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Lessons learned from conducting disease monitoring in low-dose exposure conditions as a counter-measure after a nuclear disaster

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ABSTRACT

The complex disaster of the Great East Japan Earthquake and the Fukushima nuclear accident caused concern about their various health impacts. Many types of intervention are desired as a countermeasure, depending on the phase of the disaster cycle. The importance of developing and applying codes of conduct has recently been emphasized for post-disaster investigations. Thyroid examination as a type of cancer screening survey was launched from October 2011 after the Fukushima nuclear accident as part of the Fukushima Health Management Survey. In this article, we reviewed the results of three rounds of thyroid examination from 2011 to 2018, and summarized the points to consider in the health survey conducted after the Fukushima nuclear accident. Large-scale mass screening by ultrasound thyroid examination resulted in many cancer diagnoses, >200 cases from a large reservoir of thyroid cancer that goes mainly unnoticed without screening. To prevent the harms of such over-diagnosis, we should be aware of the disadvantage of mass-screening based on the expected natural history of thyroid cancer. A change in strategy from mass-screening to individual monitoring is urgently needed according to international recommendations that are opposed to thyroid ultrasound cancer screening even after a nuclear disaster. To guarantee autonomy and informed choice on post-disaster disease monitoring for residents in a disaster-zone, it is important to set protocol participation and on a voluntary code of conduct basis.

Keywords: disease screening; disease monitoring; over-diagnosis; thyroid cancer; code of conduct

INTRODUCTION

The Great East Japan Earthquake and Fukushima Daiichi nuclear accident caused concern about direct and indirect health impacts. It is often thought that various types of intervention are needed, depending on the phase of the disaster cycle [1]. Even with low-dose radiation levels like the Fukushima accident [2], it is thought that health surveillance is advantageous, to provide scientific data and to communicate with affected individuals, as well as individual dose monitoring using a whole-body counter or dosimeter [3]. A health survey, especially cancer screening, is also expected to potentially contribute toward a reduction in health risks, combined with assessment of individual radiation dose. However, factors affecting carcinogenesis generally not only involve radiation but also environmental factors and individual factors, such as smoking, diet and exercise habits, body mass index (BMI), infections, age, sex and genetic background [4]. Moreover, various factors are related to cultural and socio-economic backgrounds, such as the system for access to screening and medical treatment. Low-dose health effects are considerably affected by factors other than radiation, leading to the epidemiological challenge of how to correct these effects. Thus, further detailed investigations tend to encourage studies to correct confounding factors. However, it is necessary to carefully consider whether such complexity of investigation is meaningful for the health of the affected population.

Post-disaster investigations and interventions have been increasing, even in situations other than nuclear disasters; however, these are

Table 1. Results of thyroid examination in three rounds[a]

Primary screening round	1st round	2nd round	3rd round[b]
Fiscal year	FY2011–13	FY2014–15	FY2016–17
Primary screening			
No. of examinees	300 472	270 540	217 904
Examination rate, %	82	71	65
Confirmatory examination			
No. of recommended examinations	2293	2227	1501
Examination rate, %	93	84	73
No. of thyroid cancer cases	116	71	30
Gender (male: female)	39:77	32:39	12:18
Mean age at diagnosis, years	17.3	16.9	16.4
Mean tumor size at diagnosis, mm	13.9	11.1	13.0
Median tumor size at screening, mm	10.5	8.5	NA
PTC[c] proportion in surgical cases, %	98	98	100

[a]Data update at 30 September 2019. http://fukushima-mimamori.jp/ at February 2020 [46]
[b]Confirmatory examination of 3rd round was still on-going at 30 September 2019
[c]PTC = papillary thyroid cancer.

often disadvantageous to residents of the affected areas. The importance of developing and applying codes of conduct has recently been emphasized [5]. Post-nuclear disaster cancer screening requires careful consideration of a code of conduct [6].

