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Communicating with residents about 10 years of scientific progress in understanding thyroid cancer risk in children after the Fukushima Dai-ichi Nuclear Power Station accident

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ABSTRACT

After the Fukushima Dai-ichi Nuclear Power Station (FDNPS) accident in 2011, radiation-related risk of childhood thyroid cancer remains a matter of concern among residents living in areas affected by radioactive plumes. As a countermeasure to that, the Fukushima Prefectural Government—in conjunction with Fukushima Medical University—began the Fukushima Thyroid Examination (FTE) campaign in 2011. As 116 definite or suspected thyroid cancer cases were found after the first round of FTE and the total number of cases was >240 as of June 2020, residents' concerns have deepened. Some researchers claim that these cases are radiation-induced, while others claim a screening effect (because FTE uses high-resolution ultrasound equipment) and express concern about over-diagnosis. Researchers therefore must address two conflicting issues: one is to elucidate radiation effects on thyroid cancer, which requires continuation of FTE; the other is to solve ethical problems associated with FTE. As to over-diagnosis, surgeons claim that early diagnosis benefits children by reducing the side-effects of treatment and prolonging disease-free survival, while cancer epidemiologists claim that early diagnosis will result in overtreatment without reducing the death rate. 'To receive FTE or not' and 'to stop FTE or not' are ongoing dilemmas for children (and their parents) and other stakeholders, respectively. To facilitate building a consensus among stakeholders, I overview recent findings about dose reconstruction, the dose–response relationship of thyroid cancer, over-diagnosis, and the natural history of thyroid cancer, all of which contribute to judging the risk–benefit balance of thyroid screening.

Keywords: nuclear accident; thyroid cancer; risk; radiation dose; thyroid screening

INTRODUCTION

After the Fukushima Dai-ichi Nuclear Power Station (FDNPS) accident in March 2011, 120 PBq of ^{131}I was released into the environment [1]. Since radioiodine tends to accumulate in the small thyroid gland, thyroid doses are inversely proportional to thyroid mass and thus higher in young children than in adults. After the Chernobyl accident, the incidence of childhood thyroid cancer began to increase 4 or 5 years later and peaked at 10 to 15 years [2], and about 4000 thyroid cancer cases were diagnosed among those who were children and adolescents at the time of the accident [3]. Although both the Chernobyl and FDNPS accidents were ranked as level 7 in the International Nuclear and Radiological Event Scale, the total amount of ^{131}I released from the FDNPS was only one tenth of that from the Chernobyl NPS, and half of the activity of released ^{131}I was deposited over the Pacific Ocean [1]. Nevertheless, as many people in Fukushima Prefecture were afraid of an increased risk of childhood thyroid cancer, the Fukushima Prefectural Government and Fukushima Medical University began conducting the Fukushima Thyroid Examination (FTE) campaign in 2011 by using high-resolution ultrasound equipment [4].

After the first cycle of FTE, 116 definite or suspected thyroid cancer cases were found, and an additional 71 cases were diagnosed after the second cycle of FTE. Now, as of June 2020, the total number of cases is >240. Because these numbers are much larger than the sporadic occurrence expected from the National Cancer Registry in Japan, Tsuda *et al.* [5] warned that radiation risk after the FDNPS accident could be much higher than expected and thyroid cancers found in FTE could include radiation-induced ones. On the other hand, Katanoda *et al.* [6] pointed out that systematic screening for thyroid cancer using high-resolution ultrasound equipment might be responsible for the high detection rate of thyroid cancer by revealing pre-clinical manifestations. Since most thyroid cancers detected by FTE are well differentiated papillary thyroid carcinoma (PTC), prognosis of which is generally good, the authors warned about over-diagnosis. If over-diagnosis indeed occurred, FTE could not be justified as a public health measure—the purpose of which is to reduce cancer mortality [7].

As mentioned before, FTE has been conducted as a countermeasure against residents' fears of radiation health effects, not to reduce cancer death as a public health measure. It is ironic that the countermeasure against residents' fears causes another social problem. Surgeons claim that early diagnosis and treatment of 'clinically relevant' thyroid cancer would be beneficial for children by reducing the side-effects associated with surgery and radiotherapy [8] and by increasing the disease-free survival, though evidence of neither has been fully established, as discussed later. After the FDNPS accident, ongoing FTE does not appear to have led to a consensus among Fukushima residents and other stakeholders about the issues, i.e. 'to receive FTE or not', or 'to discontinue FTE or not' [9]. The present review will be informative by sharing relevant scientific findings, as described below.

