

RAPID COMMUNICATION

The protocol and preliminary baseline survey results of the thyroid ultrasound examination in Fukushima

Shinichi Suzuki¹⁾, Shunichi Yamashita^{1), 2)}, Toshihiko Fukushima^{1), 2)}, Keiichi Nakano¹⁾, Sanae Midorikawa²⁾, Akira Ohtsuru²⁾, Seiji Yasumura²⁾, Mitsunori Hosoya²⁾, Kenji Kamiya²⁾, Hiroki Shimura²⁾, Satoru Suzuki^{1), 2)}, Izumi Nakamura¹⁾ and Masafumi Abe²⁾

¹⁾ Department of Thyroid and Endocrinology, Fukushima Medical University School of Medicine, Fukushima 960-1295, Japan

²⁾ Radiation Medical Science Center for the Fukushima Health Management Survey, Fukushima Medical University, Fukushima 960-1295, Japan

Abstract. After the Fukushima nuclear power plant accident on March 11, 2011, the public of Japan became particularly concerned about the possibility of an increased risk of childhood thyroid cancer, similar to what was observed after the Chernobyl's accident. Due to serious public health perception, there was an urgency to evaluate the baseline levels of childhood thyroid status in Fukushima prefecture. Therefore we have commenced a thyroid ultrasound examination (TUE) survey of the approximately 360,000 pediatric inhabitants (0 to 18 years of age) who lived in Fukushima at the time of the accident in October 2011. The subjects were divided into three categories according to the standardized diagnostic criteria of ultrasound findings. Category A contained the subjects whose TUE findings were intact or benign. Category B were recommended a confirmatory TUE. Category C was recommended an immediate confirmatory TUE. Results: The survey of 40,302 subjects in the first year was completed in March, 2013. There were 40,097 (99.5%), 205 (0.50%) and 0 subjects in categories A, B and C, respectively. Of the 82 category B subjects who underwent fine needle aspiration cytology (FNAC), 12 were diagnosed with a malignant tumor or were suspected to have malignancy. The 12 subjects received thyroid surgery and 11 thyroid cancers and one benign nodule were confirmed histologically after surgery. This is the first large-scaled TUE survey to employ sophisticated ultrasound screening and aim to evaluate the baseline frequency of childhood thyroid nodules and cysts. The results will become the golden standard of future comparative TUE in Fukushima, Japan.

Key words: Fukushima, Chernobyl, Ultrasound examination, Nodules, Thyroid cancer

ON MARCH 11, 2011, a massive earthquake and tsunami occurred in East Japan. This was followed by a serious nuclear accident at Tokyo Electric Power Company's (TEPCO) Fukushima Daiichi nuclear power plant (NPP). Four to five years after the Chernobyl NPP accident, there was a significant increase in childhood thyroid carcinoma in Belarus and Ukraine; this was found to be the consequence of prolonged exposure to radioactive iodine fallout mainly through the food chain [1-4]. This late nuclear accident-related increase in childhood thyroid cancer caused great worry among the Japanese public in the

first few months after the Fukushima disaster.

Due to the issue of concern and a strong request from the central and local governments, the Fukushima Health Management survey (FHM) body initiated several health protection surveys [5], including one that involved thyroid ultrasound examinations (TUE) of all pediatric inhabitants who lived or were staying in Fukushima at the time of the accident. The first objective of this survey was to evaluate the baseline rates of childhood thyroid nodules and cancer in Fukushima as this information was not yet available. The baseline survey commenced on October 9, 2011 [6, 7] and was conducted by Fukushima Medical University (FMU). Since it is essentially important to follow the standardized ultrasound diagnostic criteria as a part of quality control when any large-scaled screening, the protocol and the initial data of the baseline TUE survey in Fukushima are reported concretely here for the first time.