THYROID EXAMINATIONS IN THE FUKUSHIMA HEALTH MANAGEMENT SURVEY

There is a risk of thyroid cancer owing to exposure to radioactive iodine after a nuclear disaster; thus, thyroid cancer screening using ultrasonography tends to be socially demanded even with a low equivalent thyroid dose estimated [2, 7]. Thyroid cancer screening testing was launched from October 2011 after the Fukushima nuclear accident as part of the Fukushima Health Management Survey [8]. The first round of screening took place from fiscal year (FY) 2011 to FY2013, the second round in FY2014 and FY2015, the third round in FY2016 and FY2017, and the fourth round in FY2018 and FY2019. The thyroid examination comprised two stages: primary screening and confirmatory examination [9, 10]. Table 1 presents a summary of the three rounds of thyroid screening over the 8-year period. Recipients of thyroid ultrasound examinations included all residents of Fukushima aged ≤18 years at the time of the accident. Residents aged 6–18 years at the time of the examination round are screened at their school, so if someone wants to refuse the examination, a parent must sign an opt-out agreement. Since the default of the screening examination protocol is set to participate, participation rate in primary screening was high, i.e. 82% in the first round and 71% in the second round (Table 1) compared to many other opt-in type surveys (e.g. 26.4% participation rate in a basic survey estimating individual external doses for the first 4 months after the Fukushima accident [11]). As the number of people >18 years old increases and the number of people who are subject to school examination decreases in the second and third rounds, the participation rate gradually declines, but is 65% even in the third round. Primary screening focused mainly on detecting nodules and cysts using ultrasonography. The results of primary screening were classified according to three categories: A1, A2 and B. Category B included individuals for whom further examination was recommended; category A (A1 and A2) comprised individuals who did not require further examination. This classification in the screening criteria of the thyroid examination is in accordance with the Japan Society of Ultrasonics in Medicine clinical diagnositic criteria [12], but is not generally used as a screening criterion, because thyroid cancer screening is not recommended to asymptomatic adults [13, 14]. Moreover, findings such as cysts and nodules are commonly observed in healthy people.

In the confirmatory examination, malignant or suspected malignant cases were detected using fine-needle aspiration cytology. In total, 116 cases in the first round and 70 cases in the second round were diagnosed with thyroid cancer, and 1 case was benign [15]. Although confirmatory examinations are ongoing, 30 cases in the third round and 16 in the fourth round were diagnosed. Accounting for >98% of surgical cases, the most common pathological type was papillary carcinoma.

In the first round of thyroid examinations, potential over-diagnosis was reported by Katanoda *et al.* [16]. The observed age-specific prevalence of thyroid cancer was found to be ∼30 times the expected rate, according to the cancer registry in Japan. The distribution pattern by age at the time of the accident, where the number of detected thyroid cancer cases was adjusted according to the number of examinees, increased with age in both the first and second screening rounds [15]. The distribution pattern of incidence by age at the time of screening in the second round also increased with age. The incidence of cancers detected by screening was 48 cases per 105 person-years for the age group 18–20 years; this was ∼50 times the incidence estimated using the data of young people retrieved from the national cancer registry. This pattern according to age at the time of the accident differs from findings in Chernobyl; there was a higher frequency of younger cases with a relatively short latent period after the Chernobyl nuclear accident [17, 18]. Thus, a relationship between a large number of detected thyroid cancers and radiation exposure is considered highly unlikely in light of the very low doses in Fukushima. These results indicate a large reservoir of thyroid cancers that are not recognized as clinical cancers without ultrasound screening [15].

Principle of disease screening

From the perspective of general disease screening, not just after a nuclear disaster, the World Health Organization (WHO) issued guidelines including 10 norms in 1968 [19]. This guideline recommend that any screening program should not be started unless all 10 norms are met. For example, the condition sought should be an important health problem (the first norm). The screening test should be acceptable to the population (the sixth norm). The natural history of the condition, including development from latent to clinical disease, should be adequately understood (the seventh norm). For thyroid cancer, especially for papillary cancer that can be easily detected by ultrasonography, screening is not recommended according to WHO guidelines [20]. Worldwide over the past 20–30 years, an increase in the detection of small thyroid tumors has led to a dramatic rise in the diagnosis of small thyroid cancers, many of which are unlikely to progress to clinical disease. Autopsy studies show that up to 30% of people have latent thyroid cancers. Therefore, thyroid cancer ultrasonography screening is listed as Grade D, or not recommended, in people of all ages by the US Preventive Services Task Force [13, 14]. Over-diagnosis can harm patients by leading to diagnosis-associated anxiety/depression, labeling/stigmatization, or a financial burden as well as over-treatment, with potential complications [21]. However, it may be difficult to understand that screening for early detection of cancer, leading to over-diagnosis, can be more harmful than not screening. Thus, we need to better understand the natural history and oncogenic mechanisms of papillary thyroid cancer.

