Knowledge Gaps and Research Ideas Proposed by the IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents

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Introduction

Background

Since the nuclear power plant accident at Chernobyl, Ukraine (in 1986), epidemiological studies of the potential health consequences of the accident have contributed significantly to advances in scientific knowledge, particularly in the field of ionizing radiation and thyroid cancer risk. The evidence yielded by those studies, particularly the cohort studies, served to improve overall preparedness and response to nuclear emergencies, and contributed to the implementation of successful countermeasures against radiation exposure and associated adverse health effects. However, several questions remain to be answered.

The observed increasing trends in thyroid cancer incidence rates worldwide have drawn attention to the issues related to overdiagnosis associated with the increased use of sensitive imaging technologies (Pellegriti et al., 2013; Vaccarella et al., 2016; IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018). This has raised the question of whether and how to implement thyroid health monitoring after a nuclear accident that involves the release of radioiodine, and has also emphasized the importance of establishing guidelines on this topic. To address this gap, the International Agency for Research on Cancer (IARC) convened an international, multidisciplinary Expert Group in 2017 to develop recommendations on long-term strategies for thyroid health monitoring after nuclear accidents. The recommendations developed by the Expert Group are described in detail in IARC Technical Publication No. 46, which was published in September 2018 (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018; Togawa et al., 2018). In short, the Expert Group recommends against population thyroid screening after a nuclear accident, and it recommends that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals after a nuclear accident (higher-risk individuals are defined as those exposed in utero or during childhood or adolescence with a thyroid dose of 100–500 mGy or more).

The thyroid monitoring programme referred to in IARC Technical Publication No. 46 is an elective activity offered to higher-risk individuals, who may choose how and whether to undergo thyroid examinations and follow-ups. If the society affected by the nuclear accident and the relevant authorities decide to implement a thyroid monitoring programme, it is of the utmost importance to ensure its high quality, and to optimize in all communications the balance between the potential benefits and harms of undergoing thyroid examinations. For asymptomatic individuals, undergoing thyroid examinations entails potential benefits, such as early detection of a thyroid cancer, which enables treatment of less advanced disease and thus a lower risk of treatment-related complications, as well as the potential harm of overdiagnosis, which exposes participants to treatment that carries with it the side-effects and known risks of complications, without clinical benefit. It is important that all the potential benefits and harms are discussed among individuals, families, and clinicians, and that the decision about whether to undergo thyroid examinations and follow-ups is consistent with the person's values, preferences, and context.

During the development of the recommendations, the Expert Group identified some gaps in knowledge (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018; Chapter 5). The identified gaps included, among others, detailed characterization of the dose–risk relationship between thyroid radiation dose and thyroid cancer risk, the natural history of paediatric thyroid cancer, and the psychosocial impacts of thyroid health monitoring. In addition, guidelines on thyroid dose assessment and standardized protocols for ultrasonography imaging and subsequent diagnostic tests are currently lacking. Further work should be encouraged to address those gaps and help guide the decision-making process as well as the planning and implementation of a high-quality thyroid monitoring programme in case of a nuclear accident.

Scope and objectives

The Expert Group supports the notion that well-designed studies after a nuclear accident are warranted, because the additional scientific knowledge yielded can guide the preparedness, response, and recovery phases of any future nuclear accident that involves the release of radioiodine. The present report was developed with the aim of encouraging the relevant scientific community, health-care providers, and research funding bodies around the world to create and strengthen the evidence base for future public health and other interventions in case of a nuclear accident, such as a thyroid monitoring programme.

The present report covers the following four domains:

Research Area 1: Definition and identification of higher-risk individuals;

Research Area 2: Protocol and interpretation of thyroid examination;

Research Area 3: Clinical management of thyroid cancer; and

Research Area 4: Long-term health impacts of nuclear accidents.

The objectives of this report are: to present the current state of knowledge and the gaps in knowledge; to propose further work to fill those knowledge gaps; and to discuss potential limitations (e.g. bias), ethical issues, and significance.

Approach

The Expert Group selected the four above-mentioned domains according to their expertise and the availability of the existing or emerging data. The Authors of the present report developed potential strategies while considering potential limitations, ethical issues, and significance. Ten Expert Group members, including Experts, a Specialist, an Adviser, and the Scientific Secretariat, contributed as Authors to the initial drafting of the present report, based on their scientific expertise in the relevant fields. The first draft was then shared with and reviewed by the remaining Experts, who were appointed as Reviewers. The draft was further revised by the Authors based on the Reviewers' comments. The revised draft was then edited by the Editors and Dr Karen Müller. The present report was reviewed and approved by the Authors and Reviewers in February 2019.

Context

The Authors of the present report recognize the great scientific value of the research opportunities described here for using or expanding on the existing data from the Chernobyl accident or the emerging data from the accident at Fukushima Daiichi, Japan (in 2011). This is because the information that can be gained from the proposed task forces or studies will help to guide the planning and implementation of a high-quality thyroid monitoring programme after a nuclear accident. However, the Authors wish to stress that these research opportunities cannot be realized without sufficient financial support and staff resources, health-care facilities, and ethical approval as well as support from the stakeholders, including the residents and relevant professionals. Therefore, the Authors place great importance on having a continuous dialogue among scientists, residents, health professionals, and local and national authorities, which helps to improve the trust relationship and align the values of research with the values of the society.

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Research Area 1: Definition and identification of higher-risk individuals

1A. Individual thyroid dose assessment

Current knowledge

In general, in the case of a nuclear accident with environmental release of radioactive material, including radioactive iodine, the following exposure pathways contribute to the thyroid dose received by members of the public: (i) internal exposure from inhalation and ingestion intake of ^{131}I; (ii) internal exposure from inhalation and ingestion intake of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and of short-lived radiotelluriums (^{131m}Te and ^{132}Te); (iii) external exposure from radionuclides in the radioactive cloud and radionuclides deposited on the ground and other surfaces; and (iv) internal exposure from incorporated long-lived radionuclides such as radiocaesiums (^{134}Cs and ^{137}Cs) as a result of inhalation and ingestion intake (Gavrilin et al., 2004). The relative importance of the contribution of these exposure pathways to the thyroid dose depends on the history of an individual's location (e.g. residence), as well as their dietary habits and actions taken to reduce the dose for the individual considered.

As a rule, estimates of the thyroid dose from external exposure can be reliably derived from measurements of the exposure rate profile in the areas where members of the public lived or spent time after the accident. However, it is a more complex task to assess the thyroid dose from internal exposure to radioiodines. The most objective assessment of individual thyroid doses from internal exposure to radioiodines, which is associated with the least uncertainties, can be obtained by combining the following three elements: (i) individual direct measurements of the radioiodine activity in the thyroid gland of exposed people within a few weeks after a nuclear accident; (ii) personal interviews about the individual's history of locations (e.g. residence), dietary habits, and actions taken to reduce the dose at the time of and after the accident; and (iii) calculation of the dose, considering all sources of the thyroid dose from internal exposure to radioiodines. These three elements are discussed in more detail below.

