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Lessons learned from Chernobyl and Fukushima on thyroid cancer screening and recommendations in case of a future nuclear accident☆

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ABSTRACT

Exposure of the thyroid gland to ionizing radiation at a young age is the main recognized risk factor for differentiated thyroid cancer. After the Chernobyl and Fukushima nuclear accidents, thyroid cancer screening was implemented mainly for children, leading to case over-diagnosis as seen in South Korea after the implementation of opportunistic screening (where subjects are recruited at healthcare sites). The aim of cancer screening is to reduce morbidity and mortality, but screening can also cause negative effects on health (with unnecessary treatment if over-diagnosis) and on quality of life.

This paper from the SHAMISEN special issue (Nuclear Emergency Situations - Improvement of Medical And Health Surveillance) presents the principles of cancer screening, the lessons learned from thyroid cancer screening, as well as the knowledge on thyroid cancer incidence after exposure to iodine-131.

The SHAMISEN Consortium recommends to envisage systematic health screening after a nuclear accident, only when appropriately justified, *i.e.* ensuring that screening will do more good than harm. Based on the experience of the Fukushima screening, the consortium does not recommend mass or population-based thyroid cancer screening, as the negative psychological and physical effects are likely to outweigh any possible benefit in affected populations; thyroid health monitoring should however be made available to persons who request it (regardless of whether they are at increased risk or not), accompanied with appropriate information and support.

Abbreviations: DTC, differentiated thyroid cancer; FHMS, Fukushima Health Management Survey; FNA, fine-needle aspiration; FTC, follicular thyroid cancer; IARC, International Agency for Research on Cancer; PTC, papillary thyroid cancer; SHAMISEN, Nuclear Emergency Situations - Improvement of Medical And Health Surveillance; TC, thyroid cancer; WHO, World Health Organization.

☆ **Concise and informative title**Thyroid cancer screening after nuclear accidents.

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1. Introduction

The SHAMISEN (Nuclear Emergency Situations - Improvement of Medical And Health Surveillance) international experts' consortium was set up to review the lessons learned from the experience of past nuclear accidents, in particular those which occurred at the Chernobyl and Fukushima nuclear power plants and develop recommendations for preparedness and health surveillance of populations affected by a nuclear accident (past or future) (Liutsko et al., this issue; Ohba et al., this issue; Schneider et al., 2020). The current paper, part of the SHAMISEN special issue, presents the lessons learned from thyroid cancer screening in the wake of both accidents and the SHAMISEN Consortium recommendations on the topic in the case of a future accident.

Thyroid nodules are very common, in liquid (cysts) or solid form, and are generally benign, with only 10 to 15% of nodules revealing a thyroid malignancy. Thyroid cancer (TC) occurs about three times more often in women than in men, and TC incidence varies substantially between countries. In 2012, the age-standardised rates per 100,000 women were 88.6 in South Korea, 20.0 in the USA, 14.7 in Italy, 12.6 in France, 8.0 in Finland and 6.5 in Japan (GLOBOCAN, 2012). Over the last three decades, TC incidence has increased worldwide, in both genders: the percent of temporal change in 1973–2002 was 63% and 29% in Finland, and 86% and 52% in Japan in women and men, respectively (Pellegriti et al., 2013). Only 2.3% of all TCs are diagnosed in children aged 0–19 years (Bernier et al., 2019). Most of the cases have a good prognosis, as the 5-year survival rate for all TCs is 98% (Bibbins-Domingo et al., 2017). There are different TC types: differentiated TC (DTC) including papillary thyroid cancer (PTC) and follicular (or vesicular) thyroid cancer (FTC), anaplastic (undifferentiated), and medullary TC. PTCs represent >80% of thyroid cancers; they are mainly diagnosed in young people (mostly between age 30 and 50) and have a good prognosis. FTCs represent around 10% of thyroid cancers; they are generally not very aggressive and have a slow progression. FTC prognosis is slightly worse than that for PTC, with a survival rate of 80% after 35 to 40 years as compared with 95% for PTC. Medullary TC is rare (3–5% of TC) and corresponds to familial cancers with a genetic mutation in 30% of cases; patients with medullary TC have a survival rate of 65% after 10 years. Anaplastic TC is very rare (1% of TC), occurring mainly in elderly people; it has a rapid growth and high risk of spreading or metastasis, resulting in a poor prognosis with a survival rate below 10% at 6 months after the initial diagnosis (Niccoli-Sire and Conte-Devolx, 2007; Raue and Frank-Raue, 2016).

