, ≥ 5 to 10 mSv, > 10 to 100 mSv, > 100 to 1000 mSV, and > 1000 mSv, respectively). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression to examine the association between the radiation-exposed dose and the prevalence of thyroid disease.[11] The P value for trend was calculated as level of significance of regression coefficient (indicative of amount of increase in risk per unit change in ORs) for each variable (or exposure group) in

logistic regression model.

Results

The relationships between radiation-exposed dose and prevalence of thyroid disease are shown in Tables 1 to 8. The prevalence of simple goiter (euthyroid, diffuse hyperplasia of the thyroid, and without thyroid antibody in the serum) was related to the radiation-exposed dose (Table 1). The prevalence of autoimmune thyroiditis without goiter was related to the radiation-exposed dose only in the group of age more than 15 years (Table 5). The prevalence of abnormal thyroid function was related to the radiation-exposed dose only in the group of age less than 15 years (Table 8). High serum triiodothyronine instead of abnormality of serum thyroxine or thyrotrophin, was the major finding in this group. Elevated serum triiodothyronine was noted in 25 of 35 patients. Elevated serum thyroxine was noted in 7 of 35 patients. Elevated serum thyrotrophin was noted in 3 of 35 patients. Decrease of serum triiodothyronine or thyroxine was noted in 1 of 35 patients, respectively. There was no relationship between the radiation-exposed dose and the prevalence of nodular goiter, thyroid cyst, thyroid cancer, Hashimoto's thyroiditis, and presence of anti-thyroid microsomal antibody, respectively.

Discussion

Thyroid g1and may be exposed to external and internal source of ionizing radiation.[12] External radiation may be related to the radiotherapy of lesions of the head, neck or upper thorax, which includes thyroid in the radiation fields. The internal radiation may be related to oral intake of diagnostic or therapeutic doses of radioactive iodine, or radioactive iodine from fallout. The radiation exposure of the residents in ^{60}Co-contaminated rebar buildings belongs to external radiation, and is a kind of chronic low-dose, low-dose-rate γ-radiation.

External radiation of the thyroid may increase the risk of Graves' disease or euthyroid Graves' ophthalmopathy, silent thyroiditis, cystic degeneration, benign adenoma, and thyroid cancer. [13] There was report that thyroid cancer developed following external radiotherapy for scalp tinea.[14] A sixfold increase in the risk of thyroid cancer in childhood was observed. The original mean dose given to the thyroid was less than 9 rads.[14] However, external irradiation of the thyroid at doses higher than 2,000 rem is not clearly associated with the induction of thyroid cancer. [12] The protective mechanism is complete destruction of thyroid cells at such high dose. Radiation doses to the thyroid that exceed approximately 26 Gy frequently produce hypothyroidism.[13] Using thyroid ultrasonography, Healy et al[15] also demonstrated diffuse atrophy in 45 of 46 survivors of childhood Hodgkin's disease who had received radiotherapy to the neck in childhood. The radiation dose to the thyroid gland in these patients ranged from 2,250 to 4,000 cGy. In our present study, the radiation exposure dose of the residents in ^{60}Co-contaminated rebar buildings was usually below 1000 mSv (100 rem). We found that simple goiter, which means euthyroid, diffuse hyperplasia of the thyroid, and absence of thyroid antibody in the serum, is the major change, instead of thyroid nodule, thyroid carcinoma, or atrophy of the thyroid gland.

The study of thyroid lesions in children and adolescents after Chernobyl disaster showed in addition to the increase in incidence of thyroid carcinomas, benign thyroid lesions were also found to be increased in the exposed population.[16,17] Among benign thyroid lesions, cystic adenomatoid nodules of papillary type and diffuse hyperplasia with cellular atypia and nodularity seem to be commonly associated with radiation exposure to the thyroid gland.[17] In the Chernobyl disaster, the most biologically significant isotopes released in the fallout were radioiodines, primarily iodine 131 and other short-lived iodines (132, 133). The absorption of radioiodines from ingestion of contaminated food and water and through inhalation resulted in serious internal exposure to the thyroid gland. Additional

sources of radiation to the thyroid came from protracted gamma radiation from external sources and internal exposure caused by longer-lived isotopes, such as cesium, strontium, plutonium, and others. [18,19] In our present study, although the radiation is a kind of chronic low-dose, low-dose-rate γ-radiation, we also found the prevalence of diffuse hyperplasia was dose dependent. However, it is contrary to the finding of Antonelli et al[20] who showed that occupational exposure to radiation had a higher significant risk for thyroid nodules.