Direct thyroid measurements

Direct thyroid measurements will enable the quantification of the thyroidal ^{131}I content at the time of measurement. According to experience from the two most recent nuclear power plant accidents (at Chernobyl and Fukushima), the direct thyroid measurement is conducted by placing a gamma-radiation detector against the neck to measure the exposure rate of gamma-rays arising from the radioactive decay of ^{131}I in the thyroid. Special attention should be paid to reducing the contribution from gamma-ray-emitting sources other than the ^{131}I accumulated in the thyroid to the measured exposure rate against the neck (for further details, see Gavrilin et al., 1999, 2004).

The net exposure rate, which is related to the ^{131}I activity in the thyroid, is the difference between the measured exposure rate against the neck and the measured background exposure rate. The calibration coefficient, which provides the correspondence between the net exposure rate and the ^{131}I activity in the thyroid at the time of measurement, depends on the device that was used, the geometry of measurement, and the size of the thyroid (Ulanovsky et al., 1997; Khrutchinsky et al., 2012). The uncertainty associated with the determination of the ^{131}I activity in the thyroid can be reduced substantially if a portable spectrometric device with a lead collimator is used rather than a simple survey meter.

For most members of the public, intake of ^{131}I is the primary source of dose to the thyroid if ingestion intake of radioiodines is the dominant exposure pathway. However, short-lived radioiodines may be substantial contributors to the thyroid dose, mainly ^{133}I and ^{132}I (due to the intake of ^{132}Te and its radioactive decay to ^{132}I in the body). For example, after the Fukushima accident, a typical contribution of short-lived radioiodines to the thyroid dose for residents who lived in contaminated areas and did not consume contaminated drinking-water and foodstuffs was estimated to be as great as 30–40% of the dose to the thyroid from ^{131}I (Shinkarev et al., 2015). Therefore, selected measurements of ^{132}I and ^{133}I in the thyroid should be performed in addition to measurement of ^{131}I.

For thyroid dose assessment, direct thyroid measurements should be performed in a sufficiently large number of residents of all ages from a given settlement in order to objectively determine the dominant pathway of radioiodine intake (inhalation or ingestion) for the considered group of the public (IAEA, 2015). Given the greater susceptibility of young children and of women who were pregnant or breastfeeding at the time of the exposure, priority should be given to direct thyroid measurements for these groups (UNSCEAR, 2014).

Personal interviews

Personal interviews enable the reconstruction of the time-dependent intake of ^{131}I from the time of the accident to the time of the measurement (assuming that no additional intake of ^{131}I would occur after the direct thyroid measurement is conducted) (Gavrilin et al., 1999, 2004). After the Chernobyl and Fukushima accidents, concise questionnaires were prepared to conduct personal interviews with members of the public to collect information on the dynamics of ^{131}I intake from the time of the accident to the time of direct thyroid measurements (Gavrilin et al., 1999; Uyba et al., 2018). Those questionnaires were prepared to clarify the individual’s locations, actions taken to reduce the dose, and dietary habits, so that the dose incurred from the exposure to the radioiodines could be estimated (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018).

Dose calculation

The thyroid dose from ^{131}I can be assessed as a product of two parameters: (i) the thyroidal ^{131}I content at the time of measurement and (ii) the function describing the kinetics of ^{131}I content in the human thyroid. The type of the function for an individual depends on how ^{131}I was distributed in the environment after the accident, how the person interacted with the environment contaminated with ^{131}I, whether the person had only inhalation intake or both inhalation and ingestion intake, the duration of the ingestion intake, whether the person took potassium iodide pills (to preclude the uptake of radioactive iodine by the thyroid) and, if so, on what dates, and other factors (Gavrilin et al., 2004).

The thyroid dose from short-lived radioiodines is usually calculated as a fraction of the thyroid dose from ^{131}I, accounting for different dose coefficients for inhalation and ingestion intake related to short-lived radioiodines and ^{131}I, and for the kinetics of radioiodine intake (Gavrilin et al., 2004; Shinkarev et al., 2015). The thyroid dose from external exposure depends on the measured exposure rate outdoors in the area of residence, the average time spent outdoors, and the type of residential home.

Knowledge gaps

Despite the recommendations by the Nuclear Emergency Situations: Improvement of Medical and Health Surveillance (SHAMISEN) Consortium (Oughton et al., 2017) to prepare action frameworks focused on dose assessment, currently there are no comprehensive international guidelines that outline how to assess individual thyroid dose, including the preparation and implementation of measurement of the thyroidal ^{131}I content during a short time period after an accident in a large population living in a contaminated territory. Such comprehensive international guidelines would enable better preparation for possible future nuclear power plant accidents with respect to providing members of the public with realistic estimates of dose to the thyroid after radioiodine releases into the environment.

Proposed future work

To minimize uncertainties in the estimation of thyroid dose from internal exposure to ^{131}I, the above-mentioned three elements should be taken into account. Furthermore, several lessons can be learned from the two most recent nuclear power plant accidents (at Chernobyl and Fukushima) about the assessment of individual thyroid doses (Gavrilin et al., 2004; Uyba et al., 2018).

An international task force should be implemented to develop guidelines on the procedure for assessing individual thyroid dose after a nuclear accident with the least uncertainty. To help develop international guidelines, it would be worthwhile to review the available experience from the three previous nuclear power plant accidents involving meltdown (at Three Mile Island, Chernobyl, and Fukushima) with respect to preparing for and conducting direct thyroid measurements and personal interviews.

Potential limitations

Potential limitations that need to be considered are related to deviations from the protocol for the preparation and conduct of the direct thyroid measurements. Experience from the past nuclear power plant accidents showed that in many cases the operators who conducted the direct thyroid measurements did not follow a protocol (e.g. selecting measurement sites in non-contaminated areas, removing contaminated clothing and washing the person before the measurement, conducting a background measurement, correct recording of the result of the measurement in the units of the devices, recording the date of the measurement, and conducting the personal interview). Therefore, it is important to ensure that the relevant professionals are familiar with the guidelines that are developed and are trained accordingly.

Successful conduct of direct thyroid measurement after nuclear accidents relies on timely action by trained professional staff and on the availability of appropriate measuring devices. Enough trained staff should be available to measure and to assess the thyroid radioiodine content of individuals as soon as possible in a sufficiently large population (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018). Experience from the past nuclear power plant accidents showed that one operator is able to conduct 150–200 direct thyroid measurements during an 8-hour working day, but there may be unexpected demands on emergency response teams that may hinder the conduct of direct thyroid measurements. This potential problem of lack of resources needs to be taken into account in the planning and preparation for direct thyroid measurements, including the need to train operators.

Potential significance

Establishing international guidelines on the assessment of individual thyroid dose will help local authorities, relevant professionals, and communities to plan for and implement the assessment of thyroid dose from internal exposure to radioiodines in an emergency situation. Having a reliable estimate of thyroid ^{131}I dose will help to accurately identify higher-risk individuals and also to elucidate an association between radiation exposure and health outcomes.

