

THYROID HEALTH MONITORING AFTER NUCLEAR ACCIDENTS

IARC EXPERT GROUP ON THYROID HEALTH MONITORING
AFTER NUCLEAR ACCIDENTS

IARC TECHNICAL
PUBLICATION NO. 46

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

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Distributed by
WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27,
Switzerland
(tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

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Cover image: *Upscale Neighborhood*, Dominic Piperata, Paradigm Arts Group,
www.arts-group.com.

This book is also available in electronic format from
<http://publications.iarc.fr>.

IARC Library Cataloguing in Publication Data

Thyroid health monitoring after nuclear accidents / IARC Expert Group on Thyroid
Health Monitoring after Nuclear Accidents (2018: Lyon, France)

(IARC Technical Publications; 46)

1. Thyroid Neoplasms 2. Early Detection of Cancer 3. Radioactive Hazard Release
4. Radiation Exposure 5. Risk Factors

I. International Agency for Research on Cancer II. Title III. Series

ISBN 978-92-832-2465-5

(NLM Classification: W1)

ISSN 1012-7348

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Acknowledgements

The Expert Group would like to thank Catherine Chassin (IARC Section of Environment and Radiation) for her skilful administrative support, Jennifer Brandt for editing the report, and the production team of Karen Müller and Sylvia Lesage (IARC Communications Group) for checking and formatting the report.

The Expert Group would like to express gratitude to the Ministry of the Environment, Japan, for their financial support of the project and to the Nuclear Safety Research Association of Japan for managing the grant. IARC would like to make it clear that the sponsor had no involvement in developing the recommendations or in the writing of this report.

Disclaimer

The Scientific Secretariat (the Expert Group Chair and the Scientific Coordinator), Experts, Specialists, and Advisers served in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Experts, Specialists, and Advisers participated in the project based on their scientific expertise in the relevant fields. Experts participated in drafting the present report and revising it critically with support from the Scientific Secretariat. Specialists were invited to provide additional input to specific chapters, in collaboration with Experts. Advisers contributed to the discussions but did not have designated writing responsibilities. The present report is based on the contributors' individual evaluations of the scientific evidence and does not necessarily reflect the opinions of their employers. All chapters were reviewed by the entire project team. Only authors have the final responsibility for the contents.

Abbreviations

¹²⁷I	iodine-127
¹³¹I	iodine-131
^{131m}Te	tellurium-131m
¹³²I	iodine-132
¹³²Te	tellurium-132
¹³³I	iodine-133
¹³⁴Cs	caesium-134
¹³⁷Cs	caesium-137
AJCC	American Joint Committee on Cancer
BelAm	USA–Belarus
Bq	becquerel
C cells	parafollicular cells
CT	computed tomography
CTDSG	Chernobyl Thyroid Diseases Study Group
DTC	differentiated thyroid cancer
EAR	excess absolute risk
ERR	excess relative risk
ETE	extrathyroidal extension
FA	follicular adenoma
FAP	familial adenomatous polyposis
FNAC	fine-needle aspiration cytology
FNMTC	familial non-medullary thyroid cancer
FTC	follicular thyroid cancer
Gy	gray
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IGHG	International Late Effects of Childhood Cancer Guideline Harmonization Group
ITB	iodine thyroid blocking
J/kg	joule per kilogram
JABTS	Japan Association of Breast and Thyroid Sonology
JSUM	Japan Society of Ultrasonics in Medicine
KI	potassium iodide
L-T4	levothyroxine
MAPK	mitogen-activated protein kinase
mGy	milligray
MRI	magnetic resonance imaging
mSv	millisievert
μSv	microsievert
MTC	medullary thyroid cancer
mU/L	milliunits per litre

ng/mL	nanograms per millilitre
PA	protective action
PTC	papillary thyroid cancer
PTMC	papillary thyroid microcarcinoma
RAI	radioactive iodine
RCT	randomized controlled trial
RR	relative risk
SI	International System of Units
Sv	sievert
Tg	thyroglobulin
TMI	Three Mile Island
TSH	thyroid-stimulating hormone
TUE	Thyroid Ultrasound Examination
UkrAm	USA–Ukraine
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

CHAPTER 1. Executive Summary

Nuclear power has been a major source of energy supply in many countries. Although nuclear power plants must comply with high safety standards, history shows that severe nuclear accidents can occur under unexpected circumstances. Nuclear accidents may result in a release of various radionuclides into the environment and the contamination of surrounding areas, which can lead to public health problems. An increase in the incidence of thyroid cancer after exposure during childhood and adolescence is a well-documented health consequence of exposure to radioiodine as a result of the Chernobyl nuclear power plant accident.

After the Fukushima Daiichi accident, public health fears and concerns, particularly about thyroid cancer risk, were heightened. In response to those concerns, thyroid examinations of children and adolescents were implemented as part of the Fukushima Health Management Survey. The increasing public awareness about the risk of thyroid cancer as a consequence of radiation exposure, and public fears about thyroid cancer and interest in undergoing a thyroid examination, raise questions about whether and how to conduct thyroid health monitoring after future nuclear accidents. This underscores the need for the development of guidelines on thyroid health monitoring in case of a nuclear accident.

Within this context, one needs to be aware of the apparent rise in thyroid cancer incidence observed in several countries where the practice of conducting thyroid ultrasonography screening of adults has increased. This phenomenon has led to ongoing discussion over the potential issue of overdiagnosis as a result of thyroid screening (i.e. detection of thyroid cancer that would not have been detected without the screening or would not have caused symptoms or death during a person's lifespan), as well as questions about the benefits of early diagnosis of thyroid cancer, which is known to have a very favourable prognosis for the majority of patients irrespective of screening. This needs to be carefully considered when planning for thyroid health monitoring after a nuclear accident.

With this in mind, the International Agency for Research on Cancer (IARC) convened a multidisciplinary, international Expert Group to develop recommendations on long-term strategies for thyroid health monitoring after a nuclear accident based on the current scientific evidence and previous experiences. The recommendations developed by the Expert Group refer to possible future nuclear accidents with exposure of large populations to volatile radioiodine, and to a

great extent are informed by the lessons learned from previous nuclear accidents. Although the report draws on information from past nuclear accidents, the objective of the report is not to evaluate actions taken during past nuclear accidents, or to provide guidance on the continuation of actions and programmes that are in progress. The available evidence was reviewed by subject-specific experts and is presented as a series of chapters as a basis for recommendations by the authors of this Technical Publication.

After reviewing the scientific evidence, the Expert Group made the following two recommendations:

Recommendation 1: The Expert Group recommends against population thyroid screening after a nuclear accident.

The Expert Group defines “population thyroid screening” as actively recruiting all residents of a defined area, irrespective of any individual thyroid dose assessment, to participate in thyroid examinations followed by clinical management according to an established protocol. The Expert Group recommends against population thyroid screening, because the harms outweigh the benefits at the population level.

Recommendation 2: The Expert Group recommends that consideration be given to offering a long term thyroid monitoring programme for higher risk individuals after a nuclear accident.

The Expert Group defines a “thyroid monitoring programme” as including education to improve health literacy, registration of participants, centralized data collection from thyroid examinations, and clinical management. A thyroid monitoring programme is an elective activity offered to higher-risk individuals, defined herein as those exposed in utero or during childhood or adolescence with a thyroid dose of 100–500 mGy or more, who may choose how and whether to undergo thyroid examinations and follow-ups in an effort to benefit from early detection and treatment of less advanced disease. A “thyroid monitoring programme” is distinct from population screening, with the starting point being the individual instead of the population. Within the thyroid monitoring programme, there should be a shared decision-making process between individuals, families, and clinicians about whether and how to engage in thyroid examinations and follow-ups. Under the principle of “people-centred health services”, the potential benefits and harms of examining the thyroid by either palpation or ultrasonography in asymptomatic individuals should be

discussed with the support of well-designed educational materials to optimize informed decision-making consistent with the person's values, preferences, and context.

These recommendations were developed in the context of considerations relevant to exposure to any toxic (including radioactive) substances, and preparedness and response to nuclear accidents, given their implications for decision-making about thyroid health monitoring. They include having in place a health monitoring programme, including cancer registration, as well as a dynamic risk communication programme before a nuclear accident. Also considered was having an active and timely dosimetry monitoring programme and protective actions to minimize radiation exposure, such as an iodine thyroid blocking programme after a nuclear accident.

The Expert Group acknowledges that there may be important considerations in addition to the scientific evidence during such decision-making processes, including socioeconomic implications, health-care resources, and social values, and that the final decisions are made by the government, the relevant authorities, and the society affected by the nuclear accident. These recommendations are intended to serve as a reference primarily for government officials, policy-makers, and health professionals who would be involved in the decision-making, planning, and implementation of thyroid monitoring in case of a nuclear accident.

CHAPTER 2. Introduction

2.1 Rationale

Nuclear power has been a major source of energy supply in many countries. Worldwide, there are more than 400 nuclear power plants in operation. Although nuclear power plants must comply with high safety standards to ensure that the likelihood of accidents is minimal, history shows that severe nuclear accidents can occur under unexpected circumstances. Since the first operation of a nuclear power plant for commercial use, in 1954, accidents involving meltdown have occurred at three nuclear power plants: Three Mile Island, USA (in 1979); Chernobyl, Ukraine (in 1986); and Fukushima Daiichi, Japan (in 2011).

These accidents underscore the importance of adequate preparedness and response for the management of and recovery from the aftermath of these accidents. Since the time of the Chernobyl accident, international guidelines for preparedness and response to nuclear emergencies have evolved and have contributed to the implementation of successful countermeasures against radiation exposure from and adverse health effects of nuclear accidents. However, new challenges emerge as technology, knowledge, and views change; therefore, guidelines for nuclear accident preparedness and response are continuously changing and being updated.

Nuclear accidents may result in a release of radionuclides into the environment and contamination of surrounding areas, including leafy vegetables, air, open water sources, and soil. These radionuclides can be inhaled by humans, penetrate into a human body, or be ingested via contaminated foodstuffs, including milk and water. It has long been scientifically established that exposure to ionizing radiation can cause adverse health effects. Epidemiological studies, for example, have shown that increased exposure to ionizing radiation is associated with increased risk of various diseases, including cancer. An increase in the incidence of thyroid cancer among residents who were exposed to ionizing radiation during childhood or adolescence is a well-documented health consequence of the Chernobyl accident.

Given the established association of thyroid cancer risk with radiation exposure, particularly during childhood and adolescence, public fears about thyroid cancer and a high interest in examination of the thyroid are likely after any future nuclear accident. Therefore, appropriate preparedness and response regarding thyroid cancer-related issues are crucial. After the Fukushima Daiichi accident and the Chernobyl accident, thyroid examinations of the affected children and adolescents were performed. The

extensive efforts that were made after the respective accidents yielded knowledge and lessons learned, which are invaluable in guiding preparations for any future nuclear accidents.

Although it is the goal of every country to maintain safe nuclear facilities, the accidents at Three Mile Island, Chernobyl, and Fukushima are reminders of the real possibility of an accident and the importance of establishing guidelines for how to plan and implement thyroid health monitoring after nuclear accidents. There is continuing discussion about the potential issue of overdiagnosis (i.e. detection of thyroid cancer that would have remained asymptomatic and been undetected during a person's lifespan) as a result of thyroid screening, as well as questions about the benefit of an early diagnosis of thyroid cancer, which is known to have a very favourable prognosis for the majority of patients. With this in mind, IARC convened a multidisciplinary, international Expert Group to develop recommendations on long-term strategies for thyroid health monitoring after nuclear accidents based on the current scientific evidence and previous experiences.

2.2 Aims and scope

This report addresses a specific aspect of emergency preparedness for and response to the release of volatile radionuclides, in particular radioiodine, from a nuclear facility into the environment, resulting in the exposure of the population living in the vicinity of the facility. To date, all instances where this has occurred and has involved a large population were caused by nuclear power plant accidents, hereafter referred to as “nuclear accidents”.

2.2.1 Aims

The multidisciplinary, international Expert Group aimed to: (i) develop recommendations on long-term strategies for thyroid health monitoring after a nuclear accident based on experiences from past nuclear accidents, as well as current scientific knowledge on cancer screening in general and thyroid cancer in particular, and on the incidence, pathology, treatment, and outcome of thyroid cancer in general and in the context of radiation exposure; and (ii) identify knowledge gaps that need to be addressed to better guide the planning and implementation of thyroid health monitoring after nuclear accidents.

2.2.2 Scope

The forward-looking recommendations of the Expert Group are intended to specifically address whether thyroid health monitoring should be implemented in a resident population in the vicinity of a nuclear accident and, if so, how such thyroid health monitoring should be prepared for and implemented. Thyroid health monitoring for emergency workers is not addressed in this report.

These recommendations have been developed for countries that produce nuclear power or their neighbouring countries, with the intention to serve as a reference primarily for the government officials, policy-makers, and health professionals who would be involved in the decision-making, planning, or implementation of thyroid health monitoring. The Expert Group acknowledges that decision-making may also require considerations other than the scientific evidence. Therefore, the Expert Group's recommendations should be used as a reference; the final decision should be made by the government, the relevant authorities, and the society affected by the nuclear accident.

The Expert Group's recommendations should not be confused with the recommendations developed by the different international bodies for emergency preparedness or for radiation protection after nuclear accidents. For the overall guidelines on emergency preparedness and response in the case of radiological and nuclear accidents, readers are referred to the international safety standards published by the International Atomic Energy Agency (IAEA, 2006, 2014a, 2015a), the World Health Organization (WHO, 2017a), the International Commission on Radiological Protection (ICRP, 2009), and other international organizations.

Lastly, the Expert Group would like to stress that this report is not an evaluation of the thyroid health monitoring activities that were implemented after the past nuclear accidents, and does not include any recommendations related to thyroid health monitoring activities currently in progress, in particular the Fukushima Health Management Survey.

This report contains the Expert Group's recommendations and considerations related to thyroid health monitoring in the context of preparedness for and response to nuclear accidents (Chapter 3), summaries and syntheses of the scientific evidence base used by the Expert Group when developing the recommendations (Chapter 4), and the identified gaps in scientific knowledge (Chapter 5).

2.3 Approach

The multidisciplinary, international Expert Group was convened by IARC to develop the recommendations according to the objectives outlined in Chapter 2.2. The Expert Group consisted of 14 experts from a variety of scientific and medical disciplines, including cancer screening, radiation epidemiology, radiation dosimetry, pathology, endocrinology, nuclear medicine, and surgery, and was supported by three Specialists, four Advisers, and an IARC Scientific Secretariat (the Expert Group Chair and the Scientific Coordinator). The available evidence was reviewed by subject-specific experts and is presented as a series of chapters as a basis for recommendations by the authors of this Technical Publication. Specialists were invited to provide additional input to specific chapters, in collaboration with chapter authors. Advisers contributed to the discussions but did not have designated writing responsibilities.

For the preparation of this report, three in-person meetings were held at IARC in Lyon, France. The first Expert Group meeting was held on 23–25 October 2017 to discuss the current scientific evidence, as well as lessons learned from past nuclear accidents. Afterwards, the members of the Expert Group generated drafts for the Scientific Evidence chapter. On 25–26 January 2018, a meeting with a subgroup of the Expert Group was held to synthesize the evidence and prepare the first draft of the recommendations. The first drafts of the Introduction, Scientific Evidence, and Recommendations chapters were then shared with and reviewed by the whole Expert Group. On 21–23 February 2018, the second Expert Group meeting was held to discuss the details of the report and modify it further. After this meeting, the draft was further revised based on the decisions made. The present report was reviewed and approved by the authors of the Expert Group in August 2018.

Randomized controlled trials (RCTs) are often used as the strongest evidence when developing evidence-based public health guidelines. However, because RCTs are unlikely to be applicable to an evaluation of emergency preparedness for or response to environmental hazards, such as radiation exposure due to nuclear accidents, this report was generated based on the Expert Group's collective assessment and interpretation of the evidence from observational studies.

CHAPTER 3. Recommendations on thyroid health monitoring in case of nuclear accidents

Emergency preparedness and response regarding thyroid-related issues are critical in mitigating adverse health effects that can occur as a result of both a nuclear accident and measures that might be put in place afterwards intended to promote the well-being of the population. The guiding principle for any health intervention should be to maximize benefit and minimize harm, and this approach should also be considered with respect to thyroid health monitoring.

With this in mind, the Expert Group developed the following forward-looking recommendations on thyroid health monitoring after nuclear accidents. The recommendations are based on experiences from past nuclear accidents, as well as the state of scientific knowledge on cancer screening in general and thyroid cancer in particular. Published data, and expert opinion when data were not available, on the incidence, pathology, screening, treatment, and outcome of thyroid cancer in general and in the context of radiation exposure, were summarized and used in the creation of the recommendations.

Although these recommendations are intended to specifically address whether and how thyroid health monitoring should be conducted in case of a nuclear accident, the Expert Group recognizes the great importance of considering additional areas of preparedness and response to optimize the decision-making process, planning, or implementation of thyroid health monitoring.

The Expert Group also recognizes that decisions about thyroid health monitoring after a nuclear accident may take into account aspects beyond the scientific evidence, including socioeconomic and health-care resources, as well as social values unique to each potential situation and local population. Therefore, the recommendations of the Expert Group should be used as a reference and the final decisions should be made by the respective government(s), the relevant authorities, and the society affected by the nuclear accident within this greater context.

Recommendations

Recommendation 1: The Expert Group recommends against population thyroid screening after a nuclear accident.

Recommendation 2: The Expert Group recommends that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals after a nuclear accident.

Explanation and elaboration

1. Population thyroid screening

The Expert Group defines “population thyroid screening” as actively recruiting all residents of a defined area to participate in thyroid examinations through either ultrasonography or palpation and subsequent diagnostic or follow-up tests as indicated. This includes population thyroid screening for children and adolescents. A key aspect of this definition is that the starting point for the screening is at the population level; namely, recruiting all eligible subjects in a defined population irrespective of any thyroid radiation dose assessment.

The Expert Group recommends against population thyroid screening, because the harms outweigh the benefits at the population level. There is evidence from observational studies in adults that thyroid screening leads to overdiagnosis with no mortality reduction. Data on thyroid cancer biology suggest that this may also be true for children and adolescents. Radiation-induced thyroid cancer, as suggested by data from the Chernobyl accident, appears to have a similar favourable prognosis as sporadic thyroid cancer. Therefore, screening populations of children and adolescents regardless of risk levels (i.e. thyroid radiation dose) is expected to also result in issues related to overdiagnosis without clear public health benefits.

For further details, please refer to Chapter 4.1, Chapter 4.2.2, Chapter 4.3.1–4.3.4, and Chapter 4.4.1.

2. Thyroid monitoring for higher-risk individuals

The Expert Group defines a “thyroid monitoring programme” as including education to improve health literacy, registration of participants, and centralized data collection from thyroid examinations and clinical management. Thyroid monitoring is an elective activity offered to higher-risk individuals, who may choose how and whether to undergo thyroid examinations in an effort to benefit from early detection and treatment of less advanced disease. A thyroid monitoring programme is distinct

from population screening, with the starting point being the individual instead of the population.

The Expert Group defines “higher-risk individuals” as those exposed in utero or during childhood or adolescence with a thyroid dose of 100–500 mGy or more. Evidence suggests a dose–response relationship with increasing thyroid cancer risk with increasing thyroid dose. In an effort to balance the potential harms of excessive thyroid monitoring with identification of the highest-risk cases, the Expert Group proposes a thyroid dose of 100–500 mGy for a practical definition of an actionable level to offer inclusion into the long-term thyroid monitoring programme. Ideally, the thyroid doses should be determined by measurements of thyroid radioiodine content. For individuals with no direct measurements, dose estimations from modelling exposure and contributing factors, such as iodine status or incorporation of iodine thyroid blocking (ITB), should be applied rather than assuming exposure simply due to geographical area of residence.

The recommendation of the Expert Group of establishing a thyroid dose actionable level does not mean that nothing should be offered to an individual below this exposure level. If an individual with lower dose is willing to have or interested in having a thyroid examination, after receiving a detailed explanation of potential benefits and harms, then they should be offered a thyroid examination in the framework of the long-term thyroid monitoring programme.

Within the thyroid monitoring programme, there should be a shared decision-making process between individuals, families, and clinicians about whether and how to engage in thyroid examinations. Under the principle of “people-centred health services”, the potential benefits and harms of examining the thyroid by either palpation or ultrasonography in asymptomatic individuals should be discussed with the support of well-designed educational materials to optimize informed decision-making consistent with the person’s values, preferences, and context.

Well-informed individuals who elect to participate in monitoring should receive high-quality services from qualified medical professionals in an organized monitoring programme, with governmental authority oversight, quality assurance, and a financing strategy.

For those who decide to undergo thyroid examination, care should be taken to communicate findings without causing undue anxiety: communication should be timely and should avoid creating labels for findings with no clinical significance, such as findings of normal anatomical variations. To minimize potential harms of thyroid

examinations, management strategies of abnormal findings from examining the thyroid (i.e. a thyroid nodule) should not differ from those that would be applied to non-radiation-exposed persons in accordance with published guidelines.

There is evidence that thyroid cancer risk from radiation exposure during childhood or adolescence continues into adult life. The Expert Group proposes that thyroid monitoring of the identified higher-risk individuals should be initiated as soon as is practically feasible and should extend through adulthood. Intervals between individual thyroid examinations may range between 2 years and 5 years and can be adjusted based on clinical findings and screening modalities. Benefits and harms of thyroid examinations should be balanced against the presence of comorbidities, and a decision to stop should be an informed individual choice.

For further details, please refer to Chapter 4.3.1, Chapter 4.3.2, Chapter 4.3.4, Chapter 4.5.4, Chapter 4.6.5, and Chapter 4.6.6.

Remarks

The practical definition of an actionable level defined above for offering the long-term thyroid monitoring programme should not be confused with radiation protection limits from international bodies such as the International Commission on Radiation Protection. In fact, the recommended thyroid dose of 100–500 mGy as an actionable level is higher than those proposed for implementation of protective actions to minimize the risks of radiation exposure. Furthermore, the Expert Group wishes to clarify that the choice of a thyroid dose range reflects the option to be more inclusive (lower actionable levels) or to be more efficient (higher actionable levels) in monitoring and identifying radiation-associated thyroid disease in higher-risk individuals. The Expert Group acknowledges that further research is necessary and the optimal actionable level might need to be revised as new evidence emerges.

Considerations

General consideration

Monitoring infrastructure to assess the likely health consequences of release of any toxic (including radioactive) substances

According to good practice of public health monitoring of the general population, infrastructure needs to be in place to monitor the incidence of disease and the well-being of the resident population when there is a potential risk of exposure to a toxic substance from any industrial activity, including radiation. Therefore, the Expert

Group strongly supports the creation of, and continued investment in, accurate national health registries, including cancer registries. Such registration systems allow for characterization of geographical variation and trends in disease incidence and prevalence in the event of an accident with the release of toxic substances. Within the context of thyroid cancer and a nuclear accident, without accurate, baseline (pre-event) population data, there is a limited ability to identify and quantify a potential link between radiation exposure and a change in the incidence or prevalence of a disease. Mechanisms need to be in place to serially monitor both the physical and the mental health of the residents and the evacuated population in case of a nuclear accident. This includes specifically:

- an accurate and regularly updated census of the population, to enable timely identification of the potentially affected population;
- information on the general health of the resident population, for example through periodic evaluation of health indicators or systematic linkage of health records with the population registry (World Health Organization [WHO] guidance on civil registration and vital statistics; http://www.who.int/healthinfo/civil_registration/en/); and
- knowledge of baseline cancer rates, ideally from a population-based cancer registry, in line with the quality indicators of the IARC Global Initiative for Cancer Registry Development (GICR; <http://gicr.iarc.fr/>).

Considerations specific to release of radioactive substances, and radioiodine in particular

Dosimetric monitoring in case of a radiological or nuclear accident involving release of radioiodine

Accidents at nuclear facilities release several different radionuclides, but of major significance to the future health of the general population is radioiodine and the resultant radiation exposure to the thyroid gland.

The health consequences to the thyroid from a nuclear accident are dependent on the thyroid dose that the individuals have been exposed to, particularly from radioiodine. Initially, to assess the probable severity of the consequences in any affected population of a given geographical location, information is needed on the magnitude and timing of the release from the nuclear facility as well as meteorological attributes that predict wind transport of radioactive materials. Furthermore, certain measures and expertise that allow for an accurate and timely

assessment of individual doses of radioactive iodine to the thyroid gland are required in order to better understand the potential thyroid cancer risk and to identify higher-risk individuals.

Trained professional staff should be available to measure and to assess the thyroid radioiodine content (i.e. thyroidal ^{131}I content) of individuals as soon as possible, preferably within 4 weeks, but within 6 weeks after the nuclear accident at the latest (if the equipment's minimum detectable activity of ^{131}I in the thyroid is smaller than 500 Bq, the assessment may be conducted later than 6 weeks after the accident). This should be carried out on a sufficiently large representative sample of the affected population to give a useful overview of exposures for a better understanding of the dominant pathways of exposure. Direct measurements of thyroid radioiodine content of the exposed population are essential, with priority given to children and adolescents (younger than 19 years) and women pregnant at the time of exposure. When it is not possible to measure the thyroid radioiodine content of the infants, measurements of breast milk should be obtained from women who are breastfeeding. If resources are available, thyroid measurements in adults exposed to higher doses of radioiodine are also very informative, because they enable the determination of additional factors to those observed in children that may be important in estimating dose, including the dominant pathway of exposure.

Adequate radiation measurement devices and guidelines and training for their use, along with basic questionnaires on diet and behaviour, should be available. The questionnaire should be completed by at least those individuals who undergo measurements of thyroid radioiodine content.

For further details, please refer to Chapter 4.5.3 and Annexes 1 and 2.

Oral administration of potassium iodide (thyroid blocking) given to minimize uptake of radioiodine by the thyroid

WHO guidelines on ITB in case of a nuclear emergency provide recommendations on administration of potassium iodide (KI) (WHO, 2017a). The planning basis for this protective action is provided in the International Atomic Energy Agency safety standards (GSR Part 7; IAEA, 2015a) with regard to the avertable thyroid dose at which KI administration should be considered. It should be noted that in case of emergency, KI should be administered before or shortly after the beginning of exposure to radioactive iodine, with the priority given to children, pregnant women, and breastfeeding women. A properly implemented ITB

programme, coupled with other interventions such as sheltering, evacuation, and monitoring of food and drinking-water, will effectively reduce uptake of radioactive iodine in the affected population, especially children.

For further details, please refer to Chapter 4.5.2.