The thyroid gland is an organ which is particularly sensitive to radiation-induced cancer as demonstrated in several studies on TC risk after radiation exposure, especially following exposure in childhood (Lubin et al., 2017; Ron et al., 1995; Veiga et al., 2016). The magnitude of TC/nodule radiation-related risk estimates varies widely from about 1.3 to 20 per Gy depending on exposure type (external or internal), TC histological type, age at exposure, attained age, time since exposure, soil iodine deficiency, screening, *etc.* After the Chernobyl accident, exposure to radioiodine, mainly iodine-131, in childhood was associated with increased risk of thyroid nodules (Cahoon et al., 2017) and thyroid cancers in Ukraine, Belarus and the Russian Federation as early as 1991 (Astakhova et al., 1998; Cardis et al., 2005; Davis et al., 2004; Ivanov et al., 2012; Stsjazhko et al., 1995; Tronko et al., 2017; Yamashita and Thomas 2017; Zablotska et al., 2011). The average doses to the thyroid in children tended to be high: 1.8 Gy to the thyroid among over 116,000 children aged 0–7 evacuated in 1986 (Cardis et al., 2006); 0.2–0.8 Gy in the epidemiological studies of young people in the most contaminated territories of the three countries (Liutsko et al., this issue); the highest recorded doses were over 10 Gy in Belarus and Ukraine (UNSCEAR, 2000). Many of the cases resided in areas with low moderate to high levels of iodine deficiency (Cardis et al., 2005; Shakhtarin et al., 2003). PTC was the primary histologic type in people exposed during childhood and adolescence to the fallout (Cardis and Hatch, 2011; IARC, 2009; Sinnott et al., 2010). Most cases in young people were diagnosed in the absence of mass screening (as incidental findings or because of symptoms); they were aggressive tumours, a large proportion with extracapsular involvement and distant metastases (Cardis and Hatch, 2011), suggesting that even those found incidentally would have become clinically apparent. Despite these features, survival from these tumours has been excellent (UN Chernobyl Forum, 2006). Despite the large increased risk observed after the Chernobyl accident, thyroid cancer remained a rare disease, with an incidence of childhood thyroid cancer in Belarus of the order of 4 per 10^5 persons in 1995 and of adolescent thyroid cancer of 11 per 10^5 persons in 2001, the years with the highest incidence of childhood and adolescent thyroid cancer respectively.

Periodic thyroid screening including ultrasound imaging and clinical examination was established in two cohorts of children (nearly 13,000 in Ukraine and 12,000 in Belarus) who had undergone direct thyroid activity measurements in the 2 months after the accident. This started 11–12 years after the accident, once the increased incidence of TC in young people had been well established, and the aim was to better characterise the increase (Tronko et al., 2006; Zablotska et al., 2015) (see Table 2 and (Liutsko et al., this issue) for details). In the Russian Federation, population based annual clinical examination (complemented with ultrasound or other imaging procedures where necessary) was setup in 1991 among the nearly 110,000 residents of the most contaminated oblasts who were less than the age 18 at the time of the accident (Ivanov et al., 2016).

Based on the observed increased TC risk seen after the Chernobyl accident, the Japanese Government, soon after the Fukushima accident, launched the Fukushima Health Management Survey (FHMS) including thyroid ultrasound examination for the approximately 300,000 children who resided in Fukushima prefecture at the time of the accident (Yasumura et al., 2012). In contrast to the Chernobyl situation, doses to the thyroid among young people tended to be quite low in Fukushima, of the order of a few mGy in the different groups in which this was estimated, with a maximum thyroid equivalent dose of the order of 65 mGy among the 1-year-old children, that is 10 to 100 times lower than doses received after Chernobyl (Barquinero et al., 2020; UNSCEAR, 2014). The impact of this screening is discussed in detail below.

2. Lessons learned from thyroid cancer screening after a nuclear accident

Table 1 presents five types of screening according to the World Health Organization (WHO) classification (ANAES, 2004; Wilson and Jungner, 1968): systematic or mass, selective or targeted, community, opportunistic, and multiple screening. By definition, screening targets both unrecognized symptomatic and pre-symptomatic diseases. According to the WHO, screening is legitimate when it contributes to a

Table 1
Classification of screening types according to the World Health Organization (from the guide "How to judge a proposal for a screening programme", ANAES 2004).

Type of screening	Definition
Systematic or mass	The population recruited is not selected, but is defined as large-scale population. If there is a criterion (age, sex, geographical unit), screening is regarded as applying to all individuals in the relevant group.
Selective or targeted	The population recruited is selected on previously defined criteria (risk factors based on strong scientific evidence, such as radiation exposure for example).
Community	The population is recruited from within the community. Screening is carried out as part of a specific campaign and is based on voluntary participation.
Opportunistic	People are recruited for screening when they use healthcare resources (*i.e.* a hospital, doctor's surgery, health centre or screening centre, or when they see a company doctor).
Multiple	A battery of tests is used to screen for a number of diseases or conditions.