DOSE–RESPONSE RELATIONSHIP OF CHILDHOOD THYROID CANCER

If mothers had known that thyroid doses and risk of thyroid cancer were extremely low, they would not have worried about their children's risk of thyroid cancer. However, thyroid doses were not known except for 1080 children in Fukushima, and the risk of thyroid cancer from low doses of radiation was not well-known to stakeholders. After the FDNPS accident, the Japanese Nuclear Safety Commission (NSC) released a dose distribution map of thyroid equivalent dose around FDNPS on 23 March 2011, which was simulated by an atmospheric transport, dispersion, and deposition model (ATDM) [10]. Based on the map, the Local Nuclear Disaster Headquarters implemented a thyroid measuring campaign using an NaI (Tl) scintillation survey meter in Iwaki city, Kawamata town, and Iitate village, because the ATDM simulation predicted thyroid doses of >100 mSv in these municipalities even though they are located ≥ 30 km from the FDNPS. After the campaign, NSC announced that there were no subjects with thyroid doses >100 mSv. Although <100 mSv is defined as 'low dose' by international organizations, it does not assure 'extremely low risk' or 'acceptable risk level'. To develop a consensus among stakeholders about radiation-related risk of childhood thyroid cancer at doses <100 mSv, we have to familiarize ourselves with the epidemiological studies.

With regard to radiation effect on childhood cancer, we rely on cohort studies of externally exposed children, i.e. A-bomb survivors and medically exposed children, and studies of internally exposed children after the Chernobyl accident. Before the FDNPS accident, the Japanese NSC decided (in 2002) that a thyroid equivalent dose (TED) of 100 mSv, if expected, was an intervention threshold for stable iodine prophylaxis. This decision was based on a document published by the International Atomic Energy Agency [11]. However, the document did not imply that there is no radiation risk under 100 mSv. At that time, a pooled analysis of externally exposed children based on seven cohort studies, by Ron *et al.* [12] in 1995, was the most sophisticated epidemiological study on radiation and childhood thyroid cancer; it demonstrated a significant radiation effect at $\sim$0.1 Gy. Additional information became available from epidemiological studies after the Chernobyl accident, and Jacob *et al.* [13, 14] reported an increased risk of childhood thyroid cancer below 0.1 Gy [13, 14]. In 2016, Veiga *et al.* [15] conducted a pooled analysis of childhood thyroid cancer that included 12 cohorts of externally exposed children; they demonstrated a significant linear dose effect at $<$0.1 Gy. In 2017, Lubin *et al.* [16] investigated the dose–response curve below 0.2 Gy by utilizing nine cohort studies selected from those of Veiga's study; they found that a linear dose–response relationship was the preferred model under 0.2 Gy, but a threshold model with a possible threshold dose of $\sim$0–0.03 Gy was also compatible with the data. Relative risk at 0.2 Gy was estimated as 3.2, higher than the values reported after the Chernobyl accident—1.9 from a Russian Federation study [17], 1.4 from a Ukraine study [18] and 1.4 from a Belarus study [19]. As Fukushima people had been exposed mainly to ^{131}I via inhalation and ingestion, risk coefficients from epidemiological studies after the Chernobyl accident will be informative. If a threshold dose of 0.03 Gy is real, one need not worry about thyroid cancer risk below 0.03 Gy. If a linear dose–response relationship holds, relative risk at 0.03 Gy via internal exposure is calculated as 1.06–1.14: i.e. a 6–14% excess of thyroid cancer incidence will be observed in a population exposed to 0.03 Gy.

RADIATION SIGNATURES

If radiation-induced thyroid cancer possessed a unique marker (radiation signature), it would be easy to judge the radiation effect. So far, no such marker has been found. RET/PTC rearrangement was once thought to be a candidate for radiation signature [20]. However, it is not unique to radiation-induced PTC because it is commonly found in sporadic PTC among young children [21, 22]. It has been proposed that common fragile sites might be responsible for RET/PTC rearrangement [23]. Hess found an overexpression of CLIP2 gene in PTC tissue samples after the Chernobyl accident and proposed it as a radiation signature [24]. However, it is not known whether CLIP2 overexpression can be consistently found in radiation-associated PTCs from areas other than Chernobyl.