Education/risk communication to the population living in the vicinity of a nuclear power plant

Ongoing education of health professionals and the general public living and/or working in the vicinity of a nuclear plant, with respect to exposure and radiation health effects, in times when there is no immediate risk, is essential to ensure timely implementation of urgent protective actions in case of a nuclear accident, and to prevent unjustified and possibly harmful interventions. Early and ongoing stakeholder dialogue, including risk communication, is important, as evidenced by other public health emergencies, such as infectious disease outbreaks. Risk communication is an integral part of any public health emergency response and will engender trust between community groups. It should be ensured that the local population, including relevant professionals, is aware of what actions to take in the event of a release of radiation from a nuclear power plant. This includes specifically:

- sheltering and evacuation plans;
- withdrawal of contaminated food, milk, and water;
- ITB instructions, including distribution locations for KI, dosage, and timing of administration;
- measurement of the thyroidal ^{131}I content;
- what thyroid monitoring might entail, basic information about the evaluation and diagnosis of thyroid nodules and thyroid cancer, as well as baseline prevalence for the population;
- having established reliable and known communication channels for the public (e.g. newspaper, radio, television, website, text, email, and new media), as well as call centres for access to risk communication experts available to manage information sharing; and
- having established on the government level (e.g. federal or regional government) a coordination centre supervising the long-term monitoring of the health status of the population exposed to radiation as a result of a nuclear accident, as endorsed in the above-mentioned considerations, with the key functions of ensuring high-quality data collection on radiation (space and

time), health in the population, and the implementation of countermeasures to mitigate any risk, as well as preparation of periodic press releases.

For further details, please refer to Chapter 4.3.1, Chapter 4.3.4, Chapter 4.5.2, Chapter 4.5.3, and Chapter 4.6.6.

CHAPTER 4. Scientific evidence

4.1 Pathology, natural history, and risk factors for thyroid cancer

The thyroid gland is an endocrine gland that is situated in the base of the neck and produces hormones that regulate the body's metabolism. The thyroid is composed of two epithelial cell types: follicular cells and parafollicular cells (C cells). Structurally, the gland is composed of spherical follicles, which consist of a single layer of follicular cells and a lumen filled with colloid. The colloid contains a large-molecular-weight protein, called thyroglobulin, within which the iodine-containing thyroid hormones triiodothyronine and thyroxine are stored until they are released into the circulation. The C cells, which are located in the centre of the thyroid gland and behind the follicular cells lining the lumen of the follicle, are responsible for secretion of calcitonin and are involved in the regulation of bone metabolism.

The stable (non-radioactive) form of iodine (^{127}I) is present at low levels in the natural environment and is ingested in food and passes into the bloodstream. To ensure that there is always sufficient iodine for thyroid hormone production, the thyroid operates a mechanism that both concentrates iodine from the circulation and binds it within the follicular lumen. There is a natural flow of iodine in and out of the gland, and this gives rise to a biological half-life for iodine (the time taken for half of the atoms of iodine entering the follicular cell to pass back out) of 60–80 days.

The thyroid follicular cells give rise to two distinct morphological types of differentiated cancer – papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC); PTC is the more common of the two. The two morphological types show differences in both molecular biology and clinical characteristics, although both produce thyroglobulin (Xing, 2013). The C cells give rise to medullary thyroid cancer (MTC), which is identified by its production of calcitonin; this distinguishes MTC from the tumours derived from the follicular cells (PTC and FTC). PTC, FTC, and MTC can give rise to a more poorly differentiated version of thyroid cancer, and the cancers of follicular origin (PTC and FTC) may dedifferentiate to the highly aggressive anaplastic thyroid carcinoma.

FTCs occur less frequently than PTCs and do not show the classic nuclear features associated with PTCs. They can, however, show a variety of morphologies, such as macrofollicular or microfollicular structures within the tumour. FTCs more commonly invade and metastasize via the venous system, whereas PTCs tend to invade and metastasize through the lymph vessels. In contrast to PTCs, FTCs are

thought to arise in pre-existing benign lesions called follicular adenomas. However, because the purpose of this volume is to discuss the monitoring of the at-risk population after a nuclear accident, the focus here is only on cancers of the thyroid follicular cells, and primarily on PTCs.

PTC can also exhibit a variety of morphologies, including papillae that are formed by epithelial cells lining a fibroblastic core (the classic papillary subtype) and follicular structures that are similar to those of the normal thyroid but may be larger (macro) or smaller (micro) than the normal follicles (the follicular variant of PTC). PTCs composed of solid sheets of cells (solid variant PTC) are more common in children younger than 10 years at diagnosis and with a history of radiation exposure. Diffuse sclerosing variant PTC is also more common in children and young adults (younger than 30 years), with tumours characterized by prominent lymphocytic infiltration, stromal fibrosis, abundant psammoma bodies (dystrophic calcification), squamous metaplasia, and diffuse involvement of the thyroid without distinct formation of a nodule. However, although the architecture is variable, and sometimes more than one variant is present in a single cancer, PTCs all show altered morphology of the nucleus of the cell. This is the feature that distinguishes them from follicular cancers. The nucleus may be fissured into a coffee-bean shape, with hypodense chromatin that results in a ground glass appearance. The nuclei are often irregular and often contain inclusions of cytoplasm. The presence of these nuclear changes is diagnostic of PTC, but not all of the cells that compose the cancer may show these changes. Psammoma bodies are also a finding in PTC with high specificity. There is no benign precursor to PTC, so even very small tumours that occupy the equivalent of one or two normal follicles are regarded as cancers. In adults, PTC less than 1 cm in diameter is termed papillary thyroid microcarcinoma (PTMC); in children, there is no such distinction.

Both PTCs and follicular carcinomas are associated with activating mutations in the mitogen-activated protein kinase (MAPK) pathway that lead to the dysregulated growth associated with cancer. PTCs are commonly associated with point mutations of the *BRAF* oncogene in adult patients, whereas in childhood PTCs, rearrangements of the *RET* oncogenes are more common (Vaisman et al., 2011a). The *RET* oncogene is normally silent in follicular cells; rearrangement of part of the gene to a promoter region of other genes that are active in the follicular cell leads to constitutive activation of the MAPK pathway via *RET* gene signalling. Follicular cancers are associated with point mutations in other genes in the MAPK pathway

(e.g. *RAS*) or with rearrangements of *PPARg*. A recent comprehensive study on primarily adult-onset PTC confirmed the association between molecular biology and subtype of PTC, as well as the higher frequency of fusion events found in PTCs in younger patients, although only 44 patients younger than 30 years at diagnosis were studied, and no patients younger than 19 years were included (Agrawal et al., 2014). That study also showed that PTCs in older adults tend to have more genetic alterations than PTCs in younger patients. This might indicate a slow accumulation of genetic errors over time in a slowly growing tumour. The greater genetic heterogeneity seen in PTCs in older patients may contribute to a tendency for more widespread metastases and the ability for a tumour to grow in a variety of metastatic sites, as well as a loss of the key marker of a differentiated thyroid cell – the ability to take up iodine. The ability of the tumour to absorb iodine (to maintain differentiation) explains why PTCs in younger patients can only be considered as either stage 1 or stage 2, as determined by the American Joint Committee on Cancer staging system, because even patients with extensive lung metastases show low disease-specific mortality compared with older patients with a similar extent of disease. The increase in the genetic heterogeneity of PTCs in older patients might be regarded as support for the early-onset, multistep carcinogenesis theory of thyroid carcinogenesis (suggested by Williams, 2015), rather than being the result of a late-onset, multistep process or of the presence of retained fetal stem cells in the thyroid (reviewed in Takano, 2017). The cribriform-morular variant of PTC associated with familial adenomatous polyposis (FAP) is often multicentric and with lymph node involvement, but is usually clinically indolent and has also been shown to spontaneously regress, which suggests that some PTCs do have a limited growth potential. This also lends weight to the argument that multiple genetic alterations contribute to the clinical phenotype of PTC.

Several risk factors are associated with developing thyroid cancer, including environmental factors, a history of radiation exposure, and familial tumour predisposition syndromes. In geographical areas where the population has a low dietary intake of stable iodine, there is a higher incidence of goitre and follicular cancer, which is believed to be related to chronic stimulation of thyroid-stimulating hormone. However, in children, exposure to radiation, including radioiodine, is probably the major risk factor for an increase in the incidence of tumours of the thyroid follicular cells, particularly PTC. Age at exposure has an effect on radiation dose, because of the relatively small size of a child's thyroid. Iodine deficiency also

has an effect on radiation dose, because an unsaturated thyroid will take up more radioactive iodine and therefore the dose is increased (Iglesias et al., 2017). In the immediate aftermath of the Chernobyl accident, there was concern that radiation-induced thyroid cancer in exposed children tended to be more aggressive, with more extensive local invasion, lymph node involvement, and distant metastases than in non-exposed children. However, subsequent analysis suggests that this observation was related to several variables, including the increased number of children younger than 10 years at the time of exposure, chronic exposure to radioiodine in an iodine-deficient population, and the initial lack of an active surveillance programme for patients at increased risk of developing thyroid cancer. When the clinical presentation of exposed and non-exposed children of the same age was compared, the suspected difference in clinical aggressiveness could not be proven (Pacini et al., 1997; Williams et al., 2004; Reiners et al., 2013).

There are several hereditary conditions that are associated with increased risk of thyroid cancer of different cellular origins. A germline activating mutation in the *RET* oncogene is associated with an increased risk of developing MTC, which in paediatric patients is most commonly associated with multiple endocrine neoplasia type 2. There are also inherited medical conditions that are associated with an increased risk of tumours of the follicular cells. These include *PTEN* hamartoma tumour syndrome (Cowden's disease), which is caused by germline mutations in the *PTEN* gene; *DICER1* pleuropulmonary blastoma syndrome; Carney complex type 1, which is caused by germline mutations in the *PRKAR1A* gene; and FAP. FAP is primarily associated with tumours in the colon and is caused by a loss of one copy of the *APC* gene on chromosome 5. A rare variant of PTC, the cribriform-morular variant, is identified almost exclusively in some, but not all, females with FAP (Cetta, 2015). There are also documented families that have an increased incidence of tumours of the follicular cells of the thyroid (familial FTC or PTC) but do not harbour any of the germline mutations listed above. It is thought that the genes responsible may lie on chromosomes 1 and 19, but the individual genes have not yet been identified. The risk of familial FTC and PTC increases with having two or more first-degree relatives with thyroid cancer in families without a known inherited familial tumour predisposition syndrome.

4.2 Epidemiology of thyroid cancer

4.2.1 Incidence and mortality rates of thyroid cancer

Current incidence and mortality rates around the world

Thyroid cancer incidence varies dramatically by country and level of social and economic development (Fig. 1 and Fig. 2), with elevated incidence rates observed in countries with a higher Human Development Index. Age-standardized incidence rates of thyroid cancer vary more than 50-fold, from a high of 53 per 100 000 in the Republic of Korea to less than 1 per 100 000 in Malawi and other countries (Ferlay et al., 2013). Thyroid cancer is less commonly diagnosed in children and adolescents compared with adults. The most common type of thyroid cancer is PTC, followed by FTC. For example, in the USA, the proportions of PTC and FTC are 84% and 11%, respectively (Lim et al., 2017). The majority of thyroid cancer cases are either localized within the thyroid or have regional lymph node disease at the time of diagnosis (Howlader et al., 2017).

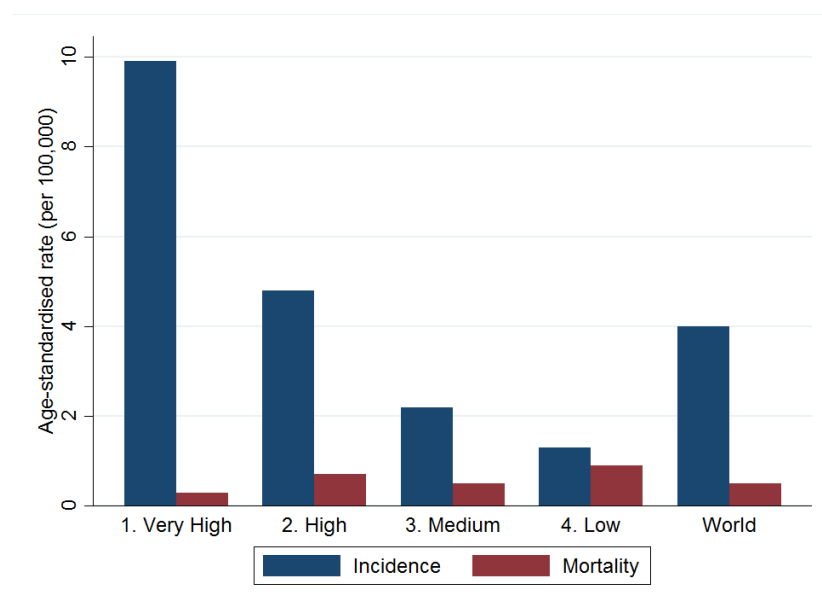


Fig. 1. Age-standardized incidence and mortality rates of thyroid cancer in 2012 by Human Development Index (extracted from Ferlay et al., 2013). Human Development Index is a composite index measuring average achievement in three basic dimensions of human development: life expectancy, education, and per capita income (http://hdr.undp.org/sites/default/files/hdr2016_technical_notes.pdf).

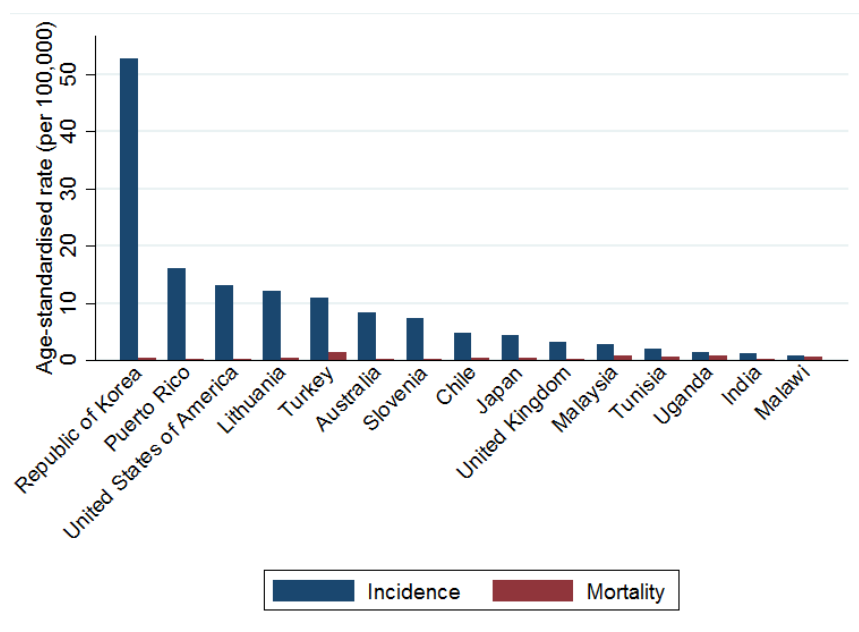


Fig. 2. Age-standardized incidence and mortality rates of thyroid cancer in 2012 by country (extracted from Ferlay et al., 2013). Countries were selected to illustrate the variation in the thyroid cancer incidence rate across countries.

Mortality rates are almost always low, about 1 per 100 000 or less (Fig. 1 and Fig. 2). Notably, even among countries with a higher incidence rate than 10 per 100 000, the mortality rates are mostly less than 1 per 100 000 (Ferlay et al., 2013). Although thyroid cancer mortality appears to be somewhat higher in countries with a lower Human Development Index, the socioeconomic gradient is not monotonic. Overall, the thyroid cancer survival rate is excellent. For example, in adult patients younger than 55 years, the expected 10-year disease-specific survival is 98–100% for localized or regional disease and 85–95% for distant metastases (Perrier et al., 2018). PTC, the type which is of concern after exposure to radiation, has a particularly high survival rate; 97–99% of patients with PTC limited to the thyroid gland are alive 20 years after diagnosis (Davies and Welch, 2010; see Chapter 4.4.2).

Relative to other cancers such as those of the breast, prostate, colon, and lung, deaths due to thyroid cancer are rare. Because of the small numbers, the estimated mortality rates can become unstable and highly variable across countries and over time. Furthermore, the quality of registries, including cancer registries and cause-of-death registries, can also influence the estimates and contribute to the variations. Together, these facts underscore the need to maintain high-quality, ideally population-based, cancer registries, from which changes in incidence or mortality over time can be understood in the local context.

As described in Chapter 4.1, the main established environmental risk factor for thyroid cancer is exposure to radiation, especially during childhood and adolescence. The increased risk of thyroid cancer has been shown to persist for at least five decades after exposure during childhood in the follow-up of Japanese atomic bomb survivors (Furukawa et al., 2013). Although other proposed risk factors for thyroid cancer exist, such as exposure to volcanic metals, intake of nitrites, and obesity, the evidence is currently limited. The major source of the variation in incidence observed by country appears to be the result of access to health-care services, imaging, testing and surgical practices of the local health-care providers, and management of pathological specimens (Davies et al., 2015). Specifically, the more closely the thyroid gland is examined, the more thyroid cancers are found. The variations in thyroid cancer incidence observed across countries that are expected to have similar environments (e.g. lifestyle, radiation exposure) are therefore likely to be a result of the differences in the medical practices, particularly thyroid gland examination. This has been exemplified in countries where thyroid ultrasound examinations have become more common, such as the Republic of Korea (see Chapter 4.3.2).

Recent trends in incidence and mortality

During the past two or three decades, the incidence of thyroid cancer among adults has doubled, tripled, or more in several high-income countries worldwide (La Vecchia et al., 2015), and this is without proportionate increases in mortality (Davies and Welch, 2014; Davies et al., 2017; Lim et al., 2017). In middle-income countries, dramatic increases in incidence have also been seen in some areas, for example Brazil, China, and Turkey, as shown by the newly released *Cancer incidence in five continents, Volume XI* (Bray et al., 2017). Studies from a few of the countries with detailed registries show that almost the entire increase in the incidence has been due to the detection of PTC, the most common subtype. The size of the cancers now being detected is also notable: the majority of the increased incidence has come from the detection of PTCs ≤ 2 cm in diameter (Ahn et al., 2014; Davies and Welch, 2014). Given that cancers of this size are usually difficult to detect through physical examination (palpation), the increased incidence of these small cancers is most likely to be because of the increased use of sensitive imaging technologies, such as ultrasonography and computed tomography (CT) scans, which is driven by the practice patterns of health-care providers (Davies et al., 2010; Brito et al., 2015).

Analyses performed specifically for this report showed that the incidence among children and adolescents (aged 0–19 years) in Denmark, France, Italy, the United Kingdom, and the USA increased from 1990 to 2005 in patterns that are similar to the time trends observed in adults (Fig. 3). During the same period, a total of 10 deaths due to thyroid cancer were captured in the registries maintained by these countries. Because deaths due to thyroid cancer in children and adolescents are very rare, trends in mortality in these specific age groups are difficult to estimate.

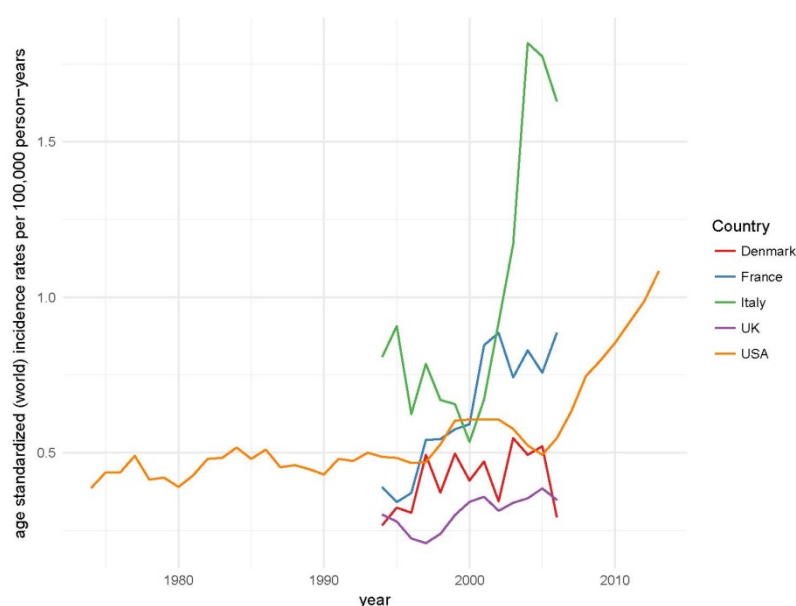


Fig. 3. Age-standardized incidence rates (per 100 000) of thyroid cancer for five selected countries, for individuals aged 0–19 years (extracted from *Cancer incidence in five continents, Volume XI*; Bray et al., 2017).

4.2.2 Overdiagnosis and thyroid cancer

Overdiagnosis is the identification of a (histologically confirmed) cancer as a result of testing that would not have been diagnosed if the testing had not taken place or would not have caused symptoms or death during the patient's lifetime. The concept of overdiagnosis is important because it affects the utility of screening programmes (see Chapter 4.3.1). If a cancer is of the type in which overdiagnosis can occur, then not only significant cancers but also indolent cancers will be found as a result of a screening programme. Although screening programmes are usually thought of as beneficial because early detection of a cancer can lead to reduced mortality, people who have an indolent cancer identified in such a screening programme would undergo treatment without clinical benefit. It is not possible in a population screened for thyroid cancer to identify with certainty which cancers are

indolent and which cancers are clinically significant, and as a result if a screening programme was implemented (including after a nuclear accident), all cancers would need to be addressed as potentially significant.

Evidence for thyroid cancer overdiagnosis

The pattern described in Chapter 4.2.1 of the dramatically increasing incidence of thyroid cancer around the world, particularly of small cancers, with largely stable mortality rates, suggests that the main cause is overdiagnosis (Davies and Welch, 2006). For overdiagnosis to occur, three factors must be present: (i) a reservoir of subclinical disease that is detectable by the screening test, (ii) a mechanism by which the tumours can be identified, and (iii) health-care activities that lead to the detection (Welch and Black, 2010). The necessary components for overdiagnosis of thyroid cancer are all present, as explained below.

Thyroid cancer is a disease that is known to have a subclinical reservoir. Differentiated thyroid cancer (DTC) is commonly found at autopsy in people who died of other causes. Depending on the method of examination of the thyroid, about 4% (partial examination) to 11% (whole examination) of thyroid glands can be shown to contain DTC, and this rate has been stable over time (Furuya-Kanamori et al., 2016).

Thyroid cancer also has a mechanism by which tumours can be found. Asymptomatic thyroid nodules are very common and are easily seen on medical imaging studies: up to 16% of CT scans and magnetic resonance imaging (MRI) scans that include the thyroid gland show nodules (Yoon et al., 2008), and with ultrasonography about two thirds of people will be found to have at least one nodule (Ezzat et al., 1994). Although radiation is known to cause thyroid cancer, along with several other candidate risk factors (see Chapter 4.2.1), the remarkable recent upward trend in incidence, particularly of small cancers, has been ascribed to identification of these asymptomatic nodules.

Access to health-care services, the last component needed for overdiagnosis to occur in thyroid cancer, shows strong associations with rates of incidence (Ahn et al., 2014; Davies et al., 2015; Davies, 2016; Vaccarella et al., 2016; Brito and Hay, 2017). The larger the numbers of imaging tests ordered and the more health-care providers intervene for increasingly smaller findings, the more thyroid cancers are uncovered (Smith-Bindman et al., 2012; Udelsman and Zhang, 2014; Zevallos et al., 2015).

Magnitude of thyroid cancer overdiagnosis

A method to obtain estimates of the magnitude of thyroid cancer overdiagnosis has been described (Vaccarella et al., 2016). Briefly, the magnitude of overdiagnosis can be estimated by comparing the observed incidence rate with the expected incidence rate (i.e. the rate expected in the absence of advances in diagnostic technology). In the study by Vaccarella et al. (2016), the expected rate was estimated using historical incidence data from Nordic countries, combined with the assumptions of the multistage model of carcinogenicity of Armitage and Doll (Doll, 1971) (Fig. 4).

The same study concluded that a large fraction of thyroid cancer diagnoses in developed countries is likely to be due to overdiagnosis (Vaccarella et al., 2016). In women, this fraction could be as high as 70–80% in Australia, France, Italy, and the USA and 90% in the Republic of Korea, whereas in men the estimated fraction is about 70% in France, Italy, and the Republic of Korea and 45% in Australia and the USA. These estimates correspond to approximately half a million overdiagnosed thyroid cancer cases in 12 countries; the large majority of these patients underwent total thyroidectomy (with some also having lymph node dissections), and many also received radioactive iodine treatment. These numbers are useful for understanding the potential impact on populations and health-care systems if population screening were to be undertaken in a given area. It is important to note that distinguishing overdiagnosed cases from cancers destined to cause harm is not possible in practice. Even though some cases can be identified as likely to be more aggressive based on morphological characteristics, not all overdiagnosed cases are distinct from cases where treatment would improve the outcome.