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1B. Characterization of the relationship between radiation and thyroid cancer

Current knowledge

Inhalation or ingestion of radioiodines (^{131}I and short-lived radioiodine isotopes) released during nuclear accidents results in radiation exposure primarily of the thyroid gland. About 4–5 years after the Chernobyl accident, an increase was observed in the number of thyroid cancers among children in highly contaminated areas of Belarus, Ukraine, and parts of the Russian Federation (UNSCEAR, 2006, 2011, 2018), with a risk of thyroid cancer occurrence increasing 1.4–4.7-fold after 1 Gy of thyroid gland exposure (Cardis et al., 2005; Brenner et al., 2011; Zablotska et al., 2011; Ivanov et al., 2016; Tronko et al., 2017). A younger age at exposure was associated with a higher radiation-related risk of thyroid cancer both after exposure to ^{131}I (Heidenreich et al., 2004; Brenner et al., 2011; Zablotska et al., 2011; Tronko et al., 2017) and after external irradiation (Furukawa et al., 2013; Veiga et al., 2016; Lubin et al., 2017).

In the range of low thyroid doses (< 0.2 Gy), a significant linear dose–response association between thyroid dose and thyroid cancer risk has been reported (Lubin et al., 2017). Similarly to what was observed at higher doses, the dose–effect association was greater at a younger age at exposure and persisted more than 45 years after exposure (Veiga et al., 2016; Lubin et al., 2017).

In addition to age at exposure, both intake of stable iodine for thyroid blocking and nutritional iodine status have been suggested to modify the effect of radiation on thyroid cancer risk. People who took stable iodine for thyroid blocking immediately after the accident had a lower radiation-related risk of thyroid cancer than those who did not (Cardis et al., 2005). Moreover, residents of iodine-deficient areas could have a higher risk of thyroid cancer after ^{131}I exposure than residents of iodine-sufficient areas (Nauman and Wolff, 1993; Cardis et al., 2005). Also, an increased risk of thyroid cancer was reported in Chernobyl clean-up workers (liquidators) in relation to the total thyroid dose due to ^{131}I and external exposure (Kesminiene et al., 2012).

For other suspected effect modifiers, the findings have been inconsistent. For example, although spontaneous thyroid cancer occurs more frequently among women than among men, no consistent difference in radiation-related thyroid cancer risk was found between men and women (Zablotska et al., 2011; Furukawa et al., 2013; Veiga et al., 2016; Lubin et al., 2017; Tronko et al., 2017). Furthermore, papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in the general population as well as in the population affected by radiation exposure; no clear differences in radiation-related risk between thyroid cancer subtypes (i.e. papillary vs non-papillary tumours) have been observed (Veiga et al., 2016).

Knowledge gaps

Over the past decades, the relationship between radiation exposure and thyroid cancer has been relatively well established and quantified in several major epidemiological studies. However, to better define higher-risk individuals, the following knowledge gaps (uncertainties) should be further addressed.

Natural history of thyroid cancer

More insights are needed into the natural history of thyroid cancer, i.e. the origin of thyroid cancer cells, cancer initiation and progression, transformation from a small and asymptomatic cancer into an aggressive one, and what factors could influence these processes. To elucidate the biological mechanisms through which radiation exposure can cause the development of thyroid cancer, a better understanding is needed of the mechanisms of spontaneous thyroid carcinogenesis. This knowledge is crucial in helping to distinguish cancers that remain asymptomatic and do not require active interventions from more aggressive cancers (see also Research Area 3). To assess the genetic predisposition and to define the molecular mechanisms that promote thyroid carcinogenesis, it would be necessary to conduct integrated multidisciplinary research on thyroid cancer, i.e. research that incorporates not only epidemiological and dosimetry aspects but also epigenetic and molecular biology aspects of thyroid cancer in relation to exposure to ^{131}I.

Dose–risk relationship at low doses and by age at radiation exposure

Overall, the relationship between radiation exposure and thyroid cancer risk is well established, but uncertainties remain about the magnitude and shape of the dose–risk relationship at the low thyroid doses (< 100 mGy) that are typically received by the affected population after environmental exposure to ionizing radiation. Therefore, follow-up and risk assessment in populations with relatively low exposure to the thyroid are important to provide additional insights into thyroid cancer risk at low doses. As mentioned above, risk of thyroid cancer after exposure was found to be higher in children and adolescents than in adults (NCRP, 1985; Cardis and Hatch, 2011). However, little is known about thyroid cancer risk, and its magnitude, after thyroid exposure in utero and in infancy (Hatch et al., 2009, 2018). A more precise characterization of risk, especially after low-dose radiation exposure in utero, during early life, and during young adulthood, merits additional research.

Dose–risk relationship by tumour type

Controversy remains about the magnitude of the dose–risk relationships by thyroid tumour type (benign nodules, PTC, follicular thyroid cancer, and other, rarer types) and by thyroid tumour characteristics, such as benign versus malignant, size, frequency of tumour foci, and signs of aggressiveness (Mushkacheva et al., 2006; Imaizumi et al., 2015; Cahoon et al., 2017). Further research with careful consideration of tumour characteristics is required to better quantify the dose–risk relationships.

Latency period

The minimum latency period, defined as the minimum period after exposure after which an excess risk is detectable, is currently estimated to be 3–5 years for radiation-induced thyroid cancer. Nevertheless, latency may vary with age at exposure, radiation dose, and other host and environmental factors. Furthermore, the minimum latency period between exposure and thyroid tumour detection may be shorter for malignant nodules of very small diameters ($\leq$ 5 mm), simply because they are detected at an earlier state of disease development. More data are required to better estimate the time sequence between radiation exposure and thyroid cancer development, and to characterize possible variations with host and environmental factors. This information would help to better characterize higher-risk populations and plan an efficient thyroid monitoring programme.

Lifetime risk of radiation-induced thyroid cancer

Radiation-related risk of thyroid cancer after exposure during childhood has been shown to persist for decades after exposure, meaning that a number of thyroid cancers initiated by exposure in early life would develop later on, in adulthood (Furukawa et al., 2013; Lubin et al., 2017; Tronko et al., 2017). However, there is uncertainty about how risk varies with time since exposure and with age, especially during periods of intense hormonal stimulation, such as pre-puberty, puberty, and, for women, pregnancy.

Potential interaction with, or effect modification by, other risk factors

Besides radiation, several other factors have been suggested to influence thyroid cancer risk, such as ethnicity, anthropometric factors (e.g. weight, body mass index, and body surface area), physical activity, diet (e.g. nutritional iodine status), reproductive factors, and environmental chemicals (e.g. nitrates and polybrominated diphenyl ethers) (Ron and Schneider, 2006). However, further data are required to clarify their associations with thyroid cancer risk (see Research Area 4A) and also to investigate a potential interaction (joint effect) between radiation and these factors in relation to thyroid cancer risk.