Table 2
Number of thyroid cancer cases detected through population-based thyroid cancer screening after the Chernobyl accident.

Country	Follow-up period	Screened population	Diagnosed TC	Mean thyroid dose, Gy	ERR per Gy [95% CI]
Ukraine (UkrAm cohort)	1998–2007, first four screening examinations [1,2,3]	13,243 individuals <18 years at the time of the accident with direct thyroid activity measurements	110 cases, including 104 PTCs, 5 FTCs, 1 medullary carcinoma	1st screening cycle: 0.68 / 2nd-4th screening cycles: 0.65	5.2 [1.7;27.5] [2]/ 1.9 [0.4;6.3] [3]
	2012–2015, fifth screening examination [4]	10,073 individuals <18 years at the time of the accident with direct thyroid activity measurements	47 cases, including 44 PTCs and 3 FTCs	5th screening cycle: 0.62	1.4 [0.4;4.2]
Belarus(BelAm cohort)	1996–2008, three screening examinations [5]	11,664 individuals <18 years at the time of the accident with direct thyroid activity measurements	158 cases, including 157 PTCs and 1 FTC	1st screening cycle: 0.56	2.2 [0.8;5.5] [6]
The Russian Federation	1991–2013 [7]	108,166 individuals <18 years at the time of the accident – general population of contaminated regions	316 cases, including 247 TCs in 1991–2008	0.17	4.7 [2.5;7.7]
		219,544 individuals ≥18 years at the time of the accident – general population of contaminated regions	925 cases, including 746 TCs in 1991–2008	0.04	−0.60 [-2.9;1.5]

CI, confidence interval; TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.
[1] (Bogdanova et al., 2015).
[2] (Tronko et al., 2006).
[3] (Brenner et al., 2011).
[4] (Tronko et al., 2017).
[5] (Zablotska et al., 2015).
[6] Based on results of the first screening cycle, for thyroid dose range < 5 Gy (Zablotska et al., 2011).
[7] (Ivanov et al., 2016).

decrease in morbidity and/or mortality in a population and delivers more good than harm. A decision to launch screening should be based on the knowledge of a disease's natural history, the acceptance of the screening programme by the population, the quality of diagnosis and availability of treatment of the disease. The analysis of advantages and disadvantages of a screening programme should take into account health, social and economic costs.

2.1. Natural history of thyroid cancer

To date, it is theorized that the initial mutation leading to thyroid carcinogenesis in many cases occurs in infancy and childhood, but the TC natural history, which corresponds to the description of spontaneous evolution of the disease with time and without any treatment, is not well known (Takano, 2017; Williams, 2015). Four general steps of the natural history of any disease are as follows (ANAES, 2004): 1) initial biological changes, which are generally undetectable; 2) first preclinical manifestation of abnormality (*i.e.* there are no clinical signs of disease yet, but the disease can be detected by appropriate tests); 3) symptoms appear (*i. e.* clinical manifestations of the disease which make it possible to detect its presence and identify it); 4) outcome of the disease (recovery, complications, death). Regarding differentiated thyroid cancer, the first two steps are sometimes the only ones because TC progression is usually slow and indolent without clinical symptoms expressing for many years (or ever). There are findings demonstrating a presence of a substantial reservoir of subclinical TCs (*i.e.* cancers for which symptoms are absent or are not numerous or severe enough to meet the diagnostic criteria for TC) which may never develop into clinically presented cases, but which may be identified in the framework of mass screening using advanced imaging techniques. In 1985, a systematic autopsy study estimated that at least one third of adults harbour small PTCs, the vast majority of which will not produce symptoms during a person's lifetime (Harach et al., 1985). More recently, a *meta*-analysis of 35 studies on prevalence of DTCs in autopsy between 1949 and 2007 confirmed the existence of a substantial reservoir of incidental case findings. This reservoir has not increased over the past decades, and the authors suggest that the increase in the incidence of DTC is related to the increase in detection of stable incidental case (Furuya-Kanamori et al., 2016).

2.2. Thyroid cancer detection

Over the last 30 years, TC incidence has increased worldwide, and detection capacities have also progressed, with many TC now being diagnosed at a very early stage (La Vecchia et al., 2015). Until the 1970s, most of the cancers were found in patients with nodules causing compression symptoms or visible neck masses. Palpation and biopsy were used to detect nodules and most were 20 mm or larger, because it is hard to detect by palpation those which are smaller; also, articles at the time suggested lesions smaller than this were unlikely to be a problem (Greenspan, 1974; Wiest et al., 1998). From the 1980s onward, smaller nodules could be identified by the advent of neck ultrasonography and then ultrasound-guided fine-needle aspiration (FNA) biopsy, and the availability of portable ultrasound machines spread in the late 1990s (Davies and Welch, 2006).