Some activists in Japan insist that the small female/male ratio of 1.6 in childhood thyroid cancers in Fukushima is an indicator of a radiation effect, because the ratio was 1.6 in Belarus and 1.8 in Ukraine after the Chernobyl accident [2]. However, it is not logical to conclude *a priori* that all thyroid cancers detected in Belarus and Ukraine were radiation-induced ones. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates that the radiation-induced fraction (attributable fraction) may be 0.6 among evacuated children and 0.25 among non-evacuated children after the Chernobyl accident [25]. According to Demidchik's review paper [2], the sex ratio of childhood and adolescent thyroid cancers in 37 studies ranged from 1 to 7.6, and the sex ratio was 2.3 when all 37 studies were pooled. In addition, a small sex ratio is a feature of occult thyroid cancer that is found at autopsy in Japan [26–30] (Table 1). Thus, a small sex ratio is not unique to radiation-associated thyroid cancer, but is observed in childhood thyroid cancer in general and occult thyroid

Table 1. Prevalence and female/male ratio of occult (latent) thyroid cancer in Japan

Author	Area	Slice interval (mm)	Prevalence of occult thyroid cancer		
			Male (M)	Female (F)	F/M
Yamamoto *et al.* [30]	Tokushima	Serial 3 mm interval	26/247 (10.5%)	20/161 (12.4%)	1.2
Sampson *et al.* [26]	Hiroshima Nagasaki	Serial 2–3 mm interval	254/1614 (15.7%)	282/1453 (19.4%)	1.2
Fukunaga and Yatani [27]	Sendai	Serial 2–3 mm	16/59 (27.1%)	13/43 (30.2%)	1.1
	Honolulu	interval	29/140 (20.7%)	31/108 (28.7%)	1.4
Yatani *et al.* [29]	Mie	A single slice	10/665 (1.5%)	11/437 (2.5%)	1.7
		Serial 2–3 mm interval	18/68 (26.5%)		
Seta and Takahashi [28]	Iwate	Serial 5 mm interval	27/181 (14.9%)	32/198 (16.2%)	1.1

Table 2. Estimated thyroid doses among 1-year-old children

	Minamisoma city	**Iitate village**	**Namie town**	**Futaba town**	**Naraha town**	**Tomioka town**
WHO (mSv) [31]	**10–100**	**10–100**	**100–200**	**10–100**	**10–100**	**10–100**
UNSCEAR 2013 (mGy) [1]	**53, 47**	**56**	**81, 83**	**15, 19**	**82, 69**	**47**
Our estimates (mSv) [a]	**12.1**	**14.3**	**8.2**	**7.8**	**4.9**	**5.0**
Inhalation dose [36]	**8.1**	**4.5**	**5.7**	**5.3**	**2.3**	**1.2**
Ingestion dose [42][c]	**3.2**	**6.2**	**1.6**	**1.7**	**2.0**	**3.1**
External dose [43] [d]	**0.8**	**3.6**	**0.9**	**0.8**	**0.5**	**0.7**
	Okuma town	**Soma city**	**Shinchi town**	**Hirono town**	**Iwaki city**	**Kawamata town**
WHO (mSv)	**10–100**	**10–100**	**10–100**	**10–100**	**10–100**	**10–100**
UNSCEAR 2013 (mGy)	**36**	**35**	**35**	**34**	**52**	**65**
Our estimated total dose (mSv)[a]	**6.4**	**14.5**	**12.3**	**4.5**	**7.9**	**5.4**
Inhalation dose [36]	**2.9**	**9.4**[b]	**9**[b]	**2.2**[b]	**5.4**[b]	**1.6**[b]
Ingestion dose [42][c]	**2.6**	**4.5**	**2.8**	**1.8**	**2.0**	**2.5**
External dose [43][d]	**0.9**	**0.6**	**0.5**	**0.5**	**0.5**	**1.3**

[a] Sum of inhalation, ingestion and external doses. Total dose and inhalation dose are correlated ($P = 0.001$), while total dose and external dose are not ($P = 0.179$).
[b] Preliminary estimation for this manuscript utilized data collected under research protocols approved by the Institutional Review Boards as reported elsewhere [36, 42].
[c] Ingestion doses in the original article are modified so as to reflect the lower iodine uptake rate by the thyroid in Japanese people [36].
[d] External dose in the first 4 months after the accident was calculated on the basis of published data (http://kenko-kanri.jp/en/health-survey/document/pdf/31_18Jun2018.pdf).

cancer in particular. If over-diagnosis occurred, the sex ratio would become smaller.