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Correspondence to: Shinichi Suzuki, M.D., Ph.D., Department of Thyroid and Endocrinology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima City, Fukushima 960-1295, Japan. E-mail: shsuzuki@fmu.ac.jp

Subjects and Methods

Primary and secondary TUE and subjects

The subjects were the approximately 360,000 children who lived or were staying in the Fukushima Prefecture at the time of the accident and were aged 18 years or younger on March 11, 2011. FMU conducted two concurrent screening programs: the primary screening, where all children underwent ultrasound examination of the thyroid gland, and the secondary screening, where all children who were shown to have a thyroid nodule in the primary screening underwent a second confirmatory TUE. The overall objective in this survey was to include 360,000 children and adolescents, however it was initially started for those who may have been relatively exposed to radiation. This comprised 47,766 children and adolescents who were living in the areas closest to the nuclear power plant at the time of the accident, 13 target municipalities, which were Kawamata city, Namie town, Iitate village, Minami-Soma city, Ookuma town, Futaba town, Tomioka town, Naraha Town, Hirono Town, Kawauchi village, Katsurao village, Tamura city and Date city.

Ultrasonographic diagnosis

The primary screening mainly detected nodules and cysts in the thyroid gland. The ultrasound devices used were the LOGIQ e Expert (GE healthcare co.) with a 12RS linear probe (10-12MHz) and the Noblus (Hitachi-Aloka co.) with a 12MHz linear probe. This highly sophisticated method is able to detect masses smaller than 1 mm in size. The examiners were mostly board-certified fellows from various Japanese medical associations, namely, the Japan Thyroid Association, the Japan Association of Endocrine Surgeons, the Japanese Society of Thyroid Surgery, the Japan Society of Ultrasonics in Medicine (JSUM) (Seno-thyroidology and General), the Japanese Society of Pediatric Endocrinology, the Japanese Society of Sonographers (JSUM-registered Medical Sonographer, Seno-thyroidology), and the Japan Association of Breast and Thyroid Sonology (JABTS). Both devices were mobile and of high resolution. After each TUE, the suspicious findings among ultrasound images stored on site were retrospectively reviewed twice by the doctors and sonographers in the Radiation Medical Science Center who participated in the FHM Survey. In the first judgment, the record was completed, corrected and selected for the second

inspection by medical doctors and sonographers. In the second inspection, final decision was made by the some specialized doctors. The person of judgment can watch all stored images.

Categories of TUE findings

The children were classified according to the primary screen into three categories designated A, B and C. Category A contained the subjects without thyroid nodules or cysts (subcategory A1) and the subjects with benign findings (≤ 5.0 -mm nodules and/or ≤ 20.0 -mm simple or colloid cysts) that did not require further confirmatory TUE (subcategory A2). In our survey, the mixed solid-cystic type tumor (Fig. 1a), which is a cyst with a solid component, was not classified as a cyst; instead, it was classified as a nodule because this mixed-type tumor sometimes occurs in thyroid cancer. Cysts with colloid clot were identified during the TUE on the basis of the comet tail sign (Fig. 1b) [8]; fine needle aspiration cytology (FNAC) was not required. All category A subjects were recommended to undergo the next round of TUE two years later.

The category B subjects all had a ≥ 5.1 mm nodule and/or a ≥ 20.1 mm cyst and were recommended to undergo a secondary, confirmatory TUE. The category C subjects required immediate re-examination due to highly suspicious TUE findings such as huge tumor or extremely aggressive cases including major extrathyroidal invasion or multiple, large lymphnode metastasis.

The patients who retained their category B and C classifications after the primary screening underwent a detailed examination at FMU that involved a precise ultrasound examination using the highest resolution devices and a more detailed medical examination together with blood and urine analyses. Ultrasound screening criteria [9, 10] were used to determine whether a benign or malignant tumor was present. If not, the subject was re-classified as A1 or A2 and was recommended to undergo the next primary examination two years later. However, subjects diagnosed with a benign or malignant tumor or suspected malignancy diagnosed by FNAC underwent follow-up or surgical treatment. The accuracy of FNAC may not be 100%, and the final decision was made by the pathological findings of the surgically operated tissues. Most cases other than those of malignancy or suspected malignancy according to the FNAC were not considered eligible for surgical treatment. They were planned to undergo re-evaluation after 6 months to a year.