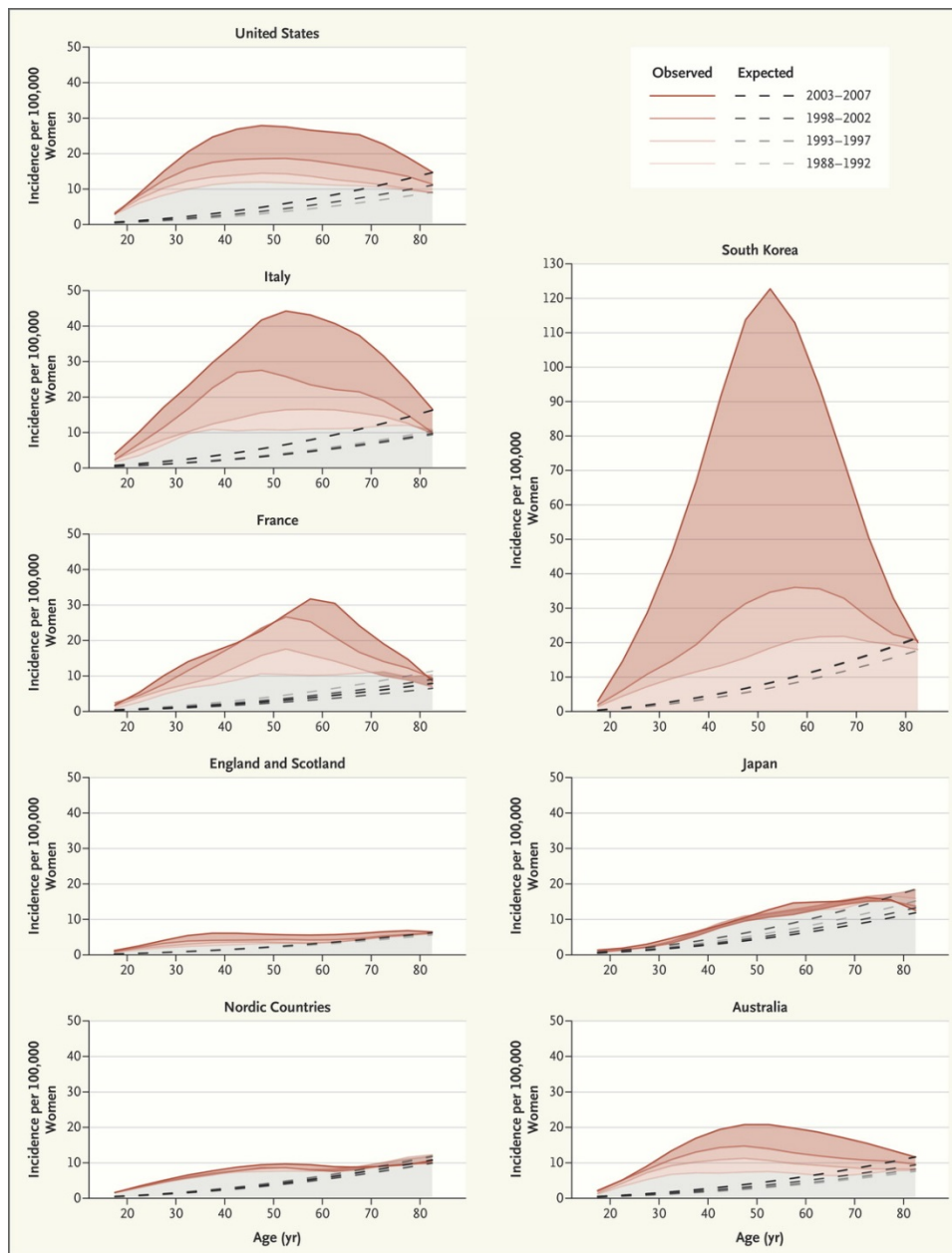


Fig. 4. Observed versus expected changes in age-specific incidence of thyroid cancer per 100 000 women, 1988–2007. Source: Vaccarella et al. (2016). Copyright © 2016, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Overdiagnosis in paediatric thyroid cancer

Autopsy studies have shown that there is a subclinical reservoir of thyroid cancer in children older than 10 years (Franssila and Harach, 1986). In addition, baseline data from the Fukushima Health Management Survey showed higher rates of thyroid cancer than had previously been observed in cancer registries in Japan. Analysis of the data, comparing cancer rates with radiation exposure and expected time to cancer development, suggested that the detected cases may have been prevalent, subclinical cases, rather than radiation-induced cancers (Suzuki, 2016).

Furthermore, a simulation study using data from the Japan National Cancer Registry indicated that the number of thyroid cancer cases observed among individuals younger than 19 years can be expected in Fukushima under conditions of no nuclear accident (Takahashi et al., 2017).

Now, recent data from the Fukushima Health Management Survey further suggest that among children and adolescents, it is possible to identify some thyroid cancers that might stop growing (Midorikawa et al., 2017a). This hypothesis comes from a mathematical model, and the analysis is limited by a short time frame and small numbers; therefore, it may not be possible to establish this for certain. Continued prospective surveillance will be needed for confirmation. If the hypothesis is confirmed, it is possible that the phenomenon of identifying clinically indolent thyroid cancers in adults might also apply to children and adolescents.

4.3 Cancer screening

4.3.1 Principles of cancer screening

The goal of cancer screening is to reduce deaths and morbidity from cancer through early detection of cancer or prevention of malignant disease through the management of pre-cancerous lesions (e.g. cervical or colorectal cancers) (WHO, 2002). Cancer screening can be a valuable public health strategy for improving population health when it is appropriately and effectively implemented. Benefits and risks of screening must be carefully assessed in an effort to avoid overestimation of potential benefits and unfounded risks from screening associated with no reduction in morbidity and mortality of the targeted disease (Auvinen and Hakama, 2014).

The settings and circumstances in which cancer screening should be a priority require complex decision-making. The appropriateness (i.e. whether to screen, as well as whom to screen) and effectiveness (i.e. how to implement a screening programme) must be informed by the best available scientific evidence and social values and contextualized to a particular health system (WHO, 2007).

Definition and types of cancer screening

Cancer screening is the application of a screening test in a presumably asymptomatic population, to identify individuals with an abnormality suggestive of a specific cancer with the intent of reducing mortality and morbidity. It can be classified as organized or opportunistic, as well as population or selective screening.

An organized screening programme includes: coordination and centralization at the national or regional level; a protocol for screening frequency and identification of a defined target population; a mechanism to invite the target population and recall individuals with a screen-positive result; a robust health information system; and a mechanism for programme monitoring and evaluation (Taplin et al., 2006). If a programme does not meet the criteria for an organized programme but is still carried out, then it is classified as opportunistic (or unorganized). Generally, organized cancer screening is the most effective, equitable, and efficient approach to cancer screening.

Failure to achieve the elements of organized screening can result in low participation rates, low quality of screening tests, and low rates of completion of the screening process. This, in turn, can significantly lower the effectiveness of the screening programme and potentially harm individuals through tests and treatments where there are potential risks of treatment-related complications, as well as the psychosocial impact of being a cancer survivor. It can also harm health systems by diverting essential resources and causing doubt about public health programmes, which can result in a loss of credibility.

Population screening (or mass screening) is defined as large-scale screening of large target populations (or whole populations), usually regardless of risk, but with restrictions by sex, age, and geographical units. Selective screening, in contrast, provides a narrower definition of the target population, taking other predictive factors into account that increase the likelihood of finding disease in the asymptomatic population (i.e. screening of selected high-risk groups in the population). Selective screening may be more effective and less costly, and therefore less harmful, than population screening, but it requires a strong scientific evidence base on how to define such a selective target population. For the reasons of lower effectiveness and potential harms to individuals as described above, both population and selective screening are usually carried out as organized screening programmes.

In contrast, monitoring, particularly as defined in the context of this report, is distinct from screening, with the starting point being the individual rather than the population; the same clinical examinations may be used in monitoring as in screening. The aim in both strategies is early detection of cancer in asymptomatic individuals, but the public health approach and objectives are distinctly different. Monitoring is defined here as an elective activity generally offered to higher-risk individuals who may choose how and whether to participate. These individuals could

potentially benefit from early detection by having treatment options of less advanced disease, although no benefit in terms of reduced mortality has been demonstrated. A monitoring programme includes education to improve health literacy, registration of detected cases, and individual clinical examinations and treatment.

Monitoring may be a useful approach when an earlier diagnosis means that more treatment options are available, for example including less invasive procedures, less pain during treatment, shorter recovery from treatment, or other benefits. However, when there is no expected reduction in mortality for the patient, there should be a shared decision-making process between family and clinicians about whether and how to engage in a monitoring programme (including performing the clinical examinations). The decision is whether one would prefer to have an earlier diagnosis, to potentially reduce the aggressiveness of the treatment (without reducing the risk of dying from the disease), or not to search for the disease, with the possibility of more extensive treatment later in life but also the potential to never be diagnosed, and hence to undergo no treatment at all.

The Expert Group notes that what is defined as “monitoring” in this report may be called “screening” in other publications, but prefers to keep the two processes clearly distinct by using the terminology introduced above to highlight the differences in objectives and programmatic targets (Table 1) and for the ease of keeping the two recommendations clearly distinct (see Chapter 3).

Table 1. Characteristics of screening and monitoring programmes as used in this report to better distinguish the recommendations (see Chapter 3)

Characteristics	Screening programme	Monitoring programme
Aims	Early detection of disease in asymptomatic individuals	Same as screening programme
Objectives	Reduce mortality and, if applicable, morbidity, with public health benefits outweighing the harms	Empower higher-risk individuals to make an informed decision, with personal decisions about individual benefits outweighing the harms
Recruitment approach	Active recruitment	Passive recruitment
Recruitment goal	Achieve high participation to ensure the effectiveness of the screening programme	Shared decision-making between family and clinicians
Participants	Target population defined based on high-quality scientific evidence	Individuals who choose to participate after shared decision-making process
Process	Screening process with call mechanism through link to treatment	Same as screening programme
Evidence on effectiveness	Well established for breast, cervical, and colorectal cancers	None

Deciding whether to develop a screening programme

Whether to perform cancer screening should be determined by first assessing whether there is sufficient evidence to promote the screening among a defined target population. This decision should be based on the availability of a screening modality with high accuracy, effective treatment, and evidence to show a benefit of earlier diagnosis within the context of available resources of a particular health-care system. In 1968, criteria for screening were defined by Wilson and Jungner as an understanding of the epidemiological burden of the cancer, the biology of the cancer, the efficacy of the screening modality, and the health system capacity – including the accessibility and effectiveness of diagnosis and treatment (Wilson and Jungner, 1968). If the screening criteria of Wilson and Jungner are not met or are not feasible, cancer screening should not be implemented. Modelling can be used to quantify the benefits, harms, and resource requirements (including cost) of screening in a particular setting, to inform policy-making. Public health officials may find that cancer screening is not cost-effective or that the health system infrastructure is insufficient to effectively deliver screening services.

Public health decision-making in cancer screening must involve the community, as well as health-related regulatory and funding agencies. Cancer screening requires a balance of medical ethics principles – autonomy, beneficence, non-maleficence, and justice – and input from key stakeholders. Services should be integrated and

people-centred, consistent with guidelines from the World Health Organization (WHO) (WHO, 2015, 2016). Screening participants should be counselled on the potential risks and benefits of undergoing a screening test, as well as about alternatives to screening, including evidence-based, unbiased information, to allow a fully informed choice. This should be done before the initial test, because it is very difficult to halt the process after a positive screening result. Cancer screening is a significant and complex public health intervention; evidence-based decision-making, high-quality implementation, monitoring and evaluation, and community engagement are critical to its success.

Potential benefits of cancer screening programmes

There is well-established evidence from developed countries that cancer screening programmes for some types of cancer (e.g. cancer of the cervix, colon and rectum, and breast) can reduce cancer-specific mortality. The extent of the overall benefits varies with the type of cancer, the target populations, the screening modalities and frequency, the capacities and resources of the country or health system, and other factors, including social values. The type of cancer must meet the Wilson and Jungner criteria to confer a benefit to the screened population.

Understanding the risk of a population cohort is particularly important to define a target population that is at high risk, in order to maximize the benefits and reduce the harms of cancer screening. A target population is generally established by an age range and, depending on cancer type, by sex, but can also be based on high-risk behaviours or exposures (e.g. tobacco use in lung cancer screening). Although the latter situation, as introduced above, is called selective screening, in the case of restricting the target population only by age, sex, and geography, it is still referred to as population (or mass) screening.

Potential harms from cancer screening programmes

There are generally three major potential harms to individuals from screening programmes. These can be partially mitigated through quality assurance practices.

First, only a minority of individuals who receive a positive result from a cancer screening examination will ultimately be found to have cancer on subsequent diagnostic tests. A false-positive result can produce psychological harm, physical discomfort, or even injury when the subsequent diagnostic test is invasive, as well as significantly increase the resource requirements of a screening programme. An additional harm is the potential for overdiagnosis (see Chapter 4.2.2). Finally, a

poorly implemented screening programme can also cause harm through failure to access high-quality treatment, which may lead to suboptimal treatment outcomes.

Routine monitoring and evaluation linked to quality assurance programmes can reduce harms from screening. It is recommended that 10–20% of the budget of a screening programme be allocated to monitoring and evaluation (Anttila et al., 2015). This mandates a strong health management information system that includes registration and tracking of participants and their outcomes, as well as collection of a minimum set of quality indicators for programme performance.

Implementation of cancer screening programmes

Population screening has been proposed or shown to be effective for various types of cancer in adults. According to the evaluation within the context of the European Code Against Cancer, participation in organized population screening for colorectal cancer for men and women, and cervical cancer and breast cancer for women, has been shown to reduce the risk of developing or dying from the respective cancer (Armaroli et al., 2015). Currently, implementation of these population screening programmes differs considerably across countries. For other cancers, such as population screening for prostate cancer and selective screening for lung cancer, the evidence on benefits and harms is not sufficient to recommend participation in screening activities outside of research projects. However, some countries recommend prostate cancer screening, and some have started selective lung cancer screening, using low-dose computed tomography (CT). Screening for thyroid cancer is discussed in depth in Chapter 4.3.2.

The only childhood cancer type for which organized screening programmes have been implemented is neuroblastoma, mainly because there is an inexpensive, non-invasive, and sufficiently accurate early detection method (urine catecholamine metabolites). The National Cancer Screening Programme in Japan, population-based screening studies in Canada and Germany, and further pilot studies in several places in Europe and in the USA have shown that although there was an increased detection of early-stage neuroblastoma, there was no reduction in mortality or increase in survival in children with neuroblastoma. This finding is partly attributable to the peculiar natural course of neuroblastoma, with relatively frequent spontaneous regression of the tumour. The screening resulted in overdiagnosis, leading to unnecessary treatment with complications that sometimes resulted in death. Because of this, screening was discontinued and medical associations advised

against any screening for neuroblastoma (Schilling et al., 2003; Tsubono and Hisamichi, 2004; Shinagawa et al., 2017).

4.3.2 Thyroid cancer screening

In principle, there are two main ways to screen for thyroid cancer: through palpation or through ultrasonography. Palpation is a physical examination of the neck and surrounding lymph nodes. Ultrasonography imaging is a non-invasive test that is performed by a trained clinical provider.

The characteristics of a screening test are one component of determining whether screening programmes are advisable. The sensitivity and specificity of palpation to detect thyroid nodules are dependent on the health professional administering it, but overall the sensitivity and specificity of this method are poor, with only about 40% of nodules larger than 15 mm in diameter palpable on physical examination (Wiest et al., 1998). The accuracy of the interpretation of the ultrasonography images depends on the degree of experience of both the sonographer and the person interpreting the images. When suspicious nodules are found by ultrasonography, they must be biopsied to confirm a malignancy. There are systems for categorizing both ultrasonography features of thyroid nodules and fine-needle aspiration biopsy results to maximize the chances of accurate interpretation and stratification for the risk of malignancy (Haugen et al., 2016; Tessler et al., 2017). For example, when the American Thyroid Association classification system is used to interpret the ultrasonography images of thyroid nodules, the reliability for indication to fine-needle aspiration is good, with diagnostic accuracy of 86% (Persichetti et al., 2018). For fine-needle aspiration biopsy results, using the Bethesda System for Reporting Thyroid Cytopathology criteria, the sensitivity, specificity, and diagnostic accuracy are 97%, 50.7%, and 68.8%, respectively (Bongiovanni et al., 2012).

The goal of cancer screening is to reduce deaths and morbidity from cancer through early detection of cancer or prevention of malignant disease through the management of pre-cancerous lesions (see Chapter 4.3.1). Whether thyroid cancer screening reduces thyroid cancer-specific mortality has never been evaluated by any randomized controlled trial. There are, however, four observational studies that included mostly women in the Republic of Korea who underwent elective thyroid ultrasonography examination during screening or follow-up for breast cancer (Lin et al., 2017b). These studies represented opportunistic rather than population

screening, with the detection rate ranging from 9 to 30 per 1000 persons. Nearly all of the detected cancers were papillary thyroid cancer (PTC) (Lin et al., 2017a), the most common type of thyroid cancer and the type that was found in approximately 11.2% (95% confidence interval, 6.7–16.1%) of autopsies in people who died from unrelated causes (Furuya-Kanamori et al., 2016). This suggests that screening activities are likely to identify indolent thyroid cancers that would not have affected a person's health during their lifetime, as well as cancers that may be of clinical significance. In addition, analyses of trends in incidence and mortality of thyroid cancer across several countries show steep increases in incidence, probably related to opportunistic screening and greater use of imaging technology, and no measurable changes in mortality during the same period (see Chapters 4.2.1 and 4.2.2). The most compelling example of this observation from the Republic of Korea is detailed later in this chapter.

The United States Preventive Services Task Force (USPSTF) is an independent and widely respected panel of experts that systematically review evidence and develop recommendations for clinical preventive services. The USPSTF recommends against screening for thyroid cancer in otherwise healthy, asymptomatic populations (Bibbins-Domingo et al., 2017). This recommendation is based on concerns that screening for thyroid cancer in an adult population with no identified risk factors may be associated with the discovery of incidental, indolent thyroid tumours, as well as a lack of evidence to show a reduction in disease-specific mortality from early identification of thyroid cancers before clinical detection. The systematic review conducted to support the USPSTF in updating its recommendations on thyroid cancer screening concluded that although ultrasonography and fine-needle aspiration of identified nodules “can identify thyroid cancers, it is unclear if population-based or targeted screening can decrease mortality rates or improve important patient health outcomes” (Lin et al., 2017b). Key to the recommendation against screening is that screening identifies benign thyroid nodules and indolent thyroid cancers that subsequently need further interventions, which may increase the risk of patient harms, and that thyroid cancer is a disease with in general excellent prognosis and low mortality rate. However, this recommendation by the USPSTF does not apply to higher-risk populations (e.g. those at an increased risk of thyroid cancer due to a history of exposure to ionizing radiation, or inherited genetic syndromes associated with thyroid cancer).

The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) consortium evaluated evidence on benefits and harms of screening for differentiated thyroid cancer (DTC) in survivors of childhood, adolescent, and young adult cancer whose thyroid had been in the field of radiation exposure (at-risk survivors) (Clement et al., 2018). They did not recommend that all at-risk survivors be followed up with serial ultrasonography, because the benefit of early treatment in children is uncertain and ultrasonography can identify a benign nodule or indolent cancer, which can lead to potential harms (e.g. treatment without clinical benefit, side-effects caused by treatment, distress, and cost). The report, however, recommended that at-risk survivors should be counselled about the increased risk of thyroid cancer, as well as options (palpation vs ultrasonography) for thyroid screening, and that at-risk survivors be fully informed, be engaged in discussions, and be allowed to choose between screening with ultrasonography and screening with palpation, or to consider no active screening. No consensus was reached on the radiation dose that should trigger the thyroid screening programme or on the timing for when the programme should be initiated after exposure.

There have been data showing some clinical utility of screening for thyroid cancer in high-risk populations within several different clinical contexts, including tumour predisposition syndromes associated with an increased risk of developing DTC and familial non-medullary thyroid cancer (FNMTC). The lifetime risk of developing thyroid cancer is 1–12% in familial adenomatous polyposis (Jasperson et al., 2017) and 35% in *PTEN* hamartoma tumour syndrome (Eng, 2001). In individuals with *DICER1* syndrome, the risk of developing thyroid cancer is increased 16-fold compared with the general population (Khan et al., 2017). FNMTC is defined by the presence of two or more first-degree relatives with DTC; however, even in families with only one person previously diagnosed with DTC, there is a 9-fold risk of another family member developing DTC (Mazeh et al., 2012). For all of these syndromes, selective screening for DTC is initiated at the time of diagnosis, and in FNMTC, as an example, the incorporation of thyroid ultrasonography screening is associated with detection of smaller tumours and a lower rate of central neck lymph node metastasis, requiring less extensive surgery, and a lower rate of radioactive iodine therapy (Rosario et al., 2012; Klubo-Gwiedzinska et al., 2017).

The thyroid screening experience after the Chernobyl accident may provide more salient and critical information on the potential benefit of thyroid screening for the present discussion on children and adolescents exposed to radiation after a nuclear accident. Two screening cohorts of children and adolescents who lived in areas contaminated by the Chernobyl accident were established in the mid-1990s: the USA–Belarus (BelAm) cohort and the USA–Ukraine (UkrAm) cohort. Using the data from these screening cohorts, various features of PTC were evaluated in relation to ^{131}I dose (Bogdanova et al., 2015; Zablotska et al., 2015a). The analysis of the BelAm cohort included 158 PTC cases diagnosed during three cycles of screening in 1997–2008, and the analysis of the UkrAm cohort included 115 PTC cases, including 104 cases diagnosed during four cycles of screening in 1998–2007 and 11 cases treated before the first cycle of screening. Both the BelAm and UkrAm studies concluded that higher thyroid doses of ^{131}I may be associated with some features of tumour aggressiveness (e.g. lymphatic vessel invasion). Thyroid cancers that were diagnosed before the establishment of the screening cohort were more likely to be larger and more invasive, possibly associated with higher thyroid doses of ^{131}I (Bogdanova et al., 2015).

In a study of thyroid cancer treatment outcome in a cohort of Chernobyl-exposed Belarusian children and adolescents who received post-surgical radioiodine therapy, cancer outcomes were favourable even in those patients with advanced disease (Reiners et al., 2013). If, however, treatment of aggressive thyroid cancer at an earlier state brings other benefits, such as a need for less aggressive treatment (i.e. reduced extent of surgical dissection, reduced radioactive iodine therapy) and reduced risk of complications, then offering timely thyroid screening may be justified. However, the evidence is currently lacking on the benefit of early treatment in children and adolescents. Even within the present Expert Group, there is a debate about whether and how prospective data could be obtained to ultimately determine whether the benefits of selective thyroid screening outweigh the harms (e.g. overdiagnosis, treatment without clinical benefit, treatment-related complications, and anxiety due to diagnosis or false-positive test results) in a higher-risk population.

Based on the available scientific evidence, the Expert Group recommends against population thyroid screening in case of a nuclear accident, because the harms outweigh the benefits at the population level (i.e. risk of overdiagnosis with no mortality reduction) (see Chapter 3). Population screening is defined herein as actively recruiting all residents of a defined area to participate in thyroid

examinations irrespective of any individual thyroid dose assessment (see Chapter 4.3.1 for the general definition of population screening). However, given the increased risk of thyroid cancer associated with exposure to ionizing radiation after nuclear accidents as well as the aforementioned potential clinical benefits of early disease detection in higher-risk individuals, the Expert Group recommends that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals after a nuclear accident. A thyroid monitoring programme is distinct from population or selective screening, with the starting point being the individual instead of the population. Thyroid monitoring is an elective activity offered to higher-risk individuals, who may choose how and whether to undergo thyroid examinations and follow-ups in an effort to benefit from early detection and treatment of less advanced disease. In an effort to balance the potential harms of excessive thyroid monitoring with identification of the highest-risk individuals, the Expert Group proposes a thyroid dose of 100–500 mGy received in utero, during childhood, or during adolescence at the time of exposure to radiation for a practical definition of an actionable level to offer inclusion into the elective long-term thyroid monitoring programme for higher-risk individuals.

The reason why the Expert Group recommends that such a programme be an elective activity is that the current data on whether thyroid screening brings more benefits than harms in terms of outcome, including morbidity, mortality, and quality of life in children and adolescents as well as in adult higher-risk populations, are limited (Lin et al., 2017b). Given the uncertainty, there should be a shared decision-making process between individuals, families, and clinicians about whether and how to engage in a thyroid monitoring programme (including performing the clinical examinations). The decision is whether one would prefer to have an earlier diagnosis, to potentially reduce the aggressiveness of the treatment (without reducing the risk of dying from thyroid cancer), but also the potential to be overdiagnosed and undergo treatment with the risks of complications and negative psychosocial impacts, or not to search for the disease, with the possibility of more extensive treatment later in life, but also the potential to never be diagnosed, and hence to undergo no treatment during one's lifetime at all. The next chapters (Chapters 4.3.3 and 4.3.4) discuss the patient perspective on screening and approaches to avoid overdiagnosis in a thyroid monitoring programme.

Experience in the Republic of Korea

Thyroid cancer screening in adults is commonly practiced in the Republic of Korea (Han et al., 2011), even though thyroid screening is not formally included in the government-initiated cancer screening programme. The data from the Republic of Korea serve as an example of what the impact might be of thyroid screening in the general adult population if it were implemented after a nuclear accident.

Screening gained popularity with the spread of health check-ups among the Korean population in the early 2000s. In 1999, the National Cancer Screening Program initiated screening services for major cancers, including gastric, liver, colorectal, cervical, and breast cancers (Ahn et al., 2014). Thyroid ultrasonography was frequently conducted in addition to other cancer screenings, because it was inexpensive and easy to perform (Kim et al., 2009; Park et al., 2016). According to the Korea Community Health Survey, in 2012, 23% of the population reported that they had participated in thyroid cancer screening during the previous 2 years (Korea Centers for Disease Control and Prevention, Korea Community Health Survey, unpublished data, 2012).

According to data from the Korea Central Cancer Registry, the age-adjusted incidence of thyroid cancer increased 15-fold between 1993 and 2011 (Ahn et al., 2014; Jung et al., 2017; Fig. 5). Because this dramatic increase in thyroid cancer incidence coincided with the year of the introduction of the National Cancer Screening Program, it was thought to be the result of the increased practice of thyroid cancer screening. The regional-level analysis demonstrated that areas with high levels of thyroid cancer screening uptake were strongly associated with high incidence rates (Fig. 6). Furthermore, an analysis of data from the Korea Central Cancer Registry showed that the increase in thyroid cancer incidence was mostly due to the detection of a specific subtype, papillary carcinoma, which has been observed in autopsy studies of asymptomatic people (see Chapter 4.2.2).