Proposed study design

A screening cohort study on thyroid cancer after exposure to ^{131}I during childhood, supported by the National Cancer Institute of the United States National Institutes of Health (Stezhko et al., 2004), should be continued in Ukraine and recommenced in Belarus to provide additional insights into changes in radiation-related risk of thyroid cancer with time since exposure, age, and other potential radiation effect modifiers. The use of a standard screening protocol and similar methods of thyroid dose reconstruction, based on individual direct measurements of thyroid radioactivity, ensures comparability between the studies and enables a pooled data analysis, which quantifies the risks and evaluates potential radiation effect modifiers, such as sex, age at exposure, attained age, time since exposure, thyroid disorders that precede thyroid cancer, iodine deficiency, and others.

In addition to cohort studies, epidemiological monitoring of time trends in thyroid cancer incidence in highly contaminated areas of Belarus, Ukraine, and the Russian Federation among populations exposed as children or adults is warranted, as defined by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2018). Such monitoring would enable timely detection of any changes in thyroid cancer incidence, followed by detailed analyses of non-radiation and radiation risk factors and possible public health interventions. Furthermore, it would also enable a case–control study to be performed among the entire population in Belarus and Ukraine who were exposed in utero to fallout from Chernobyl (Tronko et al., 2014; Hatch et al., 2018).

Two cohorts of people exposed to ^{131}I in utero in Belarus and Ukraine are currently undergoing periodic thyroid screening examinations (Hatch et al., 2009, 2019; Yauseyenka et al., 2016). Individual thyroid doses are available for every study cohort member, taking into account the exposure pathway (external and internal) and mode (in utero and postnatal). Cohort-specific and pooled analyses of these two cohorts would provide important information on the magnitude and time-related changes of ^{131}I-related thyroid cancer risk after exposure at various trimesters of intrauterine development and during the first months of life.

Other potential cohorts with exposure to ^{131}I, largely in the low-dose range, include rural residents in the area around the Semipalatinsk nuclear test site, in Kazakhstan, and people who lived downwind of the Mayak Production Association nuclear facility, in the Russian Federation. However, substantial efforts would be required for retrospective thyroid dose reconstruction, because no direct thyroid measurements were performed among these groups of people.

For thyroid cancer risk after external and ^{131}I exposures in adults, priority should be given to a well-planned case–control study of thyroid cancer nested in a combined cohort of liquidators. This cohort study of liquidators has estimated thyroid doses using the Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) method, which was developed and extensively tested by an international group of experts (Kryuchkov et al., 2009). Such a study could yield more precise estimates of the increase in risk of thyroid cancer among liquidators.

Also, the pooled analysis of nine cohorts on thyroid cancer after low-dose exposure to external radiation during childhood (Lubin et al., 2017) can be used to improve the quantification of dose–risk relationship by some effect modifiers, such as time since exposure, ethnicity, or anthropometric parameters.

Potential limitations

A major limitation that needs to be considered when conducting studies involving thyroid screening is that thyroid screening influences the risk assessment of radiation-induced thyroid cancer. Thyroid screening has an impact on the baseline rates of thyroid cancer (i.e. increased incidence due to detection of subclinical thyroid cancers), on the tumour characteristics (i.e. screening data on tumour size and malignant potential are different from epidemiological data from a cancer registry, mainly due to detection of microcarcinomas in screening), and potentially on the estimated minimum latency period (which could be different according to the malignancy and size of nodules). These points should be taken into account when interpreting findings from a study population where screening activities were undertaken.

Another potential limitation is the relatively small size of some study populations, for example those exposed in utero. To enable informative analyses, international data pooling may be necessary.

Finally, for reliable retrospective individual thyroid dose reconstruction, the collection of personal information about an individual's whereabouts at the time of the accident and afterwards, and their behaviour, diet, and iodine prophylaxis plays an essential role (see Research Area 1A). However, the retrospective collection of the necessary information could be logistically or financially challenging or could even be biased, for example in the case of poor memory recall or due to the health of the individuals in the study.

Potential significance

Currently, higher-risk individuals are defined only by thyroid dose and the age of the individuals (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018). Further information on effect modifiers, including nutritional iodine status and time since exposure, would enable a more precise definition of higher-risk individuals. This information will help optimize the balance between the benefits and harms of thyroid health monitoring by identifying a possible excess of thyroid disease in higher-risk individuals, and also by reducing overdiagnosis and associated potential harms.

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Research Area 2: Protocol and interpretation of thyroid examination

2A. Clinical examination

Current knowledge

In case of a nuclear accident, it is important to assess the individual thyroid radiation dose while making the uncertainty as small as possible (see Research Area 1A). If the decision derived from thyroid dose assessments and other decisional factors, such as societal values and available resources, is to implement a thyroid monitoring programme after a nuclear accident, the programme should entail: (i) assessment of medical history (e.g. thyroid diseases in the individual and their family, familial tumour predisposition syndromes, diet (including dietary iodine intake), smoking history, exposure to environmental pollutants, and exposure to ionizing radiation from previous medical surveillance and from treatment of a non-thyroid disease and malignancy) and (ii) clinical examination (e.g. visualization and palpation of the neck [if the informed decision is to undertake palpation], height, weight, and signs of thyroid dysfunction).

Information derived from the above-mentioned assessments plays an important role in determining the person's risk of developing thyroid cancer. To ensure the highest quality of the programme, standard operating procedures (SOPs), including standard forms for documentation need to be established before the programme is implemented.

Knowledge gaps

Currently, there are no electronic SOPs for the assessment of medical history or for clinical thyroid examination after a nuclear accident. For the development of SOPs, real-world data and experience from past nuclear accidents would be very helpful to tailor the SOP for thyroid monitoring after nuclear accidents.

In addition to the SOPs for the assessment of medical history and for the clinical examination, an optimal design should be developed for an electronic health record database that enables the storage and future analysis of data from these assessments.

Proposed study

A task force could be launched to create electronic SOPs and develop an optimal design for an electronic health record database for a thyroid monitoring programme after a nuclear accident. This would enable the efficient and effective collection and storage of medical history data as well as clinical examination data in an effort to improve the care of populations affected by a nuclear accident.

Potential limitations

Although a standard set of questions and an electronic health record can facilitate accurate and complete collection of data for a large population, there may still be limitations related to cultural and language barriers or recollection for members of the population to answer historical queries, as well as limitations in resources to implement the SOPs.

Potential significance

Having the SOPs for thyroid clinical examination prepared in advance will facilitate a prompt and appropriate response after a nuclear accident. Furthermore, the SOPs, including standard forms for documentation, and an electronic health record database will help to harmonize the information collected across different examination centres and countries. Development of these documents as part of preparedness for a nuclear accident will also afford an opportunity to translate the SOPs into multiple languages.

