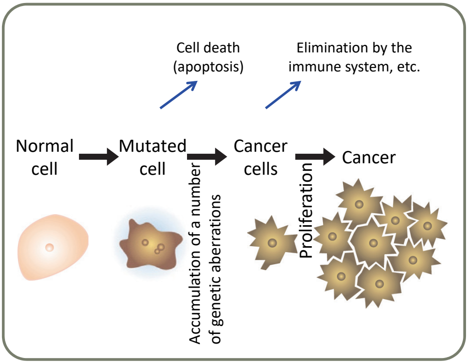
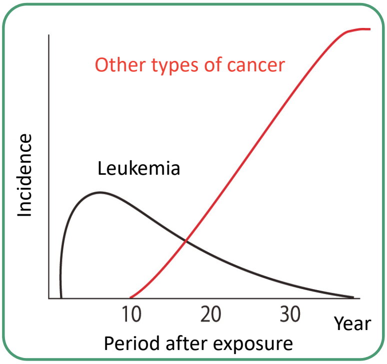
Cancer and Leukemia

Mechanism of Carcinogenesis





- Radiation is only one of various factors that induce cancer.
- Mutated cells follow multiple processes until developing into cancer cells.
  → It takes several years to decades.

Not only radiation but also various chemical substances and ultraviolet rays, etc. damage DNA. However, cells have a mechanism to repair damaged DNA and DNA damage is mostly repaired quickly. Even if repair was not successful, the human body has a function to eliminate cells wherein DNA damage has not been completely repaired (p.82 of Vol. 1, "Damage and Repair of DNA").

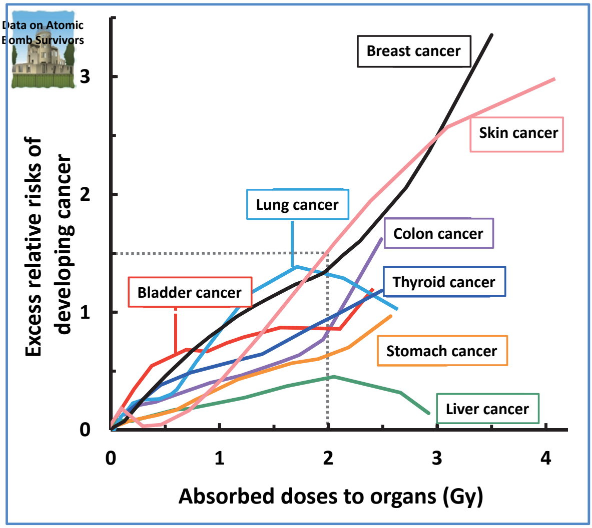
Nevertheless, cells with incompletely repaired DNA survive as mutated cells in very rare cases. Such cancer germ repeatedly appears and disappears.

In the process, genetic aberrations may be accumulated in cells that happen to survive and these cells develop into cancer cells. However, this process requires a long period of time. After the atomic bombing, leukemia increased in around two years, but the incidence decreased thereafter. On the other hand, cases of solid cancer started to increase after an incubation period of around 10 years.

(Related to p.85 of Vol. 1, "Lapse of Time after Exposure and Effects")

Included in this reference material on March 31, 2013
Updated on March 31, 2016

Tissues and Organs Highly Sensitive to Radiation



Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

Tissue	Tissue weighting factor$_{WT}$*
Red bone marrow, stomach, lungs, colon, breasts	0.12
Gonad	0.08
Bladder, esophagus, liver, thyroid	0.04
Bone surface, brain, salivary gland, skin	0.01
Total of the remaining tissues	0.12

Source: 2007 Recommendations of the International Commission on Radiological Protection (ICRP)

* The tissue weighting factor is larger for organs and tissues for which risks of radiation effects are higher.

This figure shows how cancer risks have increased depending on where in the body was exposed to how much doses of radiation, targeting atomic bomb survivors. The horizontal axis indicates the absorbed doses to organs through a single high-dose exposure at the time of the atomic bombing, while the vertical axis indicates excess relative risks, which show how cancer risks have increased among the exposed group compared with the non-exposed group. For example, when the absorbed dose to organs is 2 Gy, the excess relative risk for skin cancer is 1.5, meaning that the risk increased in excess of 1.5 times compared with the non-exposed group (in other words, among the group of people exposed to 2 Gy of radiation, the risk of developing skin cancer is 2.5 times higher (1 + 1.5) than among the non-exposed group).

As a result of these epidemiological studies, it was found that the mammary gland, skin, and colon, etc. are tissues and organs that are easily affected by radiation and develop cancer. The 2007 Recommendations of the ICRP specify tissue weighting factors while taking into account the radiosensitivity of each organ and tissue and the lethality of each type of cancer.

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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Updated on February 28, 2018

Cancer and Leukemia

Difference in Radiosensitivity by Age

Children are not small adults.

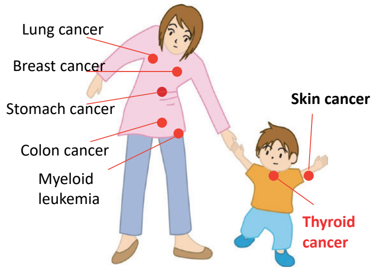
	Committed effective dose coefficients for I-131*1 (mSv/Bq)	Committed effective doses when having taken in 100 Bq of I-131 (mSv)	Equivalent doses to the thyroid when having taken in 100 Bq of I-131*2 (mSv)
3 month-old infants	**0.18**	**18**	**450**
1 year-old children	**0.18**	**18**	**450**
5 year-old children	**0.10**	**10**	**250**
Adults	**0.022**	**2.2**	**55**

*1: Committed effective dose coefficients are larger for children due to difference in metabolism and physical constitution.
*2: Calculated using the tissue weighting factor of 0.04 for the thyroid

Source: International Commission on Radiological Protection (ICRP), ICRP Publication 119, Compendium of Dose Coefficients based on ICRP Publication 60, 2012

Risks of thyroid cancer and skin cancer are higher for children than for adults.

mSv/Bq: microsieverts/becquerel



In the case of adults, bone marrow, colon, mammary gland, lungs and stomach easily develop cancer due to radiation exposure, while it has become clear that risks of developing thyroid cancer and skin cancer are also high in the case of children.

In particular, children's thyroids are more sensitive to radiation and committed effective doses per unit intake (Bq) are much larger than adults. Therefore, the exposure dose to the thyroids of 1-year-old children is taken into account as the standard when considering radiological protection measures in an emergency. Additionally, much larger values are adopted as children's committed effective dose coefficients per unit intake (Bq) than those for adults.

(Related to p.114 of Vol. 1, "Relationship between Ages at the Time of Radiation Exposure and Oncogenic Risks")

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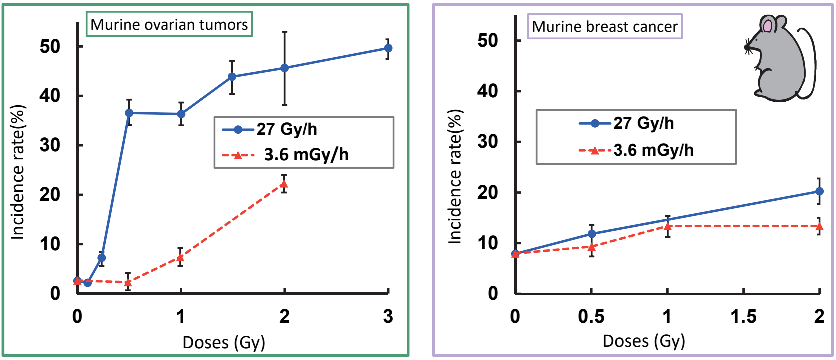
Cancer-promoting Effects of Low-dose Exposures



Source: United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993

Risks of low-dose and low-dose-rate exposures

$$= \frac{\text{Risks of high-dose and high-dose-rate exposures}}{\text{Dose and dose-rate effectiveness factor}}$$

Organizations	Dose and dose-rate effectiveness factors
UNSCEAR 1993	Less than 3 (1 to 10)
National Academy of Sciences (NAS) 2005	1.5
International Commission on Radiological Protection (ICRP) 1990 and 2007	2

Surveys targeting atomic bomb survivors have examined effects of the high-dose exposure at one time, while occupational exposures and exposures caused by environmental contamination due to a nuclear accident are mostly chronic low-dose exposures.

