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PREVALENCE OF THYROID NODULAR LESIONS IN CHILDREN AND ADOLESCENTS

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1. INTRODUCTION

The Great East Japan Earthquake on March 11, 2011 and its subsequent tsunami caused the accidents at the Fukushima Daiichi Nuclear Power Plant, in which extensive damage to the nuclear power reactors resulted in massive radioactive contamina-

tion. The amount of radioactive materials released into the environment was estimated to be 18 PBq of ¹³⁴Cs, 15 PBq of ¹³⁷Cs, 2.0 PBq of ⁸⁹Sr, 0.14 PBq of ⁹⁰Sr, and 160 PBq of ¹³¹I¹⁾, which is approximately 10% of those released by the Chernobyl accident, 47 PBq of ¹³⁴Cs, 85 PBq of ¹³⁷Cs, 115 PBq of ⁸⁹Sr, 10 PBq of ⁹⁰Sr, and 1760 PBq of ¹³¹I²⁾.

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Following the Chernobyl accident, a population-based case-control study in Belarus and the Russian Federation³, and a cohort study with residents younger than 18 years old in Ukraine⁴ both showed a positive relationship between childhood thyroid cancer occurrence and thyroid iodine-131 exposure. Insufficient information and iodine-131-contaminated milk consumption induced radiation-associated thyroid cancer in children, especially those aged 0-5 years at the time of the accident. However, no statistically significant increase in risk of thyroid cancer was observed below 100 mGy⁵. Cohort studies for atomic bomb survivors or children treated with ionizing radiation showed that the external exposure of the thyroid gland to radiation is also a risk factor of thyroid cancer for individuals younger than 20 years old^{6,7}. A linear relationship between the radiation doses and incidence of thyroid cancer was observed in 200-2000 mGy of exposure⁷.

Experiences in the last century have taught us that the influences of radiation on health should be estimated by individual radiation dose measurements. After the Fukushima accidents, various groups have reported such measurements in residents of Fukushima^{8,9}. Fukushima prefectural government and Fukushima Medical University estimated the external radiation doses based on the residents' behavior in the 4 months following the accidents¹⁰. In 99.8% of 421,394 residents in Fukushima Prefecture, the estimated doses were <5 mSv, and the maximal dose was 25 mSv¹¹. Further, thyroid radiation doses analyzed using an NaI (TI) scintillation survey meter in children in the evacuation and deliberate areas were <10 mSv in 95.7% of children (maximum : 33 mSv)⁹. Thus, reported external and internal radiation doses of residents in Fukushima Prefecture were less than 50 mSv.

Despite the low radiation doses relative to the level to be a risk factor of thyroid cancer in childhood, the Fukushima prefectural government decided to conduct the Fukushima Health Management Survey to assist in the long-term health management of residents, which is being carried out by Fukushima Medical University, in response to anxieties among residents of Fukushima Prefecture. As one of four detailed surveys, thyroid ultrasound examinations targeting all prefectural inhabitants between 0 and 18 years of age on March 11, 2011 (approximately 360,000 inhabitants), were started in October 2011.

In this review article, through a modern standardized approach of thyroid ultrasound examination, one of the results of the Fukushima Health Manage-

ment Survey will be briefly introduced in comparison with those obtained from other prefectures in Japan and also the previous reports in the world.

2. THYROID ULTRASOUND EXAMINATION IN FUKUSHIMA

The Fukushima Health Management Survey was established as a long-term program to address public health concerns arising from all aspects of the Great East Japan Earthquake, including the nuclear accident^{10,12}. This program includes a comprehensive thyroid ultrasound examination program for approximately all 360,000 residents of Fukushima Prefecture who were 18 years old or younger as of April 1, 2011¹². Thyroid ultrasound examinations began on October 9, 2011, and will continue for the lifetime of all those who participate. Since the incidence rate of childhood thyroid cancer increased 4 to 5 years after the Chernobyl nuclear accidents¹³, thyroid ultrasound examinations performed until March 2014 were deemed to be a preliminary baseline survey.