Natural history of papillary thyroid cancer

From 2015 cancer registration data in Japan, the lifetime cumulative cancer incidence of all cancers was 65.5% for men and 50.2% for women, and that of thyroid cancer was 0.5% for men and 1.6% for women [22]. However, the lifetime cumulative mortality of all cancers was 23.9% for men and 15.1% for women, and that of thyroid cancer was 0.06% for men and 0.1% for women. According to Cancer Registry statistics, the 5-year cancer survival rate for people diagnosed with cancer between 2009 and 2011 is 62.0% for men and 66.9% for women; the 5-year survival rate for thyroid cancer is 91.3% for men and 95.8% for women. Based on the 10-year survival rate for people diagnosed with cancer from e.g. 2002 to 2006, that of gastric cancer is 61.3% for men and 58.2% for women, that of lung cancer is 18.1% for men and 31.2% for women, that of prostate cancer is 78.0%, and that of breast cancer is 79.3% for women; the 10-year survival rate for thyroid cancer is 87.1% for men and 94.8% for women [22]. These good 5-year and 10-year survival rates for thyroid cancer include anaplastic and poorly differentiated thyroid cancer with a poor prognosis, so are even better if limited to papillary thyroid cancer. Thus, papillary thyroid cancer is among the cancer types with the best prognosis.

The incidence of differentiated thyroid cancer, mostly papillary thyroid carcinoma, has been reported to have increased 3- to 15-fold in the past few decades [23]. Welch *et al.* used 40 years of data to examine patterns of incidence and mortality in various cancers and speculated about what the epidemiologic signature might reveal about the true cancer increase, over-diagnosis and advances in prevention and treatment [24]. As exemplified by the female lung cancer signature before 2000, a concordant rise in incidence and mortality indicated a true cancer increase. In contrast, discordant signatures have indicated that the incidence of thyroid cancer is rising, yet mortality remains stable; this is also true in renal cancer and melanoma. Stable mortality is viewed as a marker for stable true cancer occurrence and increased detection of cancers not destined to cause death, i.e. over-diagnosis. Furuya-Kanamori *et al.* conducted a meta-analysis using 42 data sets and 12 834 autopsies [25]. The prevalence of differentiated thyroid carcinoma among the entire examination subgroup averaged 11.2% between 1949 and 2007 and stabilized from 1970 onward; no time effect was observed. Increasing incidence is also not mirrored in prevalence within autopsy studies, strongly suggesting that the current increasing incidence of thyroid cancer reflects over-diagnosis.

Because the prognosis of differentiated thyroid cancer is excellent, in 2003 Ito *et al.* first proposed active surveillance for patients diagnosed with low-risk small thyroid cancers, with close follow-up management instead of immediate surgery [26]. Since then, active surveillance has been implemented throughout the world. The results of active surveillance for differentiated thyroid cancer show that most cancers remain the same size and patients who undergo active surveillance have similar or better overall prognosis than those who receive immediate surgery [27–29]. Furthermore, no cancers with poor prognosis develop during active surveillance [27]. A recent meta-analysis showed that older age was associated with a reduced risk of tumor enlargement in adult patients under active surveillance [30].

There are two hypothesized patterns of natural thyroid cancer progression. One is the exponential cell growth pattern, the other is a growth arrest pattern. Our study concerning tumor growth rates among young people who were screened in thyroid examinations of the Fukushima Health Management Survey showed that cell growth rates were positive in smaller tumors; in contrast, this rate was almost zero in larger tumors [31]. These data suggest that nearly all cancers followed a growth arrest pattern, even after having shown early growth, as indicated. Recently, Miyauchi *et al.* also suggested growth arrest after a similar initial growth phase at a young age, based on long-term analysis of active surveillance for micropapillary thyroid carcinoma [32].

Considering these results together, most papillary thyroid cancers are characterized by self-limiting growth in a growth arrest pattern, forming a large pool of latent cancer as a reservoir that cannot be detected without screening (Fig. 1) [10, 15, 33, 34]. It is thought that most papillary thyroid cancers show a self-limiting course like type ① in the figure. Even though the tumor growth pattern is self-limiting, some tumors develop into clinical cancer and require surgery (star mark), like type ②. In addition, some cancers show a regrowth pattern, as in type ③. Tumors like type ③ may gain a small benefit from early detection in middle-aged or older individuals. However, if most advanced clinical cancers with poor prognosis develop following the type ④ pattern, the possibility of improving prognosis is low with screening of young people. Therefore, even if the screening criteria are changed to a conservative larger screening population, the disadvantage of over-diagnosis may not diminish [35].