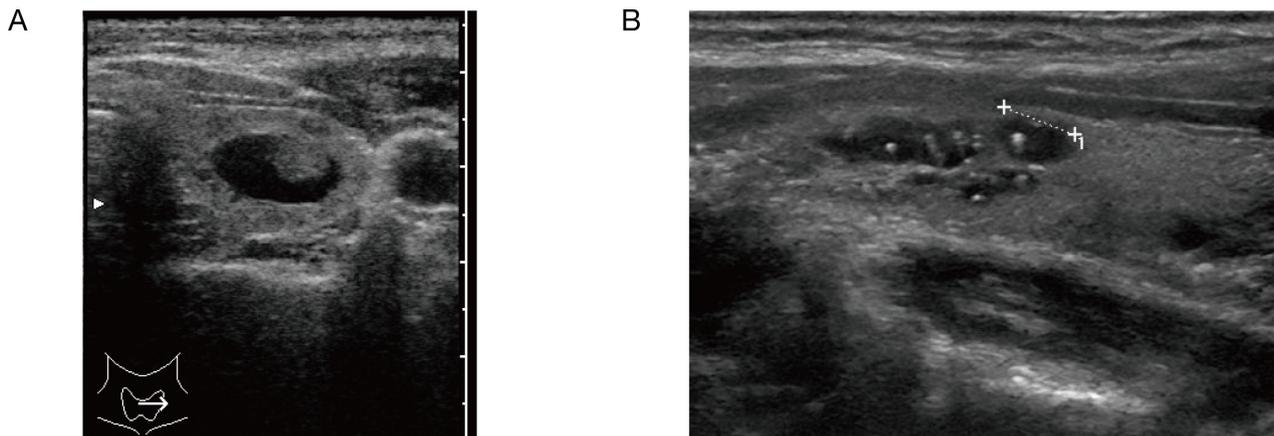


Fig. 1 Ultrasound findings and criteria of thyroid cyst

A) Mixed cystic-solid nodule. Mixed cystic-solid nodule is included as the category of “nodule” in this survey.

B) Ultrasound finding of multiple cysts with colloid clot (colloid cysts). These cysts were well shown in most of the A2 cases, which is rare in children aged five and below, but rather common in elementary and junior high school children.

Survey schedule

The survey was divided into a first round survey and a full-scale survey. The preliminary survey began on October 9, 2011 and was completed at the end of March, 2014. The full-scale survey began in April, 2014 and will finish at the end of March, 2016. Thereafter, all subjects will then be included in further full-scale surveys every two years until they reach the age of 20, and every five years after that for the rest of their lives. There are no differences between either survey method. It is well known that there is a latent period in the development of a radiation induced tumor. As we do not have survey records from before the accident, we named “the first round survey” as the baseline survey. The second survey was denoted as the “full-scale survey”.

Ethics

This survey was approved by the ethical review committee of Fukushima Medical University (No. 1318). Written informed consent was obtained from the surveyed children’s parents.

Statistics

The age and sex with the proportion of category B were calculated using logistic regression models, with adjustment for age (years) or sex. SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) was used for analyses. All probability values for statistical tests were two-tailed, with p -values < 0.05 regarded as statistically significant.

Results

Primary-screen results of the preliminary baseline survey

Between October 9, 2011 and March 31, 2013, 40,302 subjects was living in 13 municipalities targeted for the fiscal year 2011, underwent the primary screening of the preliminary baseline survey (Fig. 2). The participation rate for the TUE at this time was 84.4%.

There were 40,097 (99.5%), 205 (0.50%) and 0 people in categories A, B and C, respectively. Of the category A subjects, 25,670 (63.7% of the whole cohort) and 14,427 (35.8% of the whole cohort) were further divided into subcategories A1 and A2, respectively (Fig. 2). The A2 subjects consisted of 14,350 subjects (35.8% of the whole cohort) with <20.0 mm cysts and 218 subjects (0.53% of the whole cohort) with <5.0 mm nodules. There were 141 cases with both nodules and cysts. Of the 205 subjects in category B, one (0.002% of the whole cohort) had a cyst exceeding 20.0 mm and 204 (0.5% of the whole cohort) had a nodule exceeding 5.0 mm (mixed cystic-solid nodules were considered as nodules). Thus, overall, 14,351 (35.6%) and 422 (1.01%) of the whole population had cysts and nodules, respectively.