ESTIMATED THYROID DOSES AFTER THE FDNPS ACCIDENT—ESTIMATION BEFORE 2015

The World Health Organization (WHO) published preliminary dose estimates in 2012 [31], in which thyroid doses of a hypothetical 1-year-old infant ranged from 100 to 200 mSv in Namie town, and from 10 to 100 mSv in the rest of Fukushima Prefecture (Table 2). However, WHO estimated doses on the basis of information available before October 2011, and the doses in that range were overestimated compared with the latest estimates. Kim *et al.* analyzed 1080 children in Iwaki city, Kawamata town, and Iitate village, who received direct thyroid measurements, and reported that the 90th percentile of TED was <16 mSv [32]. However, the total number of children measured was small and insufficient to represent the full demographic and spatial distribution of thyroid doses in Fukushima. In 2014, UNSCEAR released a report on the FDNPS accident [1] in which estimated average thyroid absorbed doses for 1-year-old infants ranged from 47 to 83 mGy in deliberately evacuated municipalities, while it ranged from 33 to 52 mGy in other municipalities of Fukushima Prefecture (Table 2). UNSCEAR noted that 'the doses to the thyroid varied considerably among individuals, indicatively from about 2 to 3 times higher or lower than the average for a district'. As a comparison, our estimates for 1-year-old children are included in Table 2 and will be discussed later.

ESTIMATED THYROID DOSES AFTER THE FDNPS ACCIDENT—ESTIMATION AFTER 2016

There were several sources of uncertainty in the UNSCEAR dose estimates, which could be reduced by utilizing data newly obtained after the UNSCEAR 2013 Report. First, ^{129}I concentrations in soil at >900 points in Fukushima were published [33]. Second, hourly ^{137}Cs concentrations in air that had been trapped at monitoring stations for suspended particulate matter (SPM) measurement were also published [34]. These data are useful for improving the ATDM simulation. Third, by utilizing ^{137}Cs concentrations in air at many SPM stations in the Kanto area, Terada *et al.* [35] updated the source term, improved the ATDM simulation, and released a database—Worldwide System for Prediction of Environmental Emergency Dose Information_2019 Data-base (WSPPED_2019DB)—that describes spatiotemporal radionuclide concentrations. Fourth, evacuation scenarios for children were re-evaluated. In the UNSCEAR 2013 Report, only one or two evacuation scenarios per municipality were used to estimate inhalation and ingestion doses during evacuation. Ohba *et al.* [36] analyzed 100 or 300 randomly sampled 'whereabouts' questionnaire sheets to estimate inhalation doses during evacuation by utilizing WSPEEDI_2019DB. Fifth, Hirouchi *et al.* [37] investigated sheltering from radioactive plumes in Japanese houses as a radiological protection factor. In the UNSCEAR 2013 Report, sheltering was not considered in the dose estimation. Sixth, it has been known that, as Japanese consume substantial quantities of stable iodine from food, iodine uptake by the thyroid is lower than that in the International Commission on Radiological Protection (ICRP) model. Ishikawa *et al.* reported that the differences between Japanese and ICRP models in terms of thyroid weight, as well as fractional uptake and retention times of ^{131}I in the thyroid, would contribute to uncertainties in the thyroid dose estimates in Japanese people [38]. However, it has not been officially proposed to correct the ^{131}I-dose coefficient of the ICRP dose estimation to reflect the lower iodine uptake rate among Japanese people. Once Kudo *et al.* [39] demonstrated the distribution of thyroid weight, iodine uptake rate and other bio-kinetic parameters in Japanese people, it became possible to propose a correction factor for the ^{131}I-dose coefficient. Seventh, in contrast to UNSCEAR's supposition that Fukushima residents consumed contaminated vegetables and other foodstuffs grown in Fukushima Prefecture, Hirakawa *et al.* [40] investigated the food and water supply in Fukushima immediately after the accident and concluded that most Fukushima residents consumed non-contaminated food that had been stocked before the accident and did not consume contaminated milk or vegetables. This was because of destruction of the food supply chain after the accident and the closure of retail stores in Fukushima [40]. After reopening, retail stores sold fish, vegetables and milk that were produced in areas other than Fukushima, and these foods had been screened for contamination before shipment [10]. On the other hand, most Fukushima residents had to consume potentially contaminated tap water for drinking and cooking. Water supply systems in Fukushima were temporarily stopped after the earthquake on 11 March due to the loss of electricity and damage to pipelines, but they resumed service on 14 March in most municipalities. As radioactive plumes after 15 March affected water sources in Fukushima, tap water was contaminated with ^{131}I [41]. As the monitoring of tap water did not begin until several days after the accident [41], and drinking tap water was not prohibited before monitoring results were available, tap water might be a major source of ^{131}I-exposure via ingestion.

