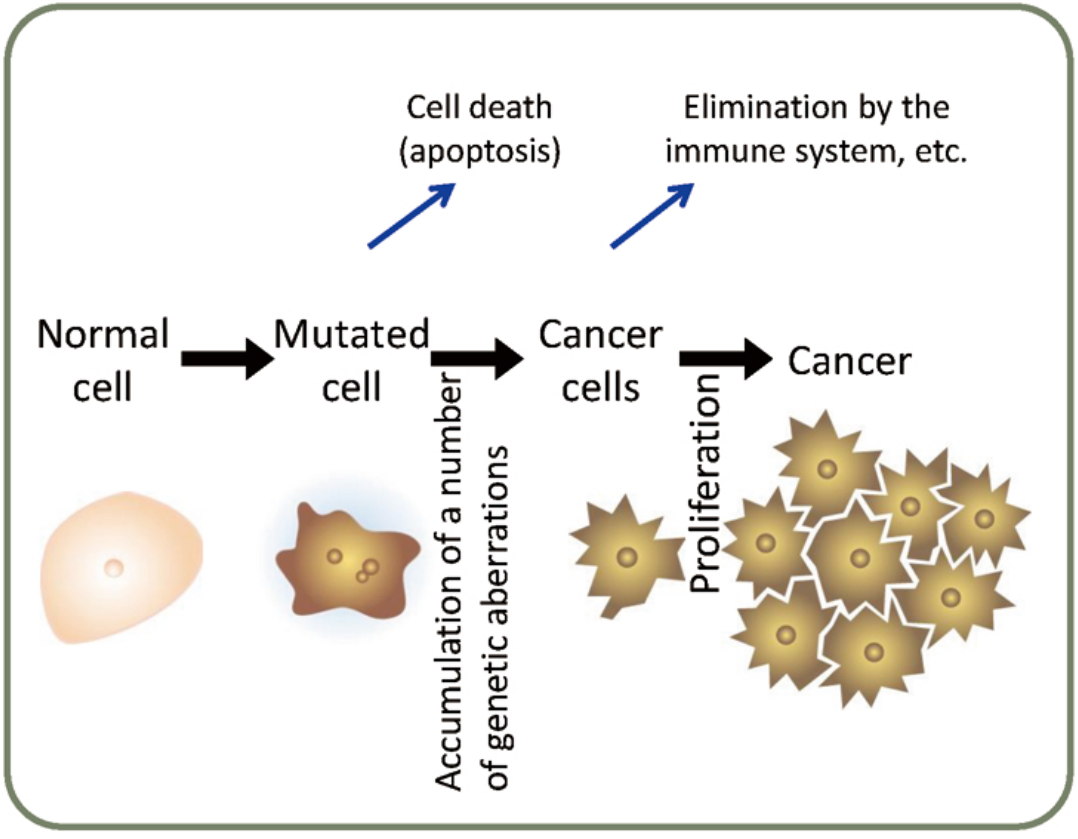
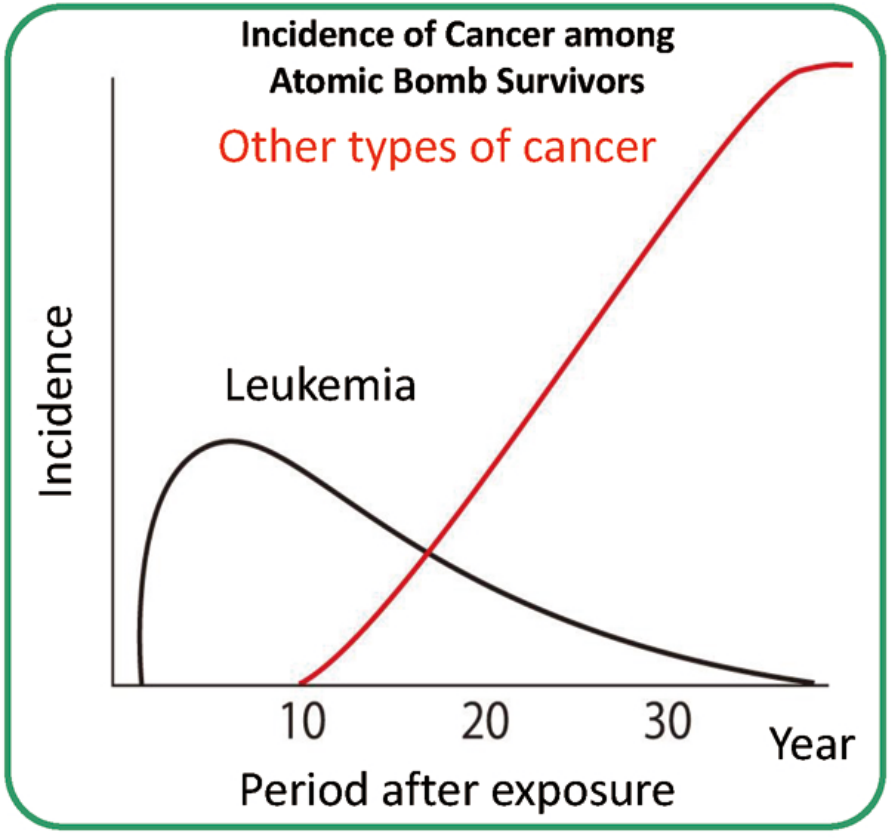
Mechanism of Carcinogenesis