About 12 years after the Chernobyl accident (1986), ultrasonography (with 7.5-MHz frequency probes) and palpation became widely used to examine the thyroid gland in Belarus, Ukraine and the Russian Federation, followed by FNA biopsy to determine benign or malignant nature of thyroid nodules with a diameter of 5 mm or more (Tronko et al., 2006; Zablotska et al., 2011). After the Fukushima disaster in 2011, a thyroid survey, planned to be conducted every 2 years at first and every 5 years once the subjects reach adulthood, was setup focusing on the close to 360,000 children residents of Fukushima prefecture aged below 18 at the time of the accident. The survey uses advanced thyroid ultrasound examinations (with 18-MHz or higher frequency probes compared to the 7.5-MHz frequency probes used earlier) to identify potential TC cases (with FNA biopsy performed for cases of detected cancers and suspicious for malignancy: thyroid nodules >5 mm or cysts >20 mm) (Yamashita et al., 2018; Yasumura et al., 2012).

It should be noted that, since the 2000s, new imaging technologies have markedly increased the number of TC diagnoses (Brito et al., 2013; Vaccarella et al., 2015). A study in 11 selected high-resource countries showed that diagnostic changes may account for >50% of TC cases diagnosed in 2003–2007 in women younger than 80 years in all studied countries, except for Japan where it accounted for only 30%. The authors concluded that this proportion is expected to increase in the future, and the danger of TC over-diagnosis and overtreatment should be considered as a matter of urgency (Vaccarella et al., 2015).

2.3. Over-diagnosis

Because most individuals with DTC have good prognosis, thyroid screening may result in over-diagnosis, *i.e.* the identification of TCs that would never have caused any symptoms, problems or death in a lifetime (Davies and Welch, 2006; Feinstein, 1968) and consequently of over/unnecessary treatment. Indeed, diseases such as DTC, which progress slowly, particularly when the preclinical stage is long, are more likely to be detected using new imaging technologies. Consequently, screening will detect not only the most severe cases that would ultimately cause symptoms and been identified clinically, but also more favourable cases with the slowest growth natural history (Welch and Black, 2010). Since DTC usually progresses slowly causing symptoms only at an advanced stage and rarely causing death, there is a potential for over-diagnosed cases that will not affect patient's health and survival (Pellegriti et al., 2013). From 1988 to 2012, the estimated proportion of TC cases attributable to over-diagnosis, which is lower in men than in women, increased in several countries (Li et al., 2020; Vaccarella et al., 2016). In 2008–2012, over-diagnosis in women was estimated to account for 93% of TCs in South Korea, 91% in Belarus, 83% in France and Italy, 75% in Spain, Australia and the United States, 65% in Norway and Denmark, 58% in the United Kingdom, and 55% in Japan (Li et al., 2020). It is likely that the over-diagnosis using the most recent and potent ultrasound technology that is being used in Fukushima prefecture would be larger still.

Given the very good prognosis and low mortality of DTCs related to radiation even when they present clinically, ultrasound detection of a latent TC or small thyroid nodule will provide little benefit to the patient either in terms of prognosis or reduction of mortality. Indeed, as indicated above, the vast majority of the TC cases diagnosed in the first 10–15 years after the Chernobyl accident were not detected by screening and, though they were aggressive, they had excellent prognosis. Ultrasound detection of a latent TC or small thyroid nodule has, however, been shown to cause negative effects in the affected populations, including avoidable distress and anxiety in patients and their relatives and possible negative health consequences in the patients related to unnecessary treatment (surgery, lifetime medication) (Brito et al., 2013; Lamartina et al., 2020; Midorikawa et al., 2017). Thyroid surgery carries a risk of complications such as hypoparathyroidism or vocal cord paralysis (Chisholm et al., 2009) and total thyroidectomy, as performed after the Chernobyl accident, implies patients must live the rest of their lives with thyroid hormone supplementation. Additional treatment using radioactive iodine-131 therapy in some cases may result in potentially short- or long-term adverse effects. One out of three patients develops altered taste and inflammation of salivary glands; and one out of five patients has dry eyes and a transient decrease in fertility. In the long term, risk of second primary malignancies and worsening of quality of life of treated patients have been also reported (Brito et al., 2013; Davies and Morris, 2017; Lamartina et al., 2020; Rubino et al., 2003; Singer et al., 2012).

To reduce the high human and economic costs associated with over-diagnosis and overtreatment of small latent TCs, some solutions have been suggested, including improved risk communication (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents 2018; Ohtsuru et al., 2015), avoidance of TC screening, as well as the use of alternative terminology. For example, Williams suggested that the term "carcinoid" or "micro-tumour" should be used for thyroid tumours ≤10 mm with a prognosis indistinguishable from normal life expectancy (with a low TC risk); while the term "cancer" should be applied only to tumours likely to cause suffering and death (Vaccarella et al., 2015; Williams, 2015).