Therefore, animal testing using mice has been conducted to ascertain differences in oncogenic risks between a single high-dose exposure and low-dose exposures over time. Although test results vary by type of cancer, it has become clear that radiation effects are generally smaller for low-dose exposures over a long period of time.

Dose and dose-rate effectiveness factors are correction values used in the case of estimating risks of low-dose exposures, for which no concrete data is available, on the basis of risks of high-dose exposures (exposure doses and incidence rates), or estimating risks of chronic exposures or repeated exposures based on risks of acute exposures. Researchers have various opinions on specific values to be used for considering radiological protection, but the ICRP uses 2 as the dose and dose-rate effectiveness factor in its Recommendations and concludes that long-term low-dose exposure would cause half the effects as those caused by exposure at one time, if the total exposure dose is the same.

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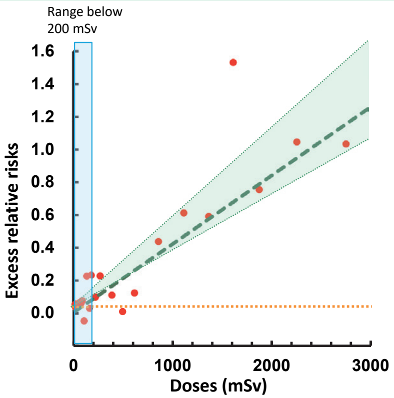
Cancer due to Acute External Exposure

Relationship between Solid Cancer Deaths and Doses

Deaths from solid cancer (results among atomic bomb survivors)



Source: Prepared based on Ozasa et al., Radiat Res., 177, 229, 2012

Excess relative risks: How cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people

Health effects surveys targeting atomic bomb survivors have revealed that cancer risks increase as exposure doses increase. The latest epidemiological survey on solid cancer risks shows proportionate relationships between doses and risks, i.e., between exposure doses exceeding 100 mSv and the risk of developing solid cancer and between exposure doses exceeding 200 mSv and the risk of death from solid cancer.

However, there is no consensus among researchers concerning a relationship between cancer risks and exposure doses below 100 to 200 mSv. It is expected that studies will be further continued into the future to clarify whether a proportionate relationship can be found between cancer risks and all levels of exposure doses, whether there is any substantial threshold value, or whether any other correlations are found (p.158 of Vol. 1, "Disputes over the LNT Model").

*Source:
1: E. J. Grant et. al., "Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958-2009," Radiation Research 187, 513-537 (2017)
2: K. Ozasa et. al., "Studies of the Mortality of Atomic Bomb Survivors, Report 14, 1950-2003: An Overview of Cancer and Noncancer Diseases," Radiation Research 177, 229-243 (2012)

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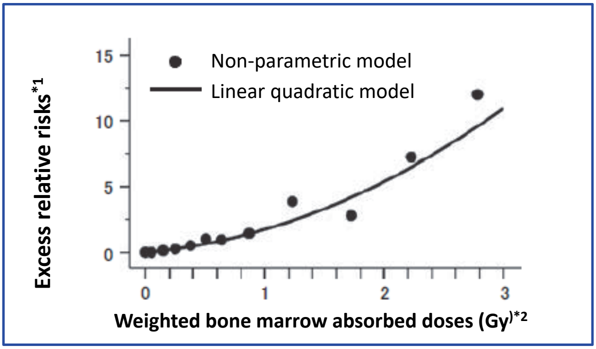
Cancer due to Acute External Exposure

Dose-response Relationship of Radiation-induced Leukemia

Dose-response relationship of radiation-induced leukemia among atomic bomb survivors in Hiroshima and Nagasaki



*1: An indicator to show increments in the mortality rate (or incidence rate) in the case of having been exposed to radiation against the mortality rate (or incidence rate) in the case of having been free from radiation exposure; showing how many times increase was caused by radiation exposure

*2: In the case of leukemia, weighted bone marrow doses (sum of 10 times the neutron doses and total amount of γ-rays) are used.

Source: Prepared based on Wan-Ling Hsu et al. The Incidence of Leukemia, Lymphoma and Multiple Myeloma among Atomic Bomb Survivors: 1950–2001, Radiation Research 179, 361–382 (2013)

Surveys targeting atomic bomb survivors made it clear that the dose-response relationship of leukemia, excluding chronic lymphocytic leukemia and adult T-cell leukemia, is quadric, and the higher an exposure dose is, the more sharply risks increase, showing a concave dose-response relationship (the linear quadratic curve in the figure). On the other hand, risks posed by low-dose exposure are considered to be lower than estimated based on a simple linear dose-response model.

In the figure above, black dots show excess relative risks depending on levels of bone marrow absorbed doses and the black line shows excess relative risks based on a linear quadratic model.

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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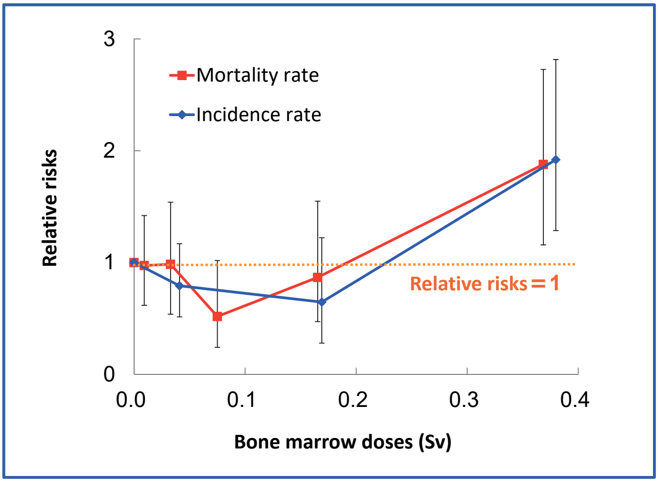
Cancer due to Acute External Exposure

Risks of Developing Leukemia

Data on Atomic Bomb Survivors

Risks of developing leukemia among atomic bomb survivors



Source: Prepared based on the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2006 Report

Relative risks of developing leukemia (values indicating how many times larger the risks are among people exposed to radiation when assuming the risks among non-exposed people as 1) among atomic bomb survivors do not increase notably among those whose bone marrow doses are below 0.2 Sv but increase significantly among those whose bone marrow doses are around 0.4 Sv.