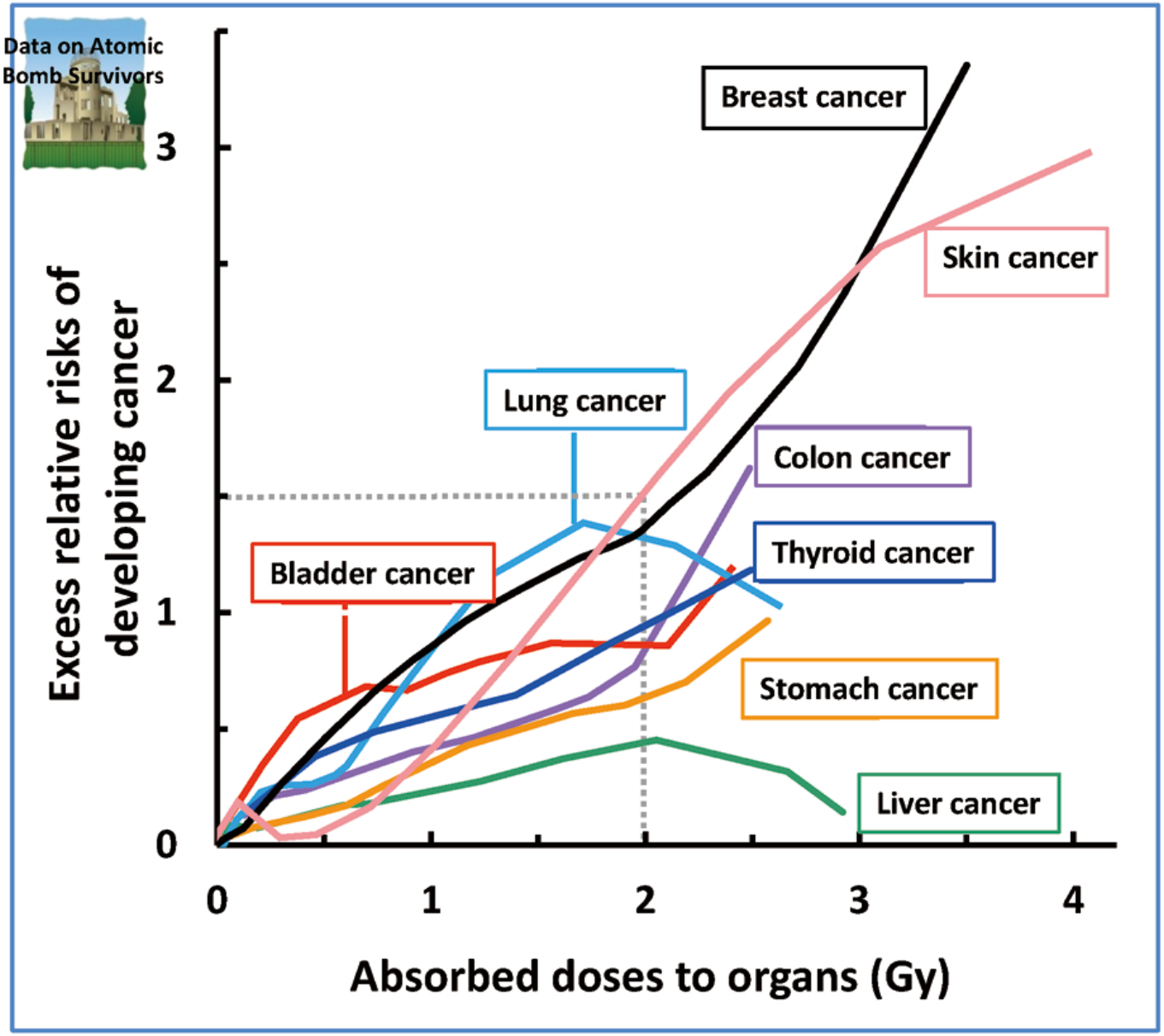


- Radiation is only one of various factors that induce cancer.

- Mutated cells follow multiple processes until developing into cancer cells.
  → It takes several years to decades.

Cancer and Leukemia

Tissues and Organs Highly Sensitive to Radiation



Tissue	Tissue weighting factor w_T*
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.

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

Cancer and Leukemia

Difference in Radiosensitivity by Age

Children are not small adults.

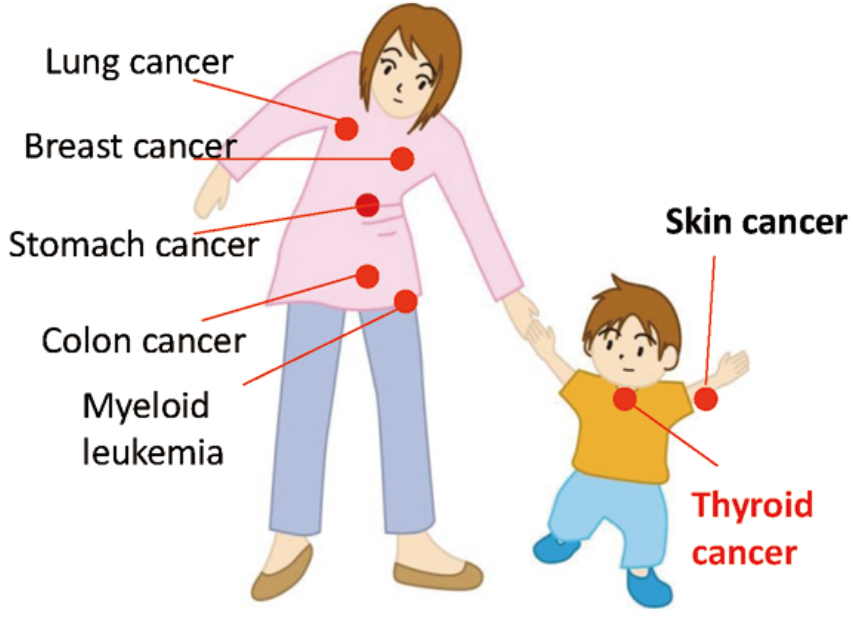
	Committed effective dose coefficients for I-131*1 (μSv/Bq)	Committed effective doses when having taken in 100 Bq of I-131 (μSv)	Equivalent doses to the thyroid when having taken in 100 Bq of I-131*2 (μSv)
3 month-old infants	0.18	18	450
1 year-old children	0.18	18	450
5 year-old children	0.10	10	250
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: Prepared based on International Commission on Radiological Protection (ICRP), ICRP Publication 119, Compendium of Dose Coefficients based on ICRP Publication 60, 2012

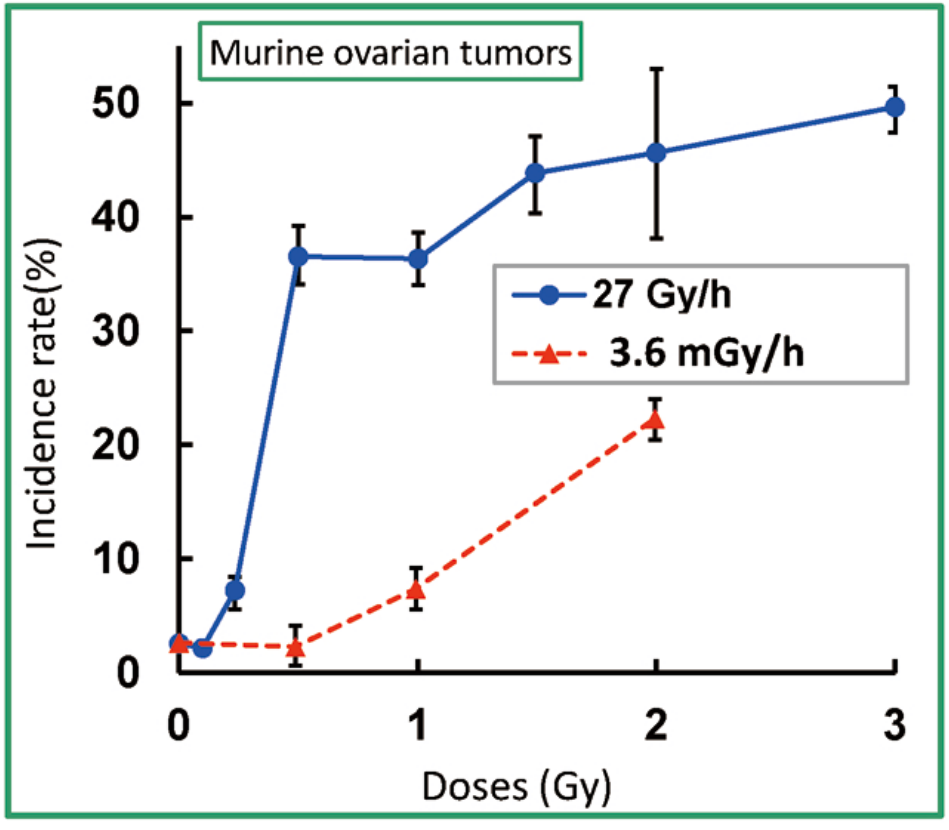
Risks of thyroid cancer and skin cancer are higher for children than for adults.