2B. Ultrasonography

Current knowledge

Imaging

Ultrasonography imaging technology has advanced and is widely used to aid diagnostics. Different techniques are available, such as greyscale ultrasonography, Doppler ultrasonography, elastography (ultrasound elasticity imaging), and three-dimensional imaging. These techniques enable the detection of thyroid nodules and help differentiate benign nodules from malignant nodules on the basis of certain features. The ultrasonography data from thyroid examinations conducted after the Chernobyl accident showed that perfusion of suspect thyroid lesions derived from colour Doppler imaging may be a relevant indicator of malignancy (Lyshchik et al., 2005). Elastography is a more recent ultrasonographic procedure, which has the potential to improve the identification of thyroid malignancies (Hu and Liu, 2017). Three-dimensional image acquisition enables the capture and storage of data from a complete sweep with the ultrasonography probe over the whole neck (Lyshchik et al., 2004a, 2004b). The advantage of this mode of data acquisition, which has recently been used more frequently, is that the complete sonographic scan can be analysed (or re-analysed) off-site with reduced acquisition time and improved sensitivity for detecting malignancy and invasive behaviour (Kim et al., 2016).

The diagnostic quality of ultrasonography is strongly investigator-dependent (Lyshchik et al., 2005; Schlögl et al., 2006). For instance, the resolution of standard B-mode sonographic imaging depends strongly on the transmitting frequency of the probe. Therefore, it is mandatory that an identical patient position and probe resolution (and image post-processing) are used for acquisition of images across the whole population, irrespective of risk level, to ensure comparability (Reiners et al., 2019). Furthermore, the application of colour Doppler imaging and of newer imaging modalities, such as elastography and three-dimensional imaging, may be considered if resources are available.

Reporting scheme

Several reporting schemes have been developed for risk stratification of thyroid nodules to help determine whether fine-needle aspiration is indicated. Examples are the American College of Radiology Thyroid Imaging Reporting and Data System (TI-RADS), the ultrasonographic classification of the American Thyroid Association, and the European Thyroid Imaging and Reporting Data System (EU-TIRADS) (Cooper et al., 2009; Russ et al., 2017, Tessler et al., 2018). TI-RADS has been shown to discriminate well between benign and malignant thyroid nodules, both in adults and in paediatric patients (Lim-Dunham et al., 2019). The inclusion of additional parameters may further improve the accuracy of these existing reporting schemes. For example, the specificity of TI-RADS for selecting patients who need fine-needle aspiration biopsy can be increased by the inclusion of elastography parameters without a decrease in sensitivity (Mao et al., 2018). The combination of the TI-RADS scoring system with colour Doppler flow parameters, and virtual touch imaging parameters derived from elastography, may additionally improve the accuracy of predicting central compartment lymph node metastasis in patients with papillary microcarcinoma of the thyroid (Xu et al., 2016).

Knowledge gaps

Imaging

To ensure high quality, standardized imaging protocols, quality assurance measures, and training programmes need to be developed and implemented. In this context, ultrasonography thyroid phantoms with simulated thyroid glands and thyroid lesions of definite size and density are recommended for training and quality control (Schlögl et al., 2001, 2006; Baba et al., 2017). Another approach would be to use human volunteers for training. For example, after the Fukushima accident, Japanese clinicians started a local education programme, which included written instructions and hands-on examinations to certify medical doctors and technologists as thyroid sonographers. In this programme, healthy adult volunteers were used rather than thyroid phantoms. This approach is preferable for training; for the quality assurance of an ongoing thyroid ultrasonography examination programme, thyroid phantoms could additionally be used for blinded quality checks.

Reporting scheme

The ability to discriminate between benign and malignant nodules may be improved by incorporating additional parameters, such as colour Doppler flow parameters, or by using newer technologies, such as elastography and three-dimensional imaging. The utility of such newer technologies in risk stratification has not been tested in large numbers of children and adolescents.

Proposed study

Imaging

To ensure high quality, standardized imaging protocols should be developed before initiation of an ultrasonography thyroid examination programme. Investigators need to be trained according to these protocols. Imaging protocols and training methods used to carry out a large-scale thyroid examination programme, such as the Fukushima Health Management Survey (FHMS), should be documented and published to help guide any ongoing or future ultrasonography thyroid examination programme, including thyroid health monitoring after a nuclear accident.

Reporting scheme

From the scientific viewpoint, creating an SOP for reporting of imaging findings using TI-RADS with the addition of newer technologies, including colour Doppler perfusion parameters (if available), elastography, and three-dimensional imaging, would be valuable. Evaluation of the diagnostic accuracy of this reporting system with existing ultrasonography scans, such as those stored in the FHMS database, could help validate the utility of the SOP. Finally, artificial intelligence (AI) algorithms could be developed for the evaluation of the three-dimensional volumetric greyscale, power Doppler sonography, and elastography data, if available.

Potential limitations

In the FHMS, a standardized acquisition protocol for thyroid sonography in the primary examination was used. Cine clips covering an area including and surrounding the nodular lesion in both B-mode and colour Doppler mode were captured and stored electronically. Elastography was used in the confirmatory examination. These approaches do not cover the whole thyroid, and therefore a complete re-evaluation would not be possible. Nevertheless, thyroid ultrasound image analysis using AI should be feasible with the ultrasonography data stored electronically.

The review of thyroid health records, including whole original data sets from imaging and fine-needle aspiration cytology (including sequencing data), constitutes an enormous workload. Although such large amounts of information cannot be managed without sophisticated algorithms and bioinformatics scientists familiar with handling and analysing “big data”, the first reports about the utility of this technology are promising (Tagliaferri et al., 2018).

Potential significance

The use of AI and machine learning approaches, including deep learning or neural networks, improves image segmentation and, in the case of thyroid ultrasonography, volume definition of the whole gland and of focal lesions (Poudel et al., 2018). Even more importantly, the data derived with these technologies may achieve a high accuracy in discriminating between malignant and benign lesions (Song et al., 2018). According to the first results derived with these technologies, the sensitivity for discrimination of malignant thyroid nodules using AI is at least equal to that of experienced radiologists, whereas the specificity of the AI approach may not yet be satisfactory (Chang et al., 2016; Wu et al., 2016; Chi et al., 2017). Furthermore, such computer-aided diagnosis may alleviate the burden on doctors and decrease the related cost. Finally, establishing AI algorithms based on the FHMS “big data” may help to improve the diagnostic accuracy, so that this technique could subsequently be applied generally for thyroid diagnostics in children and adolescents worldwide.

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Research Area 3: Clinical management of thyroid cancer

3A. Natural history and treatment outcomes of thyroid cancer

Current knowledge

About 80–90% of thyroid cancers are PTC histology; the proportion varies across the globe based on iodine status and rates of detection. PTC has a substantial subclinical reservoir: some people die with the disease, never knowing that they had it. Emerging baseline data from the Thyroid Ultrasound Examination (TUE) programme, which was initiated in those aged 18 years or younger as part of the FHMS, suggest that the subclinical reservoir may begin to develop during childhood and adolescence (Suzuki et al., 2016). This finding has ramifications for thyroid screening activities implemented in children and adolescents after a nuclear accident: it could create an apparent increase in the incidence of thyroid cancer.