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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Cancer due to Acute External Exposure

Relationship between Ages at the Time of Radiation Exposure and Oncogenic Risks

Atomic bomb survivors' lifetime risks by age at the time of radiation exposure

Age	Gender	Lifetime risks of death from cancer per 100-mSv exposure (%)	Lifetime risks of death from cancer when having been free from acute exposure (%)	Lifetime risks of death from leukemia per 100-mSv exposure (%)	Lifetime risks of death from leukemia when having been free from acute exposure (%)
10	Males	2.1	30	0.06	1.0
	Females	2.2	20	0.04	0.3
30	Males	0.9	25	0.07	0.8
	Females	1.1	19	0.04	0.4
50	Males	0.3	20	0.04	0.4
	Females	0.4	16	0.03	0.3

Source:
・Preston DL et al., Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. Radiat Res., 2003 Oct; 160(4):381-407
・Pierce DA et al., Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990 Radiat Res., 1996 Jul; 146 (1): 1-27

This table shows lifetime risks of death from cancer due to radiation exposure based on data obtained through epidemiological surveys targeting atomic bomb survivors. Specifically, comparisons are made between lifetime risks of deaths from cancer and leukemia per 100-mSv acute exposure and respective death risks when having been free from acute exposure, i.e., background death risks due to naturally developing cancer and leukemia.

The table suggests that a 10-year-old boy, for example, is likely to die of cancer in the future with a probability of 30% (the background risk of death from cancer for 10-year-old boys is 30% as shown in the table), but if the boy is acutely exposed to radiation at the level of 100 mSv, the risk of death from cancer increases by 2.1% to 32.1% in total.

The table shows the tendency that in the case of acute exposure to 100 mSv, lifetime risks of death from cancer are higher for those who are younger at the time of the exposure.

The reasons therefor include the facts that younger people have a larger number of stem cells that may develop into cancer cells in the future and cell divisions are more active and frequent compared with aged people.

(Related to p.109 of Vol. 1, "Difference in Radiosensitivity by Age," and p.115 of Vol. 1, "Ages at the Time of Radiation Exposure and Cancer Types")

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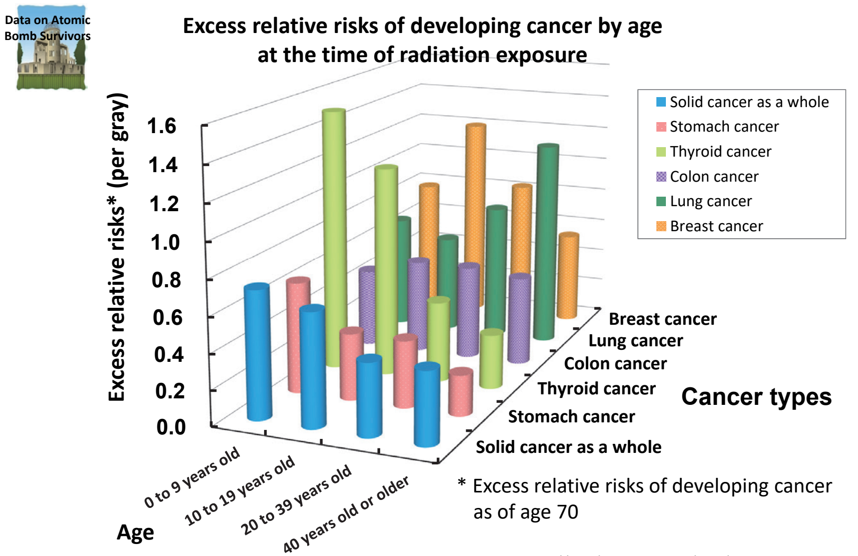
Updated on February 28, 2018

Cancer due to Acute External Exposure

Ages at the Time of Radiation Exposure and Cancer Types



Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

This figure shows a comparison of excess relative risks of developing cancer (values indicating how much cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people) per gray by age at the time of radiation exposure and by type of cancer, using the results of the surveys targeting atomic bomb survivors. Risks of thyroid cancer, stomach cancer and solid cancer as a whole are higher among people who were younger at the time of radiation exposure, risks of lung cancer are high among people aged 40 or older, risks of breast cancer are high during puberty, and risks of colon cancer do not show notable differences by age. In this manner, the figure suggests that the periods showing high radiosensitivity vary by type of cancer.

The excess relative risks in the figure show oncogenic risks due to exposure to respective organs when the survey targets become 70 years old.

(Related to p.116 of Vol. 1, "Oncogenic Risks by Age at the Time of Radiation Exposure," and p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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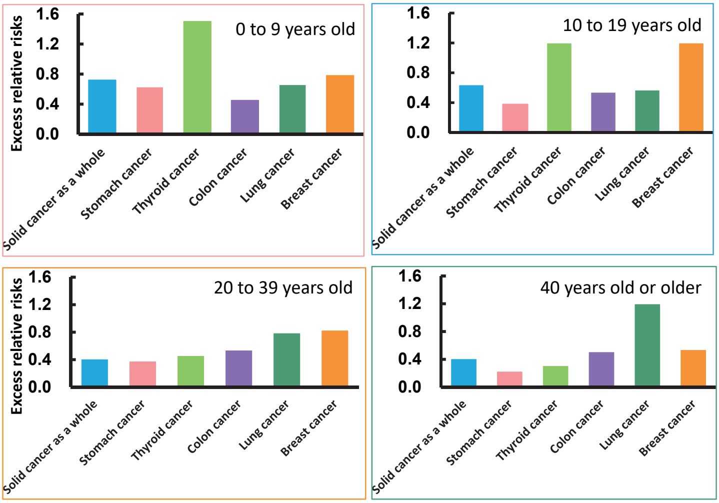
Cancer due to Acute External Exposure

Oncogenic Risks by Age at the Time of Radiation Exposure

Excess relative risks of developing cancer by age at the time of radiation exposure

* Excess relative risks of developing cancer as of age 70 (per gray)



Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

These figures show excess relative risks of developing cancer (values indicating how much cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people) in respective organs due to radiation exposure when the survey targets become 70 years old.

It can be observed that types of cancer with higher risks differ by age at the time of radiation exposure.

(Related to p.115 of Vol. 1, "Ages at the Time of Radiation Exposure and Cancer Types," and p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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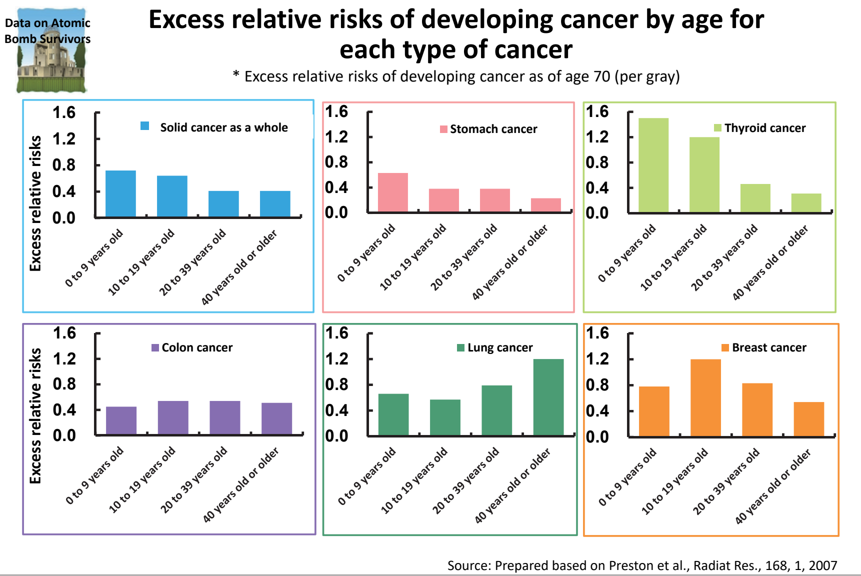
Cancer due to Acute External Exposure

Ages at the Time of Radiation Exposure and Risks by Type of Cancer



These figures show excess relative risks of developing cancer (values indicating how cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people) by age for each type of cancer, using the results of the surveys targeting atomic bomb survivors. For example, the excess relative risk of developing solid cancer as a whole for the age group of 0 to 9 years old is approx. 0.7, which means that the excess relative risk increases by 0.7 among a group of people exposed to 1 Gy compared with a group of non-exposed people. In other words, supposing the risk for a group of non-exposed people is 1, the risk for a group of people aged 0 to 9 who were exposed to 1 Gy increases by 1.7 times. The excess relative risk of developing solid cancer as a whole for people aged 20 or older is approx. 0.4 and the risk for a group of people exposed to 1 Gy will be 1.4 times larger than the risk for a group of non-exposed people.