2.4. Impact of thyroid cancer screening

2.4.1. Opportunistic screening impact in South Korea

The impact of screening is difficult to assess, but it is well known that setting up a TC screening increases the observed incidence rate. The existence of a natural reservoir of latent thyroid carcinomas, together with advancements in diagnostic practices leading to case over-diagnosis explain, at least partially, the rise in TC incidence in many countries. The opportunistic screening for TC implemented in South Korea is a clear demonstration of such screening-attributed increase in the incidence. In 1999, the South Korean Government initiated a national screening program for cancers and other diseases. Thyroid cancer screening through ultrasound examination was not included in this program, but was offered to people as an inexpensive add-on. Subsequently, TC mortality remained stable in the country, but the incidence substantially increased reaching the highest TC incidence rates in the world (GLOBOCAN, 2012; Li et al., 2020). In 2011, the incidence rate was 15 times higher than that observed in 1993. The higher was the proportion of screened population, the higher was the TC incidence. It was also shown that PTC was the only histological type associated with the TC screening in South Korea (Ahn et al., 2016; Ahn et al., 2014).

2.4.2. Selective screening impact after the Chernobyl accident

Ten to twelve years after the Chernobyl nuclear power plant accident, systematic ultrasound TC screening examinations were initiated in Ukraine and Belarus in cohorts of children who underwent direct thyroid activity measurements in May of 1986, shortly after the accident. Table 2 presents the number of screening-detected TCs in each country. The Ukrainian cohort includes 13,243 individuals <18 years at the time of the accident, who resided in the three most contaminated northern oblasts of Ukraine (Kyiv, Zhytomyr and Chernihiv) and had undergone individual direct measurements of thyroid radioactivity in May-June 1986. A total of 157 TCs were detected in the Ukrainian cohort between 1998 and 2015 (Bogdanova et al., 2015; Tronko et al., 2017). The Belarusian cohort had a similar thyroid screening protocol. The cohort included 11,664 people aged ≤18 years at the time of the accident, who resided in Gomel and Mogilev oblasts of Belarus and had individual thyroid radioactivity measurements taken within 2 months after the accident. Among them, 87 TCs were diagnosed in the first two screening cycles (1996–2004), 71 in the third (2005–2008) and 52 people had TC diagnosis established before the screening started (Stezhko et al., 2004; Zablotska et al., 2015; Zablotska et al., 2011).

Regarding the Russian screening examination, a population of 327,710 residents of the most radioactively contaminated territories of Bryansk, Orel, Tula and Kaluga regions was subjected to annual comprehensive medical check-ups including thyroid examination with or without ultrasound. In total, 1241 TCs were diagnosed between 1991 and 2013, including 316 cases in subjects who were <18 years at the time of the accident. A screening effect on TC incidence was estimated using national statistics. For the follow-up period of 1991–2013, the screening was predicted to increase baseline TC incidence by a factor of 6.7 in those exposed in childhood, and 1.5 in those exposed in adulthood. The screening effect estimate for individuals exposed in childhood was almost two-times higher for the period of 1991–1995 as compared with the period of 2006–2013, 12.8 and 6.8, respectively (Ivanov et al., 2016; Ivanov et al., 2012).

2.4.3. Mass (or systematic) screening impact after the Fukushima disaster

Twenty five years after the Chernobyl accident, the nuclear accident at the Fukushima Daiichi nuclear power plant occurred in a different socio-economic and environmental context: improvement of medical technical devices, awareness of risks of radiation-induced diseases because of previous events (experiences of the Chernobyl accident, as well as the atomic bombings in Hiroshima and Nagasaki in Japanese survivors), earthquake and tsunami, *etc*. After this disaster , the Fukushima Medical University initiated the FHMS including, as mentioned above, thyroid ultrasound examination of about 360,000 inhabitants of Fukushima prefecture who were ≤18 years at the time of the disaster in Japan (Yasumura et al., 2012). In the absence of previous health surveillance data in Fukushima, the first three years of the mass