Fig. 3 shows the results of the primary screen of the 40,302 subjects after they were divided according to sex and age. The proportion of A1 cases decreased with age. By contrast, the proportion of A2 cases increased with age: a peak was observed at the ages of 13 to 15, after which the frequency decreased. The

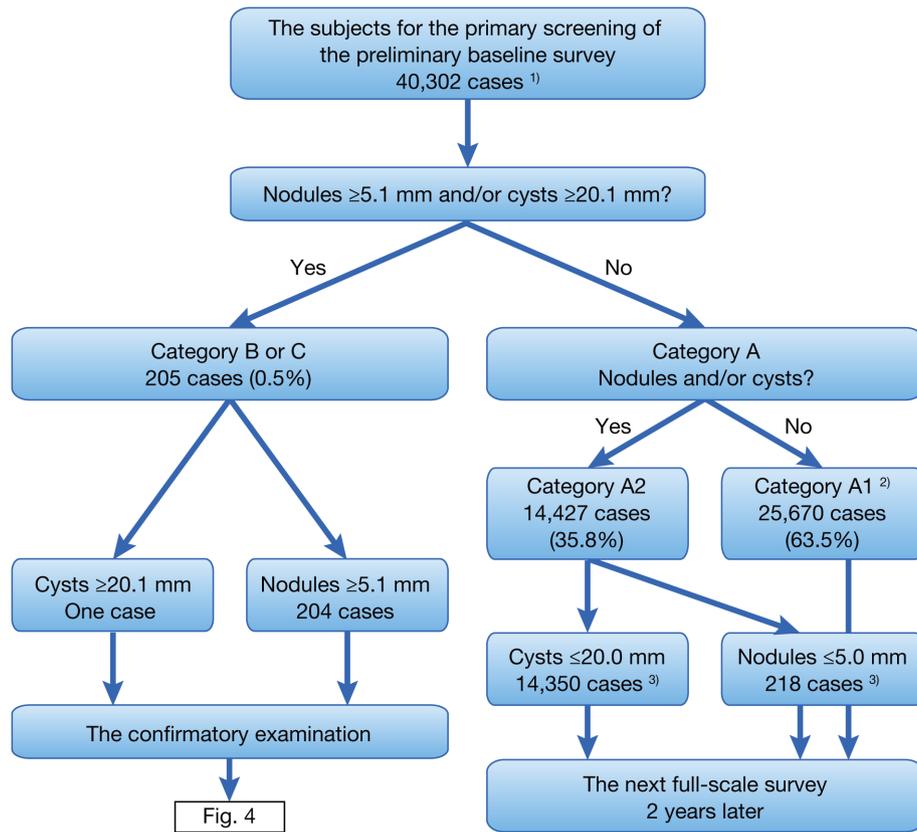


Fig. 2 Flow-Chart for the result of the primary screening in the first round survey from October 9, 2011 to March 31, 2012
Participation rate: 84.4%

1) 2,188 cases who participated in this survey from April 2012 to March 2013 were added.

2) Subjects with intrathyroidal thymus, lymph nodes, ultrasound artifacts, and vessels etc.

3) Some cases had both cyst and nodules.