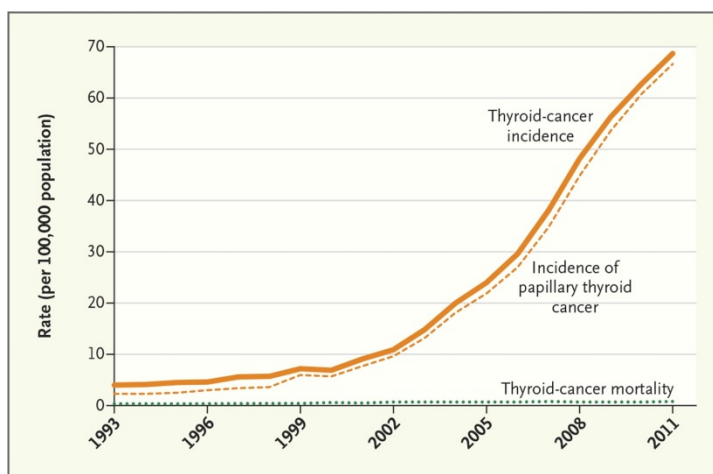


Fig. 5. Thyroid cancer incidence and related mortality in the Republic of Korea, 1993–2011. Data on incidence are from the Korea Central Cancer Registry, and data on mortality are from Statistics Korea. All data are age-adjusted to the standard population in the Republic of Korea. Source: Ahn et al. (2014). Copyright © 2014, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

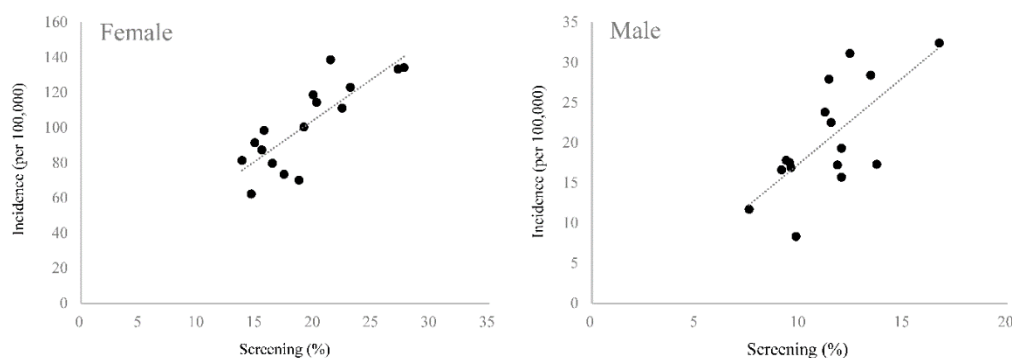


Fig. 6. Association between thyroid cancer screening rates and thyroid cancer incidence rates in the 16 regions in the Republic of Korea, in females and males, in 2010. Data on screening are from the Korea Community Health Survey, Korea Centers for Disease Control and Prevention. Data on incidence are from the Korea Central Cancer Registry, Statistics Korea.

Despite the rapid increase in incidence, the thyroid cancer-specific mortality rate remained stable or decreased marginally, from 0.65 per 100 000 in 2000 to 0.53 per 100 000 in 2014 (Choi et al., 2017). The regional-level analysis showed no substantial difference in thyroid cancer mortality rates across regions with high and low thyroid cancer screening rates. In short, the experience in the Republic of Korea suggests that screening of otherwise asymptomatic people leads to the increased detection of a subclinical reservoir, resulting in an apparent epidemic without

proportionate mortality reduction, although the long-term impact of screening on mortality should be considered (Brito et al., 2013, 2015; Davies and Welch, 2014).

In 2014, a group of physicians expressed their concerns about the overdiagnosis of thyroid cancer, which initiated a social debate in the country. This process led to the creation of the Korean National Cancer Screening Guidelines, which state that “thyroid screening by ultrasonography is not recommended for a healthy asymptomatic person” (Yi et al., 2015). Also, there was a marked decrease in thyroid cancer incidence and surgeries after the physicians expressed their concerns. The age-adjusted incidence of thyroid cancer decreased from 84.9 per 100 000 in 2013 to 49.1 per 100 000 in 2015, according to the Korea Central Cancer Registry (Cancer Registration & Statistics Branch, 2017), and the number of thyroid surgeries declined from 40 124 in 2013 to 22 321 in 2015 (National Health Insurance Corporation, National Health Insurance Database, unpublished data, 2015). The analysis of insurance data suggests that the decrease in incidence and in the number of surgeries was the result of less screening rather than less aggressive management, such as active surveillance. Although the incidence of thyroid cancer remains high, the trend has been reversed as a result of lessons learned from the experience of overdiagnosis in the country.

4.3.3 The patient perspective

There is a strong belief in the benefits of screening among both health professionals and the public. This must be taken into account, because it will affect any efforts to educate the public about thyroid monitoring after a nuclear accident. Historic messaging has cultivated a cultural enthusiasm about the value of early detection. Some of the other important influences include financial incentives where insurance coverage is available, and marketing efforts by device and pharmaceutical companies (Moynihan et al., 2015; McCaffery et al., 2016).

Many cultures value action in medical care over inaction (Feinstein, 1985), and in many populations health literacy and numeracy is limited. In addition to numeracy limitations, the public school curriculum usually does not include cancer epidemiology and the natural history of cancer, and therefore most people would not have baseline knowledge in this area. Lastly, the power of anecdotal evidence typically overrides the logic of risk information; it is much easier to focus on the one “saved” person than on all the others to whom nothing happened (Jenni and Loewenstein, 1997).

Although thyroid cancer screening is not recommended or endorsed for asymptomatic healthy adults, in some countries where it is practiced, studies show low awareness and understanding of the issues. Specifically, in a qualitative study in women aged 30–69 years in the Republic of Korea, most were unaware of the potential for overdiagnosis of thyroid cancer from thyroid ultrasound screening; nevertheless, even after they were informed about it, they continued to see screening as beneficial (Park et al., 2015). Similar results were found in a survey of women who were asked about their intention to undergo screening for thyroid cancer, with and without information on overdiagnosis being provided. Of the participants, 87% reported an initial intention to undergo thyroid cancer screening, and when they were provided with information about overdiagnosis, 74% of the same group of women still intended to undergo screening (Lee et al., 2016a).

Although these study results seem to indicate that decision aids are not helpful because of such strong public beliefs, it is possible that as societal ideas shift, tools to support informed decision-making can become more effective. For example, in the case of prostate cancer, for which the potential for harm from screening is much better understood and information has been broadly disseminated to the public, the use of decision aids is more effective at appropriately lowering intent-to-screen rates when it is appropriate to do so and is congruent with the patient's stated values (Evans et al., 2005). If the public understands the issues around thyroid cancer overdiagnosis and its natural history, then the options for thyroid health monitoring can be more easily and effectively explained to the population affected by a nuclear accident.

4.3.4 Approaches to avoid overdiagnosis

In certain situations, higher-risk individuals, such as those exposed in utero or during childhood or adolescence with a thyroid dose of 100–500 mGy or more, may be offered long-term thyroid monitoring (see Chapter 3, Recommendation 2). These individuals may elect to undergo a periodic thyroid ultrasound examination, a periodic physical examination by a trained clinician, or no examination. The main potential benefit of monitoring is that early detection may result in treatment options that are less intensive. The main potential harm is that treatment may not have been needed – the cancer detected may never have evolved to be clinically apparent had monitoring not taken place. The decision about which path to take is “preference-sensitive”; that is, individuals would be expected to choose differently based on their

interpretation of the potential benefits, potential harms, and scientific uncertainties of each option.

Based on current evidence and knowledge, the following approaches to minimize overdiagnosis of thyroid cancer should be considered.

Education

Health professionals and the public should be made aware of the potential harms and the potential benefits of thyroid screening. In 2017, the United States Preventive Services Task Force evaluated the data on ultrasound or palpation screening; they concluded that the potential harms continue to outweigh the potential benefits of detection through screening, and recommended against screening for thyroid cancer in healthy asymptomatic adult populations (Bibbins-Domingo et al., 2017). There is no parallel document for thyroid cancer screening in children, but there is a useful report that provides guidance on how to approach thyroid cancer screening in survivors of childhood, adolescent, and young adult cancer who received radiation doses to the thyroid (Clement et al., 2018). The recommendation is that shared decision-making be implemented between a health professional and the individual's family to decide whether and how to monitor for thyroid cancer. Education of both health professionals and the public about the potential harms and the potential benefits of thyroid screening and the magnitude of its net benefit can facilitate such shared decision-making and allow individuals to make an informed decision consistent with the person's values, preferences, and context.

Programme development using principles of people-centred health services

Without an organized programme to offer monitoring to higher-risk individuals, there is the possibility of overtreatment, undertreatment, and inequitable distribution of services. The World Health Organization (WHO) *Framework on integrated people-centred health services* provides an outline for the development of a programme in which all people have equal access to high-quality health-care services and are empowered to have a more active role in their own health (WHO, 2015, 2016).

WHO recommends five interwoven strategies to achieve this vision: (i) engage, educate, and empower people and communities; (ii) strengthen governance and accountability; (iii) reorient the model of care; (iv) coordinate services within and across sectors; and (v) create an enabling environment. Health authorities are encouraged to select those policies and interventions that best fit their national,

subnational, or local needs and to customize them to match their priorities, capabilities, and resources.

Use of shared decision-making processes

Because the decision about whether to participate in thyroid monitoring is preference-sensitive, monitoring should be offered through an organized programme developed using the principles of shared decision-making (O'Connor et al., 2004). The programme should include the provision of balanced information about available options, including the potential benefits and harms of each, and consideration should be given to the values and preferences of the patient in regard to the options. In the case of thyroid monitoring after a nuclear accident, because the individuals being offered monitoring would be children or adolescents, parents or guardians will need to be involved in the decision-making process.

Shared decision-making processes can be accomplished through the development and implementation of a specific “decision aid”. Examples include the model of the Ottawa Hospital Research Institute (Ottawa, Canada; <https://decisionaid.ohri.ca>) and that of conversational tools (Mayo Clinic, Rochester, MN, USA; <https://shareddecisions.mayoclinic.org/>) and option grids (The Dartmouth Institute for Health Policy and Clinical Practice, Hanover, NH, USA; <https://health.ebsco.com/products/option-grid>).

Communication with the community and people participating in thyroid health monitoring

After the Fukushima accident, four principles were developed for effective communication with the community at large (Murakami et al., 2017): (i) setting, (ii) scale, (iii) content, and (iv) communicator. In the communication *setting*, direct contact with participants was more effective and was better received than broad distribution of information. In the *scale* of communication, small, face-to-face group meetings were better than large meetings. For the *content* of the communication, it is important to establish appropriate communication materials with contents that are appropriate and easy for the audience to understand. For the *communicator*, outside experts were paired with locally recognized, trusted sources, such as teachers or public health nurses. Some of the approaches used in Fukushima are described in Chapter 4.6.5.

It was noted that during the initial phase of the Thyroid Ultrasound Examination (TUE) programme, anxiety was increased by longer waiting periods for receipt of

results, and the classification scheme of identified nodules also created anxiety. Care should be taken when communicating the findings of normal anatomical variations (such as colloid cysts) with the participants and their families, in order to avoid undue confusion or anxiety.

4.4 Management of differentiated thyroid cancer

4.4.1 Pre-surgical evaluation and treatment of differentiated thyroid cancer

Clinical presentation

Although primary thyroid tumours are often asymptomatic, individuals with a large or infiltrating tumour may experience a lump on the neck, trouble breathing or swallowing, hoarseness, or localized pain. Symptoms are more frequent with metastatic disease and depend on the site and the organ. Skeletal metastases are the most symptomatic, particularly when located in the spine.

Pre-surgical evaluation

All patients being considered for surgery for suspicion of thyroid cancer should undergo a neck ultrasonography both of the thyroid gland (to document number of nodules, location, and size) and of the cervical lymph nodes (to identify any suspicious cervical lymph nodes in the central or lateral compartments) (Francis et al., 2015; Haugen et al., 2016). After this, fine-needle aspiration cytology (FNAC) should be used to determine the malignant potential of the thyroid nodule and any suspicious cervical lymph nodes. Cross-sectional imaging is recommended for patients with bulky lymph node disease or where there is suspicion of invasion of major structures.

Surgery

Total thyroidectomy and lobectomy are the primary treatment options for patients with thyroid cancer confirmed by FNAC. In adults, lobectomy may be sufficient for unifocal, intrathyroidal papillary thyroid cancer (PTC) up to 4 cm in diameter, or thyroid cancer with non-invasive histology, such as the encapsulated follicular variant of PTC or minimally invasive follicular thyroid cancer (FTC) (Haugen et al., 2016). A completion thyroidectomy should be performed if histology after lobectomy shows invasive behaviour or high-risk differentiated thyroid cancer (DTC) variants. Total thyroidectomy is indicated in the other cases. In adults, central lymph node dissection should be considered in patients who have advanced primary tumours (classification T3 or T4 [tumour > 4 cm or with gross extrathyroidal extension (ETE)])

in the American Joint Committee on Cancer [AJCC] tumour–node–metastasis [TNM] cancer staging system) or clinically involved lateral neck lymph nodes (cN1b) (Haugen et al., 2016; Tuttle et al., 2017).

For adult patients with unifocal, intrathyroidal papillary thyroid microcarcinomas (PTMC), studies are in progress to determine whether “active surveillance” (observation by serial ultrasound examinations) can be pursued as an elective alternative to immediate surgery. A recent study of adult patients with low-risk PTMC who have chosen this option has shown that the lifetime probability of disease progression decreases with increasing age, from up to 60% if active surveillance is initiated during the third decade of life to 4% if surveillance is initiated during the eighth decade of life (Miyauchi et al., 2018).

Current guidelines for paediatric patients recommend total thyroidectomy for patients with cytology suspicious for PTC, described by the Bethesda System for Reporting Thyroid Cytopathology categories V (suspicious for) or VI (consistent with) PTC (Francis et al., 2015; Cibas and Ali, 2017). Diagnostic lobectomy may be considered in paediatric patients with indeterminate cytology and may be sufficient if the pathology reveals an encapsulated follicular variant of PTC without lymphovascular invasion or a minimally invasive FTC (Francis et al., 2015; Samuels et al., 2018). Prophylactic central neck dissection should be considered for paediatric patients with PTC and should be performed in all paediatric patients with evidence of lateral neck lymph node metastasis, confirmed by FNAC, or distant (pulmonary) metastasis (Francis et al., 2015). There are no data to support consideration of active surveillance of PTMC in children or adolescents.

Radioiodine ablation/therapy

In the past, almost every patient with a diagnosis of DTC underwent adjuvant radioactive iodine (RAI) ablation after surgery. Currently, careful review of a patient’s outcome has introduced the concept of risk-based selection of patients for RAI therapy (Castagna et al., 2016). RAI ablation is only indicated in high-risk patients. In intermediate-risk patients, radioiodine remnant ablation may be indicated, but the decision must be individualized using the postoperative tumour marker thyroglobulin (Tg) together with neck ultrasonography and/or postoperative diagnostic whole-body scanning. RAI adjuvant therapy is recommended after total thyroidectomy in high-risk patients, defined as patients with gross ETE (AJCC T4) and/or distant metastasis (AJCC M1) (Haugen et al., 2016). Within the paediatric population, RAI

therapy should be considered for all patients with American Thyroid Association paediatric-designated intermediate- and high-risk disease, with the administered RAI activity determined by the postoperative Tg level, radioiodine diagnostic whole-body scanning, and the results of other imaging modalities (Francis et al., 2015).

Treatment of distant metastatic disease

Distant metastases are observed in approximately 3% of PTC cases (Lim et al., 2017), with a higher proportion observed in paediatric patients than in adult patients (Al-Qurayshi et al., 2016). Patients with lateral neck lymph node metastasis have an increased risk of distant metastasis (Lee et al., 2011; Francis et al., 2015). Distant metastases most commonly occur in the lungs (50% of metastases), followed by the bones (26%), both lungs and bones (18%), and other sites (5%) (Dionigi et al., 2014). For FTC, the risk of distant metastasis correlates with the degree of tumour vascular invasion. Treatment of distant metastases includes adjuvant RAI, as well as potential application of local treatment modalities (e.g. surgery, radiation therapy, and thermal radiofrequency or cryo-ablation) for refractory metastasis. Despite all of these methods, a complete response is observed in less than half of patients with distant metastases (Durante et al., 2006; Pawelczak et al., 2010).

Levothyroxine therapy after surgery

Immediately after total thyroidectomy, thyroid hormone therapy is initiated. If less than a total thyroidectomy is performed, the function of the remaining thyroid gland must be assessed through evaluation of thyroid-stimulating hormones (TSH). Levothyroxine (L-T₄), used to replace the thyroid gland, is given in TSH-suppressive dosage to high-risk thyroid cancer patients and may decrease progression of metastatic disease and improve survival (Diessl et al., 2012). No significant benefits for TSH suppression have been demonstrated in low-risk patients, and in these patients, serum TSH may be maintained at the lower end of the reference range (TSH of 0.5–2 milliunits per litre [mU/L]). For patients who achieve stable remission from disease, regardless of the initial risk classification, LT-4 therapy may be shifted from a suppressive to a replacement dosage (Haugen et al., 2016).

4.4.2 Follow-up and prognosis of differentiated thyroid cancer

The aim of follow-up is to discover and treat persistent or recurrent locoregional or distant disease. Patients with no clinical, biochemical, or structural evidence of disease are classified as having an “excellent response” to initial therapy (Francis et

al., 2015; Haugen et al., 2016; Sohn et al., 2017; Sung et al., 2017). This is associated with a very low risk of recurrence in long-term follow-up (1–4%) (Tuttle et al., 2010; Castagna et al., 2011; Momesso and Tuttle, 2014; Momesso et al., 2016; Pires et al., 2016). Patients who have persistently detectable or rising Tg values under TSH stimulation (or even TSH suppression), or persistent or rising anti-Tg antibodies without structural evidence of disease, are classified as having a “biochemical incomplete response” (Haugen et al., 2016). Within this category, 56–68% of patients will continue to show no evidence of disease, although 8–17% will ultimately be found to have structural disease over 5–10 years of follow-up. Patients with biochemical incomplete response should be followed up every 6–12 months, maintaining mild TSH suppression (0.1–0.4 mU/L) with appropriate cross-sectional imaging based on the serum Tg levels over time (Haugen et al., 2016; Lazar et al., 2016). Adult patients with a postoperative TSH-stimulated Tg level of greater than 10–30 nanograms per millilitre (ng/mL) have an unfavourable prognosis, with decreased disease-free survival and increased disease-specific mortality. Post-lobectomy patients should be followed up with serial physical examinations, serum Tg measurements, and thyroid and neck ultrasonography to assess for persistent or recurrent disease.

In paediatric patients, the presence of ETE more than five lymph node metastases and distant metastasis (pulmonary) predicts an increased risk of persistent and recurrent disease (Francis et al., 2015; Sung et al., 2017). After initial treatment, a single Tg level that is higher than 10 ng/mL is consistent with an incomplete response; however, there is no defined Tg level that is associated with unfavourable prognosis. Because the majority of paediatric patients have low disease-specific mortality, even for patients with pulmonary metastasis, the trend in postoperative Tg, in concert with radiological imaging, should be used to determine if and when additional therapy may be beneficial (Biko et al., 2011; Padovani et al., 2012). Biochemical and radiological surveillance are typically performed every 3–6 months and every 6–12 months, respectively (Francis et al., 2015).

Persistent disease

A patient with a “structural incomplete response” is defined as having persistent or newly identified locoregional or distant metastases. The management of these patients must be individualized based on the location of disease and the response to previous therapy. Despite additional treatments, the majority of patients classified as

having a structural incomplete response will continue to have persistent structural and/or biochemical evidence of persistent disease at final follow-up (Pawelczak et al., 2010; Vaisman et al., 2011b).

Although the response to therapy assessment described above has been validated for DTC patients treated with total thyroidectomy and RAI, fewer data are available for patients treated with lobectomy or total thyroidectomy without RAI.

Recurrent disease

Long-term studies have shown that recurrent disease occurs in about 9% (at 10 years) of adult patients and about 30% (at 40 years) of paediatric patients, mostly in those with extensive disease at initial presentation (e.g. large thyroid tumour, ETE, and lymph node metastases) (Landau et al., 2000; Bilimoria et al., 2007; Hay et al., 2010). Among patients with recurrence, three quarters will have disease in the neck only, mostly in lymph nodes or in the thyroid bed. Recurrent disease is also more commonly seen in those with an aggressive histological type, including tall cell, columnar cell, and hobnail variants in adults (Haugen et al., 2016) and diffuse sclerosing variant in paediatric patients (Koo et al., 2009).

Side-effects and complications of treatment

The main side-effects and complications of surgery for thyroid cancer are damage to laryngeal nerve function, through loss of either the superior laryngeal nerve (temporary or permanent, 0–58%) or the recurrent laryngeal nerve (~10%), and loss of parathyroid gland function (temporary, ~17%; permanent, ~2%) (Friedman et al., 2002; Francis et al., 2014; Oda et al., 2016; see Annex 3). Rates of damage to the recurrent laryngeal nerve and parathyroid gland function have been shown to be lower in surgeries performed by surgeons who perform 26 or more thyroid surgeries annually (Adam et al., 2017).

The side-effects of RAI (¹³¹I) therapy are believed to be dose-dependent. The most worrisome side-effect is the risk of a secondary malignancy. There is no direct evidence of increased risk of secondary malignancies after a single course of adjuvant therapy compared with the observed risk of a second primary cancer in thyroid cancer patients who have not been treated with ¹³¹I (Haugen et al., 2016). The risk of soft tissue and bone tumours increases by about 20%, and the risk of leukaemia increases by about 2.5-fold, relative to thyroid cancer survivors not treated with RAI (Haugen et al., 2016). The most common side-effect of RAI is xerostomia, with an increased risk of dental caries, because of the loss of salivary

gland function (Fard-Esfahani et al., 2014). Additional known side-effects are dry eyes and nasolacrimal system dysfunction, dysphagia, and, at very high cumulative activities of ^{131}I , decreased fertility.

After thyroid surgery for thyroid cancer, there is a lifelong need for thyroid hormone replacement as described above (100% after total thyroidectomy, 25% after lobectomy) (Saravanan et al., 2002; Said et al., 2013). Obtaining prescription medication requires regular blood tests and doctor visits. It has been shown that those receiving thyroid hormone replacement therapy are more likely to experience impaired psychological well-being than those who are not using thyroid hormone replacement therapy (Saravanan et al., 2002).

Disease-specific mortality

Overall, thyroid cancer survival is excellent. For example, in adult patients younger than 55 years, the expected 10-year disease-specific survival is 98–100% for localized or regional disease and 85–95% for distant metastases (Perrier et al., 2018). PTC, the type that is of concern after exposure to radiation, has a particularly high survival rate; 97–99% of patients with PTC limited to the thyroid gland are alive 20 years after diagnosis (Davies and Welch, 2014). In adults, factors that have been shown to affect PTC mortality include older age, tumour size, ETE, incomplete resection, cervical lymph node or distant metastasis, and being diagnosed with stage 3 (or higher) cancer, with cause-specific mortality approaching 30% for patients with MACIS scores (distant metastasis, patient age, completeness of resection, local invasion, and tumour size) of 6 or more (Grogan et al., 2013; Hay et al., 2018).

In paediatrics, PTC-specific 30-year survival is approximately 99–100% irrespective of sex, procedure type, or presence of regional lymph node metastasis at presentation, with a minimal decrease in survival (to 97%) for patients with distant metastasis (Golpanian et al., 2016). Disease-specific survival in radiation-induced PTC is similar to that in non-radiation-induced PTC. For children and adolescents exposed to Chernobyl fallout, survival was 98–99% (Hay et al., 2010; Tuttle et al., 2011; Reiners et al., 2013).

Based on the evidence described above (see also Chapter 4.1), the clinical management of thyroid cancer occurring as a result of radiation exposure after a nuclear accident should be conducted in the same manner as it is for children who have spontaneous thyroid cancer. Treatment should be concordant with the published guidelines.

4.5 Radiation and cancer

4.5.1 Radiation exposure

Radiation is defined as movement of energy through space. On the basis of the frequency or wavelength of emitted energy, radiation can be divided into ionizing and non-ionizing radiation. Radiation that carries enough energy to ionize atoms as it passes through matter is called ionizing radiation. It comes from both natural and artificial sources. The two major sources of natural ionizing radiation are radionuclides originating from the Earth's crust, including radon, and cosmic rays from space. The major contributor to anthropogenic sources of radiation is medical uses of radiation (X-rays and nuclear medicine). Other artificial sources of exposure include occupational exposure, fallout from nuclear weapons testing, and, in some instances, fallout from nuclear reactor accidents.

Ionizing radiation can consist of either waves (electromagnetic radiation such as X- and γ -rays) or particles (such as α or β particles). X- or γ -rays can penetrate a body, but not all of the waves will necessarily interact with the tissue in the body as they pass through. Particulate forms of ionizing radiation, except neutrons, penetrate less because they have a mass and they slow down by collisions; they deliver a dose of radiation to the body's cells mainly if ingested or inhaled.

Radioactivity refers to unstable atoms that disintegrate spontaneously. The unit of radioactivity in the International System of Units (SI) is the becquerel (Bq), which is equal to 1 disintegration per second (decay/s). Half-life is the length of time that it takes for half of the atoms of a given nuclide to decay, and may range from millionths of a second to millions of years.

To estimate radiation dose (i.e. the energy absorbed by tissue), one needs to understand the processes by which radiation interacts with tissue. Absorbed dose is defined as the amount of energy absorbed by tissue (or an organ) and is generally viewed as the most useful measure of radiation dose for epidemiological studies. The SI unit for absorbed dose is the gray (Gy), defined as 1 joule per kilogram (J/kg).

The health risks from exposure to radiation depend on various factors, including radiation type, dose, and dose rate, and the characteristics of the exposed persons such as age at exposure and sex. The unit used in radiation protection is the sievert (Sv) and is an absorbed dose weighted for potential to cause harmful effects of different radiations and for susceptibility to radiation-induced harm for different

exposed tissues. The range of radiation dose from various sources is illustrated in Fig. 7.

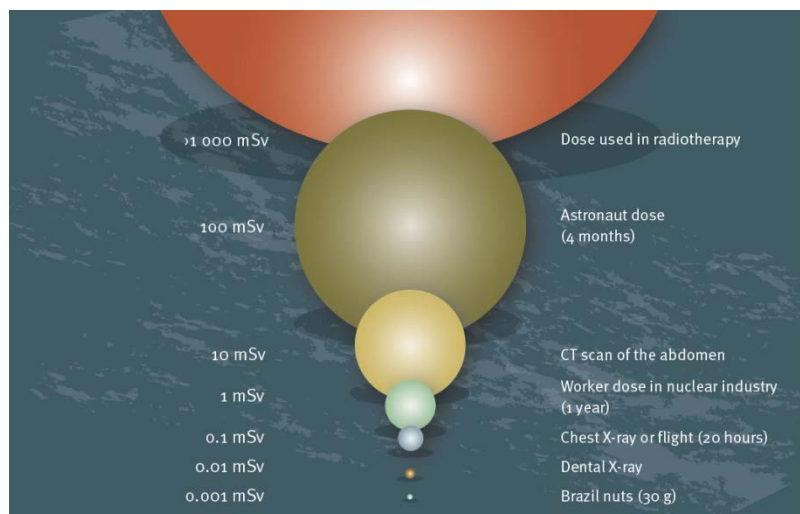


Fig. 7. The range of doses of ionizing radiation from various sources. mSv, millisieverts. Source: UNSCEAR (2016). Reproduced by permission of UNSCEAR.