Utilizing WSPEEDI_2019DB, our group re-evaluated TEDs via ingestion [42] and inhalation [36] among residents <19 years old at the time of the accident. Table 2 includes our TED estimates via inhalation [36], ingestion [42] and external exposure [43]. It demonstrates that mean TEDs in 1-year-old infants living in municipalities near the FDNPS at the time of the accident are much smaller than thyroid doses reported by WHO or UNSCEAR, and are <15 mSv. However, it is noted that the 95th percentiles of TEDs of 1-year-old infants in Namie town and Futaba town are ~30 mSv, and the uncertainty interval upper bounds are ~60 mSv (Table 2).

To validate simulation-based TEDs, we compared them with those based on the direct thyroid measurement of 1080 children. As shown in Table 3, our estimates of median and 75th percentiles are consistent with TEDs reported by Kim *et al.* [44], if zero dose estimates by Kim *et al.* are ignored. It is noteworthy that 0 mSv does not necessarily mean the absence of exposure but rather reflects difficulty in measuring low radio-activities in the thyroid under the high background levels. Thus, it is likely that most children in Fukushima received thyroid doses of <30 mSv, for which risk of thyroid cancer is very low (as discussed above). UNSCEAR is going to update the Fukushima Report in 2020, at which time the doses received by Fukushima residents will be further clarified.

RADIATION EFFECT?

As to Tsuda *et al.*'s report in the journal *Epidemiology*[5], several researchers, including UNSCEAR experts, submitted critical comments to the journal. As pointed out by the criticizers, it is inappropriate to compare prevalence or incidence of thyroid cancer among areas with different contamination levels. Such an epidemiological study design is called an ecological study, where the average exposure or dose in a municipality is used as a surrogate for individual exposures or doses in that municipality. As the dose distribution among cases might be quite different from the distribution of average doses in municipalities, an ecological study in general is susceptible to the 'ecological fallacy'. As Tsuda *et al.* utilized the radio-cesium contamination level of land in different municipalities as a surrogate for individual thyroid dose from ^{131}I, their conclusion was inevitably susceptible to the 'ecological fallacy'. Moreover, the prevalence of thyroid cancers in the first FTE was not actually associated with contamination levels defined by Tsuda *et al.* The incubation period of radiation-induced PTC was 4–5 years after exposure in Chernobyl [2, 45], while the first FTE had been conducted within 3 years of the Fukushima accident. In addition, age distribution, pathological type of PTCs and genetic alteration in PTCs in Fukushima were quite different from those of PTCs after the Chernobyl accident [20], as discussed below. The mean age, at the time of the Fukushima accident, of thyroid cancer patients detected in the first FTE was 14.9 (SD 2.6) years [46], whereas >50% of thyroid cancer patients after the Chernobyl accident were <6 years old [20]. As to the histological variant type of PTC, it was classic papillary in >90% of cases in Fukushima [47], while it was the solid or diffuse sclerosing variant after the Chernobyl accident [22]. As to genetic alterations, *BRAF*^{V600E} point mutation was observed in 63.2% of cases in Fukushima [48], whereas RET/PTCs rearrangements were the dominant genetic alterations after the Chernobyl accident [22]. These data support the conclusion that thyroid cancers detected in the first FTE might not be associated with radiation.