POTENTIAL MOLECULAR MECHANISM OF SELF-LIMITING CANCER GROWTH

Measures of tumor mutational burden in comprehensive genomic profiling show a low frequency of somatic alterations in papillary thyroid carcinoma, as compared with other carcinomas, and a few driver

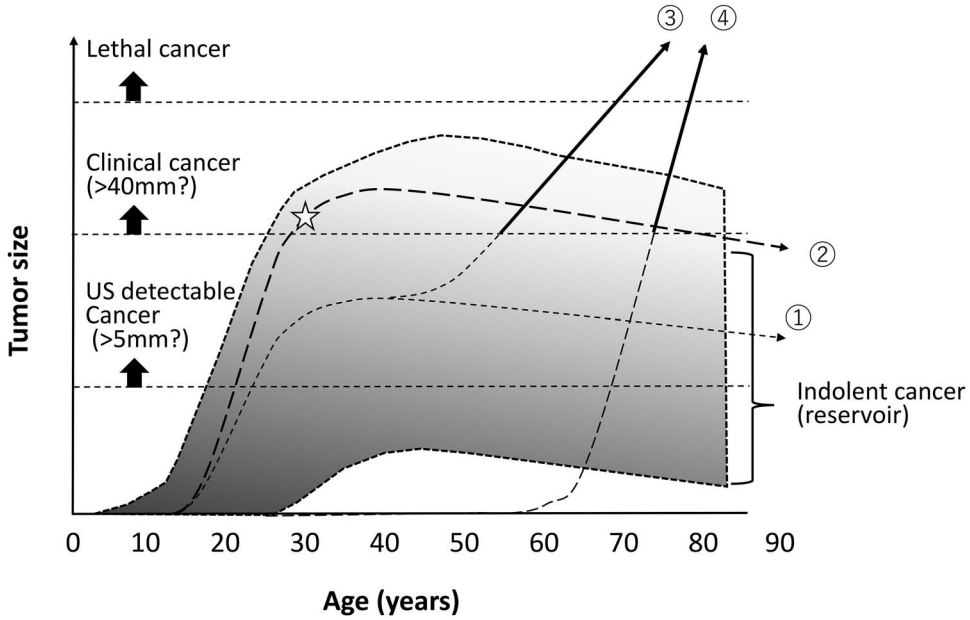

Fig. 1. Proposed natural history of papillary thyroid carcinoma. The vertical axis represents tumor size and the horizontal axis represents age. The horizontal broken lines show the size of cancer at cancer death (upper broken line), that of clinically diagnosed cancer (middle broken line), and that of cancer detected by ultrasound (lower broken line). The area surrounded by a small dotted line represents the entire natural history of papillary thyroid cancer, including the harmless tumor that is the reservoir. Arrows are examples of the natural history of individual cancers. 1 and 2 are examples of self-limiting growth patterns, 3 is an example of re-growth from self-limiting, and 4 is an example of linear growth due to *de novo* carcinogenesis. The star symbol indicates the timing of surgical treatment.

mutations such as BRAF, RAS or RET/PTC [36, 37]. Mutation in papillary thyroid cancer is thought to result from DNA replication errors, correlated with normal stem cell division [38]. Tumor mutational burden and the number of driver mutations increase significantly with age and the number of stem cell divisions. Thus, the development of papillary thyroid cancer is thought to be completed at an early age.

In the cancer mutation profile detected via the thyroid ultrasound examinations of the Fukushima Health Management Survey, Mitsutake *et al.* reported that BRAF mutation accounted for 63% and rearrangement for 16% [39]. Further, in all cases, no additional mutations were found, e.g. no telomerase reverse transcriptase (TERT) promoter mutation, indicative of poor malignancy. These patterns in Fukushima cases are markedly different from those of Chernobyl where point mutation was 26% and fusion was 71%, as reported by Efanov *et al.* [40]. Among these Chernobyl cases, the mean ^{131}I thyroid absorbed dose with point mutations was 0.2 Gy, significantly lower than the 1.4 Gy with fusion. By contrast, the profile among young cases in Fukushima was similar to that of low-risk, sporadic cases of adult thyroid cancer with the same pathological features. A recent report showed that the upper 95th percentile of thyroid equivalent doses of 1-year-old children was estimated to be <0.03 Sv in a reconstruction from internal radionuclides after the Fukushima accident [7].

BRAF oncogene mutation occurred most commonly with papillary thyroid carcinoma in sporadic adult cases as well as among young people in Fukushima, and it is possibly associated with tumor initiation. Kim *et al.* reported that a genetic modification by mutant BRAF in experiments using thyrocytes resulted in suppression of cell growth and oncogene-induced senescence [41]. Further, increased thyroid stimulating hormone (TSH) signaling overcame oncogene-induced senescence. This finding indicates that metastatic dormancy may be common in well-differentiated thyroid cancer, a disease in which many individuals with biochemically and anatomically defined distant metastases often have prolonged disease stability without undergoing therapy.