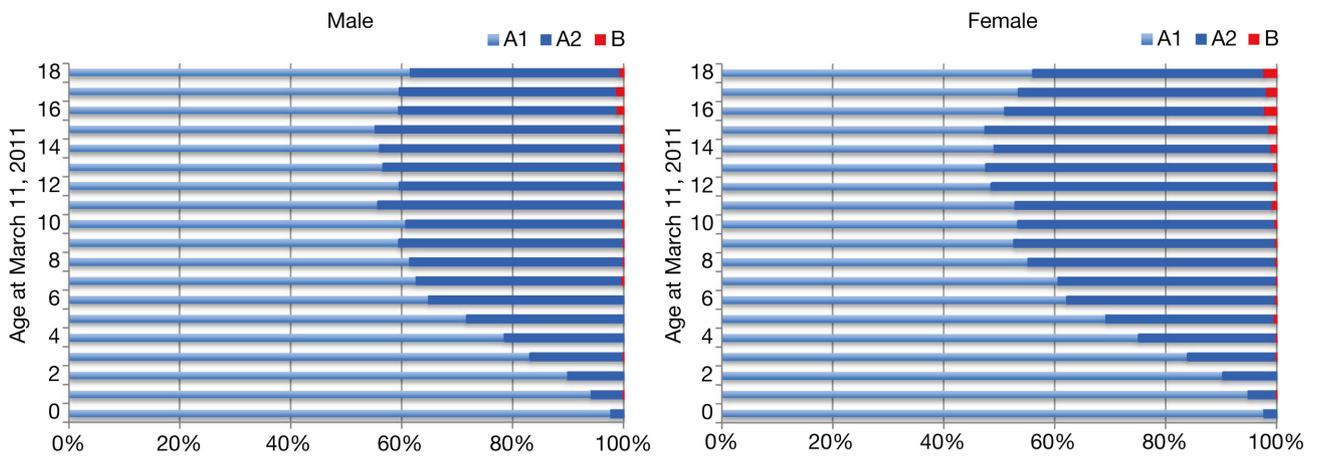


Fig. 3 Result of the first screening classified by sex and age from October 9, 2011 to the end of March 2012
In the Fukushima Health Management Survey, 40,302 children received thyroid ultrasound examination in 13 municipalities targeted for the fiscal year 2011. A1 cases decreased with age, while A2 cases increased with age with a peak at ages of 13 to 15, and decreases after that. B cases increased with age after adolescence. In terms of gender, A2 and B cases were predominantly at female after adolescence.

proportion of B cases increased with age both male and female ($P < 0.0001$). In terms of gender, the A2 and B cases were more likely to be female ($P < 0.0001$).

Secondary-screen results of the first round baseline survey

Of the 205 category B subjects, all of whom were automatically scheduled for secondary TUE, 166 underwent the examination (Fig. 4). Thus, the implementation rate of the secondary examination was 81.0%. Of the 205 subjects who participated in the secondary screen, a diagnosis could be obtained in 160. Of these 160 subjects, 34 (21.3%) were reclassified as A1 ($n=11$, 6.9% of the 160 subjects) or A2

($n=23$, 14.4%) because they did not have abnormal findings (A1) or had cysts/nodules but were deemed not to require further examination until the next full-scale follow-up survey (A2).

The precise ultrasound examination showed that the remaining 82 subjects required FNAC. The results of FNAC were 12.2% (10/82), 2.4% (2/82), 10.9% (9/82), 68.2% (56/82) and 6.0% (5/82) in the malignancy, suspected malignancy, indeterminate, normal or benign and inadequate cases, respectively. The 12 cases with malignancy or suspected malignancy following FNAC underwent thyroid surgery. Pathological examination revealed that one benign thyroid nodule ($n=1$) and 11 classical papillary thyroid cancers ($n=11$). There