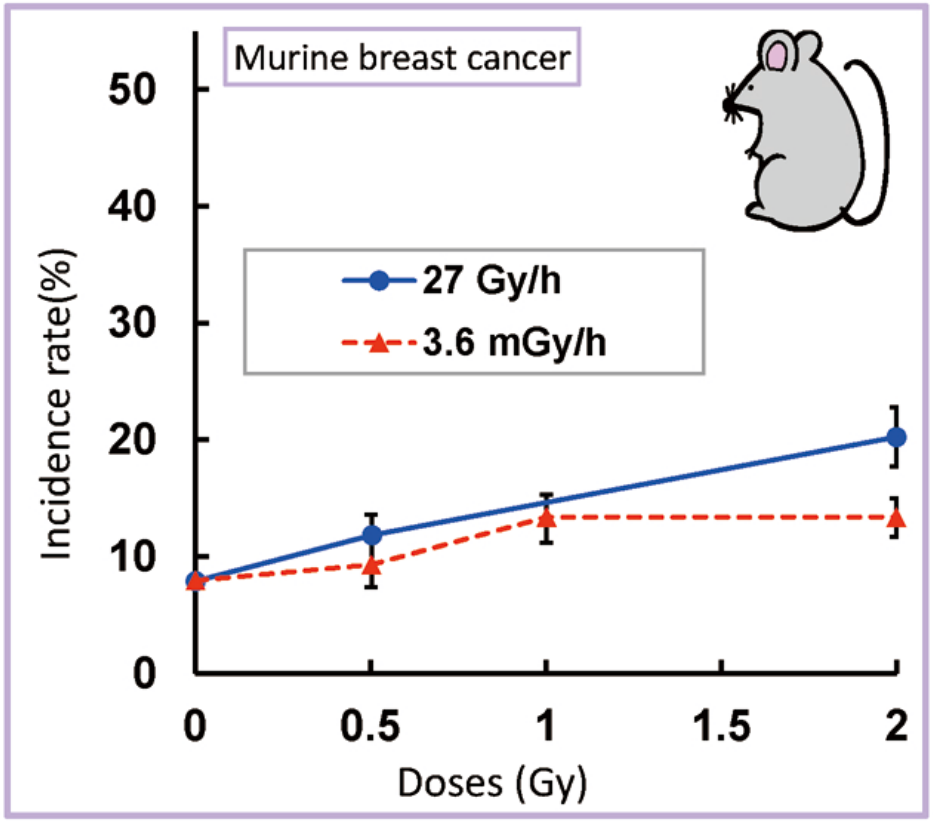
μSv/Bq: microsieverts/becquerel



Cancer and Leukemia

Cancer-promoting Effects of Low-dose Exposures





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

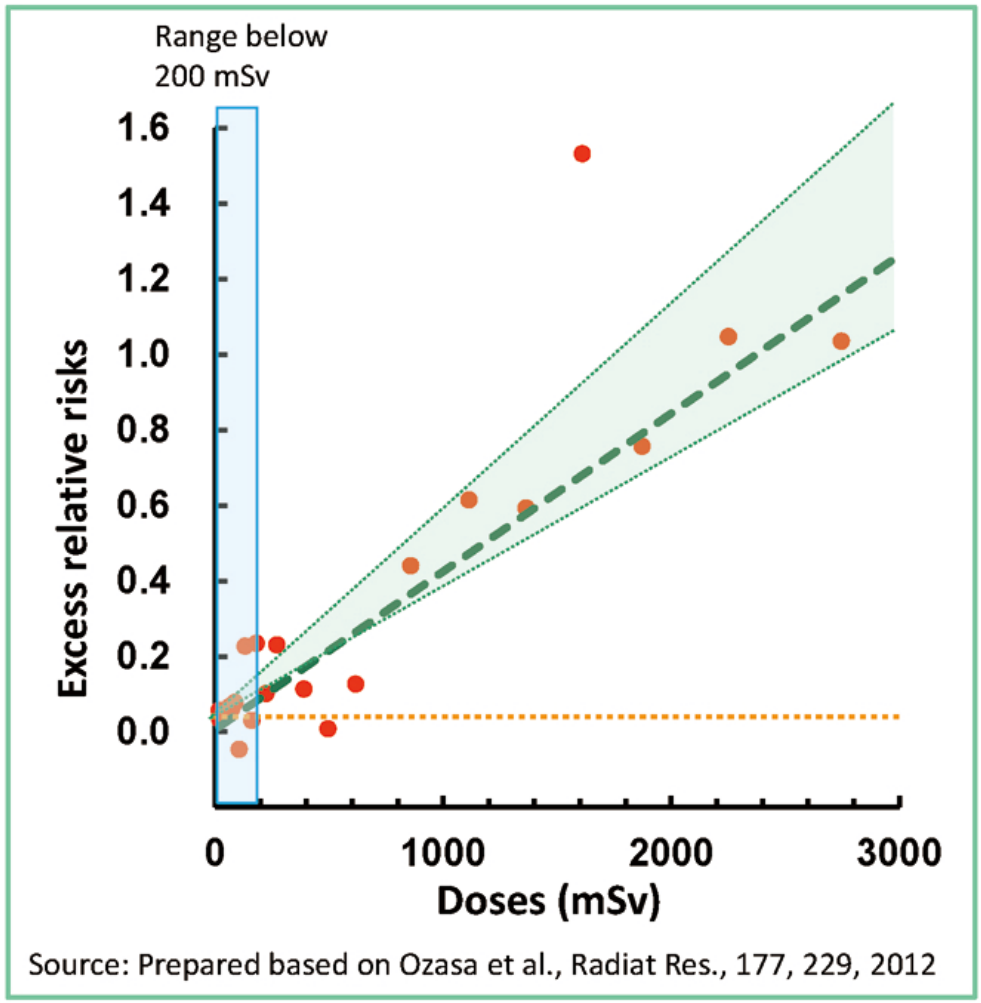
Risks of low-dose and low-dose-rate exposures

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

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

Relationship between Solid Cancer Deaths and Doses

Deaths from solid cancer (results among atomic bomb survivors)



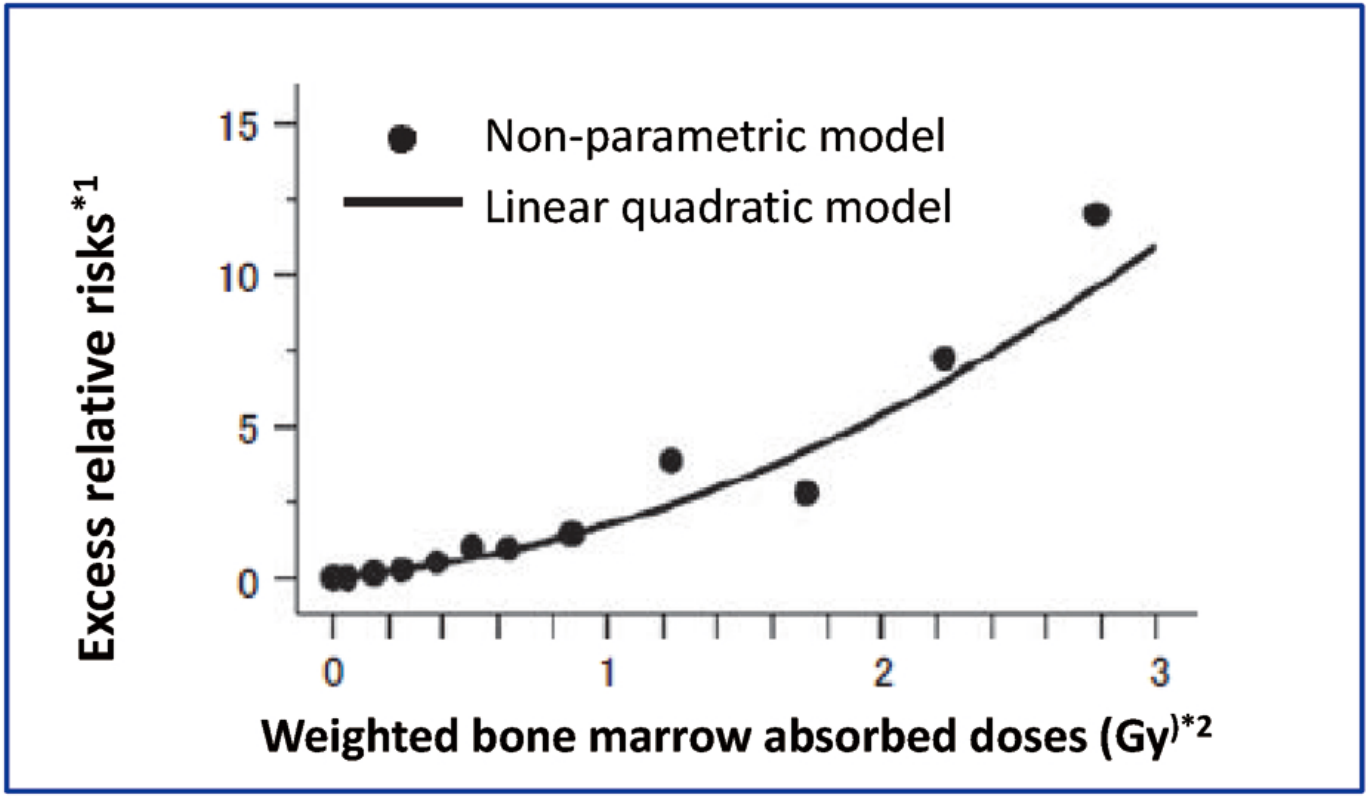
Source: Prepared based on Ozasa et al., Radiat Res., 177, 229, 2012