If immunological mechanisms are involved in the suppression of cancer growth, cancer incidence is expected to increase with immunosuppressed conditions. Kidney transplantation and associated immune suppression are recognized as posing a significantly increased risk of cancer development during long-term follow-up. Thyroid cancer is a typical cancer in terms of potential post-transplant risk. A meta-analysis identified an ∼7-fold higher standardized incidence of thyroid cancer following renal transplantation compared with the non-transplant group [42]. These data suggest that over-diagnosis of papillary thyroid cancer by ultrasonography screening can unnecessarily identify many detectable cancers from a large reservoir of dormant thyroid cancers under normal immune conditions.

NECESSITY OF FOLLOWING A CODE OF CONDUCT

What should we do in a situation where many people are worried about the health effects after a nuclear disaster? In the event of a nuclear

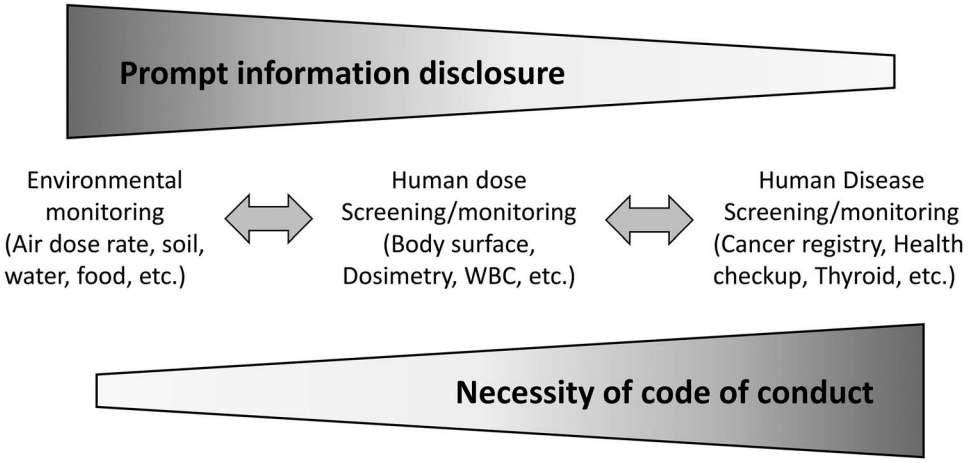

Fig. 2. Approach to code of conduct and information disclosure regarding methods for conducting environmental radiation dose monitoring, dose monitoring or screening by personal dosimeter and whole body counter, and disease monitoring or screening in a health survey.

disaster, it is necessary to quickly provide appropriate dose monitoring information to potentially affected individuals and to smoothly carry out necessary interventions to protect against radiation. Thus, intervention through environmental monitoring may require timely information disclosure rather than a code of conduct such as human rights and protection of personal information (Fig. 2). Considering the natural history of thyroid cancer and the effects of low radiation doses, the incidence of thyroid cancer is unlikely to change significantly after the Fukushima accident if it was not screened by ultrasonography. Thus, a monitoring system that includes individual health consultation and not ultrasound screening for thyroid cancer should be implemented, to support decision-making based on the harm–benefit balance as a pillar of the response to health concerns among the population after a nuclear disaster [43]. According to a recommendation issued by the WHO/International Agency for Research on Cancer (IARC) in 2018, thyroid screening of the population is not recommended, even after a nuclear accident; monitoring is performed for those who are estimated to have been exposed to $\geq$100–500 mGy of absorbed dose. In monitoring, ultrasonography is not recommended except when clearly necessary [44]. Since unnecessarily diagnosing a disease in a healthy person causes a lot of harm to the patient and society, including over-diagnosis [20, 21, 45], the countermeasures for human disease requires a code of conduct based more on evidence, compared with environmental monitoring of radiation dose, as shown in Fig. 2. If thyroid cancer monitoring is proposed, it should be on a voluntary basis and with ethical approval, as in a research setting, as long as it is accompanied by appropriate information and support.

CONCLUSION

In an ongoing survey after the Fukushima nuclear compound disaster, large-scale mass screening of thyroid cancer results in cancer diagnoses from a large reservoir, even at a young age. To prevent the harm of over-diagnosis, a change in strategy from that of screening to monitoring is urgently needed, based on a code of conduct, in addition to improved understanding of the natural history of thyroid cancer.

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CONFLICT OF INTEREST

None declared.

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