A detailed protocol has previously been reported^{10,12}. In brief, a primary survey with portable ultrasound apparatuses screened thyroid nodules and cysts. This survey also conducted measurement of thyroid volume and screening of dysgenesis of thyroid lobes, swelling of lymph nodes, intrathyroidal ectopic thymuses, ultimobranchial bodies, and ultrasonographic findings suggesting diffuse thyroid diseases. Participants of the primary screening were classified into three categories A, B and C. Category A included those with neither thyroid nodules nor cysts (subcategory A1) and those with nodules ≤ 5.0 mm and/or simple or colloid cysts ≤ 20.0 mm that did not require further confirmatory examinations (subcategory A2). In this survey, a cystic nodule with a solid component was classified as a solid nodule because thyroid cancer sometimes forms cystic components. Subjects in category B had one or more nodules ≥ 5.1 mm and/or cysts ≥ 20.1 mm. Category C subjects had sonographic findings showing a large tumor or evidence of aggressive growth. Subjects categorized into B or C were urged to undergo a secondary examination, in which medical examination, detailed ultrasound examination, as well as blood and urinary testing were conducted. Fine needle aspiration cytology (FNAC) was performed in restricted subjects approved by the FNAC criteria based on sonographic characteristics and the maximum diameter of the nodule (Suzuki *S et al.* submitted).

Detailed results of the thyroid ultrasound examination will be published separately (Suzuki S *et al.* submitted). Briefly, 296,026 children participated in the thyroid ultrasound examination program until June 2014, and its participation rate was 80.5%. 141,063 (47.7%), 2,236 (0.8%), and 1 participants were categorized into categories A2, B, and C, respectively¹¹. The solid nodules were observed in 3,888 subjects, and the prevalence rate was 1.3%. 47.8% of subjects had thyroid cysts, most of which were less than 20.1 mm in diameter. Until June 2014, 2070 participants in categories B and C were recommended to have a secondary examination. FNAC conducted in 485 subjects identified malignant cells or cells suspicious for malignancy in 104 cases. Surgery was performed in 58 cases, 57 of which had thyroid carcinoma. The prevalence rate in the participants of the preliminary survey until June 2014 was 0.03% under the condition that confirmed test results were available in 82.6% of children requiring the secondary examination.

3. THYROID ULTRASOUND FINDINGS IN CHILDREN IN THREE JAPANESE PREFECTURES

In order to interpret the results of ultrasound screening of the thyroid in Fukushima, it is important to understand the ultrasound nature in a normal population of children and adolescents. The prevalence of incidental thyroid abnormalities detected on ultrasound examinations in adults has been well documented, however no large-scale ultrasound examination of the thyroid in the general population of children had been conducted until recently. Therefore, the Investigation Committee for the Proportion of Thyroid Ultrasound Findings of Japan Association of Breast and Thyroid Sonology performed ultrasound screening of the thyroid in three Japanese prefectures was conducted in 4,365 children, aged 3 to 18 years, using the same procedures as those used in Fukushima¹⁴. The number of participants was almost equal between male and female; 2075 male and 2290 female children were enrolled in this program.

In this screening program, 4,321 (99.0%) of the total participants were classified into category A, and 55 (1.0%) were categorized as B (Table 1)¹⁴.

Table 1. Number of subjects in each gender classified according to the sonographic findings and prevalence rate in the study by the Investigation Committee for the Proportion of Thyroid Ultrasound Findings in Japan^{14,17}.

Category	Male		Female		Total		
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
A	A1	956	(46.1)	897	(39.2)	1,853	(42.5)
	A2	1,107	(53.3)	1,361	(59.4)	2,468	(56.5)
B		12	(0.6)	32	(1.4)	44	(1.0)
C		0	(0.0)	0	(0.0)	0	(0.0)

Category A included subjects with neither thyroid nodules nor cysts (subcategory A1) and those with nodules ≤ 5.0 mm and/or simple or colloid cysts ≤ 20.0 mm (subcategory A2). Category B included subjects with nodules ≥ 5.1 mm, cysts ≥ 20.1 mm, or nodules ≤ 5.0 mm advised to undergo a confirmatory examination. Category C included subjects with nodules with sonographic findings such as a large tumor or evidence of aggressive growth urging re-examination.

Table 2. Percentage of subjects by age and gender classified by the sonographic findings in the study by the Investigation Committee for the Proportion of Thyroid Ultrasound Findings in Japan^{14,17}.

Age group (years)	Category A2		Category B	
	Male (%)	Female (%)	Male (%)	Female (%)
3-5	29.2	29.0	1.0	0.0
6-10	54.1	56.4	0.2	0.3
11-15	54.6	64.1	0.7	1.6
16-18	54.7	59.7	0.8	2.5

Of those, 2468 subjects (56.5% of total subjects) were classified into a subcategory, A2. There were no participants classified as category C. The prevalence of females in categories A2 and B were significantly higher than males. The highest percentage of subjects categorized in A2 in female was seen in those aged 11-15 years (Table 2). Male subjects also showed the highest percentage of A2 in the age groups 11-15 and 16-18 years. In contrast, the percentage of the subjects classified as category B increased in parallel with age.