As shown in the figures above, risks differ by age at the time of radiation exposure and type of cancer.

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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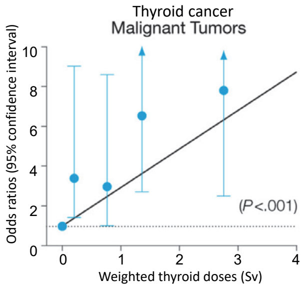
Updated on February 28, 2018

Incidence of Thyroid Cancer among Atomic Bomb Survivors



Source: Radiation Effects Research Foundation; JAMA 2006; 295(9): 1011-1022

Analysis of micro papillary cancer

mGy: milligrays

Weighted thyroid doses	Average doses (mGy)	Targets (people)	Cancer detected in (people)	Odds ratios (95% confidence interval)
<5mGy	—	755	33	1
5～100mGy	32	936	36	0.85 (0.52～1.39)
100～500mGy	241	445	22	1.12 (0.64～1.95)
500mGy<	1237	236	15	1.44 (0.75～2.67)

Source: Hayashi et al., Cancer, 116, 1646, 2010

* Odds ratio: A statistical scale for comparing the probability of a certain incident between two groups
Odds ratios larger than 1 suggest that the probability is larger. When the probability that a certain incident occurs is p (Group 1) and q (Group 2), respectively, the odds ratio is obtained by the following formula.
Odds of p / Odds of q = p / (1-p) ÷ q / (1-q)
When the 95% confidence interval does not include 1, the difference in the probability is statistically significant.

Odds ratios (statistical scales for comparing the probability of a certain incident between two groups) regarding incidence of thyroid cancer among atomic bomb survivors show that risks of thyroid cancer increase as doses increase.

No significant difference was found by a survey only targeting micro papillary thyroid cancer.* The odds ratio remains low until the weighted thyroid dose exceeds 100 mGy, but the ratio slightly exceeds 1 when the weighted thyroid dose becomes 100 mGy or larger. (When the odds ratio is larger than 1, the relevant incident is more highly likely to occur. However, in this data, as the 95% confidence interval includes 1, there is no statistically significant difference in the probability.)

* Source:
M. Imaizumi, et.al., "Radiation Dose-Response Relationships for Thyroid Nodules and Autoimmune Thyroid Diseases in Hiroshima and Nagasaki Atomic Bomb Survivors 55-58 Years After Radiation Exposure" JAMA 2006;295(9):1011-1022
Y. Hayashi, et.al., "Papillary Microcarcinoma of the Thyroid Among Atomic Bomb Survivors Tumor Characteristics and Radiation Risk" Cancer April 1, 2010, 1646-1655

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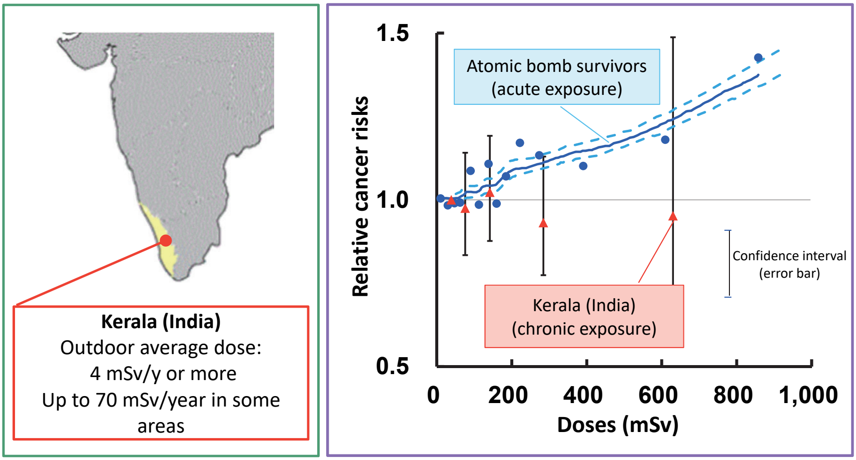
Effects of Long-Term Low-Dose Exposure

Carcinogenesis among residents in high natural radiation area in India



mSv: millisieverts

Source: Prepared based on Nair et al., Health Phys 96, 55, 2009; Preston et al., Radiat Res. 168, 1, 2007

It is considered that effects appear in different manners depending on whether it is a low-dose-rate radiation exposure or a high-dose-rate radiation exposure.

The figure on the right compares the data on atomic bomb survivors and risks for residents in high natural radiation areas such as Kerala in India. No increase is observed in relative risks for cancer (values indicating how many times cancer risks increase among exposed people when supposing the risk for non-exposed people as 1) among residents in Kerala even if their accumulated doses reach several hundred mSv. This suggests that risks are smaller in the case of chronic exposure than in the case of acute exposure, although further examination is required as the range of the confidence interval (the error bar on the figure) is very large.

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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Updated on February 28, 2018

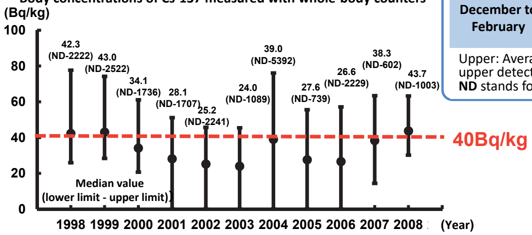
Internal Exposure due to Cesium at the Time of the Chernobyl Accident

Seasonal changes in body concentrations of Cs-137 (Bq/kg) and number of examinees

	1998 to 2001	2002 to 2005	2006 to 2008
March to May	34.6 (ND-2154.9) 10,993	27.3 (ND-5392.2) 18,722	32.0 (ND-1757.1) 9,284
June to August	71.5 (ND-399.0) 265	32.2 (ND-393.0) 268	21.2 (ND-271.1) 451
September to November	40.9 (ND-2521.7) 9,590	33.5 (ND-1089.3) 8,999	44.2 (ND-2229.3) 4,080
December to February	33.5 (ND-1735.8) 8,971	20.6 (ND-607.0) 6,603	39.8 (ND-1454.3) 6,404

Upper: Average **(Bq/kg)**; Middle: Lower detection limit to upper detection limit; Lower: Number of examinees (people); **ND** stands for below the detection limit.

Body concentrations of Cs-137 measured with whole-body counters



The annual internal exposure of 40 Bq/kg was detected in the Bryansk State from 1998 to 2008.

Bq/kg: Becquerels per kilogram

Source: Prepared based on Sekitani et al., Radiat Prot Dosimetry, 141, 1, 2010

Due to the Chernobyl accident in 1986, much larger amounts of radioactive materials were released compared with those released by the accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS. At first, the government of the former Soviet Union did not publicize the accident nor did it take any evacuation measures for residents around the nuclear facilities. In late April, when the accident occurred, pasturing had already started in the southern part of the former Soviet Union and cow milk was also contaminated with radionuclides.