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

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



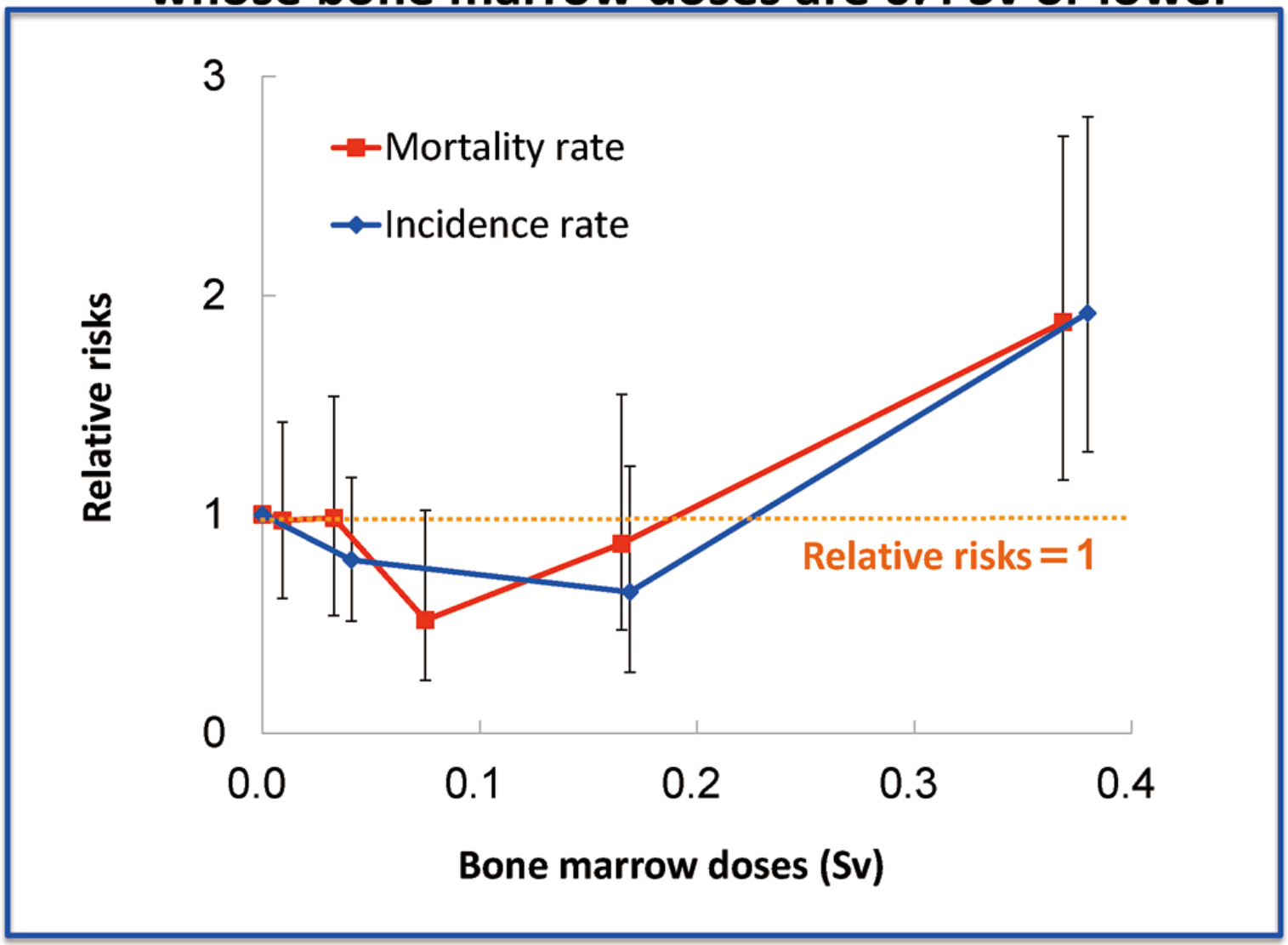
*1: An indicator to show increments in the mortality rate (or incidence rate) in the case of having been exposed to radiation against the mortality rate (or incidence rate) in the case of having been free from radiation exposure; showing how many times increase was caused by radiation exposure

*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)

Risks of Developing Leukemia

Risks of developing leukemia among atomic bomb survivors whose bone marrow doses are 0.4 Sv or lower



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

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:

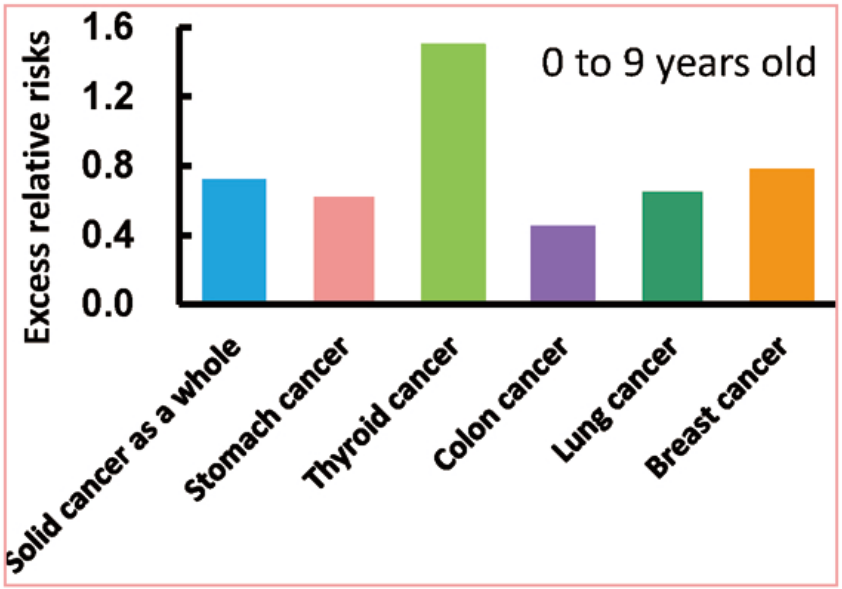
- Preston DL et al., Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. Radiat Res., 2003 Oct; 160(4):381-407
- Pierce DA et al., Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990 Radiat Res., 1996 Jul;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