To test a possible radiation effect on thyroid cancer occurrence in Fukushima, it is essential to conduct careful epidemiological analyses. As shown in Table 2, external doses and internal doses via ingestion and inhalation are not correlated. This is because external doses during

Table 3. Comparison of estimated TED (mSv) among 5-year-old children by simulation with those by thyroid measurement. It is noteworthy that 0 mSv does not necessarily mean the absence of exposure but rather reflects difficulty in measuring low radio-activities in the thyroid under the high background levels.

	Iwaki city			Kawamata town			Iitate village		
	Kim *et al.* [44] (*n* = 48)		Present study[b]	Kim *et al.* [44] (*n* = 333)		Present study[b]	Kim *et al.* [44] (*n* = 99)		Ohba *et al.* [36]
	Scenario 1[a]	Scenario 2[a]		Scenario 1[a]	Scenario 2[a]		Scenario 1[a]	Scenario 2[a]	
25th Percentile	0	0	3.0	0	0	3.1	0	0	1.5
Median	5	2.6	6.0	0	0	3.7	7.3	3	7
75th Percentile	10.6	5.2	9.8	5.9	2.7	4.2	14.7	11.9	14

[a]Scenario 1 and scenario 2 represent acute inhalation on 15 March 2011 and chronic intake from 16 March to the day before the measurement, respectively.
[b]Preliminary analyses using 336 and 99 'whereabouts' questionnaire sheets of residents $<$19 years of age in Iwaki city and Kawamata town, respectively.

the first 4 months after the accident were dependent on the level of radionuclides, especially ^{134}Cs and ^{137}Cs, deposited onto soils, whereas inhalation doses were dependent on the concentration of ^{131}I in the air in the early phase of the accident. Rain and snow enhanced the deposition of radionuclides onto soil but did not influence inhalation dose. Thus, thyroid doses must be used as an explanatory variable in future analyses, rather than external doses or deposition density of radionuclides on soils as have been used in previous epidemiological studies [49–51].

Ohira *et al.* [52] analyzed the association of incident thyroid cancer cases in the second cycle of FTE with average thyroid absorbed doses in the UNSCEAR 2013 Report. There was no positive association between thyroid doses and thyroid cancer incidence. Although Ohira's study in 2020 [52] was one step ahead of other studies [49–51], it might not be completely free of ecological fallacy. More sophisticated epidemiological studies, e.g. a case–control study using individual thyroid doses, are needed to demonstrate the presence or absence of a radiation effect on childhood thyroid cancer in Fukushima.

SCREENING EFFECT?—BIOLOGICAL NATURE OF PTC

Tsuda *et al.* [5] claimed that there might be an epidemic of childhood thyroid cancer associated with radiation exposure in Fukushima, whereas Katanoda *et al.* [6] and Williams [20] thought that many cancers were attributable to systematic screening. To understand why over-diagnosis might occur from using ultrasound equipment in cancer screening it is essential to know the biological nature of PTC [20]. It is a well-differentiated cancer that grows slowly and generally has good prognosis [20]. Many Japanese bear small PTCs without clinical manifestations (occult or latent carcinoma), which are uncovered only at autopsy in 11–28% of deaths (Table 1). The prevalence of occult PTC starts to increase in the teens and levels off in the thirties [26, 29]. In contrast to clinical PTC, the prevalence of such latent PTC is not associated with gender (Table 1). Thus, it is highly likely that many small PTCs without clinical symptoms will be observed among children and adolescents if thyroid screening is conducted with high-resolution ultrasound equipment capable of detecting 3 mm nodules. It is well documented that systematic use of ultrasound equipment for adult health checkups in Korea was associated with a dramatic increase in PTC prevalence without noticeable effect on the thyroid cancer death rate [53]. As small PTCs are generally indolent in adults, the detection of small PTCs could be called over-diagnosis [53].

In contrast, PTC in children and adolescents frequently metastasizes and its recurrence rate after operation is rather high, although the rate of death from PTC is low [54–58]. Many observational studies have demonstrated that preoperative lymph node metastases, extrathyroidal invasion, larger tumor size, and distant metastases are negatively associated with disease-free survival [55–59]. These data indicate that early diagnosis and treatment would benefit patients if 'aggressive' PTC can be diagnosed before clinical manifestation. In Japan, there is a clinical guideline established by the Japanese Association of Breast and Thyroid Sonology for detecting 'aggressive' tumors and reducing unnecessary biopsy from indolent tumors. Although it is difficult to exclude non-aggressive tumors by ultrasonographical findings alone, 92 out of 115 surgical cases in Fukushima Medical University Hospital exhibited lymph node metastasis, and only 1 fully encapsulated PTC was non-invasive [47]. Thus, most thyroid cancers undergoing surgery showed an aggressive nature in Fukushima.