TC screening were intended to serve as reference based on the fact that the significant increase in childhood TC was reported 4–5 years after the Chernobyl accident (Jacob et al., 2006). The participation rate was 82% in the preliminary baseline screening (2011–2013) corresponding to 300,476 children screened; 71% in the second round (2014–2015); and 65% in the third round (2016–2017) of full-scale screening. Data analysis on the fourth round (2018–2019) is still ongoing. From the preliminary baseline screening, 2,293 children (0.8% of the total screened children) had thyroid nodules >5 mm or thyroid cysts >20 mm, and one child had an immediate need for further investigation. A total of 2,227 (0.8%) children in the second screening round and 1,499 (0.7%) in the third round had thyroid nodules >5 mm or cysts >20 mm. Out of 6,019 children with thyroid nodules or cysts, 216 were diagnosed with nodules classified as suspicious or malignant by FNA biopsy and cytology, with 173 underwent surgical treatment. The histology examination showed 170 cases of PTC, one case of poorly differentiated carcinoma, one case of other TC, and one case of benign thyroid nodules (FHMS, 2020). The age distribution of the cases was quite different from that seen after the Chernobyl accident, with most of the cases seen among those who were older children or adolescents at the time of the accident, and at very low external and internal dose levels (of the order of 3 mGy, *i.e.* one year of average natural background radiation, and 65 mGy respectively, compared to maximum thyroid doses over 10 Gy in the Chernobyl affected populations) (Barquinero et al., 2020; UNSCEAR 2000). The FHMS thyroid screening, in addition, identified small cysts or nodules in around 50% of subjects examined (Shimura et al., 2018), too small to justify further exploration, but causing concern and stress among the children examined and the parents between the periodic examinations (scheduled every 2 years at present, for those who are still children or adolescent) (Midorikawa et al., 2017).

Thyroid ultrasound screening was also conducted in a cohort of 4,365 children aged 3–18 years between November 2012 and January 2013 in three other Japanese prefectures not radioactively contaminated (Aomori, Yamanashi and Nagasaki) from the fallout of the Fukushima accident, using the same examination protocol as in Fukushima prefecture. The prevalence of ultrasound-detected thyroid nodules of >5 mm or cysts of >20 mm in these three prefectures in children was 1.0%, similar to the prevalence in Fukushima prefecture; that of smaller nodules and cysts was also similar (Hayashida et al., 2015; Hayashida et al., 2013).

The effect of screening in Fukushima was first estimated in 2014, predicting an increase of background (spontaneous) TC incidence by a factor of 7.4 due to the ultrasonography survey as compared with the TC incidence rate in Japan in 2007. If the screening continues, TC baseline risk in the screened population in the Fukushima prefecture is predicted to be 0.2% and 2.2%, respectively during the first 20 and 50 years after the accident (Jacob et al., 2014). A second evaluation of screening impact was published in 2016 where the estimate was three to four times higher than the previous one (Katanoda et al., 2016). Difference between the two estimations underlines the difficulty in assessing the impact of TC screening.

Four years after the Fukushima accident, TC screening data from the first and second round (up to December 2014) were compared with the Japanese nationwide annual TC incidence, and with the incidence in one area of Fukushima prefecture selected as reference (Tsuda et al., 2016). The authors reported that the observed number of TCs was substantially higher than the expected number based on national and regional incidence data, and concluded that this increase could be attributed to ionizing radiation exposure from the accident. This ecological study has been strongly criticized by scientists around the world because of serious methodology limitations; further, the study conclusions are not supported by the results (Davis, 2016; Jorgensen, 2016; Korblein, 2016; Shibata, 2016; Suzuki, 2016; Takahashi et al., 2016; Takamura, 2016; Wakeford et al., 2016). Limitations of ecological study design are well-known, although the authors did not acknowledge the issue of ecologic fallacy. Another criticism was that the data from the Fukushima screening program are not directly comparable with the cancer registry data from the rest of Japan where systematic advanced ultrasound technology is not used to detect cases. The authors of these criticisms suggested that though the increased TC number could be associated with the exposure from radioactive fallout, a more plausible conclusion would be that the screening program is finding an anticipated increase in TC detection across the Fukushima prefecture. Indeed, Tsuda and colleagues did not consider the latent properties of TC, nor the fact that a prevalent cancer detected by screening might have had first preclinical manifestations of abnormality before the nuclear accident.

Thereafter, several researchers have analysed the relationship between radiation exposure (with different estimated exposure levels, mostly using an external dose) and TC prevalence and incidence in residents aged ≤18 years in the Fukushima prefecture at time of the disaster (Kato, 2019; Nakaya et al., 2018; Ohira et al., 2019a; Ohira et al., 2020; Ohira et al., 2019b; Ohira et al., 2016; Ohira et al., 2018; Suzuki et al., 2016; Toki et al., 2020; Yamamoto et al., 2019), but no radiation-related risks have been demonstrated to date.