Dosimetry, the quantification of radiation exposure, can be subdivided into internal and external dosimetry. Internal dosimetry assesses radiation from sources within the body, such as radionuclides, whereas external dosimetry measures sources of radiation outside the body.

The exposure to ionizing radiation from nuclear accidents has been predominantly particulate (α and β particles), but some radioactive elements also release γ -radiation. People can be exposed to ionizing radiation from nuclear accidents via several pathways: internal exposure from inhalation and ingestion intake of radionuclides, and external exposure from radionuclides in the radioactive cloud and radionuclides deposited on the ground and other surfaces.

4.5.2 Protective actions to minimize radiation exposure

In 2015, the International Atomic Energy Agency (IAEA) set international guidelines in the publication *Preparedness and response for a nuclear or radiological emergency: general safety requirements* (IAEA, 2015a). These guidelines on preparedness and response were established to ensure that procedures are in place to assess emergency conditions and take urgent protective actions (PAs) and other response actions after a nuclear accident.

Such emergency situations have three phases: early, intermediate, and long-term (FEMA, 2016). The early phase is characterized as the period during which

radionuclides are released into the environment. The intermediate phase of the accident response is characterized as the period during which radiological assessments are carried out. The intermediate phase starts when the source of the release has been contained and further significant accidental releases are unlikely. The long-term phase begins when the source is sufficiently secured to ensure that there will be no further releases, and the radiological conditions of affected areas are adequately characterized to support decisions about future inhabitation and land use. A plan must be in place to disseminate information and communicate with the public throughout a nuclear emergency.

In the event of an uncontrolled release of radioactive materials into the environment from a nuclear accident, the PAs taken to reduce radiation risks are a combination of one or more interventions intended to minimize internal or external radiation exposure (IAEA, 2015a). Urgent PAs include sheltering in place, evacuation, iodine thyroid blocking (ITB), and providing access to non-contaminated water, milk, and food. For PAs to be effective, they must be part of a radiological emergency plan to anticipate, respond to, and recover from a nuclear or radiological emergency. Emergency plans should include active and passive surveillance, as well as an effective education and warning system accessible to the nuclear power plant operators, local authorities, emergency responders, and the population.

In 2017, the World Health Organization (WHO) published new guidelines, *Iodine thyroid blocking: guidelines for use in planning for and responding to radiological and nuclear emergencies* (WHO, 2017a). These guidelines define the target population, the recommended timing and dosage of stable iodine, as well as the potential benefits of ITB to minimize thyroid dose from internal exposure to radioiodine. According to the WHO guidelines, ITB should be implemented as an urgent PA within the framework of a justified and optimized nuclear emergency protection strategy. In addition, other PAs, such as sheltering in place, evacuation, and providing access to non-contaminated water, milk, and food, must be considered. The most vulnerable groups likely to benefit from ITB are children, adolescents, pregnant women, and breastfeeding women. Individuals aged 40 years or older are less likely to benefit from ITB, because of the very low risk of thyroid cancer induced by radiation in this age group (see Chapter 4.5.4).

The optimal period of administration of stable iodine is less than 24 hours before, and up to 2 hours after, the expected onset of exposure. It would still be reasonable to administer ITB up to 8 hours after the estimated onset of exposure. However,

starting with ITB later than 24 hours after exposure may yield more harm than benefit, because it would prolong the half-life of radioactive iodine accumulated in the thyroid. A single administration of an ITB agent is usually sufficient. However, repeated administration of stable iodine may be necessary in the case of prolonged (beyond 24 hours) or repeated exposure (Zanzonico and Becker, 2000; Verger et al., 2001), where ingestion of contaminated food and drinking-water is unavoidable, and where evacuation is not feasible. Neonates, pregnant women, breastfeeding women, and people aged 60 years or older should not receive repeated ITB, because of the risk of adverse effects.

The nuclear accidents in Chernobyl and Fukushima highlighted the importance of timely PAs. In Chernobyl, very high activities of iodine-131 (^{131}I) were released over 10 days. The lack of immediate sheltering in place and implementation of ITB, incomplete evacuation, and continued ingestion of contaminated dietary items (milk and others) resulted in high thyroid doses (estimated mean dose > 650 milligray [mGy]) and a consequent significant rise in the incidence of thyroid cancer in children and adolescents living in highly contaminated areas of Belarus, the Russian Federation, and Ukraine (UNSCEAR, 2011, 2018). In contrast, an increase in the incidence of thyroid cancer was not observed in Poland, because of the effective removal of contaminated milk and the organization of ITB (Nauman and Wolff, 1993).

In Fukushima, the amount of ^{131}I released during four explosions of short duration was about one tenth of the Chernobyl release (UNSCEAR, 2014). As a result of the impact of the earthquake and the tsunami, the communication infrastructure was disrupted, thus limiting the available information. Therefore, decisions on PAs were made under conditions of uncertainty and stress (National Research Council, 2014). However, pre-emptive evacuation orders and the regulatory limits for contaminated food, milk, and water resulted in significantly lower radiation doses to the resident population (see Chapters 4.5.3 and 4.6.2). A systematic ITB programme was not implemented, because thyroid exposure of the population fell below the recommended intervention level of 50 mGy (UNSCEAR, 2014; IAEA, 2015a; see Chapter 4.6.2).

The education of the public, local authorities, and health professionals about PAs is essential before a nuclear power plant reactor starts operation. Once it is operational, education must continue and be accompanied by regular exercises and drills targeted at identifying critical strengths and weaknesses in response preparedness as part of an effective emergency plan.

4.5.3 Thyroid dose assessment

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 iodine-131 (^{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 ($^{131\text{m}}\text{Te}$ 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 to the thyroid dose of these exposure pathways depends on residence history, dietary habits, and actions taken to reduce the dose for an individual considered. However, for most of the members of the public, intake of ^{131}I is the primary source of dose to the thyroid. For the residents who lived in contaminated areas and consumed contaminated foodstuffs locally produced during the first few weeks after the accident (e.g. in the case of the Chernobyl accident, for the residents who drank milk from cows that had been grazing in pastures), the fraction of the thyroid dose due to exposure from short-lived isotopes of iodine and tellurium, external exposure, or radiocaesium ingestion intake is about 1% for each pathway (Gavrilin et al., 2004; Minenko et al., 2006). For those residents who lived in contaminated areas and did not consume locally produced contaminated foodstuffs, the contribution of the external exposure to the thyroid dose might be compared to that from ^{131}I . The contribution of short-lived isotopes of iodine and tellurium is estimated to be within several tens of percent of the dose to the thyroid from ^{131}I , whereas the contribution of radiocaesium remains insignificant ($< 1\%$) (UNSCEAR, 2014; IAEA, 2015b). It is important to stress that for the residents who did not consume contaminated foodstuffs, the main exposure pathway for ^{131}I is inhalation intake, which results in a much lower dose to the thyroid from ^{131}I (by a factor of 10–100) than if ingestion intake of ^{131}I had been the dominant pathway (Gavrilin et al., 2004).

Doses to the thyroid from the three minor contributors mentioned above are usually assessed on the basis of computational models that include data such as deposition densities of various radionuclides, taking into account information on the whereabouts and dietary habits of the individuals after the accident, which can be obtained through personal interviews and/or mailed questionnaires (Gavrilin et al.,

2004; Minenko et al., 2006). In addition, internal exposure from incorporated ^{134}Cs and ^{137}Cs can be assessed by using measurements of these radioactive isotopes of caesium by whole-body counters coupled with the time-dependent intake rate of radiocaesiums.

Doses to the thyroid from internal exposure to ^{131}I can be assessed by using a radioecological model simulating the transfer of ^{131}I through environmental processes from ground deposition to intake by humans. A typical radioecological model to estimate an individual thyroid dose consists of many parameters, including: (i) ground deposition density of ^{137}Cs ; (ii) ratio of ^{131}I to ^{137}Cs in the activities deposited on the ground; (iii) stage of vegetation development; (iv) initial interception of ^{131}I by vegetation; (v) elimination rate of ^{131}I from grass and milk; (vi) individual consumption rates of milk, milk products, and leafy vegetables; (vii) individual mass of the thyroid; (viii) individual level of iodine uptake by the thyroid; (ix) individual rate of elimination of iodine from the thyroid, and so on (Müller and Pröhl, 1993; Kruk et al., 2004). In addition, the influence of applied countermeasures (such as evacuation, introduction of maximum permissible level of ^{131}I concentration in milk, and intake of potassium iodide [KI] pills to preclude the uptake of radioactive iodine by the thyroid) should be taken into account. The total uncertainty of an individual thyroid dose derived from such a radioecological model is very high.

The total uncertainty in the thyroid dose can be substantially reduced if within a few weeks after the accident a thyroid measurement to determine the thyroidal ^{131}I content is conducted for an individual. To calculate the thyroid dose from internal exposure to ^{131}I , which is proportional to the time-integrated activity of ^{131}I in the thyroid, the variation with time of the ^{131}I activity also has to be assessed. Models of environmental transfer and metabolism of ^{131}I are used to determine: (i) the relative rate of intake of ^{131}I , both before and after the measurement, taking into account the information on residence history and dietary habits obtained during the personal interview; and (ii) the variation with time of the ^{131}I activity in the thyroid, taking into account the metabolism of ^{131}I in the body and its possible modification by the intake of stable iodine to block the thyroid (Bouville et al., 2007). The greater the number of direct thyroid measurements that are carried out for an individual at various times after the accident, the smaller the total uncertainty of the thyroid dose is. However, the time span of such direct thyroid measurements is within a few weeks after the accident, because of the short radioactive half-life of ^{131}I (8.04 days).

The direct thyroid measurement is conducted by placing a γ -radiation detector against the neck to measure the exposure rate of γ -rays arising from the radioactive decay of ^{131}I in the thyroid. However, if a simple non-energy-selective device is used, then the resulting measurement usually includes γ -rays due to: (i) incorporated radioactive isotopes of caesium; (ii) radionuclides deposited on the hair, skin, and clothes of the individual being measured; (iii) radionuclides deposited on the ground and in the room where the measurement is conducted; and (iv) naturally occurring radiation (Gavrilin et al., 1999).

With respect to assessment of the fetal thyroid dose, it is important to stress that human fetal thyroid tissue starts accumulating ^{131}I by the 12th week of gestation. According to the International Commission on Radiological Protection model (ICRP, 2001), in the case of a single intake of ^{131}I by the mother, there is a constant increase of dose coefficient versus fetal age from the 12th week to the end of the in utero period. The maximal fetal thyroid dose is about 2.5 times the thyroid dose to the mother.

4.5.4 Radiation-related cancer risks

Biological mechanisms

By definition, ionizing radiation has sufficient energy to remove otherwise tightly bound electrons from atoms. Ionizing radiation presents in the form of electromagnetic rays, namely X- or γ -rays, or as subatomic particles, such as protons, neutrons, and α and β particles (Kesminiene and Schüz, 2014). In biological organisms, ionizing radiation can cause cell death at high doses of exposure or mutations in the cell nuclei through DNA damage, which has been considered the primary mechanism of cell malignant transformation. Other biological phenomena, such as epigenetic effects, genomic instability, or the bystander effect, are also likely to be involved (Kesminiene and Schüz, 2014).

Measure of radiation-related cancer risks

To provide a quantitative measure of association between radiation dose and cancer occurrence, an excess relative risk (ERR) per unit of dose is typically used in addition to relative risk (RR), which compares the rate of cancer occurrence in an exposed group with that in a non-exposed group. ERR expresses the magnitude of increase in cancer rates in an exposed group compared with the respective background rates in a “non-exposed” group. Because of cosmic and terrestrial natural sources of ionizing radiation, human exposure to environmental ionizing

radiation is inevitable. In radiation studies, the term “non-exposed” therefore usually refers to the background exposure from natural sources (UNSCEAR, 2000b). For the interpretation of ERR estimates, an ERR of 0 means no excess in cancer occurrence above the background (spontaneous) rate, whereas an ERR of 1 indicates doubling of the cancer rate compared with the background rate. Another radiation effect measure is an excess absolute risk (EAR), which indicates the number of excess cancer cases in exposed persons above the background rate of cancer occurrence. An EAR of 0 means no excess, and any positive value represents some level of increased risk. ERR and EAR can be expressed per unit of exposure dose.

Scientific evidence on radiation-related cancer risks

The first radiation-induced cancers had already been described in the literature more than a century ago. The carcinogenic effects of ionizing radiation were recognized more broadly based on the follow-up results of survivors of the atomic bombardments of Hiroshima and Nagasaki, Japan, in 1945, who were exposed primarily to instantaneous (acute) γ -radiation. A few years after the atomic bombings, leukaemia was the first radiation-induced malignancy observed in the survivors, with excess leukaemia cases reaching a peak 6–8 years after exposure and higher relative risk in those exposed at younger ages than in those exposed at older ages (Ozasa, 2016). About 10 years after the bombing, an excess of various solid cancer sites became noticeable, including cancers of the oral cavity, oesophagus, stomach, colon, lung, breast, bladder, nervous system, skin (non-melanoma types), and thyroid (Preston et al., 2007). Increased cancer risks have also been reported after medical and occupational exposures to ionizing radiation (IARC, 2012). Recently, long-term follow-up of cancer mortality in a combined cohort of more than 300 000 radiation-monitored nuclear workers in France, the United Kingdom, and the USA strengthened the evidence of a no-threshold linear association with protracted low-dose radiation exposure both for leukaemia and for all solid cancers combined (Leuraud et al., 2015; Richardson et al., 2015, 2018). However, there remain uncertainties of the site-specific associations between low-dose radiation and cancer mortality, particularly for a type with low mortality, such as thyroid cancer.

For most of the radiation-induced solid cancers, the estimated minimum latency period, defined as the minimum period after exposure after which an excess risk is detectable, is 5–10 years (UNSCEAR, 2006). This could vary, however, depending on the magnitude of the doses received, the background cancer rate in the

population, and other factors (e.g. in the case of thyroid cancer, iodine deficiency in the population). As for thyroid cancer, an increase in thyroid cancer incidence was first reported in the fourth to fifth year after the Chernobyl accident. Based on the data from the Chernobyl accident, the estimated minimum latency period is 3–5 years (Heidenreich et al., 1999, 2004; WHO, 2013; UNSCEAR, 2018); an excess risk of radiation-induced thyroid cancer was observed among residents of the most heavily contaminated areas of Ukraine after a minimum latency period of about 3 years (i.e. no excess during about 3 years) after exposure (Heidenreich et al., 2004).

In summary, all types of ionizing radiation are associated with an increased risk of cancer at various anatomical sites, and there is a growing body of evidence that shows increased cancer risk at low doses of radiation exposure. This means that a nuclear accident can theoretically result in a substantial cancer burden in the vicinity of the accident, and therefore raise anxiety and fear in the population about radiation-related cancer risk. In reality, however, the number of radiation-related excess cancers is determined exclusively by the magnitude of accumulated individual radiation doses among affected persons. The risk of radiation-related cancer depends not only on the amounts of radionuclides and radiation types released after the accident, but also on the individual intake of radioactive substances with air, water, and food, and on implemented post-accident countermeasures mitigating the radiation exposure. Follow-up of the general population in the Southern Urals, Russian Federation, exposed to radiation as a result of several years of nuclear waste dumping into the Techa River, the main water supply to the population of riverside villages, showed that exposure to environmental sources of radioactivity (contaminated river water, river bottom sediments, and ground contamination) could result in sufficiently high doses in individuals to lead to an increase in the risk of both leukaemia and solid cancers (Preston et al., 2017). After the Chernobyl accident, with its massive release of radionuclides, clean-up workers (liquidators) showed increased risks of leukaemia and thyroid cancer (Kesminiene et al., 2012; Hatch and Cardis, 2017). In the affected general population, however, the only well-established post-Chernobyl cancer consequence was a substantial increase in the incidence of thyroid cancer after exposure in childhood and adolescence. There are also some preliminary suggestions of increased risks of breast cancer and leukaemia, but they remain unconfirmed (Hatch and Cardis, 2017). For Fukushima, data suggest that exposure

to the individuals is an order of magnitude lower than that from the Chernobyl radioactive fallout; therefore, the risk of cancer is considered low (see Chapter 4.6.2).

Inhalation or ingestion of radioiodines (iodine-131 [^{131}I] and short-lived radioiodine isotopes) released during nuclear accidents results in radiation exposure primarily of the thyroid gland. As a consequence of the Chernobyl nuclear accident, as mentioned above, there was a dramatic increase in thyroid cancers among children in substantially contaminated areas of Belarus, Ukraine, and parts of the Russian Federation (UNSCEAR, 2011), with the risk of thyroid cancer occurrence increasing 1.4–4.7-fold after 1 Gy of thyroid gland exposure (Table 2) (Cardis et al., 2005; Brenner et al., 2011; Zablotska et al., 2011; Ivanov et al., 2016; Tronko et al., 2017a). People who took stable iodine for thyroid blocking immediately after the accident had a lower risk of thyroid cancer after exposure to radioiodine compared with those who did not; moreover, residents of the areas where iodine deficiency is common may have had higher risks of thyroid cancer (Nauman and Wolff, 1993; Cardis et al., 2005; Brenner et al., 2011). In countries outside the former Soviet Union, thyroid doses from the fallout were at least 2 orders of magnitude lower than those in exposed populations of Belarus, the Russian Federation, and Ukraine, with studies carried out there providing no unequivocal evidence on increased risk of thyroid cancer (UNSCEAR, 2011). In relation to the Three Mile Island accident, thyroid cancer incidence was higher than expected in the 30 years after the accident in the affected nearby counties, but the correlation with the accident remains uncertain because incidence rates may coincide with other factors (Levin et al., 2013). Studies of thyroid cancer, as well as other health consequences, in relation to the Fukushima accident and in comparison with the other accidents are under way (Hasegawa et al., 2015).

Table 2. Summary of several key studies on risk of thyroid cancer after radiation exposure in childhood

Exposure (study)	Mean age at exposure (years)	Mean thyroid dose (Gy)	Number of thyroid cancers	ERR per 1 Gy (95% CI)
<i>External exposure</i>				
Tinea capitis (Sadetzki et al., 2006)	7	0.093	159	20.2 (11.8–32.3)
Enlarged thymus (Adams et al., 2010)	0.2	1.29	63	3.2 (1.5–6.6)
Childhood external radiation, 12-study pooled analysis (Veiga et al., 2016)	5	0.71	1070	5.5 (1.7–7.2)
Atomic bomb survivors (Furukawa et al., 2013)	< 20	0.142	191	1.3 (0.6–2.7) ^a
<i>¹³¹I exposure</i>				
Chernobyl, Russian Federation (Ivanov et al., 2016)	< 18	0.174	316	4.7 (2.5–7.7)
Chernobyl, Belarus, Russian Federation (Cardis et al., 2005)	7.4	0.433	276	4.5 (1.2–7.8) ^b
Chernobyl, Belarus (Zablotska et al., 2011)	8.2	0.56	87	2.2 (0.8–5.5) ^c
Chernobyl, Ukraine, 1st screening cycle (Tronko et al., 2006)	8.0	0.68	45	5.2 (1.7–27.5)
Chernobyl, Ukraine, 2nd–4th screening cycles (Brenner et al., 2011)	8.0	0.65	65	1.9 (0.4–6.3)
Chernobyl, Ukraine, 5th screening cycle (Tronko et al., 2017a)	8.0	0.62	47	1.4 (0.4–4.2)

CI, confidence interval; ERR, excess relative risk; Gy, gray; ¹³¹I, iodine-131.

^a ERR per Gy of thyroid dose at age 60 years after acute exposure at age less than 10 years.

^b Excess odds ratio, as an indicator of the radiation-induced risk in a case-control study, with interpretation similar to ERR.

^c Based on findings of the 1st screening cycle, for thyroid dose range < 5 Gy.

Until the mid-20th century, radiotherapy was used for treatment of various benign diseases, such as tinea capitis (ringworm of the scalp), and even some conditions that are no longer considered diseases, namely enlarged thymus and tonsillar hypertrophy (Table 2). Depending on the treatment target, the average thyroid doses varied from about 0.1 Gy in patients treated for tinea capitis (Sadetzki et al., 2006) to 1.3 Gy in patients with enlarged thymus (Adams et al., 2010). In studies of the long-term risk of thyroid cancer after radiotherapy for childhood cancer, the dose to the thyroid reached up to 50 Gy (Sigurdson et al., 2005; Bhatti et

al., 2010; Inskip et al., 2016). A pooled analysis of 12 studies on thyroid cancer risk after external radiation exposure in childhood (Veiga et al., 2016) showed a thyroid cancer risk that increased steeply with thyroid doses up to 10 Gy and then levelled off at doses of 10–30 Gy, followed by a gradual decrease in risk for doses exceeding 40 Gy. A closer look at the range of low thyroid doses of less than 0.2 Gy revealed a linear dose–response relationship between thyroid dose and thyroid cancer risk, with no evidence of dose threshold (Fig. 8) (Lubin et al., 2017). Within this dose range, the dose–effect association was greater at a younger age at exposure (Fig. 9) and a younger attained age, and persisted more than 45 years after exposure (Veiga et al., 2016; Lubin et al., 2017).

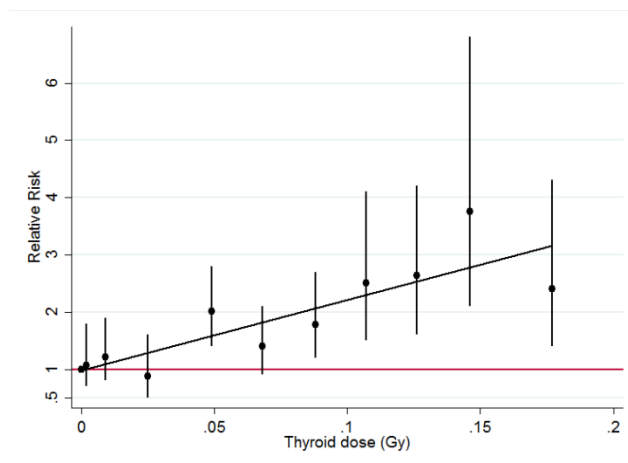


Fig. 8. Relative risk (RR) of thyroid cancer in the low-dose range (< 0.2 Gy) compared with the dose category of 0 (reference), with corresponding 95% confidence intervals. The RRs were estimated using data pooled from nine cohort studies and adjusted for study, sex, age, other study-specific factors, and chemotherapy exposure. The line was fitted based on the dose category-specific RR estimates for illustrative purposes. Adapted from Lubin et al. (2017).

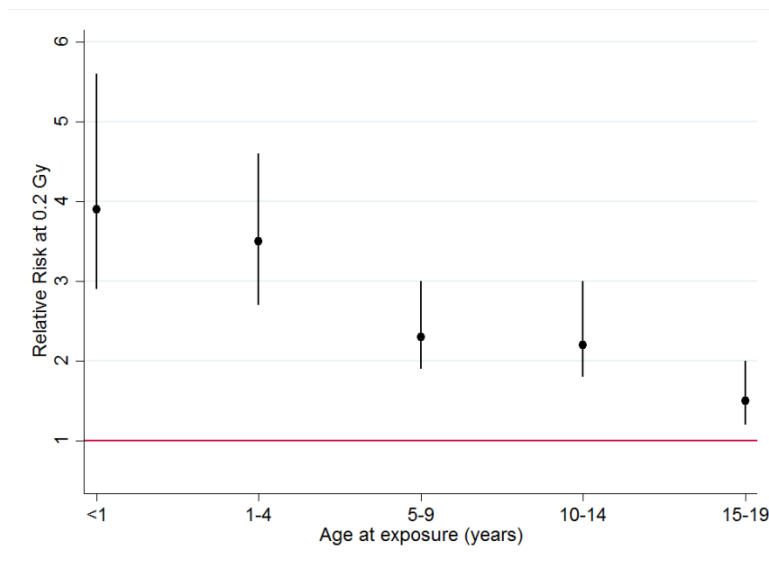


Fig. 9. Relative risk (RR) of thyroid cancer at 0.2 Gy by age at exposure, with corresponding 95% confidence intervals. The risk of thyroid cancer at 0.2 Gy is compared with that in a non-exposed group by age at exposure. The RRs were estimated using data pooled from eight studies and adjusted for study, sex, age, and other study-specific factors. Compiled from Veiga et al. (2016).

There have also been studies examining potential differences in the magnitude of radiation effects on thyroid cancer by certain characteristics. Studies on thyroid cancer risk after external irradiation in childhood provided some evidence of higher risk in those exposed at a younger age (Furukawa et al., 2013; Veiga et al., 2016; Lubin et al., 2017). A similar tendency of decreasing risk with age at exposure was also observed in studies on ^{131}I -induced thyroid cancer risk after the Chernobyl accident (Brenner et al., 2011; Zablotska et al., 2011; Tronko et al., 2017a). Although thyroid cancer occurs more frequently among women than among men, no consistent difference in radiation-induced 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., 2017a). Papillary carcinoma is the most common type and is most frequently seen after radiation exposure, but studies have not found clear differences in radiation-induced risk between thyroid cancer subtypes (i.e. papillary vs non-papillary tumours) (Veiga et al., 2016).

4.5.5 Sources of uncertainty in the assessment of the risk of radiation-induced thyroid cancer

Assessment of the risk of radiation-induced thyroid cancer

To assess the risk of radiation-induced thyroid cancer in a given population, three main elements are needed: (i) an estimate of the dose to the thyroid, considering all sources of exposure (external radiation and internal contamination due to ingestion and inhalation) and taking into account variation with age; (ii) a risk model, characterizing the relationship between the dose and the excess risk of thyroid cancer and taking into account modifying factors of this dose–risk relationship, such as sex, age at exposure, and time since exposure; and (iii) the baseline rate of thyroid cancer in the study population, taking into account variation with age and sex (WHO, 2013; Walsh et al., 2014).

Main sources of uncertainty in the assessment of thyroid cancer risk

Optimally, the dose to the thyroid can be estimated from individual measurements of the thyroid incorporated activity and measurement of the external exposure. In such cases, the uncertainties in the estimated dose may have little impact on the estimated risk (Little et al., 2014, 2015). However, in most cases, individual exposure has to be estimated from questionnaire data and environmental measurements. Then, the main sources of uncertainty in the estimated dose are related to the accuracy of retrospective dosimetry and the reconstruction of cumulative dose over time (Drozdovitch et al., 2016). The reconstruction of doses from radioiodines is especially difficult, because of the short half-lives of some of the isotopes. Models used to estimate the dose to the thyroid from estimates or activity measurements are also associated with inherent uncertainties. Level of iodine deficiency and stable iodide intake are also major elements determining the dose to the thyroid. Correction for uncertainties and measurement errors depends on the magnitude and the nature (Berkson or classical, shared or unshared) of the uncertainties (Little et al., 2014, 2015; Land et al., 2015).