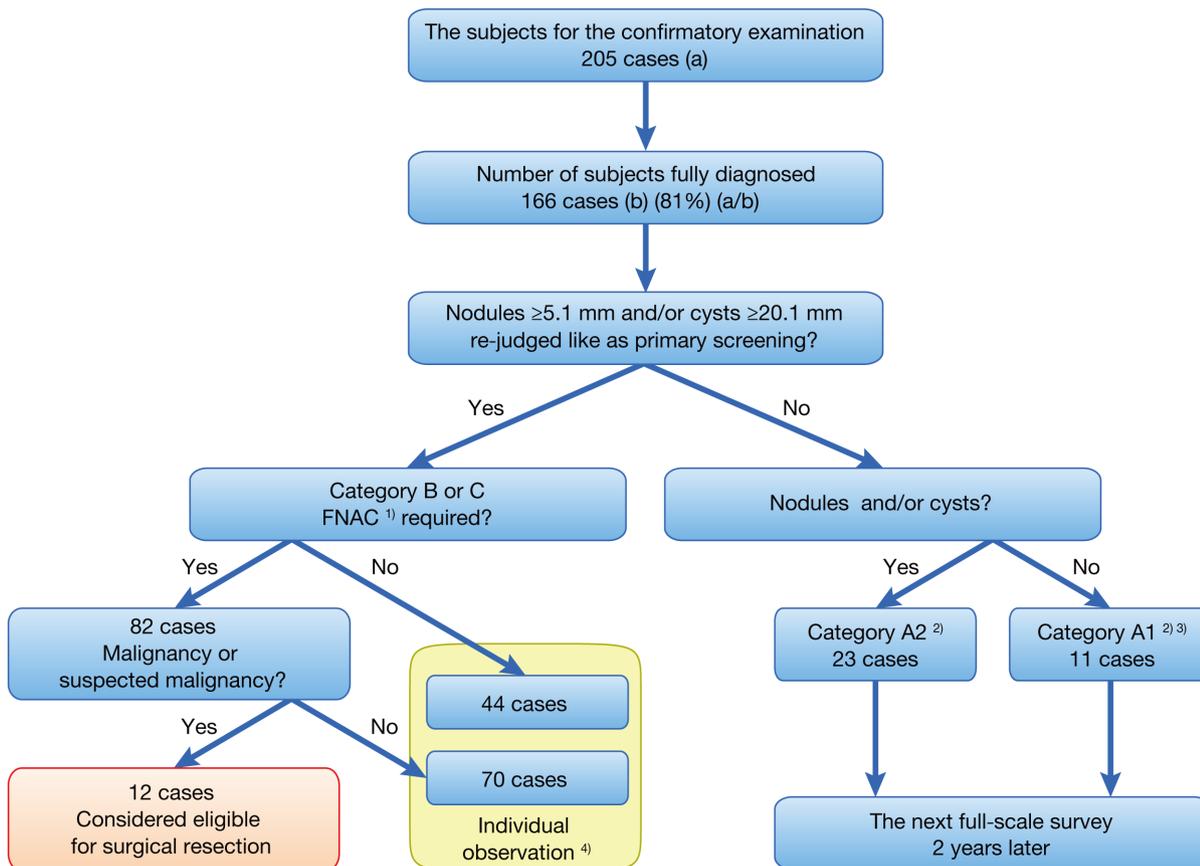


Fig. 4 Flow-Chart for the results of the secondary screening (confirmatory examination) in the first round survey

These secondary examinations were performed between March 2012 and May 2013.

1) Fine needle aspiration cytology

2) Thirty-four of the 160 cases for whom secondary screening yielded an outcome were recommended to enter the next-full-scale follow-up survey that will start in April, 2014 because their findings showed no cysts or nodules or the presence of ≤ 5.0 mm nodules or ≤ 20 mm cysts. These cases were re-judged as A1, A2, the so called “down-staging” from category B.

3) Subjects with intrathyroidal thymus, lymph nodes, ultrasound artifacts, and vessels etc.

4) One hundred and fourteen subjects underwent the routine examination (FNAC or US alone) and then either underwent surgery or were to be followed up six month to one year later.

was no solid variant form of papillary thyroid cancer. These 12 subjects were on average 17.3 (range 13–19) years old, the mean tumor size was 14.1 ± 7.6 (range 6–33) mm, and the male to female ratio was 5 to 7. Retrospectively, the ultrasound findings of all cases showed the hypoechoic nodules with irregular margin, high echo scattered spots, and hard elasticity, indicating typical papillary thyroid cancer.

Discussion

This report for the first time describes the TUE survey protocol and the findings of the preliminary baseline survey of TUE under the framework of the Fukushima Health Management Survey [5].