Following the reports of increased TC incidence after the Fukushima disaster, many alarming headlines were published, resulting in increased anxiety in the general population (Normile, 2016), particularly at the time of the fifth anniversary of the accident. The thyroid ultrasound examination in Fukushima was implemented for children to address parents' fear and anxiety about an increased TC risk, even when the Fukushima-related radiation exposure was much lower than that in the population affected by Chernobyl radioactive fallout (Suzuki et al., 2016). Despite careful consideration of the screening thyroid program, a number of psychosocial problems were found to be related to the examination. Japanese people are worried about the results of thyroid ultrasound examination and the association with radiation exposure, but also about TC screening and their own decision making immediately after the accident (Midorikawa et al., 2017). To address their concerns, Fukushima Medical University, municipalities and others have provided several services to increase understanding between residents and medical professionals. Firstly, since the second screening began, thyroid examination results are individually explained immediately after each examination to alleviate the anxieties of examinees and their parents about the results, to address concerns about radiation-related health risks, and to explain the meaning of the thyroid screening in a more comprehensive way (Midorikawa et al., 2016; Miyazaki et al., 2016). Secondly, explanatory meetings are held with parents and their screened children in order to improve understanding of the examination and the results interpretation and to reduce anxiety. The content of the explanatory meetings was found to be very understandable by 61% of participants (and moderately understandable by 35%), with a decreased anxiety about radiation thyroid effects reported by 60% of participants after the meeting. In addition, dialogues with children are also held in elementary and junior high schools because children have very little understanding of the thyroid examination and may have anxiety about the future. Through these school dialogues, the children are provided with opportunities to think about the benefits and limitations of the screening and to prepare them for discussions with their parents about radiation health risks (Hino et al., 2016; Midorikawa et al., 2017). Lastly, by adapting post-accident messages through specific media types (such as radio), it may be possible to effectively convey important information, and thus to lessen fears and combat rumours (Sugimoto et al., 2013).

3. Discussion and recommendations on thyroid cancer screening after a nuclear accident

In the case of a possible future nuclear accident, it is important that countries have already established population-based high-quality registries of diseases, especially cancer registries, to enable monitoring of diseases frequency before and after accident. A pre-existing cancer registry (*i.e.* by definition, with exhaustive and precise records on diagnosed cancers) will provide information on incidence of clinically expressed cases based on a stable monitoring system, which may help to guide decisions on launching systematic screening. Lack of information on population-based TC baseline rates makes evaluation of the possible impact of a nuclear accident on disease trends very difficult, and increases the likelihood of unfounded speculations. To date, there is little evidence of a specific signature that is 100% sensitive and specific for radiation-induced TC, and it is impossible to assess potential changes in disease frequency due to radiation without knowledge of pre-accidental incidence rates. Even when good quality disease registries are available, it is important to note that the apparent incidence of some occult or dormant diseases, in particular TC (substantial reservoir of subclinical TCs, as demonstrated in autopsy studies), may markedly increase, not only because of the radiation but mainly because of the sudden attention paid to the disease by well-meaning physicians. This has been seen clearly in the case of Fukushima where high technology ultrasound screening has led to the detection of large numbers of thyroid nodules and cysts, and large numbers of potential cancer cases which may have never had any clinical manifestation or consequence on health (overdetection) (Midorikawa et al., 2018). Given the generally very good prognosis and slow growth of the majority of TCs, screening will not only provide little benefit to a patient, but can cause negative consequences: unnecessary treatment (*i.e.* surgery with the possibility of complications, and the need for lifetime medication and monitoring), as well as considerable distress and anxiety in the population that begin early with diagnosis for examined children and their parents (Midorikawa et al., 2017; Normile, 2016) and social burdens such as disadvantages in employment or insurance coverage (more serious in survivors of childhood cancer because of their longer lifespan) (Murakami et al., 2019).

The key steps for successful implementation of a screening program include: proper communication with the target population for screening, intensive educational work both with health practitioners and screened participants explaining benefits and possible risks related to screening, the appointment of medical institutions to be involved in the screening process, and close systematic contact with them. For evaluation of screening effectiveness, it is important to take into account the avoidable costs due to over-diagnosis and overtreatment, as well as the worsening of patients' quality of life and, in some cases, health.

Systematic health screening, including cancer screening, should only be envisaged when it will bring more good than harm (Wilson and Jungner, 1968). For any type of health screening, the criteria for making such decisions will depend on a number of factors, including the availability of disease-specific registries, the natural history of disease, the magnitude of radiation doses received and the size of the affected population. In the long-term recovery phase, the SHAMISEN Consortium therefore does not recommend mass (or systematic) screening of TC in children and adults because it is unlikely to bring "more good, than harm" (Midorikawa et al., 2019; Oughton et al., 2017). The advantages of the screening program must exceed the disadvantages caused by screening test, diagnostic procedures and unnecessary treatments. Because radiation exposure dose is just one of many criteria influencing screening decisions, it is not reasonable to identify an absolute dose level at which screening would or would not be recommended. Given the challenge and potential adverse effects noted above, and because it is not conceivable to implement no TC screening in case of nuclear accident, one alternative might be to offer screening to persons who wish to undergo it, on a voluntary basis, on their own free-will and with sufficient information to support an informed decision; such a screening must be accompanied with appropriate information and support in interpreting the screening results for those who wish to be monitored: this option of screening corresponds to "community screening" according to the WHO classification (see Table 1). Good communication about the potential harms and benefits of screening to the affected populations is essential to allow them to make their own informed decisions, independent of the exposure level.