Several risk models for thyroid cancer have been derived from atomic bomb survivors (Preston et al., 2007; Furukawa et al., 2013; Jacob et al., 2014), cancer patients treated with radiation therapy (Veiga et al., 2016; Lubin et al., 2017), and people exposed after the Chernobyl accident (Brenner et al., 2011; Zablotska et al., 2011; Kaiser et al., 2016; Tronko et al., 2017a). The most important uncertainties are related to the shape of the dose–risk relationship (linear extrapolation from relatively

high dose levels to low dose levels), the impact of modifying factors (sex, age at exposure), the duration of the minimum latency period (i.e. the minimum period after exposure after which an excess risk is detectable), and the nature of the radiation-induced risk (absolute or relative excess). Variation of risk estimates with tumour type (benign vs malignant, nodule diameter, focality, singularity) has also been reported (Cahoon et al., 2017). Most health risk assessments have used models derived from atomic bomb survivors (WHO, 2013), but the applicability of such models to a situation of chronic low exposure is uncertain (UNSCEAR, 2015).

Thyroid cancer is a rare disease, especially among children. This leads to uncertainties in the assessment of baseline rates when based on a population of limited size (Matsuda et al., 2010). Large variations in thyroid cancer incidence are observed by age, sex, and region. Baseline rates are strongly influenced by diagnostic methods, and improvements in these methods have led to an increase in incidence rates in the past decades in most industrialized countries. Because most thyroid cancer cases can be cured, mortality cannot be used to define baseline rates. Substantial uncertainty also occurs when current baseline rates are used in long-term risk prediction. This method assumes the stability of baseline rates over time in the future, which is a major source of uncertainty (WHO, 2013).

Impact of screening on the assessment of thyroid cancer risk

Screening affects the assessment of the risk of radiation-induced thyroid cancer in three different ways. It has an impact on the baseline rate, the studied health outcome, and the estimated minimum latency period.

Screening has an impact on the baseline rate of thyroid cancer, because much earlier stages of thyroid cancer are detected. On the basis of results of thyroid cancer incidence after the Chernobyl accident in Ukraine, it was estimated that the impact of thyroid ultrasound examination in Fukushima may have led to an increase by a factor of 7 compared with baseline rates predicted by a cancer registry (Jacob et al., 2014). More recently, it was assumed that the impact on baseline rates of the TUE programme in Fukushima was about 3 times that of the screening performed after the Chernobyl accident (Katanoda et al., 2016). In the Republic of Korea, thyroid cancer screening is the most important determinant of the epidemic of thyroid cancer, particularly among women. Thyroid cancer screening appeared to be associated with the increase in only one tumour type, papillary thyroid cancer, and to have no impact on thyroid cancer mortality (Ahn et al., 2016).

The studied health outcome is also affected by screening. The detection of very small thyroid nodules (diameter, 5 mm) by ultrasound is very different from the diagnosis of a tumour on the basis of clinical indicators. Most of these small nodules, cancerous or benign, would have remained asymptomatic, possibly for decades. Thyroid examination may result in the detection of thyroid cancer at an earlier age and at an earlier stage compared with baseline registry data (Yamashita et al., 2018). It is uncertain whether the dose–risk relationship for such small nodules is similar to that estimated for thyroid cancer, and the applicability of the existing models to predict risk of thyroid cancer detected by screening is uncertain. A recent study of people in Belarus exposed to radioactive releases from Chernobyl during childhood estimated the dose–risk coefficient according to malignancy and size of nodules. The authors concluded that the association was much stronger for nodules larger than 10 mm than for microcarcinomas (< 10 mm) (Cahoon et al., 2017). In a Ukrainian cohort of people exposed to radioactive releases from Chernobyl during childhood, the decrease in excess relative risk observed over the past 10 years may be explained by a decrease in the diameter of detected nodules (Tronko et al., 2017a).

Screening may challenge the current estimate (3–5 years) of the minimum latency period of thyroid cancer (see Chapter 4.5.4). If some of the screened nodules will develop into thyroid carcinoma, and if there is a dose–risk relationship with such small nodules, then an excess risk of thyroid cancer in a population could be detected before 3 years after exposure. However, currently there is limited scientific evidence for a dose–risk relationship between radiation exposure and papillary microcarcinoma of the thyroid.

4.6 Experiences from previous nuclear accidents

4.6.1 Background

Although nuclear power plants must adhere to high safety standards, six decades of generating electricity with nuclear power has shown the potential hazards of both nuclear criticality and the release of radioactive materials. Since the first operation of a nuclear power plant for commercial use, in 1954, accidents involving meltdown have occurred at three nuclear power plants: Three Mile Island, USA (in 1979); Chernobyl, Ukraine (in 1986); and Fukushima Daiichi, Japan (in 2011).

Three Mile Island

On 28 March 1979, a serious accident occurred at Unit 2 of the Three Mile Island nuclear power plant near Harrisburg, Pennsylvania, USA. A relatively minor malfunction in the secondary cooling circuit initiated the accident that caused the reactor's shutdown, followed by failure of the pressure relief valve to close, allowing the coolant to drain away. As a result, the core overheated and suffered severe damage (U.S. Nuclear Regulatory Commission, 2013). Deficient control room instrumentation and inadequate emergency response training were to blame for the accident.

Although the accident did not result in major releases of radioactive materials into the environment or radiation exposures of the public, there were almost no existing emergency plans for the local communities around Three Mile Island; therefore, the response to the accident was confusion (United States President's Commission on the Accident at Three Mile Island, 1979).

Chernobyl

On 26 April 1986, the accident at the Chernobyl nuclear power plant, located in Ukraine (then a part of the former Soviet Union), occurred during an experimental test of the electrical control system as the reactor was being shut down for routine maintenance. In violation of safety regulations, the operators had switched off important control systems and allowed the reactor, which had design flaws, to reach unstable, low-power conditions. A sudden power surge caused a steam explosion that ruptured the reactor vessel, allowing further violent fuel–steam interactions that destroyed the reactor core and severely damaged the reactor building. Subsequently, an intense graphite fire burned for 10 days. The accident caused the largest release of radioactive materials into the environment ever recorded for any civilian operation (UNSCEAR, 2011).

Precipitation, occurring during the passage of the radioactive cloud, deposited radionuclides over large areas. This led to a complex and variable contamination of land, water, and biota, and caused serious social and economic disruption for large populations in Belarus, the Russian Federation, and Ukraine (UNSCEAR, 2011).

Fukushima

On 11 March 2011, north-eastern Japan was struck by an earthquake of magnitude 9.0 (the Great East Japan Earthquake), followed by a major tsunami. These two disasters affected a wide area, including the Fukushima Daiichi Nuclear

Power Plant, in Fukushima Prefecture. The severe damage to the power plant resulted in the extensive release of radioactive materials into the environment. Although the Fukushima and Chernobyl accidents were both categorized at the same level (Level 7) on the International Nuclear and Radiological Event Scale, the radiation doses to the local population were considerably lower for the Fukushima accident than for the Chernobyl accident (IAEA, 2014b).

Although the emergency response teams were dispatched by the government in a timely manner, the unprecedented demands for response to such catastrophic natural disasters hampered the response needed for the nuclear accident. Additional challenges, including disruption of critical infrastructure (e.g. electrical power, communication, and transportation), further complicated the emergency response to the nuclear accident (National Research Council, 2014).

The chapters that follow discuss experiences from previous nuclear accidents, including dose assessment, thyroid screening, psychosocial health, and lessons learned.

4.6.2 Radiation dose to the thyroid gland

Three Mile Island

The core melt at the Three Mile Island reactor led to the discharge of fission products that were mostly retained in the water, resulting in a relatively small environmental release of 5.5×10^{11} Bq of iodine-131 (^{131}I). Therefore, exposures of the public to radiation were negligible (UNSCEAR, 2011). The estimated incremental excess doses within 50 miles (~80 km) and 5 miles (~8 km) of the nuclear power plant were less than 1% and about 10% or less of the annual background level, respectively (United States President's Commission on the Accident at Three Mile Island, 1979). Radiation dose to the thyroid was not directly determined, but whole-body measurements of local residents found no detectable levels of radiation (Leung et al., 2017). The average individual dose from external γ -radiation within 80 km of the plant was 15 microsieverts (μSv) (0.015 millisieverts [mSv]), whereas the estimated maximum effective dose was 850 μSv (0.85 mSv) (UNSCEAR, 1993). The estimated individual dose to the thyroids of children aged 1 year was 0.07 milligray (mGy) or less (IARC, 2000).

Chernobyl

The Chernobyl accident caused the largest uncontrolled radioactive release into the environment ever recorded for any civilian operation. It deposited radioactive

material not only over large areas of the former Soviet Union but also, to a lesser extent, in the rest of Europe. The radionuclides released from the reactor that caused exposure of individuals were mainly ^{131}I , caesium-134 (^{134}Cs), and ^{137}Cs . The accident led to a release of about 1.76×10^{18} Bq of ^{131}I into the environment (UNSCEAR, 2000a). Consequently, a large geographical area was radioactively contaminated and millions of people were exposed to radioiodines and other radionuclides. The lack of timely implementation of countermeasures, such as management of animal fodder and milk production in the former Soviet Union, led to high thyroid doses, particularly among children.

After the Chernobyl accident in May–June 1986, large-scale monitoring was conducted in the three most contaminated countries: Belarus, the Russian Federation, and Ukraine. In total, by the end of June 1986, measurements of ^{131}I in the thyroid had been performed for more than 400 000 people, including more than 200 000 in Belarus, 45 000 in the Russian Federation, and about 150 000 in Ukraine (UNSCEAR, 2000a). Consumption of fresh milk from cows that had been grazing in pastures was the main pathway of radioiodine intake for a majority of the residents after the Chernobyl accident. The daily rate of consumption of fresh milk was found not to vary much with age; however, because the thyroid mass increases with age from birth to adulthood by a factor of about 10, the average thyroid dose for infants is about 10 times that for adults. This contributed to the large doses to the thyroid, especially in children living in rural areas in the vicinity of the damaged reactor. For example, about 55% of children younger than 3 years from evacuated villages and about 30% of children younger than 3 years from non-evacuated villages of the three southern raions (Bragin, Khoiniki, and Narovlya) of Gomel Oblast of Belarus, which neighbour the Chernobyl nuclear power station, received thyroid doses higher than 2.5 Gy (Savkin and Shinkarev, 2007). (A raion is an administrative division, and an oblast is a region.)

The distribution of individual thyroid doses estimated on the basis of direct thyroid measurements can be described with a log-normal function. This distribution can be applied to the individuals in an area with similar exposure conditions. An analysis of the distribution of the thyroid doses derived from direct thyroid measurements from 226 children younger than 17 years from an evacuated village, Pogonnoe of Khoiniki raion of Gomel Oblast, showed that the geometric mean of that distribution was equal to 2.1 Gy, with a standard deviation of 3.1. The highest estimates of thyroid doses to the children derived from direct thyroid measurements were found to be as

high as 50 Gy (Shinkarev et al., 2008). A typical contribution of short-lived radioiodines to the thyroid dose for the public was within a few percent of the contribution from ^{131}I after the Chernobyl accident. Among the short-lived radioiodines, iodine-133 (^{133}I) and ^{132}I (due to the intake of tellurium-132 [^{132}Te] and its radioactive decay to ^{132}I in the body) play a major role in terms of internal dose to the thyroid (Gavrilin et al., 2004).

Fukushima

The level of ^{131}I released because of the Fukushima accident was estimated to be about one tenth of that released as a result of the Chernobyl accident (UNSCEAR, 2014). After the Fukushima accident, in March–April 2011, in vivo monitoring of the ^{131}I content in the thyroid was conducted for slightly more than 1000 residents (WHO, 2012; UNSCEAR, 2014; IAEA, 2015b). Because of the small number, the measurements were only used to test a radioecological model of thyroid dose reconstruction. According to the UNSCEAR report, the settlement-average thyroid absorbed dose estimates in the first year after the accident for evacuated residents from Fukushima Prefecture were in the range of 0.007–0.035 Gy for adults and 0.015–0.083 Gy for infants aged 1 year. For the residents from settlements in Fukushima Prefecture and six neighbouring prefectures that were not evacuated, the thyroid absorbed dose estimates are in the range of 0.001–0.017 Gy for adults and 0.003–0.052 Gy for infants aged 1 year (UNSCEAR, 2014). However, because of the small number of direct thyroid measurements, the UNSCEAR estimates were based on an assumption that a substantial contribution to the thyroid dose was by ingestion intake of ^{131}I .

An analysis of direct thyroid measurements conducted on 26–30 March 2011 for 1080 children from three settlements – Iwaki city, Kawamata town, and Iitate village – showed that inhalation intake of ^{131}I was the dominant pathway, rather than ingestion intake (IAEA, 2015b). According to the International Atomic Energy Agency (IAEA) estimates, the geometric means of the distribution of individual thyroid equivalent doses for children aged 0–15 years derived from direct thyroid measurements were 3.2 mSv for 134 children of Iwaki city, 2.2 mSv for 647 children of Kawamata town, and 6.0 mSv for 299 children of Iitate village (IAEA, 2015b). The estimated internal thyroid doses to infants aged 1 year were mostly below 30 mSv (Kim et al., 2016). (Thyroid equivalent dose expressed in millisieverts is numerically equal to thyroid absorbed dose expressed in milligrays.)

It is worth noting that in the case of inhalation intake being dominant, the average thyroid dose to adults from ^{131}I is smaller than that to infants from the same settlement by a factor of about 2 (rather than a factor of 10 when ingestion intake with cows' milk was dominant), because a person's breathing rate decreases with age from an infant to an adult by a factor of about 5. A typical contribution of short-lived radioiodines to the thyroid dose for the residents who lived in areas where the main fallout occurred on 15 March 2011, and who did not consume contaminated drinking-water and food, is estimated to be within 15% of the dose to the thyroid from ^{131}I . The contribution to the thyroid dose for the residents who lived in areas where the main fallout occurred on 12 March 2011 might be as great as 30–40%. Among the short-lived radioiodines, the main contributors to the thyroid dose were ^{133}I and ^{132}I (through intake of ^{132}Te) (Shinkarev et al., 2015).

4.6.3 Thyroid cancer screening

Three Mile Island

Because the amount of radiation received by any one individual outside the plant was deemed to be low, no thyroid screening was performed after the Three Mile Island accident. It was determined that any increase in cancer incidence, compared with background rates, would be impossible to detect. For example, one projection was that the risk of cancer death as a result of radiation exposure was 0.7 for the 2 million exposed people. The projection indicated that there was a 50% chance that there would be 0 cancer deaths, a 35% chance that there would be 1 cancer death, and a 12% chance that there would be 2 cancer deaths as a result of radiation exposure (United States President's Commission on the Accident at Three Mile Island, 1979).

Chernobyl

Before the Chernobyl accident, knowledge about risk of thyroid cancer after exposure to ionizing radiation was mainly based on findings from epidemiological studies of external X- and γ -radiation, showing higher radiation risk for children than for adults, with an increase in thyroid cancer incidence observed 10 years after exposure (NCRP, 1985). The issue of thyroid cancer risk after exposure to ^{131}I was of special interest because of the ability of the thyroid gland to concentrate iodine. This puts the thyroid at potential risk from internal irradiation to radioactive isotopes of iodine, especially in children, who are potentially the most sensitive group (see Chapter 4.5.4). However, the data originated from long-term follow-up of patients

receiving radioiodine for diagnostic or therapeutic purposes, with very few children among the patients, precluding reliable thyroid cancer radiation risk estimates in children. The first reports on a large increase in the number of thyroid cancers in exposed children observed 4 years after the accident were published in Belarus, the Russian Federation, and Ukraine (Kazakov et al., 1992; Likhtarev et al., 1995; Goldman, 1997). After these reports, several health screening programmes, including thyroid screening, were initiated and carried out in collaboration with international organizations such as the International Atomic Energy Agency (IAEA), the World Health Organization (WHO), the Sasakawa Memorial Health Foundation, the International Federation of Red Cross and Red Crescent Societies, and others.

The humanitarian and scientific projects of the Sasakawa Memorial Health Foundation (May 1991–April 1996) focused on medical examinations for children in order to study the effects of low-dose radiation exposure on their health. These examinations were considered necessary to identify health problems in the residents of the affected areas, and to provide accurate information to the members of the population, who were experiencing significant fear and anxiety. The examination protocol included measurements of internal caesium-137 exposure dose using whole-body counters, clinical examination, thyroid ultrasonography, measurements of thyroid-related hormones (thyroid-stimulating hormone, free thyroxine), and measurements of thyroid auto-antibodies. In case of suspicious ultrasonography findings, fine-needle aspiration cytology (FNAC) and blood tests were performed in children from the five most affected regions in Belarus, the Russian Federation, and Ukraine. The protocol was developed based on experience gained during investigations of atomic bomb survivors in Nagasaki (Shigematsu, 2002).

During 1991–1996, about 160 000 children in five areas of Belarus, the Russian Federation, and Ukraine were examined. Because of the detection of an enormously high prevalence of thyroid cancers in the Gomel region of Belarus, the Chernobyl Sasakawa Health and Medical Cooperation Project was extended for 5 years in that area. In total, more than 200 000 children were screened (Shigematsu, 2002).

Soon after the Chernobyl Sasakawa Health and Medical Cooperation Project, several projects were launched, including the Chernobyl Thyroid Diseases Study Group (CTDSG), which performed thyroid screening examinations on residents exposed as children and adolescents (Stezhko et al., 2004). District-average thyroid doses in children and adolescents served as the main justification criterion for designing and implementing long-term cohort follow-up studies, such as the USA–

Ukraine (UkrAm) cohort study and the USA–Belarus (BelAm) cohort study; both focused on thyroid cancer and non-cancer thyroid disease screening (Stezhko et al., 2004). Cohort screening was developed in Ukraine and Belarus and performed jointly by radiation epidemiologists and clinicians. Supplementing the findings of the UkrAm cohort study, a screening cohort of those exposed in utero in Ukraine was initiated (Hatch et al., 2009).

A detailed summary of three screening cohorts is presented in Table 3. First, a target population of 114 537 people who were born between 26 April 1968 and 26 April 1986 and who had their thyroid radioactivity measured in 1986 shortly after the accident, was identified: 75 349 people in Ukraine and 39 188 in Belarus. A random sample of 13 243 persons was taken from 32 385 people in Ukraine, and another random sample of 11 970 persons was taken from 38 543 people in Belarus for more intensive examination (Stezhko et al., 2004). A screening cohort included individuals with low (< 0.3 Gy), medium ($0.3\text{--}1.0$ Gy), and high (> 1.0 Gy) thyroid dose estimates. The target population exposed in utero consisted of 5042 child–mother pairs in which women were pregnant at some time during the period 26 April–30 June 1986, because exposure to ^{131}I occurs for 2 months after the accident. The in utero screening cohort included 2582 child–mother pairs.

Table 3. Thyroid cancer and non-cancer thyroid disease screening cohorts in Ukraine and Belarus of people exposed to ¹³¹I in childhood or in utero

Parameters	Cohort		
	Ukrainian screening cohort (UkrAm)	Belarusian screening cohort (BelAm)	Ukrainian in utero cohort
Source population	75 349	39 188	5042
Number of people selected for tracing and recruitment	32 385	38 543	3045
Screening cohort (percentage of people selected for tracing and recruitment)	13 243 (41%)	11 970 (31%)	2582 (85%)
Percentage of women	51	51	52
Mean age at exposure \pm standard deviation, years	8.0 \pm 4.7	8.2 \pm 5.0	Mother was pregnant at some time during the period 26 April–30 June 1986
Mean ¹³¹ I dose, mGy	650	580	By trimester: 1st trimester: 2.1 2nd trimester: 7.3 3rd trimester: 131.1
Number of screening cycles, years	5 (1998–2015)	3 (1996–2008)	2 (2003–2015)
Participation rate by cycle (number of screened subjects divided by total cohort size)	1st cycle: whole cohort 2nd cycle: 94% 3rd cycle: 89% 4th cycle: 77% 5th cycle: 76%	1st cycle: whole cohort 2nd and 3rd cycles: N/A	1st cycle: whole cohort 2nd cycle: 70%
Mean age at screening (range), years	1st cycle: 22 (12–32) 2nd cycle: 24 (15–35) 3rd cycle: 26 (17–37) 4th cycle: 28 (19–39) 5th cycle: 35 (26–46)	1st cycle: 22 (12–32)	1st cycle: 18 (16–20)
Number of thyroid cancers detected	1st cycle: 43 PTCs; 2 FTCs 2nd cycle: 30 PTCs; 1 FTC; 1 MTC 3rd cycle: 16 PTCs; 1 FTC 4th cycle: 15 PTCs; 1 FTC 5th cycle: 44 PTCs; 3 FTCs	1st cycle: 86 PTCs; 1 FTC 2nd and 3rd cycles: 71 PTCs	1st cycle: 6 PTCs; 1 FTC 2nd cycle: 2 TCs (data not published yet)
Mean age at thyroid cancer surgery \pm standard deviation, years	1st cycle: 23.2 \pm 5.1 2nd cycle: 26.5 \pm 5.1 3rd cycle: 26.7 \pm 5.6 4th cycle: 29.0 \pm 4.4 5th cycle: 35.2 \pm 4.9	1st cycle: 23.0 \pm 5.9 2nd and 3rd cycles: 24.4 \pm 6.1	1st cycle: 19.1 \pm 1.2
Other non-cancer thyroid findings significantly associated with ¹³¹ I thyroid exposure	Follicular adenoma Subclinical hypothyroidism	Follicular adenoma Thyroid nodules Subclinical hypothyroidism	No evidence of statistically significant association for non-cancer thyroid outcomes

FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; N/A, not available; PTC, papillary thyroid cancer; TC, thyroid cancer.

During the period 1998–2007, the Ukrainian cohort members were screened four times (biannually) using the standard screening protocol. In 2009–2011, only people with thyroid nodules that were detected earlier were actively followed up and examined. The rest of the screening cohort, which consisted of subjects free of thyroid nodules, were passively followed up through the linkage of the cohort data with data from the Ukraine National Cancer Registry to identify thyroid and non-thyroid cancers in the cohort (Tronko et al., 2012). A fifth screening cycle was performed in 2012–2015, and 76% of the initial screening cohort was examined (Tronko et al., 2017a). Two screening cycles were performed in the in utero screening cohort in Ukraine during 2003–2015; the participation rate in the second screening cycle was 70%. In Belarus, three screening cycles were performed, and the screening was then discontinued after 2008.

The standard screening procedure included thyroid palpation, ultrasound examination, blood sampling for thyroid hormones, urinary iodine measurement, detailed dosimetric interview, and consultation and recommendations from an endocrinologist. In the case of detection of a thyroid nodule, a patient was referred for FNAC (Tronko et al., 2017b). The following criteria were used to decide whether FNAC was appropriate (Stezhko et al., 2004):

- (i) thyroid nodule or focal lesion with largest diameter greater than or equal to 10 mm detected by either palpation or ultrasonography;
- (ii) thyroid nodule or focal lesion with diameter 5–10 mm at least partially solid and with the following indirect signs of malignancy:
 - unclear or irregular borders
 - extension through thyroid capsule
 - heterogeneous or hypoechoic ultrasonic density
 - stippled calcification
 - increasing size during follow-up
 - abnormal lymph nodes of uncertain etiology;
- (iii) diffusely abnormal thyroid structure accompanied by unexplained cervical lymphadenopathy. In this case, FNAC of one or more lymph nodes is also to be done; and
- (iv) in the case of indeterminate or non-diagnostic cytology, FNAC is repeated up to three times within 1 year.

Although treatment was not a part of the protocol for the study, all individuals with thyroid disorders were/are offered standard medical care in the appropriate medical institutions in Ukraine and Belarus.

Fukushima

Based on the data from the Chernobyl accident, the increase in paediatric thyroid cancer incidence was not reported until 4–5 years after the radiation exposure (Kazakov et al., 1992). Also, the estimated internal thyroid doses were mostly below 30 mSv in Fukushima residents, including infants aged 1 year (Kim et al., 2016; see Chapter 4.6.2). Given the low radiation doses, any overall increase in thyroid cancer incidence in residents of Fukushima because of radiation exposure from the accident would probably be too small to be observed. However, the general public in Japan became particularly concerned about the potential risk of childhood thyroid cancer, similar to what was observed after the Chernobyl accident. As a result of such concerns, the Thyroid Ultrasound Examination (TUE) programme was started on 9 October 2011 (Yamashita and Suzuki, 2013). Because there are no survey records from before the accident, the “first round survey” is referred to as the “Preliminary Baseline Survey” and the “second survey” is denoted as the “Full-Scale Survey”. The protocol of the TUE programme has been described in detail elsewhere (Yamashita and Suzuki, 2013; Suzuki et al., 2016b; Yamashita et al., 2018) and is described briefly here.

Preliminary Baseline Survey

The Preliminary Baseline Survey, which was the first round of the TUE programme, was conducted from October 2011 to March 2014 for all inhabitants of Fukushima Prefecture aged 0–18 years on 1 April 2011. Among the 367 672 people in the target population, 300 473 subjects (81.7%), including evacuees currently living in other prefectures, voluntarily completed this survey (Suzuki et al., 2016a; Fukushima Medical University, 2017b; Yamashita et al., 2018). Written informed consent was obtained from the parents or guardians of all surveyed children.

Full-Scale Survey

The first Full-Scale Survey, which was the second round of the TUE programme, was conducted in the 2 years between 1 April 2014 and 31 March 2016. The participation rate in the primary examination was 71.0% of 381 256 people (Fukushima Medical University, 2017a).

The second Full-Scale Survey, which is the third round of the TUE programme, is in progress.

Methods used in the primary examination of the TUE programme

Ultrasonography was used to examine the thyroid gland (Fig. 10). The detailed protocol has been reported elsewhere (Yamashita and Suzuki, 2013; Suzuki, 2016; Suzuki et al., 2016b). In brief, the ultrasonography examination was conducted using portable equipment such as LOGIQ e Expert (GE Healthcare Co.) and Noblus (Hitachi-Aloka Co.). This highly sophisticated method was able to detect nodules and cysts smaller than 1 mm in diameter and record thyroid volume and other findings, such as congenital defects and ectopic thymus. In cases with nodules, the examiner recorded the multifocality of nodules and the location of the largest nodule, and measured the greatest dimension of the largest nodule. In cases with cysts, the examiner also recorded the multifocality of the cysts and the location of the largest cyst, and measured the greatest dimension of the largest cyst. The primary examination aimed at detecting nodules or cysts by ultrasonography and used a classification system, divided into three categories. Those in category A were recommended to undergo another primary examination. This category was also further divided into two categories: A1, for those without nodules or cysts, and A2, for those with nodules up to 5.0 mm and/or cysts up to 20.0 mm. Category B included those with nodules larger than 5.0 mm and/or cysts larger than 20.0 mm, who were then recommended to undergo a confirmatory examination. Subjects in category C required immediate examination as a result of a finding of a large or suspicious thyroid tumour or lymph node.