The treatment for thyroid cancer in children and adolescents is usually total thyroidectomy, and possibly radioactive iodine therapy, depending on the pathology and post-operative assessment for evidence of persistent disease. These treatments have known side-effects as well as risks of complications. The likely presence of a subclinical reservoir of prevalent cancer that would be detected in thyroid screening activities complicates decision-making, because some of the detected cancers might not have become clinically apparent had the patient not undergone a thyroid screening activity.

Knowledge gaps

The role of surveillance in monitoring detected paediatric thyroid cancer

There is a growing recognition that small PTCs in middle-aged to older adults can be managed with active surveillance as the first course of treatment rather than surgery, because many of the PTCs will not grow substantially while under surveillance. Given the new knowledge of a potential subclinical reservoir of PTC in children and adolescents, the benefit of uniformly aggressive treatment (total thyroidectomy and radioactive iodine therapy) is less clear. Children’s thyroid tissue is more likely to undergo radiation-induced tumorigenesis, and sporadic children’s PTCs display an increased rate of growth as well as of regional and distant metastasis compared with adults. Unfortunately, with the data currently available, it is not possible to predict which intrathyroidal thyroid cancers diagnosed during the paediatric age will grow, and at what rate.

Factors that may help predict the potential for growth may be identified with further delineation of the molecular landscape (oncogene and gene expression) of both radiation-induced and sporadic paediatric thyroid cancer. Additional factors that influence tumour growth include iodine excess or deficiency and thyroid-stimulating hormone (TSH) levels; some data suggest that TSH suppression with levothyroxine therapy may decrease the growth of PTCs under active surveillance.

Paediatric thyroid cancer treatment: thyroid lobectomy (also known as hemithyroidectomy)

Thyroid cancer treatment practices in children and adolescents are based on limited and retrospective evidence (Francis et al., 2015). Surgical recommendations are generally more aggressive than those for adults, because children and adolescents have higher rates of regional and distant metastasis and an increased risk of persistent and recurrent disease (Francis et al., 2015; Al-Qurayshi et al., 2016). With the recognition of the existence of non-invasive thyroid cancer variants, including a group of encapsulated, follicular variant PTCs (Nikiforov et al., 2016; Samuels et al., 2018), and the possibility that some cancers detected by monitoring might not continue to grow or may regress, additional studies are needed that investigate outcomes of less aggressive thyroid cancer treatment in children and adolescents (Kluijfhout et al., 2017; Samuels et al., 2018).

The extent of surgery needed in children with low-risk cancers is not clear. Traditionally, children have been treated with total thyroidectomy, which necessitates lifelong thyroid hormone replacement. If some thyroid cancers could instead be treated with removal of half of the gland (thyroid lobectomy), this may improve quality of life without reducing disease-free survival. Increasing amounts of data are available on the oncogenic landscape of paediatric thyroid cancer; however, prospective data on incorporating molecular markers into clinical decision-making in children are lacking, and this important knowledge gap should be filled (Bauer et al., 2017).

Proposed study

The optimal study design for assessing the safety and efficacy of active surveillance and lobectomy in children and adolescents is a randomized controlled trial. However, the sample sizes needed, the duration of follow-up for a slow-growing tumour, and the challenges associated with obtaining informed consent from minors in such a trial are all major barriers.

An alternative study design is an observational cohort study. The appropriate construction of the study population would probably be based on data from cancer registries, combining cases across multiple countries to obtain adequate sample sizes to answer the questions of interest. In some countries, there are mechanisms that allow the contact of families whose cases are in the registry, to obtain more detailed treatment and follow-up data. If such a mechanism could be used across a large enough cohort, for example through an international paediatric consortium, more robust data could be produced.

Furthermore, long-term follow-up data on children with PTC who have been treated with lobectomy alone may enable the identification of clinical features of disease that predict recurrence and metastasis. The data from the TUE programme is a case in point, because the majority of paediatric patients diagnosed with PTC were treated with lymph node dissection. Continued review and publication of data on the outcome of this approach, as well as delineation of the molecular landscape of the tumours (if banked and available for research purposes) from those patients would further our knowledge of care as well as molecular correlates of clinical behaviour. On the basis of those data, it may be possible to confirm for which patients surgical remission can be achieved by lobectomy with lymph node dissection as well as to identify how prophylactic central neck dissection contributes to outcomes. An assessment of potential issues related to quality of life after treatment, such as fear of recurrence, anxiety, and school and social functioning, would also be informative. In the future, if some patients in this cohort elect to pursue surveillance of small cancers rather than surgery as a first course of treatment, valuable data on the active surveillance in this age group could also be obtained.

Potential limitations

A limitation of randomized controlled trials is the many years they take to plan, conduct, and analyse. An observational cohort study entails a risk of bias due to unmeasured confounding, loss to follow-up, and dropout. However, a well-designed cohort study that minimizes these risks would provide the most rapid answers and would increase levels of knowledge and certainty, thus improving the care of children and adolescents with screen-detected thyroid cancer. Using registry data to conduct such studies has limitations, because the data were collected for registry purposes. Such studies could be expensive to conduct if registry cases had to be recontacted for follow-up or additional data collection, and would have risks of incomplete data because of an inability to locate cases years after diagnosis.

Potential significance

If participants in the TUE programme were interested in participating in such a cohort study, they would contribute tremendously to advancing the science of paediatric thyroid cancer. The risks of participating in such a study would be lower than those in virtually any other setting, given that the participants would be under active surveillance for a cancer that has a high survival rate.

The data from the TUE programme have shown that thyroid examinations in asymptomatic children and adolescents detect thyroid nodules, thyroid cancers with invasive features, and also thyroid cancers that may have been destined to remain subclinical over the person’s lifetime. A surprising finding in the TUE data was that more than 70% of thyroid cancers had lymph node metastasis at the time of diagnosis. An observational study of this cohort would provide valuable data for future populations after a nuclear accident, further refining treatment options for paediatric thyroid cancer.

The radiation exposure level in the Chernobyl accident was many times that in the Fukushima accident. After the Chernobyl accident, a number of children were diagnosed with advanced thyroid cancer and underwent extensive surgery and treatment with radioactive iodine, with its attendant side-effects (Demidchik et al., 2006; Biko et al., 2011; Hebestreit et al., 2011). There could be a benefit to early detection of thyroid cancer after a nuclear accident, so that cancers could be removed before there is extensive regional and distant metastasis, thus avoiding more extensive treatment. However, while implementation of a thyroid screening or monitoring programme would result in the detection of clinical cases at an earlier state of metastasis, it may also detect subclinical cases which would have been undetected if screening or monitoring had not occurred. Thus, it would be most desirable to have knowledge about the least invasive clinical management that is still effective. A better understanding about whether and how treatment could be de-escalated in this population would provide important information to enable patients to elect to undergo the treatment that is most likely to optimize the benefits while minimizing the side-effects of treatment.