As a result of the whole-body counter measurements of body concentrations of Cs-137, which were conducted for residents in the Bryansk State from 1998 to 2008, it was found that the median value of body concentrations of Cs-137 had decreased within a range of 20 to 50 Bq/kg until 2003 but has been on a rise since 2004. This suggests that exposure to Cs-137 due to the Chernobyl accident has been continuing over years.

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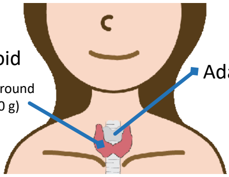
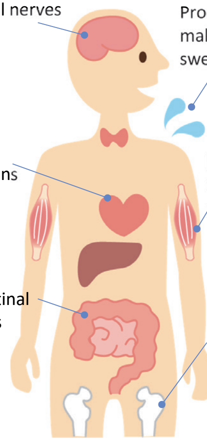
Basic Information on Thyroid

Thyroid



- **The thyroid is located in the lower center of the neck (below the Adam's apple).**
- **The thyroid takes in iodine in foods, etc., produces thyroid hormones, and secretes them into the blood.**

Actions of thyroid hormones



The thyroid is a small organ weighing around 10 to 20 g and shaped like a butterfly with its wings extended. It is located in the lower center of the neck (below the Adam's apple) as if surrounding the windpipe. The thyroid actively takes in iodine in the blood to produce thyroid hormones therefrom. Produced thyroid hormones are secreted into the blood and are transported to the whole body to act in various manners.

Thyroid hormones play roles of promoting metabolism to facilitate protein synthesis in the body and maintenance of energy metabolism and also roles of promoting growth and development of children's body and brains.

Included in this reference material on March 31, 2017

Iodine

● **Iodine = Raw material of thyroid hormones**

Intake at one meal	Amount of iodine
Kelp boiled in soy sauce (5 to 10 g)	10～20mg
Boiled kelp roll (3 to 10 g)	6～20mg
Hijiki seaweed (5 to 7 g)	1.5～2mg
Wakame seaweed soup (1 to 2 g)	0.08～0.15mg
Half sheet of dried laver seaweed (1 g)	0.06mg
Stock made from kelp (0.5 to 1 g)	1～3mg
Agar (1 g)	0.18mg

Iodine intake
Dietary Reference Intakes 2015

Estimated average requirement: 0.095 mg
Recommended intake: 0.13 mg

Japanese people's iodine intake is estimated to be approx. 1 to 3 mg/d.

Source: Zava TT, Zava DT, Thyroid Res 2011; 4: 14; Report of the "Development Committee for the Dietary Reference Intakes for Japanese 2015," Ministry of Health, Labour and Welfare; "Super Graphic Illustration: Thyroid Diseases," Houken Corp.

Iodine, which is a raw material of thyroid hormones, is contained in large quantities in seaweed, fish and seafood that are familiar to Japanese people.

The "Dietary Reference Intakes for Japanese" released by the Ministry of Health, Labour and Welfare states that the estimated average iodine requirement is 0.095 mg per day and recommended intake is 0.13 mg per day. Japanese people consume a lot of seaweed, fish and seafood on a daily basis and are considered to take in a sufficient amount of iodine (approx. 1 to 3 mg/d).

When a person habitually consumes iodine, the thyroid constantly retains a sufficient amount of iodine. It is known that once the thyroid retains a sufficient amount of iodine, any iodine newly ingested is only partially taken into the thyroid and most of it is excreted in the urine.

Accordingly, even in the case where radioactive iodine is released due to such reasons as an accident at a nuclear power plant, accumulation of the released radioactive iodine in the thyroid can be subdued among a group of people who take in iodine on a daily basis.

Included in this reference material on March 31, 2017

Basic Information on Thyroid

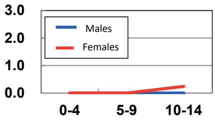
Characteristics of Thyroid Cancer

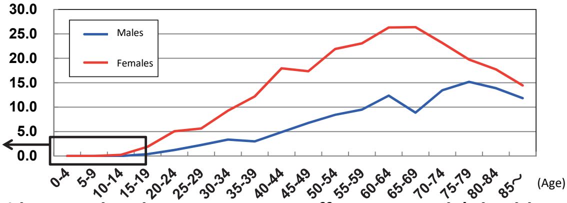
- **The incidence rate of thyroid cancer is higher for females** (estimated age-adjusted incidence rate (nationwide) (against 100,000 people), 2010).

  ⇒**Females: 11.5 (people); Males: 4.5 (people)**

- **Thyroid cancer is found in all age groups from younger people to aged people (estimated incidence rate by age group**(nationwide) (against 100,000 people), 2010).

⇒Among children(younger than 15 years old), the male-to-female ratio is almost 1:1.





- **There is also occult thyroid cancer that does not exert any effects on people's health throughout their lifetime.**
- **In many cases, prognosis after surgery is good** (crude cancer mortality rate by organ/tissue (against 100,000 people), 2010).

	Thyroid	Stomach	Liver	Lungs	Leukemia
Male	**0.9**	53.5	34.9	81.8	7.9
Female	**1.7**	26.5	17.4	30.0	5.0

(Source: "Cancer Registration and Statistics," Cancer Information Service, National Cancer Center Japan)

Thyroid cancer has some unique characteristics compared with other types of cancer.

The first is the higher incidence rate for females (11.5 females and 4.5 males against 100,000 people (national age-adjusted incidence rate)), but the male-to-female ratio is almost 1:1 among children younger than 15 years old.

It is known that breast cancer is most frequently detected in females in their 40s and 50s and the incidence rate of stomach cancer is higher among both males and females over 60 years old. On the other hand, thyroid cancer is characteristically found broadly in all age groups from teenagers to people in their 80s.

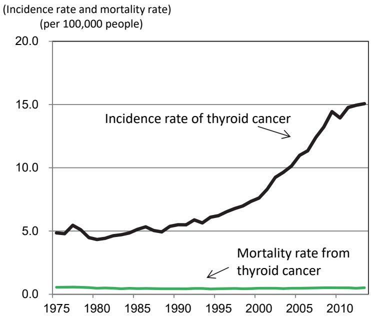
Furthermore, thyroid cancer has long been known as a type of cancer, most of which are occult cancers without exerting any effects on people's health throughout their lifetime. The crude cancer mortality rate (national mortality rate by age group (against 100,000 people), all age groups, 2010) is lower for thyroid cancer than other cancers and better prognosis after surgery is also one of the characteristics of thyroid cancer.

Included in this reference material on March 31, 2017
Updated on February 28, 2018

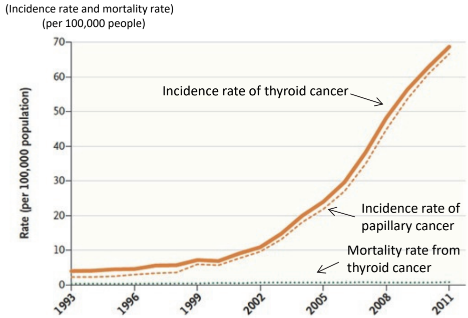
Basic Information on Thyroid

Incidence Rates of Thyroid Cancer: Overseas

Incidence rates and mortality rates (against 100,000 people) in America and South Korea



America[*1]



South Korea[*2]

*1: Prepared based on NATIONAL CANCER INSTITUTE, Surveillance, Epidemiology, and End Results Program, SEER Cancer Statistics Review 1975-2013
*2: Prepared based on Ahn HS, N Engl J Med. 2014

In recent years, sharp increases in the incidence rate of thyroid cancer have been reported, which is said to be due to increases in the frequencies of medical surveys and use of healthcare services as well as the introduction of new diagnostic technologies, resulting in detection of many cases of micro thyroid cancer (micro papillary cancer) that have no symptoms and are non-fatal.