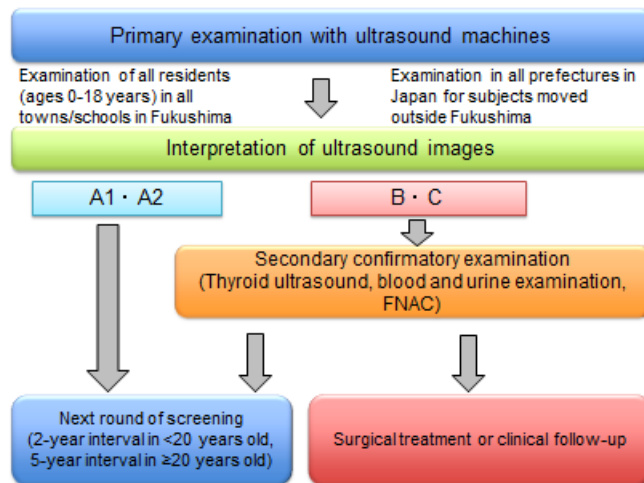


Fig. 10. Flow chart of the Thyroid Ultrasound Examination programme for residents of Fukushima aged 18 years or younger at the time of the accident. FNAC, fine-needle aspiration cytology; US, ultrasonography.

Methods used in the secondary confirmatory examination of the TUE programme

Subjects with nodules of diameter 5.1 mm or larger or cysts of diameter 20.1 mm or larger were recommended for a secondary confirmatory examination. Physicians credentialled by the Japan Thyroid Association, the Japanese Society of Thyroid Surgeons, or the Japan Society of Ultrasonics in Medicine (JSUM) performed the confirmatory examination using the highest resolution instrumentation. This confirmatory examination included a precise ultrasonography examination, blood and urine tests, and FNAC if ultrasonography findings of nodules or cysts met the FNAC criteria according to the guidelines issued by the Japan Association of Breast and Thyroid Sonology (JABTS) (Fig. 11; Suzuki, 2016; Suzuki et al., 2016a).

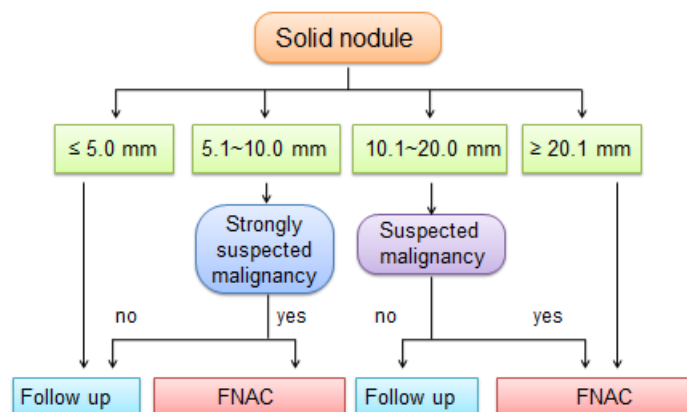


Fig. 11. Guideline for management of thyroid nodules. FNAC, fine-needle aspiration cytology. Reprinted with permission from Masafumi and Shinichi (2016).

To minimize the risk of overdiagnosis and overtreatment, criteria were developed to decide on the necessity of a secondary examination based on the primary examination, and to evaluate the indication of FNAC in the secondary examination. A secondary examination was indicated for a solid nodule of diameter 5.1 mm or larger and a cyst of diameter 20.1 mm or larger. Accordingly, nodules of 5 mm or smaller are mostly re-examined in the next round of the primary examination. In addition, for the criteria used to decide on performing FNAC in the secondary examination, a protocol was prepared based on how to proceed with the diagnosis of nodular lesions formulated by the JABTS. FNAC is recommended for: nodules greater than 5 mm in diameter, if there is strong suspicion of thyroid carcinoma using the JSUM diagnostic criteria; nodules greater than 10 mm in diameter with suspicion of carcinoma using the JSUM criteria; all nodules greater than 20 mm in diameter; and all cystic lesions greater than 20 mm in diameter (Suzuki, 2016). These guidelines were followed to avoid unnecessary FNAC, especially for nodules larger than 5 mm but smaller than 10 mm. FNAC would be performed only for nodules considered to be high-risk based on the ultrasonography findings among relatively small nodules. In addition to these criteria, if a malignancy was suspected or detected by FNAC, the malignant nodule would be assessed as to whether surgical treatment would be required.

4.6.4 Findings from thyroid screening

Chernobyl

There is a well-established association between exposure mainly to ^{131}I and risk of thyroid cancer in individuals exposed in childhood and adolescence after the

Chernobyl radioactive fallout and screened for thyroid cancer and non-cancer thyroid diseases (Brenner et al., 2011; Zablotska et al., 2011; Tronko et al., 2017a).

During the five screening cycles in Ukraine, 148 papillary thyroid cancers (PTCs), eight follicular thyroid cancers (FTCs), and one medullary thyroid cancer (MTC) were detected in the cohort. During the three screening cycles in Belarus, 157 PTCs and one FTC were detected. After the first screening cycle in the Ukrainian in utero cohort, six PTCs and one FTC were detected (Table 3). Other non-cancer thyroid disorders found during screening included follicular adenomas (FA), thyroid nodules, and subclinical hypothyroidism (Zablotska et al., 2008, 2015; Ostroumova et al., 2009, 2013; Cahoon et al., 2017).

A review of the clinical follow-up of about 5000 thyroid cancers diagnosed and treated in Belarus, the Russian Federation, and Ukraine in patients exposed to Chernobyl fallout in childhood revealed a very low disease-specific mortality ($\leq 1\%$) in these paediatric thyroid cancer patients (Tuttle et al., 2011). Although earlier reports suggested more aggressive behaviour of thyroid cancers possibly attributed to Chernobyl fallout exposure, it now seems that the initial presentation and early clinical course of most of these cases are very similar to those of both non-radiation-associated paediatric thyroid cancers and thyroid cancers that arise after exposure to external beam irradiation (Tuttle et al., 2011).

Little is known about the role of ^{131}I exposure in the development of benign thyroid nodules including FA. Thyroid screening studies in Ukraine and Belarus reported findings related to ^{131}I exposure and the development of benign thyroid nodules (Zablotska et al., 2008, 2015; Cahoon et al., 2017). A statistically significant positive dose–effect relationship between FA and thyroid exposure to ^{131}I was reported in screened individuals who were exposed when younger than 18 years, 11–15 years after the exposure in Belarus and 12–14 years after the exposure in Ukraine (Zablotska et al., 2008, 2015). The risk of FA after thyroid exposure to ^{131}I was comparable in both cohorts, with a mean thyroid dose of 0.56 Gy in the Belarusian cohort and 0.77 Gy in the Ukrainian cohort. The highest ^{131}I -related risk of FA was observed in children in Belarus who were younger than 2 years at the time of the accident, and the risks diminished with age at exposure (Zablotska et al., 2015).

Analysis of 881 thyroid nodules detected by ultrasonography followed by FNAC in the Belarusian cohort of about 12 000 screened individuals, described in Chapter 4.6.3, revealed a statistically significant positive association between ^{131}I dose and all nodule groupings, and also neoplastic nodules larger than 10 mm in

diameter and single nodules (Cahoon et al., 2017). The major factor that modifies radiation-related risk of thyroid nodules was age at exposure (Cahoon et al., 2017). Further follow-up is required in this cohort to understand the possible progression of prevalent thyroid nodules and underlying biological mechanisms.

The consequences of exposure to ^{131}I during childhood on thyroid function after the Chernobyl accident are less clear. Functional thyroid diseases (hypothyroidism and hyperthyroidism) are much more prevalent in unexposed populations – compared with thyroid cancer, which is very rare – and could result in substantial morbidity in populations exposed to radioiodine. The association between hypothyroidism and ^{131}I exposure is understood based on studies of patients treated for benign thyroid diseases with very high therapeutic doses of ^{131}I (30–80 Gy) (Ron and Brenner, 2010). The role of low to medium doses of internal exposure to radioiodine in terms of development of hypothyroidism is poorly understood and requires more research. A common pathway for induction of hyperthyroidism as well as hypothyroidism is thyroid autoimmunity, but the relevant available data from Chernobyl are inconsistent. Further analysis of longitudinal data from subsequent screening cycles is required to assess temporal trends (transitory or persistent) and shed more light on the natural history of radiation-related effects on thyroid function.

Special attention has been given to those individuals who were in utero after the 12th week of gestation at the time of the accident, because a fetus is more susceptible than an adult to the detrimental effects of ionizing radiation. In a thyroid screening cohort of 2582 child–mother pairs in Ukraine 20 years after the accident, a possible increase in the risk of thyroid carcinoma after exposure to radioiodine in utero was suggested, but no increased risks after radiation exposure were identified for ultrasonography-detected thyroid nodules or other conditions (Hatch et al., 2009). Larger studies are needed to provide more accurate risk estimates of thyroid cancer risk after ^{131}I exposure in utero, and more prospective follow-up is necessary to evaluate temporal patterns of radiation-related risks in this cohort.

Fukushima

Results of the primary examination in the Preliminary Baseline Survey

The findings of the primary examination by ultrasonography were divided into four categories: A1, A2, B, and C (see Chapter 4.6.3). The proportions of those who were classified into each of the categories were 51.5%, 47.8%, 0.8%, and 0% (1 person), respectively (Fukushima Medical University, 2017b).

The detection rates of thyroid cysts were 45.7% in males and 50.0% in females (Shimura et al., 2018). The proportion of those with cysts increased with age from 1 year to 10 years, reached a peak at 11–12 years, and then decreased with age from 13 years or older in both sexes (Fig. 12). The ages showing the highest detection rates, 55.3% in males and 60.9% in females, were 11 years in males and 12 years in females. Multifocal cysts were observed in 89.3% and 89.6% of subjects with thyroid cysts in males and females, respectively. The detection rate of thyroid cysts within each size category according to the maximum diameter, less than or equal to 3.0 mm, 3.1–5.0 mm, 5.1–20.0 mm, or greater than or equal to 20.1 mm, was 22.3%, 22.7%, 4.9%, and 0.0% in males and 28.8%, 18.0%, 3.2%, and 0.0% in females, respectively.

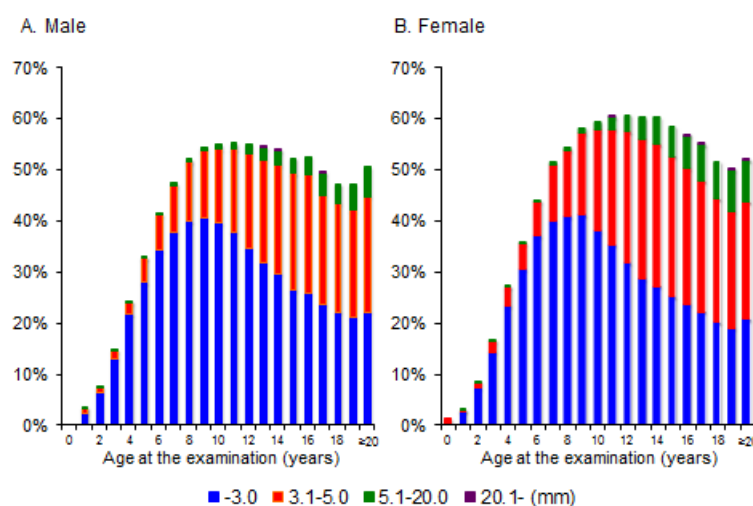


Fig. 12. Age-dependent detection rate of thyroid cysts categorized by diameter (mm). Reprinted from Shimura et al. (2018), by permission of Oxford University Press.

The detection rates of thyroid nodules were 1.0% in males and 1.7% in females (Shimura et al., 2018). A proportional increment in the detection rate of thyroid nodules with age was observed in either sex (Fig. 13). An evident difference between sexes was observed in subjects 10 years or older. There were age-dependent increases in the median nodule diameter in both sexes, and no differences between sexes were evident. The ages showing the highest detection rates, 3.5% in males and 6.7% in females, were greater than or equal to 20 years in both sexes. Multifocal nodules were observed in 13.0% and 15.0% of subjects with thyroid nodules in males and females, respectively. The detection rate of thyroid nodules within each size category according to the maximum diameter, less than or equal to 5.0 mm, 5.1–10.0 mm, 10.1–20.0 mm, or greater than or equal to 20.1 mm,

was 0.5%, 0.4%, 0.1%, and 0.0% in males and 0.7%, 0.7%, 0.3%, and 0.1% in females, respectively.

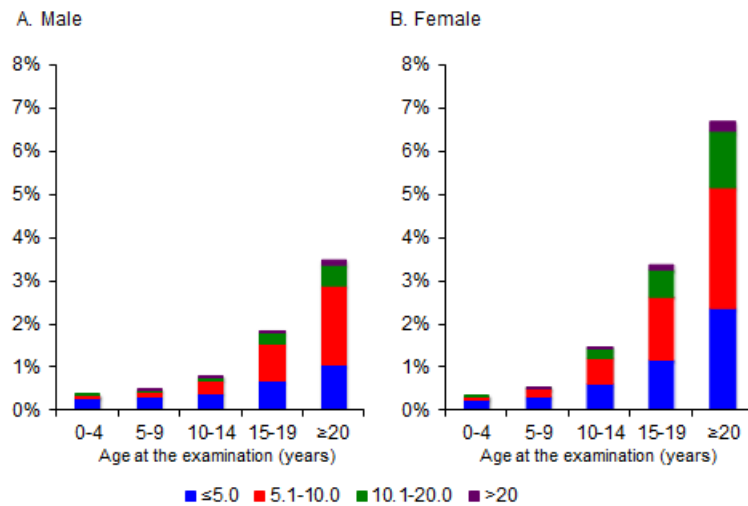


Fig. 13. Age-dependent detection rate of thyroid nodules categorized by diameter (mm). Reprinted from Shimura et al. (2018), by permission of Oxford University Press.

Results of the secondary confirmatory examination in the Preliminary Baseline Survey

A total of 2294 subjects (775 males and 1519 females) in categories B and C were recommended to undergo a confirmatory examination; 116 cases (39 in males and 77 in females) were cytologically diagnosed with a malignancy or suspected malignancy by FNAC. There was no subject with a malignancy aged 12 years or younger for males and 7 years or younger for females; after that the number of malignant cases increased with age and was consistently higher in females than in males (Fig. 14).

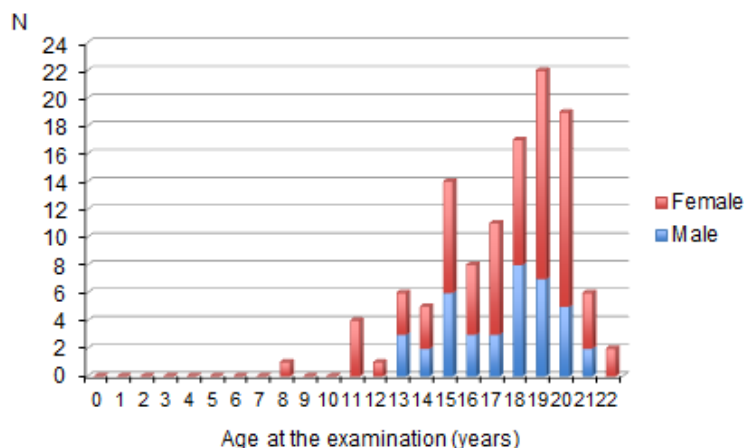


Fig. 14. The number of cases diagnosed with a malignancy or suspected malignancy by fine-needle aspiration cytology (FNAC) in the Preliminary Baseline Survey. Reprinted with permission from Fukushima Medical University (<http://fukushima-mimamori.jp/outline/report/index04.html>).

The detection rate of thyroid nodules cytologically diagnosed as malignant or a suspected malignancy within each size category according to the maximum diameter, less than or equal to 5.0 mm, 5.1–10.0 mm, 10.1–20.0 mm, or greater than or equal to 20.1 mm, was 0.000%, 0.013%, 0.018%, and 0.006%, respectively (Fig. 15) (Shimura et al., 2018). These results showed that malignant nodules of diameters 10.1–20.0 mm were predominant. The estimated number of subjects with nodules cytologically diagnosed as malignant or a suspected malignancy, as a proportion of the number of subjects with nodules in the categories of 5.1–10.0 mm, 10.1–20.0 mm, and greater than or equal to 20.1 mm, was 2.7%, 11.0%, and 17.8%, respectively.

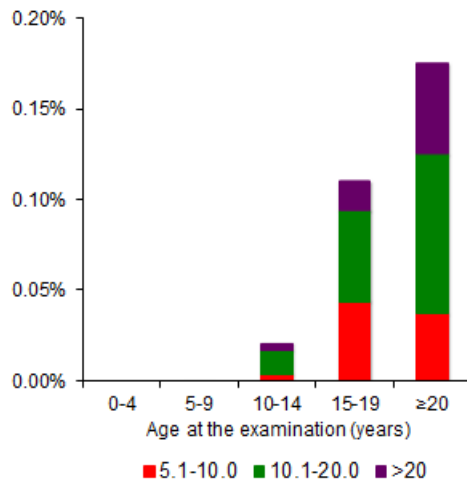


Fig. 15. Age-dependent detection rate of thyroid nodules diagnosed with a malignancy or suspected malignancy categorized by diameter (mm). Reprinted from Shimura et al. (2018), by permission of Oxford University Press.

Results of the first Full-Scale Survey

In the first Full-Scale Survey, the proportion of those who were classified into each of the categories A1, A2, B, and C was 40.2%, 59.0%, 0.8%, and 0% (no people), respectively (Yamashita et al., 2018). The rate of a category A2 finding increased from 47.8% in the Preliminary Baseline Survey to 59.0% in the Full-Scale Survey. The rate of a category B finding was 0.8% in both the Preliminary Baseline Survey and the Full-Scale Survey. Among them, 2227 subjects required a confirmatory examination because of a category B finding in the primary examination. FNAC revealed 71 subjects with a malignancy or suspicion of a malignancy; 50 of them underwent surgery, and all were diagnosed with thyroid cancer.

The second Full-Scale Survey, which is the third round of the TUE programme, is still in progress, and nevertheless shows a similar diagnostic trend.

Surgical methods

Among 187 individuals diagnosed with nodules categorized as malignant or a suspected malignancy in the Preliminary Baseline Survey and the first Full-Scale Survey, 146 underwent surgery. Of those, 126 underwent surgery at Fukushima Medical University Hospital, and all except one patient were postoperatively diagnosed with thyroid cancer: 121 were PTC, 3 were poorly differentiated carcinoma, and for 1 the final diagnosis is pending. About 9% of these patients with thyroid cancer underwent total thyroidectomy, and about 91% underwent lobectomy

or hemithyroidectomy (Yamashita et al., 2018). Lymph node dissection was performed in all cases: 82.4% underwent central compartment dissection, and 17.6% were expanded to lateral compartments.

The proportion of patients who underwent lobectomy is higher in Fukushima than in Chernobyl, because of concerns about age, the potential short- and long-term risks of radioisotope therapy, and concerns over decreased compliance with thyroid hormone replacement therapy based on age (Demidchik et al., 2006; Rumyantsev et al., 2011). Considering these reasons, as well as the consensus among thyroid experts in Japan, lobectomy was a preferred surgical method for these patients (Yamashita et al., 2018).

It will be important to follow up these patients to determine whether this de-escalation of treatment is equally effective at preventing progression and recurrence, to assess disease-specific medical and psychological morbidity, and to determine whether there are clinical and pathological features that may identify a group of paediatric patients with PTC where lobectomy may be sufficient to achieve remission.

Complications

Hypothyroidism was observed only in the patients who underwent total thyroidectomy and another patient who received thyroid hormone replacement therapy before the operation because of Hashimoto's thyroiditis. There were a few cases of subclinical hypothyroidism with a slight elevation in thyrotropin levels. Neither hypoparathyroidism nor postoperative bleeding was observed. Unilateral prolonged paralysis of the recurrent laryngeal nerve was observed in only one patient (Yamashita et al., 2018).

Pathological diagnosis

The postoperative pathological diagnosis revealed 121 (98.6%) cases of PTC, 3 cases of poorly differentiated carcinoma, and 1 case of thyroid cancer for which the final diagnosis is pending (Yamashita et al., 2018). The PTCs included 110 cases of the classical type, 4 cases of the follicular variant, 3 cases of the diffuse sclerosing variant, and 4 cases of the cribriform-morular variant. Intrathyroidal spread was observed in 61.6% of cases, and calcifications, such as psammoma bodies, were observed in 78.4%. The rates of lymph node metastasis and extrathyroidal tumour extension were also high, especially the rate of lymph node metastasis, which exceeded 70%.

Thyroid cancer risks related to radiation exposure

Large-scale thyroid ultrasound examination showed an increased detection of thyroid cancer after the Fukushima accident (Yamashita et al., 2018). However, it is difficult at this point to attribute thyroid cancers detected in Fukushima to radiation exposure after the accident, for the following reasons.

First, it is important to emphasize that thyroid exposure doses in Fukushima residents were much lower than thyroid doses in the population affected by the Chernobyl accident (see Chapter 4.6.2); that is, the estimated external radiation dose to the thyroid was less than 2 mSv for most patients with thyroid cancer (Suzuki, 2016; Fukushima Medical University, 2017b). So far, no case of thyroid cancer has been discovered in children exposed to more than 5 mSv. Doses received were similar between those with and without thyroid cancer; no higher cumulative dose was observed among the patients compared with young and adolescent residents of Fukushima. In addition, there were no significant differences in detection rate of thyroid cancer across four regions with different levels of radiation doses in Fukushima Prefecture (Suzuki, 2016). A simulation study using data from the Japan National Cancer Registry indicated that the number of observed thyroid cancer cases younger than 19 years could be expected in Fukushima under normal (no nuclear accident) conditions (Takahashi et al., 2017). Furthermore, the minimum latency period for radiation-induced thyroid cancer is currently considered to be 3–5 years based on the Chernobyl experience (see Chapter 4.5.4), suggesting that radiation-induced excess risk of thyroid cancer would not be observable during the period when the Preliminary Baseline Survey was conducted (within the 3 years after the nuclear accident). Lastly, the characteristics of thyroid nodules are different from those observed after the Chernobyl accident. The number of cases diagnosed with a malignancy or a suspicion of malignancy by FNAC increased with age in Fukushima, whereas thyroid cancer was most commonly diagnosed at a younger age in the case of the Chernobyl accident (Suzuki, 2016; Fukushima Medical University, 2017b). In addition, an analysis of genetic alterations in 68 malignant nodules from post-Fukushima cases suggested that the genetic pattern (i.e. high prevalence of the *BRAF* point mutation and low frequency of chromosomal rearrangements) was completely different from that of post-Chernobyl PTCs (Mitsutake et al., 2015).

4.6.5 Psychological outcomes

Three Mile Island

After the Three Mile Island (TMI) accident, very low levels of radionuclides were released into the environment (see Chapter 4.6.2); therefore, negligible physical health consequences were reported. However, the negative effects on the mental health of the population in the surrounding area have been documented (United States President's Commission on the Accident at Three Mile Island, 1979; Dew and Bromet, 1993).

Acute stress was quite severe after the TMI accident. It was particularly high in individuals who lived in the vicinity of the power plant or had young children at home (Fabrikant, 1983). In addition, the TMI accident resulted in heightened distrust of authority, particularly among women and those in their 30s (Fabrikant, 1983). The high level of acute stress in these particular groups could be attributed to the lack of prior knowledge about the risks after a nuclear accident, or the contradictory and confusing information they received, such as the advisory on evacuation after the accident. Whereas there was a recommendation during the crisis that pregnant women and preschool-aged children evacuate, approximately 66% of the population outside of this recommended group who lived within 5 mi (8 km) of the reactors, including many health professionals, also evacuated voluntarily (Houts et al., 1988). Of those, 80% reported that the main reason they evacuated was because of the confusing and conflicting information they had received.

Although the acute stress appeared to dissipate soon after the accident, psychological impairments persisted in the long term in some individuals. A comparative study showed that mothers of preschool-aged children who lived near the TMI power plant had more symptoms of anxiety and depression at subclinical levels during the year after the accident, compared with their counterparts who lived near another power plant (Bromet, 1982). A later study, following up the women who lived around the TMI power plant up to 10 years after the accident, further identified a sizeable minority of women whose distress levels were consistently high over the long term (Dew and Bromet, 1993).

Coping strategies commonly reported by survey respondents were taking protective actions such as evacuation, and being involved in meetings and organizations. This approach, termed "problem-focused coping", was actually less effective in reducing the psychological and behavioural consequences of stress than

seeking support and counsel from friends and family and reframing the events, termed “re-appraisal coping” (Houts et al., 1988).

Although the biggest public health problem as a result of the TMI accident is thought to be mental health issues (United States President’s Commission on the Accident at Three Mile Island, 1979), including long-term psychological impairment, no significant expansions in the mental health care system have been made to meet the long-term needs of the victims (Bromet, 2014). Given that poor mental health is associated with poor physical health, as well as early mortality and increased cost of medical services, the mental health effects of a disaster such as the TMI accident should be given high priority.

Chernobyl

The psychological consequences of natural and technological disasters have been studied extensively (Norris et al., 2002; Neria et al., 2008). Events that cause a threat to health as a result of toxic exposures are most likely to have long-term psychological impacts (Havenaar et al., 2002). The Chernobyl catastrophe was one of the most devastating and complex disasters in the history of the world, producing both ecological and social disruption. Twenty years after the Chernobyl accident, the United Nations Chernobyl Forum Expert Group “Health” concluded that the mental health impact was the largest public health impact of the accident (WHO, 2006).

Populations affected by the Chernobyl accident have increased levels of depression, suicide ideation, anxiety (including post-traumatic stress symptoms), medically unexplained physical symptoms, and subjective poor health (Havenaar et al., 1997a; Allen and Rumyantseva, 1995; Bromet et al., 2002; Contis and Foley, 2015). The risk factors that are likely to affect such psychological consequences include the severity of the disaster (e.g. death toll, scale of destruction, length of exposure, evacuation, and proximity to the epicentre), adequacy and timing of practical or emotional support, access to professional interventions, receipt of compensation and benefits, and individual- and group-level vulnerabilities (Bromet et al., 2011). The most vulnerable segments of the population were women who were pregnant or had young children in 1986, and liquidators (clean-up workers), particularly those who worked at the site between April and October 1986 (WHO, 2006).