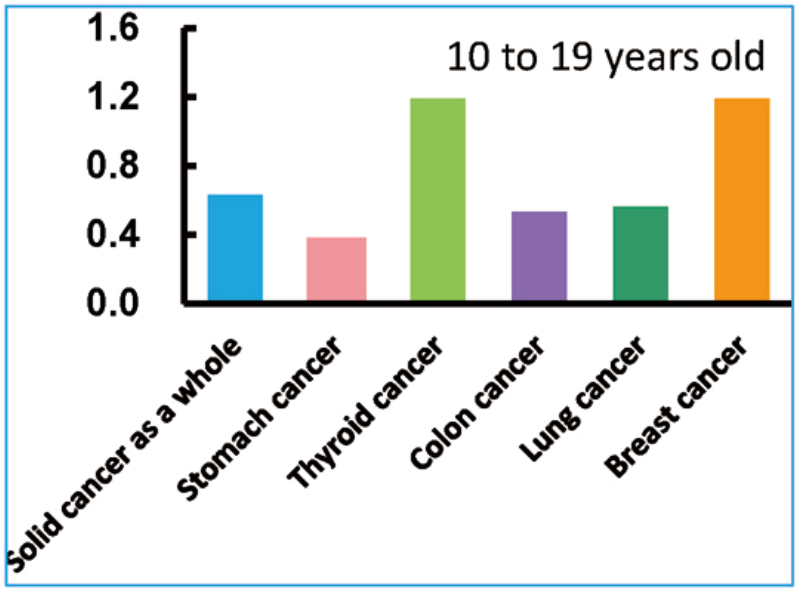
Cancer due to Acute External Exposure

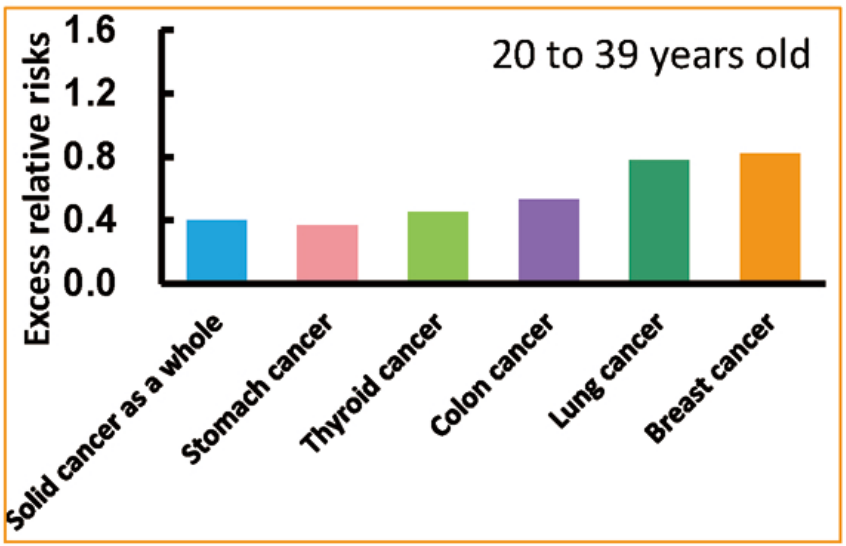
Oncogenic Risks by Age at the Time of Radiation Exposure

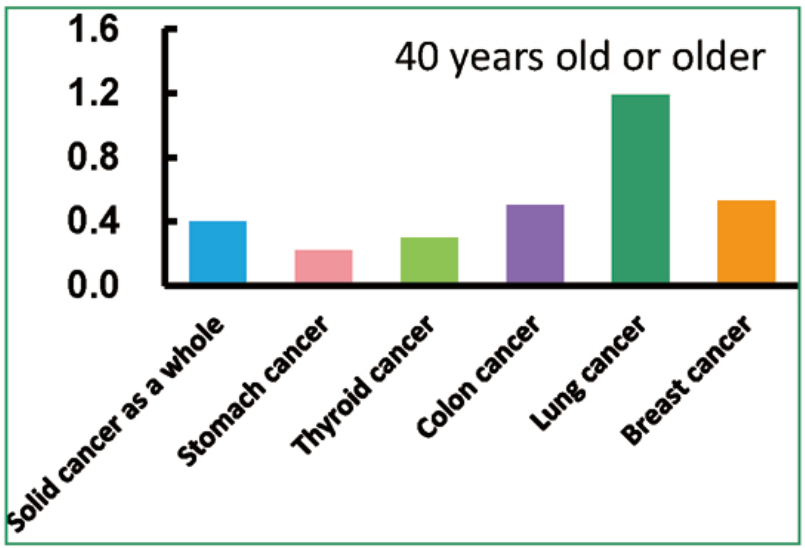
Excess relative risks of developing cancer by age at the time of radiation exposure

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









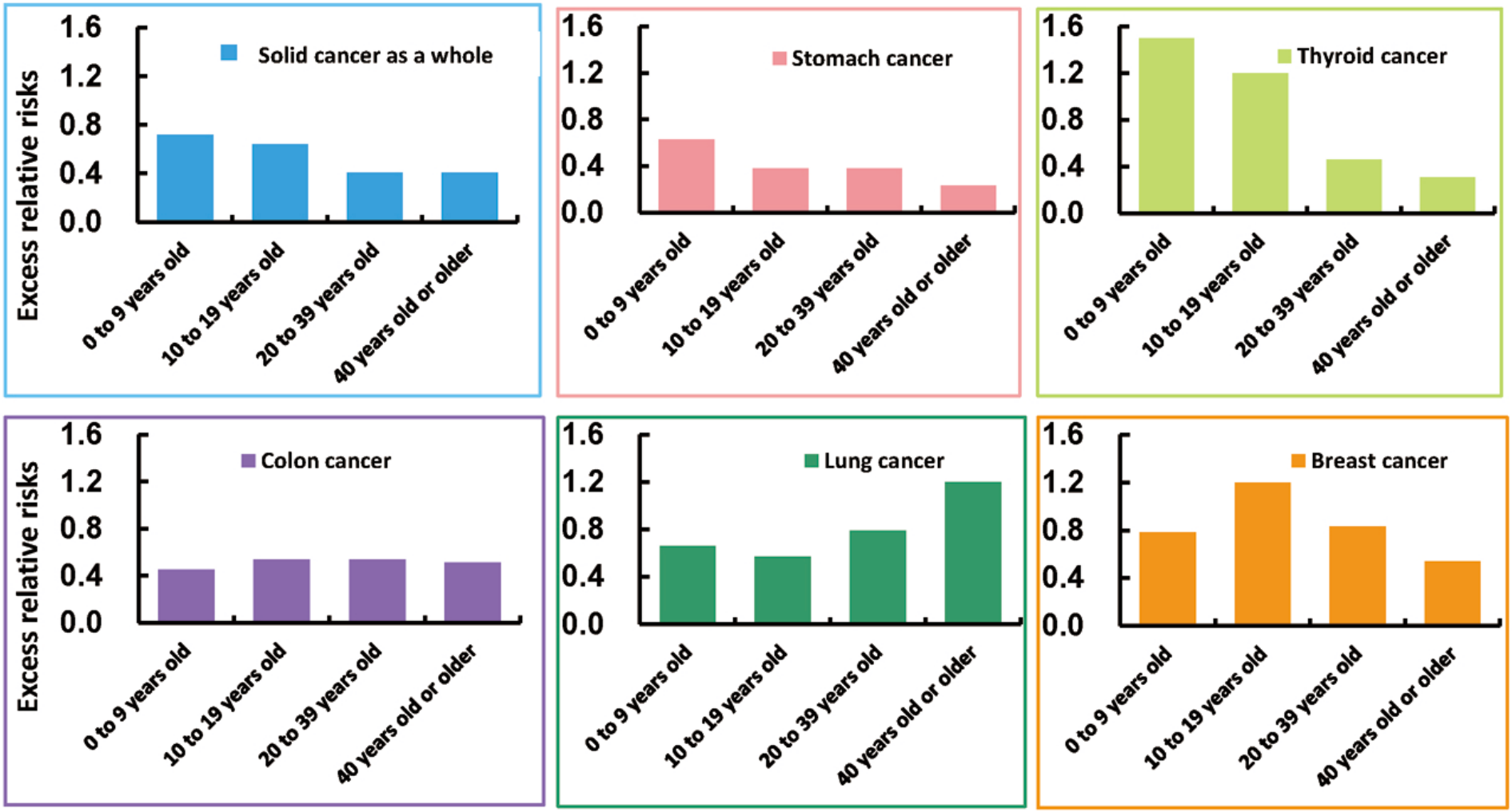
Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