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3B. Decision support for thyroid monitoring participation and thyroid cancer treatment

Current knowledge

Decision support in cancer screening and treatment is broadly recognized as a key tool for achieving high-quality support of informed choices. This would be especially true in a thyroid monitoring programme after a nuclear accident, because the challenges of education and empowerment in response to a public health catastrophe such as a nuclear accident are great. When considering a thyroid monitoring programme, it is important to recognize that there is a strong belief in the benefits of screening among both health professionals and the public (Moynihan et al., 2015; McCaffery et al., 2016). This must be taken into account, because it will affect any efforts to educate the public about thyroid monitoring choices after a nuclear accident. In addition, because many cultures value action in medical care over inaction (Feinstein, 1985), de-escalation of care, whether it be less aggressive treatment or a decision to opt out of monitoring, will be challenging.

Knowledge gaps

Most research on decision support in cancer screening and treatment has been done in adults. A critical gap is knowledge about the development, implementation, and effectiveness of decision support tools in the paediatric population. Because thyroid monitoring programmes after a nuclear accident would principally involve children, adolescents, and their caretakers, this is a crucial area of research.

This is complicated by the fact that decision support materials to fully inform people would require evidence about the benefits and harms of the options proposed, and detailed data are lacking in many areas, as outlined in the preceding sections.

The specific areas in which decision support would be beneficial are: (i) the potential benefits and harms of earlier diagnosis of thyroid cancer in a thyroid monitoring programme; (ii) the potential benefits and harms of the treatment options, including the long-term consequences of medical and surgical treatment for paediatric thyroid cancer (e.g. lobectomy vs total thyroidectomy, prophylactic central neck dissection vs no prophylactic central neck dissection, dynamic risk stratification in the use of post-thyroidectomy radioactive iodine therapy), in accordance with current treatment guidelines; and (iii) the benefits and burdens of lobectomy and active surveillance for individuals who are identified to have thyroid cancer in a thyroid monitoring programme.

An additional gap is the absence of tested, validated educational materials that could be given to the public before an accident. There is some evidence that public education before an accident could make decision support after an incident easier. Therefore, materials should be developed to inform the public about the risks of radiation-induced thyroid disease after a nuclear accident, the natural history of thyroid cancer, and how a thyroid monitoring programme would work.

Proposed study

An evaluative study of materials developed after the Fukushima nuclear accident would provide valuable information. Using the Weiss framework (Weiss, 2005), evaluation would include an assessment of what worked best in various settings and time frames as well as what approaches were not successful. In addition, the education and decision support programme should be assessed to determine what tended to enhance or detract from its effectiveness.

To support choices about whether to undertake monitoring and treatment of cancers detected by monitoring, a suggested approach is to develop decision support materials rather than specific decision aids, which are more detailed to develop and use and are limited to specific decisions. Decision support materials such as infographics and summaries of available evidence can be used to support a wide variety of discussions and educational needs. Valuable insight would be gained by submitting the developed decision support materials to evaluative testing for user comprehension, effect on anxiety and trust of public agencies, and satisfaction with utility to support decision-making.

Potential limitations

Tools developed outside the setting of a nuclear accident may be found not to work after an actual accident occurs if the needs and concerns of the population are different than anticipated. Therefore, prospective development is probably less desirable than the evaluation of tools that have already been developed or are being developed for the Fukushima population.

Potential significance

The Expert Group introduced the concept of a thyroid monitoring programme where the objective is to "empower higher-risk individuals to make an informed decision, with personal decisions about individual benefits outweighing the harms" (IARC Expert Group on Thyroid Health Monitoring after Nuclear Accidents, 2018). Efforts to develop decision support materials, to the extent possible, by building on what can be learned from the aftermath of the Fukushima accident and from the work of the FHMS would provide tremendous value, particularly to populations affected by nuclear accidents. Although each major nuclear accident has tremendous costs and losses, valuable lessons can be learned to ensure that if another nuclear accident happens, it is managed better, and the preparation of decision support materials is one such example.

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Research Area 4: Long-term health impacts of nuclear accidents

4A. Non-radiation factors associated with the development of thyroid cancer

Current knowledge

Few risk factors have been established for thyroid cancer other than sex, race, family history of thyroid cancer (Xu et al., 2012), exposure to ionizing radiation during childhood and adolescence (see Research Area 1B), and obesity during adulthood (Kitahara et al., 2016). Although the data are currently limited, studies have suggested that other factors, such as obesity during early life (Kitahara et al., 2014), exposure to endocrine-disrupting chemicals (Malandrino et al., 2016; Hoffman et al., 2017), nutritional iodine status (Cao et al., 2017), and nitrate intake (Drozd et al., 2018), might also affect the risk of thyroid cancer.

Knowledge gaps

Although epidemiological research has contributed significantly to knowledge about the association between radiation exposure and thyroid cancer risk, the etiology of thyroid cancer remains largely unknown. The current knowledge about non-radiation risk factors for thyroid cancer is limited, and most thyroid cancers cannot be explained by the known risk factors. Such knowledge is important not only to better understand the etiology of thyroid cancer but also to account for potential confounding effects on radiation risk if and when research is undertaken on radiation exposure and thyroid cancer risk.

Disasters such as nuclear power plant accidents impose many changes on people's lives. For example, after the Fukushima accident, people who were living in the evacuation zones experienced changes such as relocation, family separation, and lifestyle changes (e.g. diet, sleeping pattern, physical activity, and social life). Consequently, some negative changes in health status, such as a higher incidence of metabolic syndrome, were observed in adult evacuees (Hashimoto et al., 2017). Such negative health impacts might also have occurred in evacuees of younger ages. Such changes might have an impact on the risk of developing thyroid cancer.

Proposed study

After the Fukushima accident, in March 2011, the local prefectural government, together with Fukushima Medical University, initiated the FHMS to ensure the long-term health of Fukushima residents (Yasumura et al., 2012; Yamashita et al., 2016). As part of the FHMS, the TUE programme was initiated in those aged 18 years or younger at the time of the accident. The Preliminary Baseline Survey of the TUE programme, conducted from October 2011 to March 2014, assessed the baseline prevalence of thyroid cancer in Fukushima

(Yamashita et al., 2018; Ohtsuru et al., 2019). Follow-up surveys have been conducted, and the results have been reported regularly (Fukushima Prefectural Government, 2018).

The FHMS consists of various surveys, including the TUE programme, the Comprehensive Health Check, the Mental Health and Lifestyle Survey, and the Pregnancy and Birth Survey (Yasumura et al., 2012; Yamashita et al., 2016). The FHMS can be used as a platform to establish a prospective cohort (longitudinal) study to identify potential non-radiation modifiable risk factors for thyroid cancer in children, adolescents, and young adults. The outcome – thyroid cancer cases – can be identified through the TUE programme (thyroid cancer cases identified through other mechanisms, including through cancer registries, would have to be indicated as such). Information on non-radiation factors that might modify the risk of developing thyroid cancer, such as body mass index , waist circumference, physical activity, dietary habits in the past month (e.g. fish consumption), smoking, alcohol consumption, employment status, and other factors, if available, can be studied in relation to the risk of developing thyroid cancer in an epidemiological study. If repeated measures are available, changes in these measures over time in relation to thyroid cancer risk can also be examined.