An increased frequency of autoimmune thyroiditis with hypothyroidism has been reported in atomic-bomb survivors in Nagasaki.[21] The study of prevalence of thyroid antibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout also showed increase in thyroid autoimmunity, although without evidence of significant thyroid dysfuction.[22] Our present study showed that the prevalence of autoimmune thyroiditis without goiter, but not autoimmune thyroiditis with goiter (Hashimoto's thyroiditis), was related to the radiation-exposed dose in the group of age more than 15 years. There was also no remarkable hypothyroidism in our study. It may be due to the difference in the nature of radiation, that is acute, high dose irradiation in atomic bomb, and chronic low dose irradiation in ^{60}Co-contaminated rebar buildings. On the other hand, the incidence of circulating autoantibodies to thyroglobulin in healthy subjects increases with age.[23] The vulnerability to develop thyroid antibody in aging people may explain why only the group of age more than 15 years had relationship between autoimmne thyroiditis and radiation dose.

Another interesting finding in our present study is that the prevalence of abnormal thyroid function was related to the radiation-exposed dose only in the group of age less than 15 years. Increased serum triiodothyronine instead of remarkable hypothyroidism was the major finding in this group. Healy et al have demonstrated that 61% of the survivors of childhood Hodgkin's disease treated by external irradiation had had a raised TSH at some time following irradiation.[15] However, these patients accepted high dose irradiation. In our study, these residents received chronic low-dose irradiation. This may explain the difference. However, the reason why serum triiodothyronine is elevated is unknown. Cellular hyperplasia after irradiation may be related. On the other hand, the prevalence of abnormal thyroid function was related to the radiation-exposed dose only in the group of age less than 15 years. This may be due to the susceptibility of thyroid gland of children and adolescents to the irradiation.

The development of thyroid carcinoma after external radiation takes about 10 years, ranged from 3.4 to 28.7 years, and seemed to approach a plateau 15 to 25 years after exposure.[12] The ^{60}Co-contaminated rebar buildings were constructed since 1982 to 1984. Many families have been exposed to excessive γ-radiation for 1-11 years, mostly around 10 years, on the basis of time spent indoors.[1,2,3] Although it is a chronic low-dose, low-dose-rate γ-radiation, the chance to find a new patient with thyroid carcinoma can not be completely ruled out right now.

In conclusion, our findings suggest that chronic low-dose and low-dose-rate γ-radiation have effect on the thyroid gland of human beings. Diffuse hyperplasia is the major change, but not thyroid carcinoma or benign nodular goiter.

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Radiation-exposed dose	**Age ≤15years**			**Age >15years**		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	1	1.00	332	3	1.00
5≤ II ≤ 10	214	5	1.87 (0.22-16.23)	43	1	2.61 (0.27-25.68)
10< III ≤ 100	149	4	2.15 (0.24-19.59)	258	34	16.65*(5.05-54.86)
100< IV ≤ 1000	64	6	8.07 (0.95-68.86)	147	26	23.57*(7.01-79.27)
1000< V	10	3	33.42*(3.06-365.42)	53	9	22.43*(5.85-86.01)
Total	516	19	p=0.0003	833	73	p=0.0001

*p<0.01

Table 1: **Relationship between radiation-exposed dose and simple goiter (euthyroid, diffuse goiter without anti-thyroid microsomal antibody)**