Prior to the Fukushima accident, there were no epidemiological data on childhood thyroid cancer rates in Japan. Given that the estimated radiation exposure dose of the thyroid glands of the children residing in Fukushima was much lower than that experienced by the children in Chernobyl, it seems unlikely that the children in Fukushima will exhibit increased childhood cancer rates [11]. However, if large-scale TUE studies are performed in the absence of baseline epidemiological data, it is highly likely that they will incorrectly indicate an increase in thyroid cancer cases due to screening bias. This bias arises from the fact that while highly precise ultrasound examination is superior to palpation for detecting thyroid nodules, palpation was frequently used in clinical practice to detect thyroid nodules and thus the baseline frequency of TUE-detectable thyroid nodules in the Fukushima area is unknown. To obtain the required baseline data, the present baseline survey was instituted by the FHM body, which was completed within three years of the Fukushima accident. It is unlikely that symptoms of thyroid cancer due to radiation had developed before this time point partly because an increase in thyroid cancer was reported to start only four to five years after the Chernobyl accident [1–4].

The preliminary baseline survey data described in the present report showed that when multiple minute colloid cysts were detected, they occurred mostly in school-aged children. This suggests that small multiple colloid cysts are characteristic ultrasonographic findings in children, especially school-aged children. This is a novel finding that could only be observed because of this unique large-scale thyroid ultrasound screening survey in children and adolescents. It was difficult to draw conclusions about this at the physiological or pathological

level because the thyroid ultrasound findings of developing children have not been assessed before on such a large scale. The same system used in the Fukushima TUE survey was employed to perform TUE on 4,365 3–18-year-old children from three prefectures (Aomori, Yamanashi, and Nagasaki) that are far from Fukushima. In total, 56.6% of the subjects had an A2 status [12]. The frequency of A2 was higher in three prefectures' study than Fukushima. The study data also indicated that the A2 frequency observed in the present survey did not relate directly to radiation exposure.

The present survey identified 205 subjects with category B TUE findings. The vast majority of these cases had thyroid nodules (including cysts with a solid component and mixed cystic-solid nodules) that exceeded 5.0 mm. It should be noted that thyroid papillary microcancers with a diameter of less than 10 mm and occult cancers (many of which are also microcancers with a diameter below 5.0 mm) are not rare in children. Thus, when performing thyroid ultrasound screening, it is necessary to carefully analyze the data obtained according to the aforementioned diagnostic criteria [9, 10] to ensure detection of these microcancers.

Of the 82 subjects who underwent FNAC in the present survey, 12 were diagnosed with a malignant tumor or were suspected to have malignancy. Of these, eight underwent thyroid surgery and pathology revealed that one had a benign thyroid nodule while the remaining seven subjects had thyroid cancer. None of the thyroid cancers detected in our survey were the solid variant of papillary thyroid carcinomas that were predominantly observed in Chernobyl [13]. Our challenging commencement of TUE in Fukushima also raises another clinical problem on an appropriate treatment for early detection of childhood thyroid cancer, which should be separately discussed [14, 15].

In summary, the baseline prevalence of childhood thyroid nodules and cysts including cancers detected by the TUE in Fukushima within one year after the accident will be very useful as a golden standard to compare the future occurrence and risk of thyroid cancers either due to naturally occurring or radiation-associated causes.

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Appendix

Participating Other Expert Committee Members, Advisors and Staffs in The Fukushima Health Management Survey: Hitoshi Ohto, Kenneth E. Nollet, Kumiko Tsuboi, Shiro Matsui, Masaharu Maeda, Shigeatsu Hashimoto, Keiya Fujimori, Suguru Ishida, Hideto Takahashi, Testuo Ishikawa, Akira Sakai, Yuko Hino, Hiroshi Mizunuma, Keiichi Nakano, Hirokazu Okayama, Chiyo Ohkouchi, Tomomi Hakoïwa, Chisato Takahashi, Yukari Sato, Ayako Sato, Nobuko Sakuma,

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Disclosure Statement

The authors have nothing to disclose. There is no conflict of interest in this study.

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