NATURAL HISTORY OF JUVENILE PTCS IS NOT FULLY ELUCIDATED.

However, it is impossible to know whether a small PTC with lymph node metastasis will stop growing or continue to grow and manifest clinical symptoms in the future. Concerning this, two contradictory opinions were expressed by researchers in Fukushima. Midorikawa *et al.* [60] analyzed the change in PTC volume individually during two successive occasions and reported that a sizable fraction of thyroid cancers diagnosed by FTE demonstrated a growth arrest pattern. Meanwhile, Takahashi *et al.* [61] built a cancer-progression model for thyroid cancer by using the National Cancer Registry data in Japan and demonstrated that the numbers of prevalent cases observed by the FTE were within the 95% confidence interval of expected numbers predicted by the model.

Therefore, to reach a consensus about thyroid screening using ultrasonography more definitive data are needed. First, it would be helpful to conduct clinical observational studies on PTC that stratify disease-free survival by detailed TNM classification. If there is a certain clinical stage from which long-term disease-free survival worsens, it will help inform our judgement. Second, randomized case–control studies on the efficacy of early diagnosis and treatment, if such trials are ethically permissible, would provide definitive evidence. Without such types of evidence, it is difficult for surgeons, cancer epidemiologists and other stakeholders to arrive at a consensus about thyroid screening. To receive or not to receive thyroid screening is not a unique issue after the Fukushima accident; it is also an issue for patients irradiated for medical reasons and for their physicians as well [62, 63]. As the evidence is not clear, the international Late Effects of Childhood Cancer Guideline Harmonization Group recommended shared decision making regarding whether to undergo surveillance for differentiated thyroid cancer [63]. Likewise, the International Agency for Research on Cancer (IARC) published a guideline for thyroid screening after nuclear accidents [64]. The following two recommendations have been published: 'The Expert Group recommends against population thyroid screening after a nuclear accident' and 'The Expert Group recommends that consideration be given to offering a long-term thyroid monitoring program for higher-risk individuals after a nuclear accident.' After a one-and-a-half-year discussion in the Evaluation Subcommittee of the FTE, the Fukushima Health Management Committee revised, in October 2019, the informed consent form and accompanying document describing merits and demerits associated with thyroid screening using ultrasound equipment [65]. The revised document explicitly raises three merits and three demerits. Merit 1: the majority of subjects will be informed of no abnormality in their thyroid glands, which will reduce their fear of radiation and increase their quality of life. Merit 2: early diagnosis and treatment may reduce the side effects of surgery or other treatment modalities for advanced disease, and possibly reduce cancer recurrence. Merit 3: conducting the FTE may clarify the presence or absence of a radiation health effect in Fukushima. Demerit 1: there is the risk of diagnosing and treating 'indolent' cancer. Demerit 2: early diagnosis of cancer or suspected lesions in youth may increase mental stress as well as social and financial burdens associated with cancer diagnosis, treatment and long-term follow-up. Demerit 3: a fraction of subjects will be informed of having lesions such as nodules and cysts. Although these lesions are diagnosed as benign, the subject will be asked to undergo a secondary examination and sometimes invasive biopsy, which are stressful, and biopsy can cause injury.

CONCLUSION

Nearly ten years have passed since the FDNPS accident. TEDs have been reconstructed and estimated TEDs are compatible with values based on direct thyroid measurement. Estimated mean TEDs for 1-year-old infants are <15 mSv, and the corresponding relative risk of thyroid cancer would be very small. As to the epidemiological analyses of thyroid cancers in Fukushima, we are still awaiting studies using individual TEDs. The author hopes that information presented in this paper will help people interpret the results of ongoing FTE findings, contribute to consideration of ethical issues associated with FTE and facilitate risk communication with residents and other stakeholders.

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CONFLICT OF INTEREST

None declared.

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