When screening is voluntary, it is necessary to abandon attempts to estimate the frequency of TC and the risk attributable to radiation because assessment of risk of radiation-attributed diseases requires, in addition to data on the amount of radiation exposure, information on background disease rates in a comparable unexposed population. Because screening will necessarily affect observed incidence rates of TC (as seen with the example of South Korea above), reliable estimates of radiation induced risk would not be achievable, even in the case of mass screening, since participation rates are never 100% and participants may differ from the general target population (in risk, in dose, and in other factors which could influence their risk of TC). People who accept the constraints of screening may have a better baseline state of health and a lower incidence of disease (because they probably take better care of their health) than those who refuse, therefore results of the screening cannot be generalised to the population as a whole.

Lastly, improved knowledge on TC would be helpful for decision-making in the case of future nuclear accident (how to identify cases, latency between thyroid nodule appearance and later clinical expression, proportion and characteristics of thyroid nodules that could progress into cancer, *etc.*). It is necessary to take into account factors other than screening such as genetic factors, obesity, diet or iodine deficiency which could play a role on TC incidence variations (Pellegriti et al., 2013).

After the SHAMISEN project, the International Agency for Research on Cancer (IARC/WHO) convened a multidisciplinary Expert Group in this context that has formulated two major recommendations for thyroid health monitoring after nuclear accidents: 1) to not implement mass thyroid screening in population after a nuclear accident; 2) to consider the option of a long-term thyroid monitoring program for high-risk individuals (*i.e.* exposed *in utero*, during childhood or adolescence with a thyroid dose of 100–500 mGy or more), including a discussion of the potential benefits and harms of thyroid examination in asymptomatic individuals. Although a thyroid dose actionable level was established (with no justification or explanation as to why), it does not mean that nothing should be offered to an individual below this exposure level. If an individual with lower dose is interested in having a thyroid examination, then this examination should be offered to this individual, after receiving a clear and detailed explanation of potential benefits and harms (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018; Togawa et al., 2018). Therefore, the recommendations of the IARC Expert Group are in line with the SHAMISEN recommendations, *i.e.* making thyroid monitoring available to all persons who would request it (regardless of whether they are at increased risk or not), accompanied with appropriate information and support. Moreover, as in SHAMISEN, this Expert Group strongly supports the creation of, and continued investment in, accurate national health registries (including cancer registries) in order to have accurate baseline (pre-event) population data for being able to identify and quantify a potential relationship between radiation exposure and a change of the rate of a disease (*e.g.* thyroid cancer).

The US Preventive Services Task Force also recommends against screening for thyroid cancer in the general, asymptomatic adult population (Lin et al., 2017). For screening in high-risk population, in particular in children exposed to nuclear fallout, the recommendation consists of two principles: 1) systematic neck palpation at each outpatient visit by a general practitioner, starting 5 years after exposure and then every 5 years; 2) ultrasound screening could be considered in a clinical research setting (Lamartina et al., 2020).

The complex choice about radiation dose criteria (threshold, exposure levels) and the applicability to children require careful consideration and extensive consultation among experts (in dosimetry, oncology, paediatrics, screening, epidemiology, *etc.*) as well as with concerned stakeholders (including parents and patient organisations). The choice will by definition depend on the particular cancer outcome of interest. In the case of TC, however, given the large proportion of indolent TC and the excellent prognosis of the disease once diagnosed (with symptoms), SHAMISEN recommends not conducting mass screening for TC after a nuclear accident but proposing screening, together with adequate information and explanations, to those who request it.

4. Conclusion

The SHAMISEN Consortium recommends that any systematic health screening should be based on appropriate justification and design. It does not recommend launching a mass thyroid cancer screening after a radiation accident, but rather to make it available (with appropriate information counselling) to those who request it (Oughton et al., 2017). This recommendation, number 25 of the SHAMISEN recommendations (Liutsko et al., this issue), for the recovery phase after a nuclear accident, was elaborated on the basis of the review of TC natural history (latent and indolent TC), improvement of TC detection capacities, overdiagnosis and impact of TC screening (in South Korea, after Chernobyl accident and after Fukushima disaster).

These recommendations on thyroid cancer screening in case of nuclear accident aim to limit harms that outweigh potential benefits.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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