Most of the mental health consequences observed in the population affected by the Chernobyl accident were subclinical and did not reach the level of criteria for a

psychiatric disorder (Havenaar et al., 1997a). Nevertheless, these subclinical symptoms had an impact on the illness behaviour of the affected population, increasing their use of medical care and their adherence to safety advisories (Allen and Rumyantseva, 1995; Havenaar et al., 1997b). To some extent, these symptoms were driven by the belief that their health was adversely affected by the disaster and the fact that they were diagnosed by a physician with a “Chernobyl-related health problem” (Bromet et al., 2002; Havenaar et al., 2003).

The mental health effects were fuelled in part by an exaggerated sense of the danger from presumed exposure to radiation that was propagated by the local medical community and government officials. Liquidators, evacuees, and people living in contaminated regions were officially labelled as “sufferers” or “Chernobyl victims”, terms that were adopted by the mass media. Similarly to the atomic bomb survivors of Hiroshima and Nagasaki, the Chernobyl evacuees found themselves stigmatized when they were resettled in cities like Kiev, because the general population, and even the medical community, feared contamination (Bromet et al., 2002). Being recognized as a “Chernobyl victim” entitled people to financial, medical, and educational compensation, which, combined with continuous monitoring by local and international organizations, may also have had an iatrogenic effect on psychological well-being.

In addition to the national health follow-up programmes of populations exposed as the result of the Chernobyl accident implemented by the governments of Belarus, the Russian Federation, and Ukraine, foreign (including international) organizations conducted thyroid screening campaigns in the regions contaminated by the accident. These campaigns were welcomed by the local population, because of distrust in their physicians and medical authorities (Havenaar et al., 2003). However, there are no studies available that would allow a formal evaluation of the psychological impact of screening or other medical surveillance programmes in the populations affected by the Chernobyl accident.

Although it is recognized that the Chernobyl accident led to a series of stressors that continue to the present, the scope and magnitude of the mental health effects cannot be specified with currently available data. Given the enormity of this trauma and its many implications, there is a need for more epidemiologically sound mental health research to clarify the long-term psychological consequences.

Fukushima

After the Fukushima Daiichi Nuclear Power Plant accident in Fukushima Prefecture, the concerns of the public about radiation exposure and its health effects, particularly thyroid cancer in children, were heightened, as was observed after the Chernobyl accident. Because of the high level of public concern, the local prefectural government, together with Fukushima Medical University, initiated the Fukushima Health Management Survey, which included the Thyroid Ultrasound Examination (TUE) programme (Ishikawa et al., 2015). The primary purpose of the TUE programme was to alleviate residents' concerns by providing them with an opportunity to have their health examined as a public health service (Yamaguchi et al., 2018). Questions remain about the overall public health benefits of the TUE programme. However, not providing the residents with the opportunity to have these examinations after the Fukushima accident might have been viewed as a neglect by the government of the residents' rights to know their health status, and it might have posed an equal or greater risk of harm to the society (Yamaguchi et al., 2018).

A cross-sectional study has shown that participation in the TUE programme was associated with reduced radiation-related anxiety (Murakami et al., 2018). However, despite the best intentions, the programme did not alleviate anxieties in some residents (Ohtsuru et al., 2015), such as those who received an A2 result of "no medical problem" (Midorikawa et al., 2017b; see Chapter 4.6.3). In response to potential anxieties that might have been experienced at each step of the TUE programme, various risk communication measures were implemented (Midorikawa et al., 2017b; Murakami et al., 2017).

When the TUE programme was initiated, various protocol-related complaints and concerns kept residents from attending the prescribed primary examinations. To address these reservations, a call centre was established to allow people to ask questions of the staff of the Radiation Medical Science Center of the Fukushima Health Management Survey via phone call or email.

In addition, a booklet and biannual newsletter were sent by post to the Fukushima residents to provide detailed information about the TUE programme, including benefits and possible harms of the thyroid examination. Furthermore, explanatory meetings on thyroid examination were offered to guardians, teachers, and the general public; these have been demonstrated to be effective in reducing anxieties (Hino et al., 2016; Midorikawa et al., 2017b).

Many participants in the TUE programme and their families were very anxious about the examination results. However, because of the high volume of examinations, it often took 2–3 months before results were received. This waiting period served to increase anxiety, so information booths were set up in the examination locations and provided an opportunity for the participants and their families to speak to a medical doctor who could explain the tentative results and provide counselling services as needed. These services proved beneficial, especially for participants with cysts smaller than 20.1 mm or nodules smaller than 5.1 mm, who therefore were not subjected to the confirmatory examination (see Chapter 4.6.3). The participants also received leaflets explaining what cysts and nodules are, why thyroid cysts were not cause for alarm, and why FNAC would not be performed for all cases with nodules. Furthermore, a medical hotline was established to make counselling by medical doctors available to everyone.

During the subsequent examinations, which usually required two or three visits to one of the designated hospitals, fears about thyroid cancer and FNAC often increased among participants and their families. To address such concerns, a support team was organized consisting of clinical psychologists, medical social workers, and nurses who specialized in paediatric oncology. Members of the support team attended subsequent examinations with participants and their families to listen to their concerns and help them communicate more effectively with their doctors.

When a malignancy was suspected or detected by FNAC, it caused tremendous concern about decision-making for surgical treatment or observation, possible additional treatments, and disease outcome. Similarly, when a thyroid nodule was diagnosed as benign, concerns about thyroid disease and its relationship to the accident were raised. To address concerns encompassing both medical and social aspects, the support team assisted the patients and their families throughout the process, from the informed consent to the end of the follow-up period. This ongoing communication with participants who underwent surgical treatment or observation may have helped to alleviate self-stigmatization of children and adolescents with thyroid nodules or cancers. Moreover, continued thyroid health monitoring services may reduce fears about the future.

4.6.6 Lessons learned from past nuclear accidents

As described in the previous chapters, the three past nuclear accidents, at Three Mile Island (TMI), Chernobyl, and Fukushima, were quite different in terms of the

amount of radionuclides released, pathways and levels of radiation exposure, and interventions administered. But the negative psychological impacts on the well-being of the affected populations were similarly observed after all three accidents. The extensive efforts that were made after the respective accidents yielded knowledge and lessons learned, which will be invaluable as preparations are made for any future nuclear accidents.

Risk communication

Before all three accidents, there was limited or no communication about the possibility of a nuclear accident occurring. The public was not well informed about the potential risks of such an event, such as radiation exposure and the harmful potential side-effects, in particular thyroid cancer. Because nuclear power plants must comply with stringent safety standards, it was assumed that such risk communication was not necessary. Therefore, when each accident occurred, the affected population was not able to understand the implications, and the result was a high level of fear and distrust. In TMI and Fukushima, the health professionals were not trained about how to react to a nuclear accident. In Chernobyl, health professionals, like the rest of the public, were not informed about the accident immediately after it happened and had no idea how to respond to it. This highlights the importance of informing and engaging the public and professionals about radiation-related risks and actions to take in the event of a release of radiation from a nuclear power plant before an accident happens.

Risk communication after a nuclear accident is also critical to facilitate recovery from the accident and avoid additional adverse effects. After Fukushima, psychosocial health issues were managed through risk communication activities that involved active participation by the local residents (Yamaguchi et al., 2018). These included intensive education about thyroid ultrasound examination programmes through workshops, hotlines, leaflets, and other interventions (see Chapter 4.6.5). These risk communication activities improved participants' understanding of radiation and cancer and helped reduce their anxiety (Hino et al., 2016). This stresses the importance of developing programmes to facilitate communication with the local community, thereby reducing psychological suffering and strengthening resilience.

Helpful documents are available, such as from the International Atomic Energy Agency (IAEA) and the World Health Organization (WHO), which provide guidance and a framework for effective risk communication in health emergencies in general

(WHO, 2017b) and nuclear and radiological emergencies in particular (IAEA, 2012a), as well as tools developed by others, such as the United Nations Environment Programme, which can be used to expand public knowledge about ionizing radiation and possible associated health effects (United Nations Environment Programme, 2016).

Protective actions

Urgent protective actions relate to the need to save lives, to prevent serious side-effects, and to avert radiation doses; protective actions should be modified as more information becomes available, and discontinued when they are no longer justified (IAEA, 2012b). In contrast with the experience after the Chernobyl accident, after the Fukushima accident necessary actions to protect the population, such as sheltering, evacuation, and control of food, milk, and water, were successfully implemented, which prevented a higher exposure to radiation (IAEA, 2014b; National Research Council, 2014). However, in past accidents, stable iodine for thyroid blocking was not properly implemented, except in Poland (Nauman and Wolff, 1993). This represents a key opportunity for improvement.

Thyroid dosimetry and screening after the accidents

At the time of the Chernobyl accident, it was known that thyroid cancer could result from radiation exposure, as observed in the atomic bomb survivors of Hiroshima and Nagasaki. However, it was not yet established whether thyroid cancer could occur after a nuclear accident that resulted in the ingestion or inhalation of ^{131}I . A large-scale assessment of radiation exposure of the thyroid was carried out in Belarus, the Russian Federation, and Ukraine soon after the Chernobyl accident. More than 5 years after the accident, large-scale thyroid screening campaigns started, after symptomatic thyroid cancers were diagnosed in exposed children. International collaborations between the United States National Cancer Institute, the ministries of health of Belarus and Ukraine, the Sasakawa Memorial Health Foundation, and other scientists have resulted in epidemiological studies of causal inference between ^{131}I radiation exposure and thyroid cancer. These studies, conducted in populations exposed to substantial amounts of ^{131}I , have significantly contributed to the understanding and management of thyroid cancer, particularly in children.

In the case of the Fukushima accident, the atmospheric release of ^{131}I was estimated to be about one tenth and the doses to the thyroid to be about one

hundredth those observed after the Chernobyl accident (see Chapter 4.6.2); hence, the radiation-related risk of thyroid cancer as a result of the Fukushima accident was estimated to be very low (Fig. 16). However, because of the well-documented health consequences of the Chernobyl accident, particularly the radiation-related increase in thyroid cancer in children and adolescents, and because of the lack of understanding about the level of their radiation exposure or the associated risk, the public's concern about thyroid cancer was very high. Therefore, although they had very little radiation exposure, the residents of Fukushima strongly lobbied for attention to thyroid-related radiation effects.

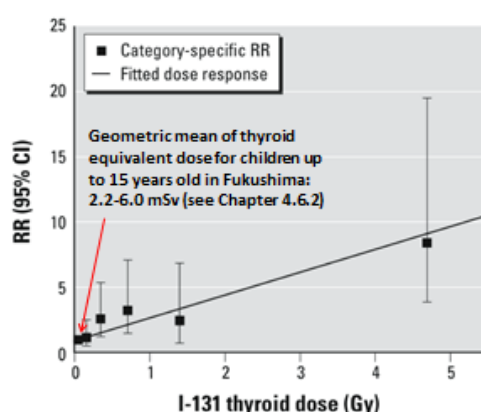


Fig. 16. Dose–response relationship between ^{131}I thyroid dose estimates and incident thyroid cancer in a prospective cohort study after the Chernobyl accident. The solid line represents fitted relative risks (RRs) based on the linear excess relative risk model adjusted for sex, oblast of residence at the first screening examination, and continuous attained age. Data points and error bars represent dose category-specific RRs and corresponding 95% confidence intervals for the respective mean doses. The fitted linear dose response was adjusted to pass through the lowest ^{131}I category. Reprinted from Brenner et al. (2011).

Unlike after the Chernobyl accident, broad recordings of thyroid dosimetry were not obtained in Fukushima, because of the extraordinary demands on emergency response teams in managing the aftermath of the devastating earthquake and tsunami. However, Fukushima Prefecture established the systematic and large-scale TUE programme, as part of the detailed Fukushima Health Management Survey, to address public concerns about the effects of a nuclear accident on the thyroid. The TUE programme has provided a more detailed scientific understanding about the thyroids of children and adolescents and the prevalence of thyroid cancer in this age group. The children and adolescents who were identified with a thyroid cancer might have developed clinical symptoms later in life or remained asymptomatic. Some of the children and adolescents have likely benefited from identification of their cancer

at an earlier state of metastasis, avoiding late clinical diagnosis with more advanced metastatic disease that would have required more extensive treatment. Others likely underwent surgery for cancers that were not destined to go on to become symptomatic. Because of this, although the benefits of the epidemiological knowledge gained from the TUE programme as well as the thyroid screening programme implemented after the Chernobyl accident are substantial, the balance of clinical benefits and harms to individuals is not entirely clear.

It is important to note that a large-scale thyroid screening or monitoring programme, like the ones conducted in Chernobyl and Fukushima, requires significant resources. In developing countries, undertaking a massive thyroid screening programme may redirect national resources from other areas of public health that would be a priority otherwise.

Conclusions from the lessons learned

Given the established association of thyroid cancer risk with radiation exposure, and the knowledge that risk is greater when exposure occurs at a younger age, thyroid cancer will remain a major concern in the case of future nuclear accidents, especially if high activities of radioiodine are released. The Expert Group members, some of whom were involved in the aftermath of the Fukushima accident, described the virtual impossibility of resisting calls for thyroid examination, even with the knowledge that the risk of thyroid cancer was very low. It is apparent from the Fukushima accident that such decision-making involves considerations beyond scientific evidence, including socioeconomic implications, health-care resources, and social values unique to each potential situation and local population. With education and a better understanding of radiation risks and thyroid cancer, perhaps in the future there will be more informed decision-making about whether and how to undertake thyroid health monitoring after a nuclear accident. Such decisions should be based on the reliable assessment of doses to the thyroid and associated thyroid health risks; communication and open dialogue among policy-makers, experts, stakeholders, and the community; and scientific evidence on the benefits and harms of thyroid health monitoring.

CHAPTER 5. Knowledge gaps

The Expert Group recommends that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals after a nuclear accident (see Chapter 3, Recommendation 2), while recognizing that some gaps in knowledge need to be addressed to optimize the balance between benefits and risks of thyroid monitoring. The Expert Group supports the notion that well-designed studies after an accident may be warranted and can add significantly to the scientific knowledge, and encourages further research in the following areas with emerging data from previous nuclear accidents where applicable.

Characterization of the relationship between radiation and thyroid cancer

Over the past decades, data from epidemiological studies have demonstrated and quantified the relationship between radiation dose and the risk of thyroid cancer. Nevertheless, there remain uncertainties in the following areas that need to be addressed in order to better define higher-risk individuals.

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

Besides radiation, several other factors have been suggested to affect thyroid cancer risk, such as ethnicity, weight, physical activity, diet (e.g. nutritional iodine status), menstrual and reproductive factors, and environmental chemicals (e.g. nitrates, polybrominated diphenyl ethers). However, little is known about potential joint effects of radiation and these factors on thyroid cancer risk, or potential effect modification of the radiation-related thyroid cancer risk by these factors.

Dose–risk relationship by age at radiation exposure

The risk of thyroid cancer appears to be much higher for exposures to children and adolescents compared with adults. A better quantification of risk associated with low-dose radiation exposure during childhood and young adulthood merits further research. In addition, the effect of low-dose radiation exposure in utero should be studied.

Dose–risk relationship by tumour type

Several recent studies have indicated variations in the strength of the association between radiation dose and thyroid cancer risk by tumour type (e.g. benign vs malignant, nodule diameter, focality, and singularity). Additional research with careful

consideration of tumour type is required for the quantification of the dose–risk relationship.

Latency period

The data from the Chernobyl accident have indicated that the minimum latency period after exposure after which an excess risk of thyroid cancer associated with radiation is detectable is about 3–5 years (i.e. no excess during at least about 3 years after exposure), but the latency period can vary by age at exposure, dose of radiation, and other factors. Further data are needed to better understand the time sequence between radiation exposure and the development of thyroid cancer by different determinants of the latency period.

Lifetime risk

Although studies of Hiroshima and Nagasaki atomic bomb survivors and studies after the Chernobyl accident indicate that the radiation-induced thyroid cancer risk remains for decades after exposure, there is still uncertainty about the risk pattern over a lifetime; that is, when it peaks and when it diminishes with age, including the period of intense thyroid gland growth and hormonal stimulation during pre-puberty and puberty.

Guidelines on thyroid dose assessment from internal exposure to radioactive iodine based on direct thyroid measurement

Before a decision is made about whether to launch a thyroid monitoring programme, it is important to obtain realistic information on individual doses to the thyroid of the public exposed 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 conducting direct thyroid measurements on exposed people within a few weeks after a nuclear accident.

Currently there are no international guidelines on how to assess thyroid dose based on direct thyroid measurements, or recommendations on how to provide large-scale measurement of the thyroidal ^{131}I content for a large population in a short period of time after the accident. Using lessons learned from previous nuclear power plant accidents (Three Mile Island, Chernobyl, and Fukushima), guidelines should be prepared that include: recommendations for selecting devices to be used for measurement of the thyroidal ^{131}I content, as well as the procedures to follow in preparing for and conducting measuring procedures; and a short questionnaire that

can be used at the time of direct thyroid measurement to conduct personal interviews on lifestyle and dietary habits from the time of the accident until the time of conducting the direct thyroid measurement.

Benefits and harms to an individual of thyroid monitoring after a nuclear accident

A person considering whether to undergo thyroid monitoring after a nuclear accident should have access to information to help them make an informed decision. However, currently information is lacking to assist individuals in decision-making. Such support for decision-making, at a minimum, should include:

- information on potential benefits and harms of earlier diagnosis of thyroid cancer from a thyroid monitoring programme in relation to the extent of treatment, risk of treatment side-effects and complications, need for repeated treatment, future interventions, morbidity, and mortality;
- information on treatment outcomes, including long-term consequences of medical and surgical treatment options for paediatric thyroid cancer (e.g. lobectomy vs total thyroidectomy, prophylactic central neck dissection vs no prophylactic central neck dissection, and indications for the use of post-thyroidectomy radioactive iodine therapy); and
- decision aids to support shared decision-making for individuals who develop thyroid cancer detected by thyroid monitoring in adult life, whether or not this is related to radiation exposure.

Emerging data and experiences from the Fukushima Health Management Survey could help with the development of such information support.

Potential psychological impacts of thyroid monitoring

Currently, little is known about the psychological impact of thyroid screening or monitoring. After the Fukushima accident, various programmes were implemented to address the residents' anxieties related to radiation and thyroid cancer risk, some of which have been demonstrated to be effective. However, longitudinal studies to evaluate the mental health impacts of a nuclear accident or of thyroid monitoring are needed to provide evidence-based guidance on how to plan and implement thyroid monitoring in a way that minimizes negative mental health consequences.

Quality assurance in thyroid monitoring

The Expert Group recognizes the importance of developing the following to minimize potential harms due to a thyroid monitoring programme.

Standardized protocols should be developed for ultrasonography imaging and reporting, as well as the potential application of newer imaging modalities, including elastography and three-dimensional imaging. Because the quality of ultrasonography is strongly investigator-dependent, a standardized protocol needs to be developed and implemented, and investigators need to be trained according to the protocol before thyroid monitoring programmes are started.

Artificial intelligence for the digital diagnosis of images is also needed. In the past, computer-aided image analysis was not very helpful in improving thyroid diagnosis by ultrasonography, fine-needle aspiration cytology (FNAC), and histology. However, the use of artificial intelligence, for instance with deep learning approaches, is promising, and therefore these approaches should be tested systematically for use in thyroid monitoring programmes after a nuclear accident.

Occurrence, etiology, and natural history of thyroid cancer

Occurrence of thyroid cancer in children and adolescents

A general understanding of thyroid cancer in children and adolescents could be advanced with research on the underlying prevalence of thyroid cancer in a screened population. Data on the ratio of thyroid cancer incidence and prevalence in screened versus non-screened children, adolescents, and young adults would also be useful.

Potential heterogeneity of molecular mechanisms involved in thyroid cancer development across different populations

Studies, although small and unvalidated, have suggested some differences in the molecular biology between thyroid cancers in Japan and in Europe. Tissue banks that contain thyroid cancer specimens exist only in developed countries. The further development of national and international biomaterial repositories and databanks that include ultrasonography images, FNAC, and histology will enable research evaluating the potential heterogeneity of molecular mechanisms involved in thyroid cancer development across different populations.

Genomic signature in thyroid cancer related to low-dose radiation exposure

The increase in papillary thyroid cancers (PTCs) in young children and adolescents after the Chernobyl accident provided a better understanding of the genomics of PTC and an opportunity to investigate whether the molecular biology was driven by etiology or by the age of the patient. Over the past decade, the rapid developments in genomics, and improved access to large, well-annotated collections of human biological samples of cancers, have increased the understanding of how age affects the molecular phenotype of cancers in general. As a result, many molecular changes that were previously thought to be biomarkers of radiation in post-Chernobyl PTC may be in the process of being reclassified as being related more to the age of the patient at diagnosis. A large study of 649 cases, including more than 50 age-matched controls, is currently being conducted using whole-genome sequencing and a variety of omics technologies by the Cancer Genome Atlas Consortium in the USA. This may afford the opportunity to validate the findings of previous studies.

Natural history of thyroid cancer in children and adolescents

Recent observational studies of adult thyroid cancer patients have shown that a significant number of papillary thyroid microcarcinomas do not grow during the active surveillance period, with the estimated lifetime probability of disease progression during active surveillance decreasing with age at presentation. Data are currently lacking on the natural course of thyroid cancer in children and adolescents.

ANNEX 1. Basic questionnaire used in Belarus after the Chernobyl accident

- 1.** Where did you live from 26 April 1986 through 31 May 1986? Indicate the dates of residence in each settlement.
- 2.** What was the date when cows (goats) were put on pasture in your village in 1986? What was the origin of the fresh milk that you were drinking at that time?
- 3.** What was the daily rate of your consumption of fresh milk between 26 April 1986 and 31 May 1986?
- 4.** What was the date when you started taking potassium iodide pills, and how many pills did you take?
- 5.** What was the date when you stopped consuming fresh milk?

ANNEX 2. Measuring protocol used 8–20 April 2011 in Tokyo for citizens of the Russian Federation after the Fukushima accident

There are four sections of the measuring protocol:

Section 1 – Passport identification

Section 2 – Characteristics of the place of measurement

Section 3 – Results of measurement

Section 4 – Results of interview

Section 1

1. Last name, first name, patronymic
2. Birth date
3. Institution, occupation

Section 2

1. Place of direct thyroid measurement
2. Date and time of direct thyroid measurement
3. Device used to measure the exposure rate near the thyroid
4. Result of measurement of the exposure rate outside ($H = 1$ m), $\mu\text{Sv/h}$
5. Result of measurement at the place of direct thyroid measurement, $\mu\text{Sv/h}$

Section 3

1. Device used to measure surface contamination
2. Results of measurement of surface contamination, particles/s/cm
 - above the head
 - hands
 - neck surface
 - clothes around chest
3. Device used for direct thyroid measurement
4. Geometry of the thyroid measurement
5. Result of direct thyroid measurement, $\mu\text{Sv/h}$

Section 4

1. Where did you live after 11 March 2011 until the date of direct thyroid measurements? Indicate the dates of residence in each locality.
2. Did you consume leafy vegetables after the accident? What was the consumption rate (g/d)?
3. Did you consume seafood (e.g. fresh fish) after the accident? What was the consumption rate (g/d)?
4. Did you take potassium iodide pills?

ANNEX 3. Side-effects of thyroid cancer surgery

Side-effect and estimated rate	Symptoms	Available rehabilitation
<p>Damage to the external branch of the superior laryngeal nerve</p> <p>Temporary or permanent, 0–58%</p> <p>(Friedman et al., 2002)</p>	<p>Vocal fatigue, loss of vocal range, breathiness, and throat clearing</p>	<p>Not reparable. Speech rehabilitation to improve dysphonia.</p>
<p>Loss of parathyroid gland function</p> <p>Temporary loss rate: 16.7%</p> <p>Permanent loss rate: 1.6%</p> <p>(Oda et al., 2016)</p>	<p>Chronic hypocalcaemia: cramping, wheezing, dysphagia, trouble thinking clearly, cardiac arrhythmia, and death if uncontrolled</p>	<p>Not reparable. Calcium replacement through oral calcium supplement and vitamin D. Parathyroid hormone injection is limited to the few refractory cases.</p>
<p>Damage to the recurrent laryngeal nerve</p> <p>Unilateral injury rate: 8.2%, 0.2% in specialized centres</p> <p>Bilateral injury rate: 1.3%, 0% in specialized centres</p> <p>(Francis et al., 2014; Oda et al., 2016)</p>	<p>Unilateral: breathiness, vocal fatigue, global fatigue, dysphagia, choking</p> <p>Bilateral: respiratory obstruction, often requiring tracheotomy</p>	<p>Surgical repair or rehabilitation possible for permanent injuries. Return to full preoperative level of function uncommon.</p>
<p>Need for thyroid hormone replacement</p> <p>After total thyroidectomy: 100%</p> <p>After lobectomy: 25%</p> <p>(Saravanan et al., 2002; Said et al., 2013)</p>	<p>Hypothyroidism if untreated: fatigue, depression, weight gain, constipation, myxoedema (weakness, hair loss, oedema, heart failure)</p>	<p>Treatable. Daily pill 1 hour before eating. Prescription medication requires regular blood tests and doctor visits. Thyroid hormone replacement therapy could negatively affect patients' psychological well-being (Saravanan et al., 2002).</p>

Disclosures of interests

Before the first meeting, all Expert Group members, including the Scientific Secretariat (the Expert Group Chair and the Scientific Coordinator), Experts, Specialists, and Advisers, completed a Declaration of Interests form for IARC/WHO experts, in which they were asked to disclose pertinent research, employment, and financial interests. Based on the information they provided, IARC determined that the participation of the experts did not constitute any conflicts of interest. Current financial interests and research or employment interests during the past four years or anticipated in the future are identified here.

Dr Louise Davies reports that her institution, The Dartmouth Institute for Health Policy and Clinical Practice and the Department of Veterans Affairs, benefited from research funding from the Mellon Foundation, and that she benefits from research funding from the Fulbright Foundation.

Dr Dominique Laurier reports that his institution, Institute for Radiological Protection and Nuclear Safety, benefits from research funding from Areva and EDF.

Dr Geraldine Thomas reports having received support for travel from TEPCO.

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