4. PREVALENCE OF THYROID NODULAR LESIONS IN CHILDREN AND ADOLESCENTS

4.1 Thyroid cyst

Few reports have studied the prevalence of thyroid cysts in children and adolescents. In the area around Chernobyl, ultrasound examination of the thyroid gland discovered that 502 of the 120,605 children had cystic lesions and its prevalence rate was only 0.42%¹⁵. Technical advances in ultrasound equipment have led to the detection of small nodules and cysts and, an increase in those prevalence rates. Avula *et al.* conducted a retrospective analysis of clinical and ultrasound findings in 287 Canadian children aged 0 to 17 years between 2006 and 2007, and detected incidental thyroid findings in 52 children (18%)¹⁶. Among these incidental thyroid findings, 35 were small (<4 mm), well-defined cysts, and the prevalence rate was 12%. In contrast, the prevalence rate of thyroid cysts detected in the thyroid ultrasound examination in the Fukushima Health Management Survey was 47.8%¹¹. Despite the high prevalence rate, 95% of the thyroid cysts were less than 5.1 mm in diameter. Small cysts without solid tissue do not require further examination and treatment. Nevertheless, affected residents continued to worry about the thyroid cysts due to lack of enough evidence. An answer for this issue was provided by the study performed by the Investigation Committee for the Proportion of Thyroid Ultrasound Findings of Japan Association of Breast and Thyroid Sonology. This study investigated the prevalence rate of thyroid cysts detected using a high-resolution sonography in a general population of Japanese children living in three prefectures distant from Fukushima^{14,17}. The prevalence rate of thyroid cysts in the participants of this study was 56.5%, which appeared to be higher than that in the study conducted in Fukushima. The bias in subjects' age in the three prefectural study should

be considered; thus no children aged 0 to 2 years and only a small number of children aged 3-5 years were recruited¹⁴. As shown in Fukushima, children aged 0 to 5 years exhibited a relatively low prevalence rate. The study in the three prefectures reported that the age-adjusted prevalence of thyroid cysts was 52.35%, which was less than the unadjusted prevalence.

4.2 Thyroid nodule

In adults, thyroid nodules are common in clinical practice. Their prevalence largely depends on the method of screening. Previous reports suggest a prevalence of 2-6% with palpation, and 19-35% with ultrasound¹⁸. The prevalence of thyroid nodules also depends on the population evaluated. Increasing age, female sex, iodine deficiency, and a history of radiation exposure raise the risk of thyroid nodules¹⁸. Technical advances in ultrasound equipment and widespread use of high resolution imaging in clinical practice increases the incidental detection of thyroid nodules.

In contrast to the adult population, few studies have been carried out in the general population of children. Rallison *et al.* examined 5,179 school children in Utah, Nevada, and Arizona for thyroid abnormalities because of possible exposure to radiation from fallout¹⁹. Palpation of the thyroid gland found nodularity of the thyroid in 98 (1.8%) subjects. A retrospective study using ultrasound was reported by Avula *et al.*¹⁶. Of 287 children, 9 (3.1%) had hypoechoic solid nodules with smooth straight margins and tiny hyperechoic foci, which were considered to be intrathyroid ectopic thymus. Three nodules (1.0%), two (0.7%) of which had target-like findings suggesting cystic nodules, and one (0.3%) was isoechoic well-defined nodule, were found. Aghini-Lombardi *et al.* also reported that thyroid nodular goiter was found in 0.5% of children (1-14 years old) and in 2.1% of adolescents and young adults aged 15 to 25 years²⁰.

The Investigation Committee for the Proportion of Thyroid Ultrasound Findings uncovered that the prevalence of thyroid nodules in Japanese children between 3 and 18 years was 1.6%, and the age-adjusted prevalence of thyroid nodules was 1.54%^{14,17}. These results are quite similar to the outcomes from the thyroid ultrasound examination in Fukushima; 1.3% of children and adolescents aged between 0 and 21 years had thyroid nodules¹¹. In both of these studies, thyroid nodules with cystic components, but not hypoechoic lesions suggesting intrathyroidal ectopic thymus, were categorized as

“nodules”. Both studies also showed that elder and female subjects exhibited a higher prevalence rate.