If any information needed for the study is not available from these surveys, the information could be collected retrospectively via additional questionnaires or from medical records. In that case, a nested case–control study design (including all cases and a sample of controls from an established cohort) may be applied for better efficiency.

Potential limitations

Follow-up of the participants may become challenging if the participants relocate for schools or jobs or if they lose interest in participation. Absence of follow-up data could decrease the validity of the study. For example, dropout or loss to follow-up reduces the study's sample size and the statistical power. Therefore, efforts should be made to minimize systematic dropout or missing information, to ensure that the study sample is representative of the study population and is of sufficient size to provide robust statistics.

Another potential bias could arise from the fact that the FHMS was not specifically designed to study associations between non-radiation factors and thyroid cancer in this population. To implement such a study, ethical approval and informed consent will have to be obtained, and this may limit the feasibility of the study. Furthermore, the questions asked in these surveys might not capture the details for exposures of interest. Retrospective collection of data may be possible, although there are several potential challenges, such as logistics, cost, and recall bias. Nevertheless, the existing information collected from people without the knowledge of having thyroid cancer is valuable, because the knowledge of having the disease can influence people's responses and bias the study results.

Although the above proposal does not primarily aim to investigate the effects of radiation exposure on thyroid cancer risk in Fukushima, it is important to remember the conclusions reached in the reports from the World Health Organization (WHO) and UNSCEAR that information on dose distribution was not sufficient at the time of evaluation to enable a firm conclusion to be drawn about any potential increase in thyroid cancer incidence in infants and children exposed to higher thyroid doses in Fukushima (WHO, 2013; UNSCEAR, 2014). Furthermore, given the small number of children and adolescents exposed to higher thyroid doses, it would be very difficult to detect an effect, if there is any, of radiation on thyroid cancer risk in the population of Fukushima residents.

Potential significance

For a rare disease, like thyroid cancer, it is challenging to design a sufficiently large cohort study. The FHMS can provide a unique opportunity to conduct a cohort study on thyroid cancer during childhood, adolescence, and young adulthood. Given the scarcity of information about the associations between non-radiation exposures and thyroid cancer during these periods of life, the proposed cohort study would have significant scientific value. Also, identifying and controlling for non-radiation risk factors for thyroid cancer will help to distinguish confounding effects from independent effects if and when an investigation is performed of the potential association between radiation exposure and thyroid cancer risk in Fukushima after the accident.

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4B. Long-term health impacts of nuclear accidents

Current knowledge

After both the Chernobyl accident and the Three Mile Island accident, the largest public health impact was impaired mental health (e.g. depression, anxiety, and stress), particularly among parents of young children (Dew and Bromet, 1993; WHO, 2006). Negative impacts of the Fukushima accident on mental health have also been observed, such as traumatic memories of the accident and fear of radiation exposure (Hasegawa et al., 2016; Maeda and Oe, 2017). Such negative impacts on the mental health of the victims can last over the long term. For example, among the Chernobyl clean-up workers from Estonia, psychological distress was clearly detectable 24 years after the accident (Laidra et al., 2015). Also, in a sizeable minority of women who lived in the area around the Three Mile Island power plant, distress levels were consistently high over the 10-year period after the accident (Dew and Bromet, 1993). The impaired mental health as a result of a nuclear accident may not always be clinical, but it could manifest as medically unexplained physical symptoms and perceived poor health.

Experience from industrial accidents has shown that the victims also face other health-related challenges after the accident, including lack of access to medical care, fewer options for a healthy diet, and reduced physical activity or social activity, all of which can affect the risks of acute or chronic diseases (Hasegawa et al., 2016). For example, the data from the FHMS have shown a higher prevalence of risk factors for cardiovascular diseases, such as obesity, hypertension, and diabetes, in evacuees compared with the prevalence of these factors before the accident (Ohira et al., 2018). Also, the aforementioned mental health effects of a nuclear accident might also cause behavioural changes, possibly worsening physical health.

Knowledge gaps

Given the potential long-term direct and indirect health effects of a nuclear accident, it is important to identify risk factors for impaired mental and physical health after a nuclear accident and to develop mechanisms for long-term risk mitigation and care. It is relatively easy to design strategies to limit exposure to radiation; it is more challenging to devise effective strategies to mitigate the human response to evacuation and fear of radiation exposure. To guide the development of strategies, well-designed epidemiological studies are needed on the long-term health of the populations affected by nuclear accidents.

Proposed study

The Cooperation on Chernobyl Health Research (CO-CHER) project, coordinated by IARC, emphasized the necessity of integrating research on mental health and risk communication into well-established cohorts to assess the attributable health effects and assist in defining public health strategies and risk communication policies in the areas affected by the Chernobyl and Fukushima accidents, or any potential future nuclear accidents (IARC, 2016). The authors of the present report share the view of the CO-CHER project about the need to integrate research on mental health and risk communication into epidemiological studies of long-term health effects after nuclear accidents.

In addition to the Chernobyl cohorts, a cohort study may be established using the FHMS platform to assess long-term mental and physical health impacts of a nuclear accident and the subsequent evacuation and resettlement. The Mental Health and Lifestyle Survey includes the Kessler Psychological Distress Scale (K6), a question about resistance to going to school, and a question about perceived health and well-being. If this assessment is repeated over the long term in the same individuals, it may enable an evaluation of individuals' long-term trajectories of these outcomes and an identification of characteristics of susceptible groups.

Furthermore, long-term physical health consequences, such as cancer other than thyroid cancer, cardiovascular disease, and diabetes, should be studied in relation to changes in lifestyle or mental health after nuclear accidents. These health outcomes could be ascertained through a linkage with registries or electronic health records, if available, or could be evaluated based on self-report. Alternatively, an ecological design may be applied to assess the trends of incidence rates of cancers or other diseases in an affected population versus a non-affected population, if a registry of the disease of interest is available.

Potential limitations

Similarly to the potential limitations mentioned in Research Area 4A, loss to follow-up or dropout is likely in a long-term follow-up study and can result in selection bias. For example, if people who had physical or mental illness during the follow-up were more likely to drop out and be lost to follow-up, it may appear from the data that there were no changes in physical or mental health over time, but the apparent absence of changes may be because those who experienced a decline in health dropped out of the study.

An ecological study design can be helpful for identifying an epidemic of a disease or generating a hypothesis, but for elucidating the causes of an epidemic, a prospective cohort study with individual-level information would be needed.

Potential significance

Understanding the long-term health impacts of nuclear accidents is important in order to identify the long-term needs of the populations affected by nuclear accidents and to determine where financial and human resources should be allocated to meet the needs in case of a nuclear accident. Furthermore, if it is possible to identify the populations that are most susceptible to impaired mental or physical health after nuclear accidents, then risk mitigation strategies can be tailored and targeted to those vulnerable populations, for greater efficiency and effectiveness.

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