Radiation-exposed dose	**Age ≤15years**			**Age >15years**		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	1	1.00	332	42	1.00
5≤ II ≤ 10	214	2	0.74 (0.07-8.23)	43	1	0.16 (0.02-1.23)
10< III ≤ 100	149	2	1.06 (0.10-11.89)	258	15	0.43^{+}(0.23-0.79)
100< IV ≤ 1000	64	2	2.52 (0.22-28.40)	147	19	1.03 (0.57-1.83)
1000< V	10	0	0.00	53	4	0.56 (0.19-1.64)
Total	516	7	p=0.4504	833	81	p=0.2255

$^{+}$p<0.05

Table 2: **Relationship between radiation-exposed dose and benign single or multi-nodular goiter**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	0	1.00	332	4	1.00
5≤ II ≤ 10	214	0		43	2	4.00 (0.71-22.52)
10< III ≤ 100	149	6		258	10	3.31 (1.03-10.67)
100< IV ≤ 1000	64	2		147	4	2.29 (0.57-9.30)
1000< V	10	0		53	2	3.22 (0.57-18.01)
Total	516	8		833	22	p=0.1100

Table 3: **Relationship between radiation-exposed dose and thyroid cyst**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	0		332	2	1.00
5≤ II ≤ 10	214	0		43	0	0.00
10< III ≤ 100	149	0		258	2	1.29 (0.18-9.21)
100< IV ≤ 1000	64	0		147	0	0.00
1000< V	10	0		53	0	0.00
Total	516	0		833	4	p=0.5007

Table 4: **Relationship between radiation-exposed dose and papillary thyroid carcinoma**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	1	1.00	332	11	1.00
5≤ II ≤ 10	214	2	0.74 (0.07-8.23)	43	2	1.42 (0.31-6.65)
10< III ≤ 100	149	3	1.60 (0.16-15.67)	258	16	1.93 (0.88-4.23)
100< IV ≤ 1000	64	0	0.00	147	15	3.32*(1.48-7.41)
1000< V	10	0	0.00	53	3	1.75 (0.47-6.50)
Total	516	6	p=0.7802	833	47	p=0.0121

*p<0.01

Table 5: **Relationship between radiation-exposed dose and autoimmune thyroiditis (positive anti-thyroid microsomal antibody without goiter)**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	2	1.00	332	12	1.00
5≤ II ≤ 10	214	0		43	0	0.00
10< III ≤ 100	149	0		258	5	0.53 (0.18-1.52)
100< IV ≤ 1000	64	0		147	8	1.54 (0.61-3.84)
1000< V	10	0		53	1	0.51 (0.07-4.03)
Total	516	2		833	26	p=0.9797

Table 6: **Relationship between radiation-exposed dose and Hashimoto's thyroiditis (goiter with positive anti-thyroid microsomal antibody)**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	2	1.00	332	23	1.00
5≤ II ≤ 10	214	3	0.54 (0.09-3.38)	43	1	0.33 (0.04-2.55)
10< III ≤ 100	149	3	0.80 (0.13-4.89)	258	15	0.84 (0.43-1.64)
100< IV ≤ 1000	64	0	0.00	147	12	1.18 (0.57-2.43)
1000< V	10	0	0.00	53	3	0.82 (0.24-2.82)
Total	516	8	p=0.3548	833	54	p=0.9661

Table 7: **Relationship between radiation-exposed dose and positive anti-thyroid microsomal antibody**

Radiation-exposed dose	Age ≤15years			Age >15years		
(mSv)	N	n	OR (95% CI)	N	n	OR (95% CI)
I < 5	79	4	1.00	332	9	1.00
5≤ II ≤ 10	214	12	1.11 (0.35-3.56)	43	1	0.85 (0.11-6.91)
10< III ≤ 100	149	7	0.92 (0.26-3.26)	258	5	0.71 (0.24-2.14)
100< IV ≤ 1000	64	11	3.89^{+}(1.18-12.88)	147	5	1.26 (0.42-3.84)
1000< V	10	1	2.08 (0.21-20.73)	53	2	1.41 (0.30-6.70)
Total	516	35	p=0.0234	833	22	p=0.7473

$^{+}$p<0.05

Table 8: **Relationship between radiation-exposed dose and T3/T4/TSH abnormality**