Cancer due to Acute External Exposure

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

Excess relative risks of developing cancer by age for each type of cancer

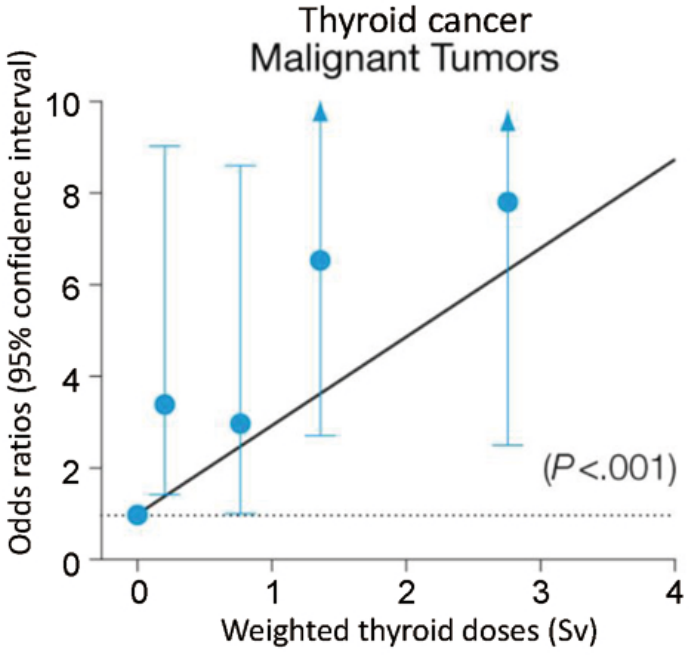
* Excess relative risks of developing cancer as of age 70 (per gray)



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

Cancer due to Acute External Exposure

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)

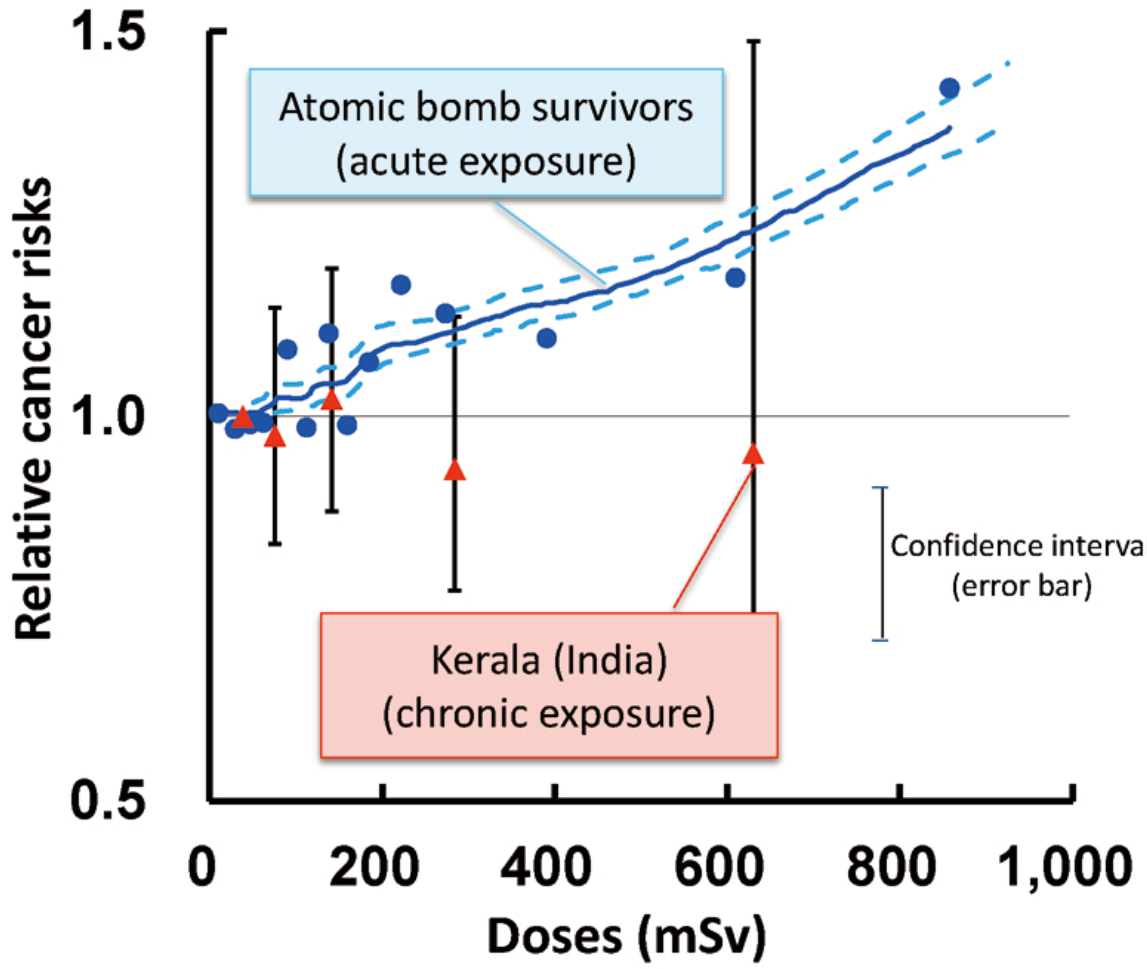
When the 95% confidence interval does not include 1, the difference in the probability is statistically significant.