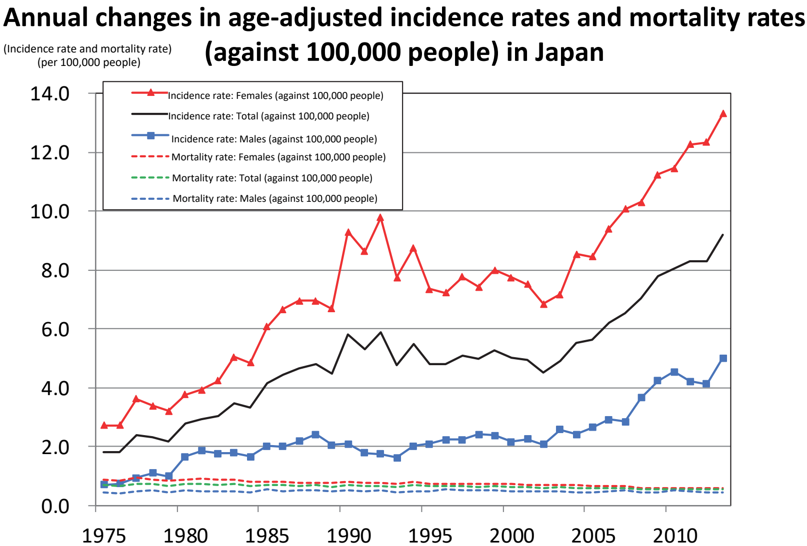
As the mortality rate has remained almost unchanged despite sharp increases in the incidence rate, the possibility of overdiagnoses (detection of many cases of such non-fatal micro papillary cancer) is pointed out.*

Increases in the incidence rate of thyroid cancer are global trends observed in such countries as America, Australia, France and Italy, but are especially notable in South Korea. In South Korea, official assistance for thyroid cancer screening was commenced in 1999 to enable people to receive the most-advanced screening at low cost. This is considered to have prompted a larger number of people to receive screening, leading to significant increases in the incidence rate of thyroid cancer.

* Source:
International Agency for Research on Cancer "Overdiagnosis is a major driver of the thyroid cancer epidemic: up to 50–90% of thyroid cancers in women in high-income countries estimated to be overdiagnoses" (August 18, 2016)

Included in this reference material on March 31, 2017

Incidence Rates of Thyroid Cancer: Japan



(Source: "Cancer Registration and Statistics," Cancer Information Service, National Cancer Center Japan))

This figure shows annual changes in incidence rates (percentage of patients against the population during a certain period of time) and mortality rates concerning thyroid cancer in Japan.

The incidence rates of thyroid cancer have been on a rise both for males and females in Japan. The increasing trend is more notable among females and the incidence rate, which was around three per 100,000 people in 1975, exceeded 13 in 2013. In the meantime, the mortality rate from thyroid cancer has not shown any significant changes and has been slightly decreasing both for males and females. The total incidence rate of thyroid cancer including both males and females per 100,000 people in 2010 was approx. 15 in America, approx. 60 in South Korea, and approx. 8 in Japan (p.124 of Vol. 1, "Incidence Rates of Thyroid Cancer: Overseas").

In Japan, palpation by doctors has long been conducted broadly as thyroid cancer screening, but ultrasound neck examination is increasingly being adopted in complete medical checkups and mass-screening. Furthermore, thanks to recent advancement of ultrasonic diagnostic equipment, diagnostic capacity has been improving and the detection rate of tumoral lesions, in particular, is said to be increasing.

* Source: Hiroki Shimura, Journal of the Japan Thyroid Association, 1 (2), 109-113, 2010-10

Included in this reference material on March 31, 2017

Risks of Thyroid Cancer among Japanese People

- The probability that Japanese people develop thyroid cancer during the lifetime without any influence of radiation exposure is*
  - 0.78% for females and 0.23% for males.

    (Kamo et al., (2008) Jpan.J. Clin Oncol 38(8) 571-576)

    * The probability that Japanese people develop cancer at least once during the lifetime, which was obtained based on the data on the number of cancer patients in Japan from 1975 to 1999

    (Kamo et al., Journal of Health and Welfare Statistics, Vol. 52, No. 6, June 2005)

- When the thyroid exposure dose is 1,000 mSv, the probability of developing thyroid cancer increases
  - by 0.58% to 1.39% for females and by 0.18% to 0.34% for males.

    (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2006 Report, Annex A)

- The probability that a Japanese person exposed to 1,000 mSv in the thyroid develops thyroid cancer during the lifetime is as follows (adding the probability of cancer incidence caused by other factors):
  - Females: 0.78 + (0.58 to 1.39) = 1.36% to 2.17%
  - Males: 0.23 + (0.18 to 0.34) = 0.41% to 0.57%

    (Kamo et al., (2008) Jpan. J. Clin Oncol 38(8), UNSCEAR 2006 Report, Annex A)

However, it is considered to be difficult to scientifically prove risk increases due to low-dose exposure of the thyroid, as effects of other factors are larger.

The probability that a Japanese person will develop thyroid cancer during their lifetime is 0.78% for females and 0.23% for males, which is the probability that they will develop thyroid cancer at least once during the lifetime, obtained based on the thyroid cancer incidence rate among the total cancer incidence data in Japan from 1975 to 1999. This is an index devised with the aim of explaining cancer risks to ordinary people in an easy-to-understand manner.

Exposure to 1,000 mSv in the thyroid increases the probability of developing thyroid cancer by 0.58% to 1.39% for females and by 0.18% to 0.34% for males, and after adding the probability of cancer incidence caused by other factors, the probability would increase by 1.36% to 2.17% for females and by 0.41% to 0.57% for males.

However, if the thyroid exposure dose is low, it is considered to be difficult to scientifically prove risk increases due to the radiation exposure, as effects of other factors are larger.

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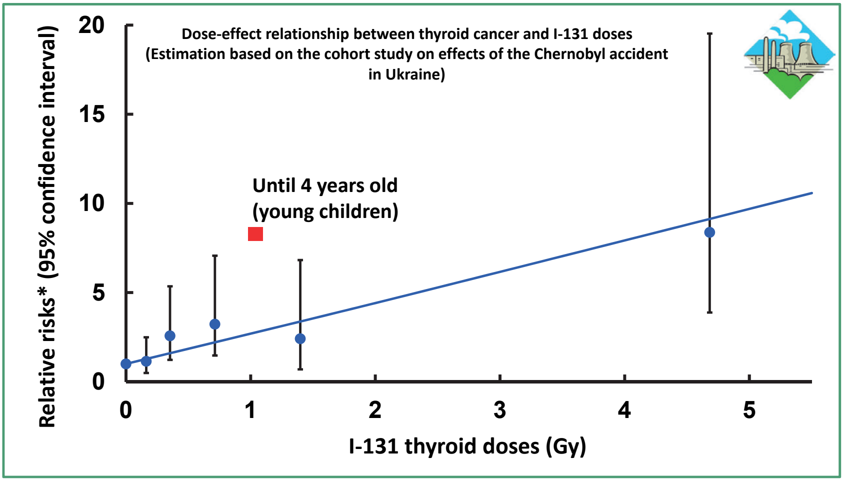
Basic Information on Thyroid

Relationship between Thyroid Cancer and Doses - Chernobyl Accident -



Source: Prepared based on Brenner et al., Environ Health Perspect 119, 933, 2011

* Relative risks indicate how many times larger the cancer risks are among people exposed to radiation when assuming the risks among non-exposed people as 1.