4.3 Thyroid cancer

As the case of thyroid nodules, the prevalence of thyroid cancer largely depends on the method of screening. In adult subjects, previous reports indicated that palpation of the thyroid gland was able to detect thyroid cancer in 0.08–0.9% of subjects^{21–25}. Higher prevalence, 0.1–1.5% in adult general population^{23,25–27}, was reported when sonographic examinations were used in a survey for thyroid cancer. Incidence of malignancy among thyroid nodules was estimated to be 3.7–15.0%²⁸. Furthermore, autopsy studies showed that the prevalence of occult thyroid cancer defined as a malignant tumor found on a specimen was up to 35.6%²⁹. As is the case in thyroid nodules, the prevalence of thyroid cancer also depends on the population evaluated. Subjects’ age, gender, amount of iodine consumption, history of radiation exposure, and family history of thyroid cancer and genetic diseases were all reported to influence the risk of thyroid nodules¹⁸.

In contrast to the adult population, few reports studying the prevalence of thyroid cancer in children and adolescents are available. Screening of thyroid disease by palpation discovered thyroid cancer in 2 of 5,179 school children in Utah, Nevada, and Arizona¹⁹. In this study, the prevalence rate of thyroid cancer was 0.04%.

Several studies for the screening of thyroid cancer in students at the age of puberty were also conducted in Japan⁸. 9988 students aged over 18 years at Chiba University underwent thyroid screening with palpation³⁰. Out of these, 4 students were diagnosed with thyroid cancer, and the prevalence rate of thyroid cancer was 0.03%. Similar prevalence were also shown by thyroid screening with palpation for high school and university students⁸. However no study investigating the prevalence of thyroid cancer by ultrasound examination in the general population of children has been reported. The Investigation Committee for the Proportion of Thyroid Ultrasound Findings in Japan is currently studying the final diagnosis of the thyroid nodules found in the study^{14,17}.

In childhood autopsy cases, Franssila *et al.* reported that 13.6% of autopsy cases aged 11–20 years had occult thyroid cancer when the thyroid gland was subserially sectioned at 2 to 3 mm intervals³¹. However, no occult thyroid cancer was found in cases aged 0 to 17 years. In addition, the prevalence of occult thyroid cancer in young adults aged 21–30

and 31–40 years were 22.2% and 35.3%, respectively³¹.

The incidence of thyroid cancer in children based on the cancer registry in United States was reported by Vergamini *et al.* as an age-standardized rate for age groups of 0–4, 5–9, 10–14, and 15–19 years with values of 0.04, 0.43, 3.50, and 15.16 per million, respectively³². It should be noted that incidence should not be confused with prevalence. While the incidence rate is the number of new cases per population at risk in a given time period, the prevalence rate is the proportion of the total number of cases to the total population. The prevalence of diseases showing long-term progression such as thyroid cancer is higher than the incidence rate, since the prevalence of chronic diseases is generated by its incidence rate and longer survival. In the last decades, thyroid cancer incidence has continuously increased all over the world³³. The reasons for such increase are under discussion; an apparent increase due to more sensitive diagnostic procedure, a true increase due to increased risk factors, or both³³.

5. SUMMARY

Studies concerning radiation doses in Fukushima Prefecture indicated that the risk of radiation-associated thyroid cancer in Fukushima would be quite low in comparison with that of the accident in Chernobyl. However, the Fukushima Health Management Survey including thyroid ultrasound examination was established in order to monitor the long-term health of residents of Fukushima Prefecture. An accurate baseline prevalence of thyroid nodule and cancer in children and adolescents is required for appropriate interpretation of the results from the thyroid ultrasound examination. Although this article reviewed several reports studying thyroid nodular lesions in children and adolescents, it is obvious that epidemiological data is still insufficient. In addition, recent advance in ultrasound technology may lead to increases in detection rates of thyroid cysts, nodules, and cancers. Revisions in diagnostic strategy for thyroid cancer may also result in changes in the prevalence and incidence of thyroid cancer. Since it was reported that the incidence rate of childhood thyroid cancer increased 4 to 5 years after the Chernobyl nuclear accidents, operation of the thyroid ultrasound examination survey with a highly standardized protocol with strict quality control within 4 to 5 years is quite important for accurate interpretations of results from the thyroid ultra-

sound survey in Fukushima over the next several decades.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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