Carcinogenesis due to Chronic Exposure

Effects of Long-Term Low-Dose Exposure

Carcinogenesis among residents in high natural radiation area in India

Kerala (India)
Outdoor average dose:
4 mSv/y or more
Up to 70 mSv/year in some areas



mSv: millisieverts

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

Radiation Effects Health Examinations – Chernobyl NPS Accident –

Country	Number of leukemia cases		Number of all types of cancer cases		Standardized incidence ratio (SIR)	
	Number of samples	Expected number	Number of samples	Expected number	Leukemia	All types of cancer
Residents in contaminated regions						
Belarus	281	302	9,682	9,387	93	103
Russia	340	328	17,260	16,800	104	103
Ukraine	592	562	22,063	22,245	105	99

Source: Prepared based on the UNSCEAR 2000 Report

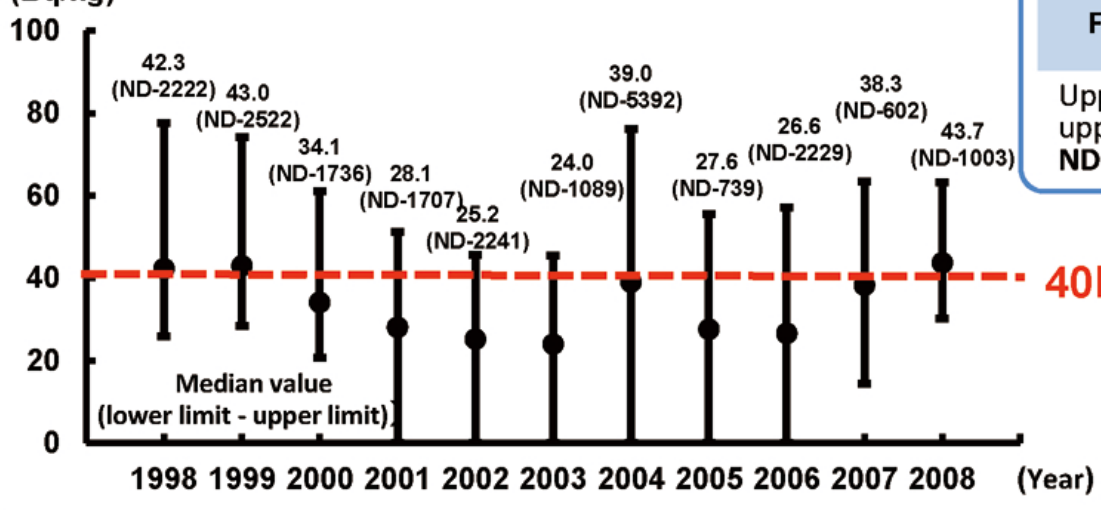
Basic Information on Thyroid
Thyroid Exposure

Internal Exposure due to Cesium - Chernobyl NPS 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.



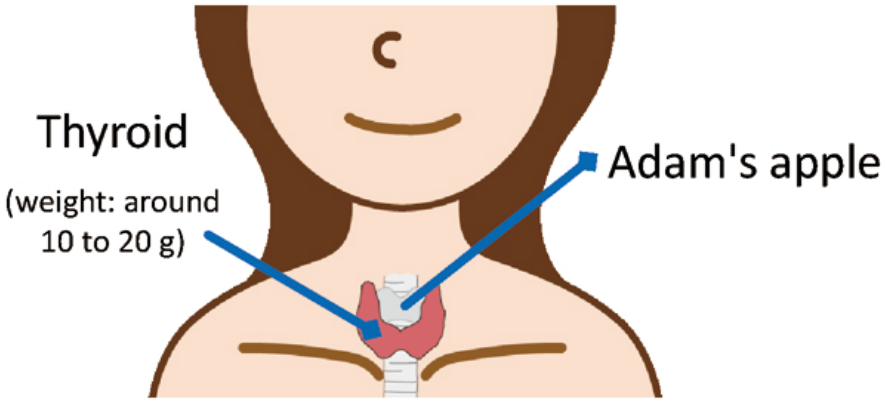
The annual internal exposure of 40 Bq/kg was detected in the Bryansk State from 1998 to 2008.

Bq/kg: Becquerels per kilogram

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

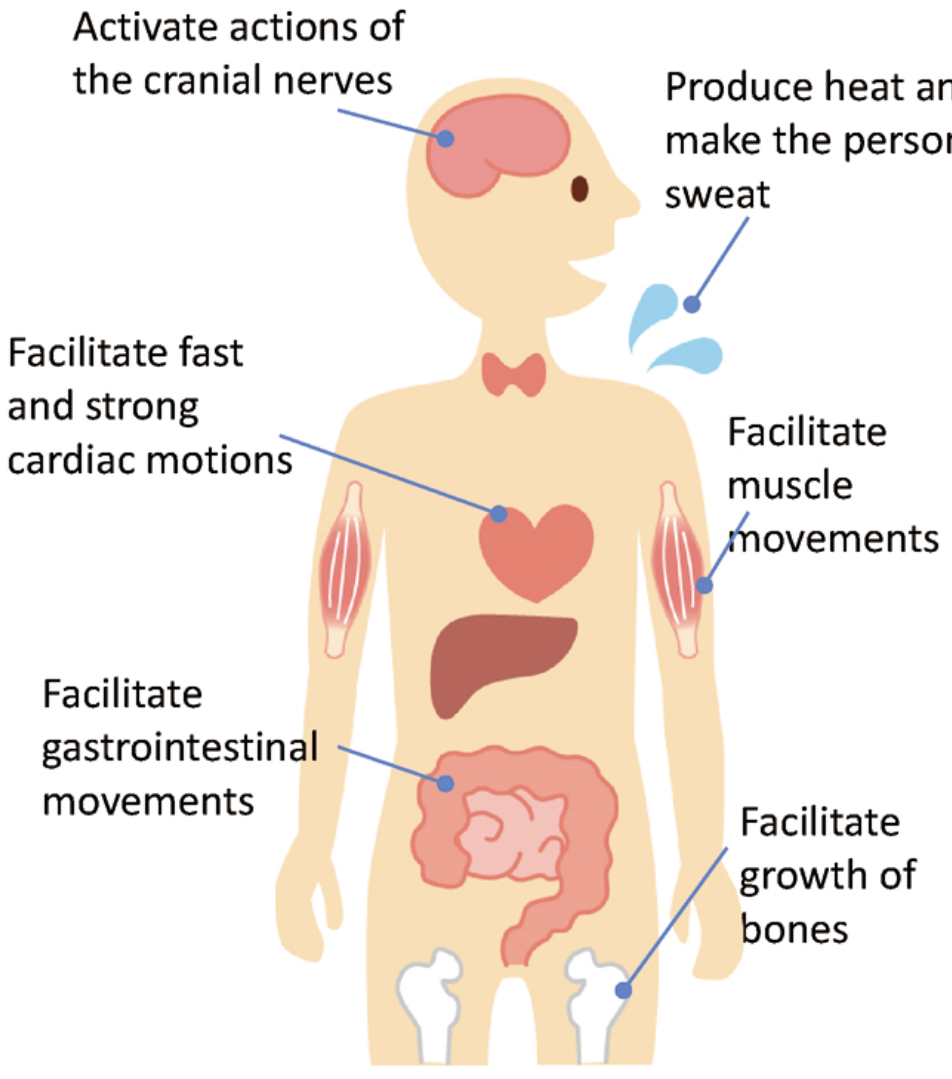
Basic Information on Thyroid

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



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.