The results of the study on the relationship between internal doses and risks of thyroid cancer among children affected by the Chernobyl accident are as shown in the figure above.

That is, exposure to 1 Gy in the thyroid doubles the probability of developing thyroid cancer. This study concludes that the double increase in risks is the average of children up to 18 years old, and for younger children up to 4 years old, risk increase would be sharper (indicated with ■ in the figure).

(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

Included in this reference material on March 31, 2013
Updated on February 28, 2018

Basic Information on Thyroid

Thyroid Cancer and Iodine Intake
- Chernobyl Accident -

Stable iodine tablets	Relative risks* of exposure to 1 Gy (95% confidence interval)	
	Areas where iodine concentration in soil is high	Areas where iodine concentration in soil is low
Administered	2.5 (0.8-6.0)	9.8 (4.6-19.8)
Unadministered	0.1 (-0.3-2.6)	2.3 (0.0-9.6)

Source: Cardis et al., JNCI, 97, 724, 2005

* Relative risks indicate how many times larger the cancer risks are among people exposed to radiation when assuming the risks among non-exposed people as 1.

As shown in the table, there has been a report that the relative risk of thyroid cancer per gray increases in areas where iodine concentration in soil is low and iodine intake is insufficient. Areas around Chernobyl, where the relevant data was obtained, are located inland away from the sea and iodine concentration in soil is low. Additionally, people there do not habitually eat seaweed and salt-water fish that are rich in iodine.

Compared to areas around Chernobyl, iodine concentration in soil is higher in Japan as a whole and iodine intake is also higher than in other countries. Accordingly, such data as obtained in areas around Chernobyl is not necessarily applicable in Japan.
(Related to p.93 of Vol. 1, "Relative Risks and Attributable Risks")

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Updated on February 28, 2018

Exposure of a Group of Evacuees
- Chernobyl Accident -

Countries	Number of people (1,000 people)	Average effective dose (mSv)		Average thyroid dose (mGy)
		External exposure	Internal exposure (in organs other than the thyroid)	
Belarus	**25**	**30**	**6**	**1,100**
Russia	**0.19**	**25**	**10**	**440**
Ukraine	**90**	**20**	**10**	**330**

mSv: millisieverts mGy: milligrays

Source: United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008 Report

Thyroid exposure doses are high for people who were forced to evacuate after the Chernobyl accident and the average is estimated to be approx. 490 mGy. The average thyroid dose for children is estimated to be even higher. One of the major causes is that they drank milk contaminated with I-131 for two to three weeks after the accident.

The average thyroid exposure dose for people who resided outside evacuation areas in the former Soviet Union was approx. 20 mGy, while that for people who resided in the contaminated areas was approx. 100 mGy. Both values were much higher than the average dose (approx. 1 mGy) for people in other countries in Europe.

The effective dose from internal exposure in organs other than the thyroid and from external exposure was approx. 31 mSv on average. The average effective dose was approx. 36 mSv in Belarus, approx. 35 mSv in Russia, and approx. 30 mSv in Ukraine. It is known that the average effective dose is larger in Belarus than in Ukraine and Russia as in the case of the average thyroid exposure dose.

(Related to p.130 of Vol. 1, "Time of Developing Childhood Thyroid Cancer - Chernobyl Accident -")

Included in this reference material on March 31, 2013
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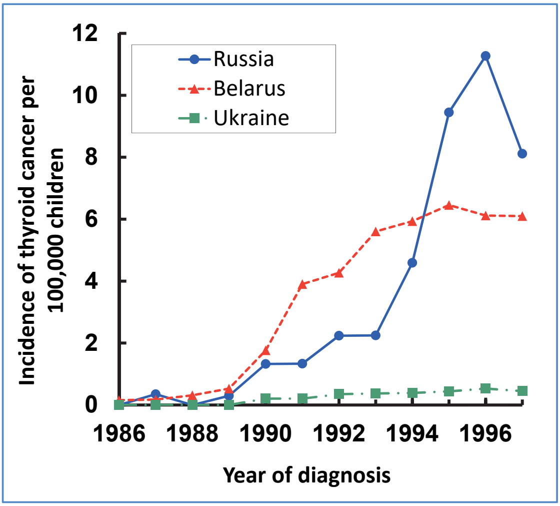
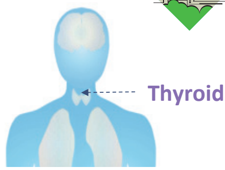
Time of Developing Childhood Thyroid Cancer
- Chernobyl Accident -

Childhood thyroid cancer (Chernobyl accident)





Iodine is a raw material of thyroid hormones.

Childhood thyroid cancer cases started to appear **four** or **five** years after the accident, and showed a sharp increase by more than **10** times after the lapse of **10** years.

Source: Prepared based on the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2000 Report

At the time of the Chernobyl accident, a large amount of radioactive materials was released and broadly spread out due to an explosion. The major cause of health hazards is said to be radioactive iodine.

Some of the children who inhaled radioactive iodine that fell onto the ground or had vegetables, milk, and meat contaminated through the food chain later developed childhood thyroid cancer. In particular, the major contributing factor is considered to be internal exposure due to I-131 contained in milk.

In Belarus and Ukraine, childhood thyroid cancer cases started to appear four or five years after the accident. The incidence rate of thyroid cancer among children aged 14 or younger increased by 5 to 10 times from 1991 to 1994 than in the preceding five years from 1986 to 1990.

However, the incidence of childhood thyroid cancer for Belarus and Ukraine is the number per 100,000 children nationwide, while that for Russia is the number per 100,000 children only in specific areas heavily contaminated (UNSCEAR 2000 Report, Annex).
(Related to p.129 of Vol. 1, "Exposure of a Group of Evacuees - Chernobyl Accident -")

Included in this reference material on March 31, 2013
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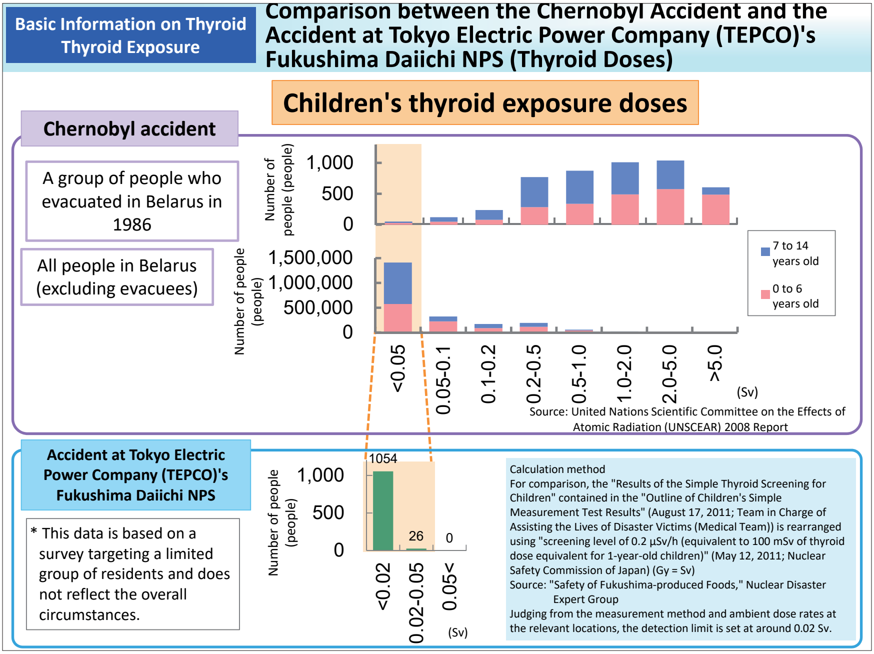


It is very difficult to accurately assess the level of exposure of children's thyroids to radioactive iodine after the accident at TEPCO's Fukushima Daiichi NPS, but rough estimation is possible using the results of the thyroid screening conducted for children as of approx. two weeks after the accident.

This screening was conducted using survey meters for 1,080 children aged 15 or younger in Kawamata, Iwaki, and Iitate, where children's thyroid doses were suspected to be especially high.

As a result, thyroid doses exceeding the screening level set by the Nuclear Safety Commission of Japan (at that time) were not detected and measured thyroid doses were all below 50 mSv for those children who received the screening.

In the UNSCEAR's analysis of thyroid doses after the Chernobyl accident, the dose range below 50 mSv is considered to be the lowest dose range. Thyroid exposure doses for children in Belarus, where increased incidences of childhood thyroid cancer were later observed, were 0.2 to 5.0 Sv or over 5.0 Sv among a group of evacuees, showing two-digit larger values than the results of the screening in Fukushima Prefecture.

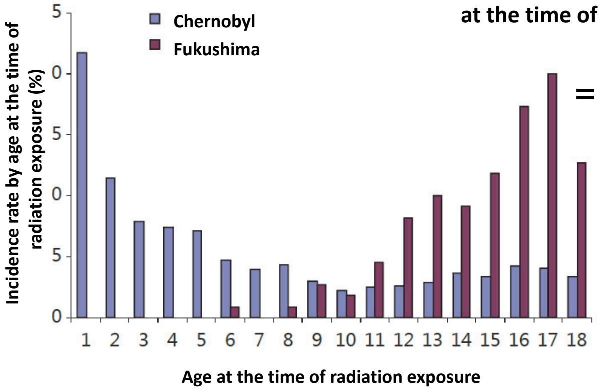
(Related to p.132 of Vol. 1, "Comparison between the Chernobyl Accident and the Accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS (Ages at the Time of Radiation Exposure)")

Included in this reference material on March 31, 2013
Updated on March 31, 2017

Comparison between the Chernobyl Accident and the Accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS (Ages at the Time of Radiation Exposure)

- **Distribution of age at the time of radiation exposure of childhood thyroid cancer patients observed in Chernobyl and Fukushima**

(Among the total number of incidence in respective regions)



Incidence rate of thyroid cancer by age at the time of radiation exposure (%)

= Number of incidence for each age / Total number of incidence of thyroid cancer

(Fukushima: Diagnosed as malignant or suspected)

Source: Williams D. Eur Thyroid J 2015; 4: 164–173

This figure shows the incidence rates of childhood thyroid cancer by age at the time of radiation exposure (aged 18 or younger), in comparison with those after the Chernobyl accident and those in three years after the accident at TEPCO's Fukushima Daiichi NPS (the percentage in the figure shows the ratio by age, i.e., what percentage the incidence for each age accounts for against the total number of incidence of thyroid cancer in respective regions; the sum of all percentages comes to 100%). The figure shows clear difference in age distribution although an accurate comparison is difficult as thyroid cancer screening in Chernobyl has not been conducted in a uniform manner as in Fukushima and such information as the number of examinees and observation period is not clearly indicated.

Generally speaking, risks of radiation-induced thyroid cancer are higher at younger ages (especially 5 years old or younger). In Chernobyl, it is observed that people exposed to radiation at younger ages have been more likely to develop thyroid cancer. On the other hand, in Fukushima, incidence rates of thyroid cancer among young children have not increased three years after the accident and incidence rates have only increased in tandem with examinees' ages. This tendency is the same as increases observed in incidence rates of ordinary thyroid cancer.

The document by Williams suggests that thyroid cancer detected three years after the accident at Fukushima Daiichi NPS is not attributable to the effects of the radiation exposure due to the accident in light of the facts that daily iodine intake from foods is larger in Japan than in areas around Chernobyl and that the maximum estimated thyroid exposure doses among children is much smaller in Japan (66 mGy in Fukushima and 5,000 mGy in Chernobyl).

(Related to p.131 of Vol. 1, "Comparison between the Chernobyl Accident and the Accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS (Thyroid Doses)")

Included in this reference material on March 31, 2017

Evaluation of the Interim Report on Thyroid Cancer Compiled by the Expert Meeting on Health Management After the Fukushima Daiichi Nuclear Accident

The Expert Meeting* compiled the Interim Report (December 2014), wherein it considered the following points concerning the thyroid cancer cases found through the Initial Screening of Thyroid Ultrasound Examination conducted as part of the Fukushima Health Management Survey, and concluded that "no grounds positively suggesting that those cases are attributable to the nuclear accident are found at this moment."

(* Expert Meeting on Health Management After the Fukushima Daiichi Nuclear Accident

i) Thyroid exposure doses of residents after the accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS are evaluated to be lower than those after the Chernobyl accident.

ii) In the case of the Chernobyl accident, increases in thyroid cancer cases were reported four or five years after the accident and this timing is different from when thyroid cancer cases were found in the Initial Screening in Fukushima.

iii) Increases in thyroid cancer cases after the Chernobyl accident were mainly observed among children who were infants at the time of the accident. On the other hand, the survey targets diagnosed to have or suspected to have thyroid cancer in the Initial Screening in Fukushima include no infants.

iv) The results of the Primary Examination did not significantly differ from those of the 3-prefecture examination (covering Nagasaki, Yamanashi and Aomori Prefectures), although the cohort was much smaller in the latter.

v) When conducting a thyroid ultrasound examination as screening targeting adults, thyroid cancer is generally found at a frequency 10 to 50 times the incidence rate.

Source: Interim Report (December 2014), Expert Meeting on Health Management After the Fukushima Daiichi Nuclear Accident (http://www.env.go.jp/chemi/rhm/conf/tyuukanntorimatomeseigohyouhannei.pdf, in Japanese)

The Expert Meeting on Health Management After the Fukushima Daiichi Nuclear Accident examines various measures concerning dose evaluation, health management and medical services from an expert perspective.

It publicized the Interim Report in December 2014 and concluded that regarding the thyroid cancer cases found through the Initial Screening of Thyroid Ultrasound Examination conducted as part of the Fukushima Health Management Survey, "no grounds positively suggesting that those cases are attributable to the nuclear accident are found at this moment."

However, the Expert Meeting points out the necessity to continue the Thyroid Ultrasound Examination as follows.

- "The trend of the incidence of thyroid cancer, which is especially a matter of concern among the residents, needs to be carefully monitored under the recognition that radiation health management requires a mid- to long-term perspective in light of the uncertainties of estimated exposure doses. (Interim Report by the Expert Meeting on Health Management After the Fukushima Daiichi Nuclear Accident; December 2014)
- "The possibility of radiation effects may be small but cannot be completely denied at this point in time. Additionally, it is necessary to accumulate information in the long term for accurate evaluation of the effects. Therefore, the Thyroid Ultrasound Examination should be continued, while meticulously explaining the disadvantages of receiving the examination and obtaining the understanding of examinees." (Interim Report by the Prefectural Oversight Committee Meeting for Fukushima Health Management Survey; March 2016)
- "Continuing the Fukushima Health Management Survey and the Thyroid Ultrasound Examination for children based on the present protocol is positioned as one of the major priorities in scientific studies." (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2013 Report)

Included in this reference material on February 28, 2018