Basic Information on Thyroid

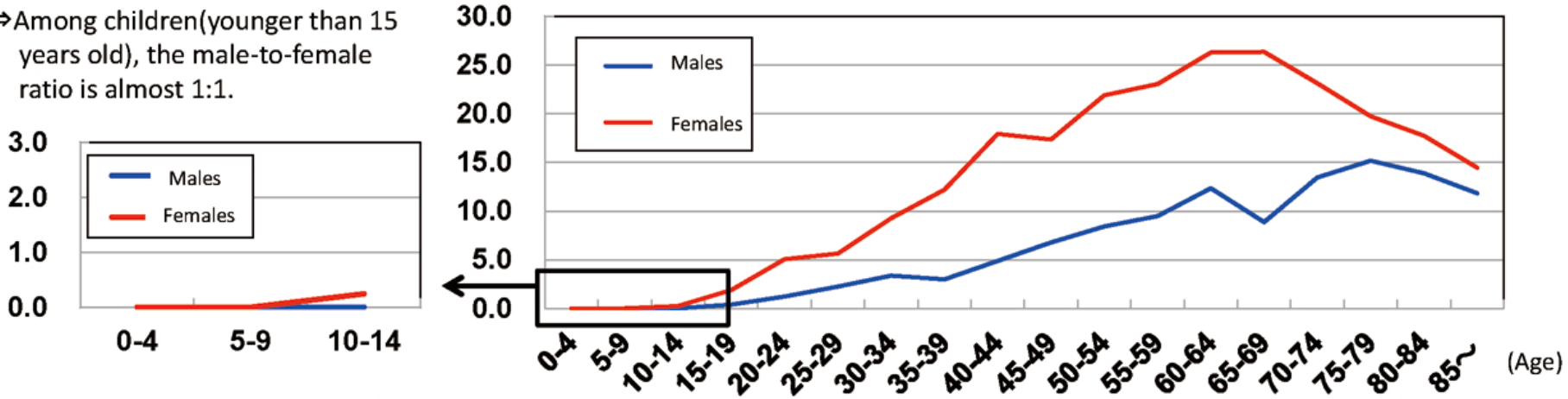
Characteristics of Thyroid Cancer

- **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: Prepared based on "Cancer Registration and Statistics," Cancer Information Service, National Cancer Center Japan

Occult (Latent) Thyroid Cancer

Some thyroid cancer is occult (latent) and presents no symptoms over a lifetime.

*** Occult (latent) cancer**

A cancer that is slow-growing with no symptoms and is found only through postmortem autopsy

Occult (latent) thyroid cancer

- Thyroid cancer is mostly a differentiated cancer and no symptoms appear over a lifetime in some cases as cancerous cell growth is slow.
- An autopsy study conducted in Japan reported that occult differentiated thyroid cancer was found in approximately 28% of 102 cases of postmortem autopsy.

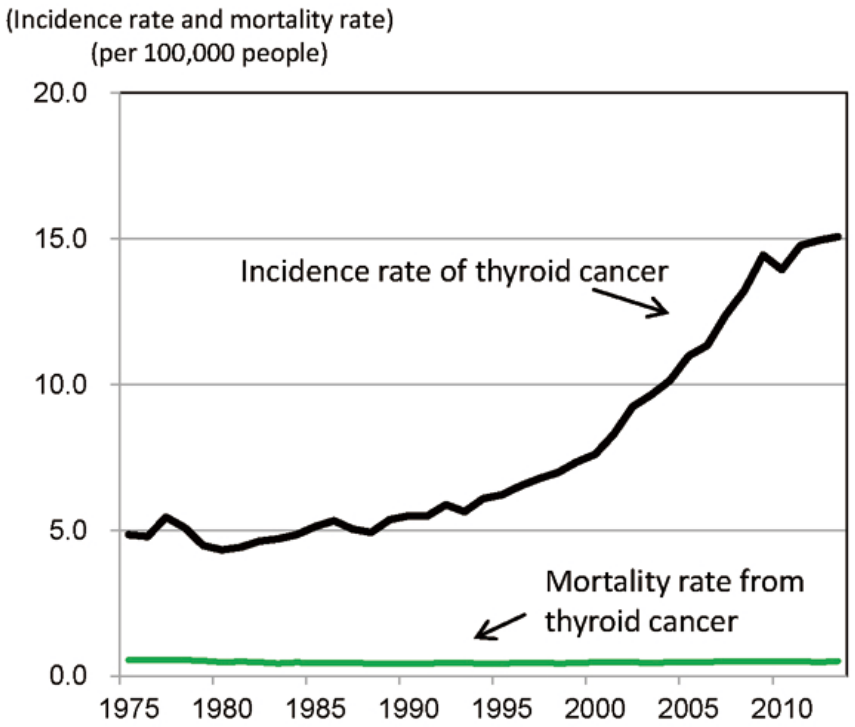
[Reference] Probabilities of developing thyroid cancer during lifetime for Japanese people* Female: 0.78%; Male: 0.23%

* Probabilities that the Japanese people develop thyroid cancer at least once during their lifetime, which were calculated based on data on the number of cancer patients from 1975 to 1999 in Japan (Kamo, et al., Journal of Health and Welfare Statistics, Vol. 52, No. 6, June 2005)

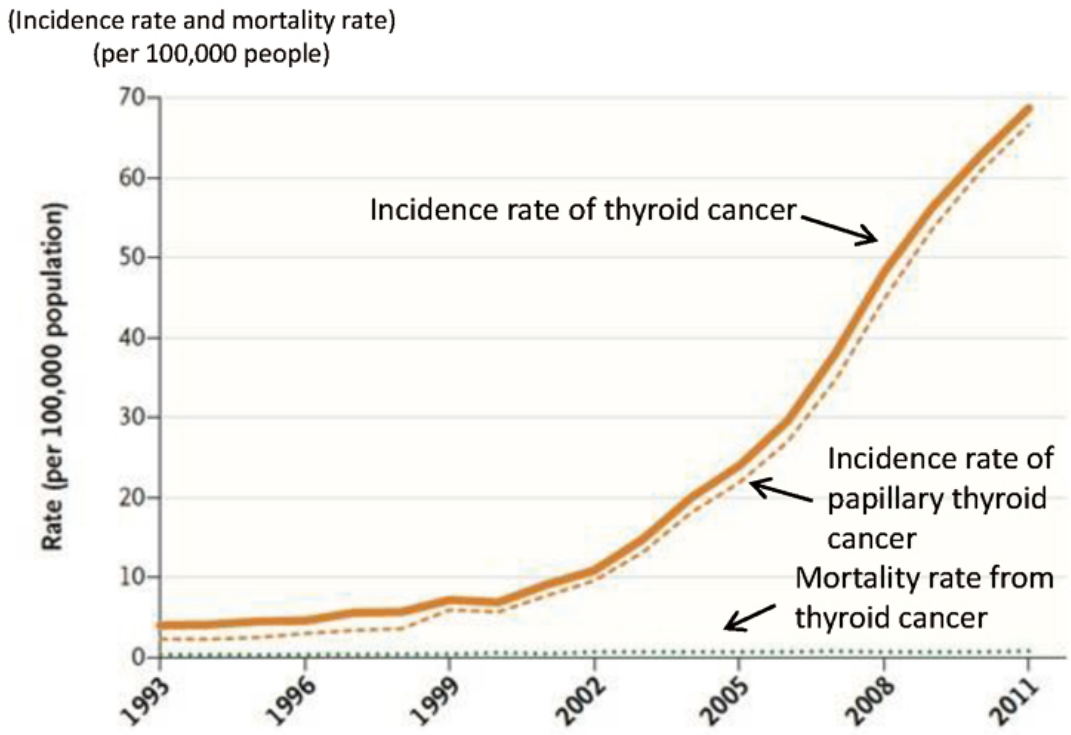
Source: Prepared based on Kamo K et al., (2008) Jpn. J. Clin. Oncol. 38(8) 571-576; Fukunaga et al., (1975) Cancer 36:1095-1099, etc.

Incidence Rates of Thyroid Cancer: Overseas

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



America*1



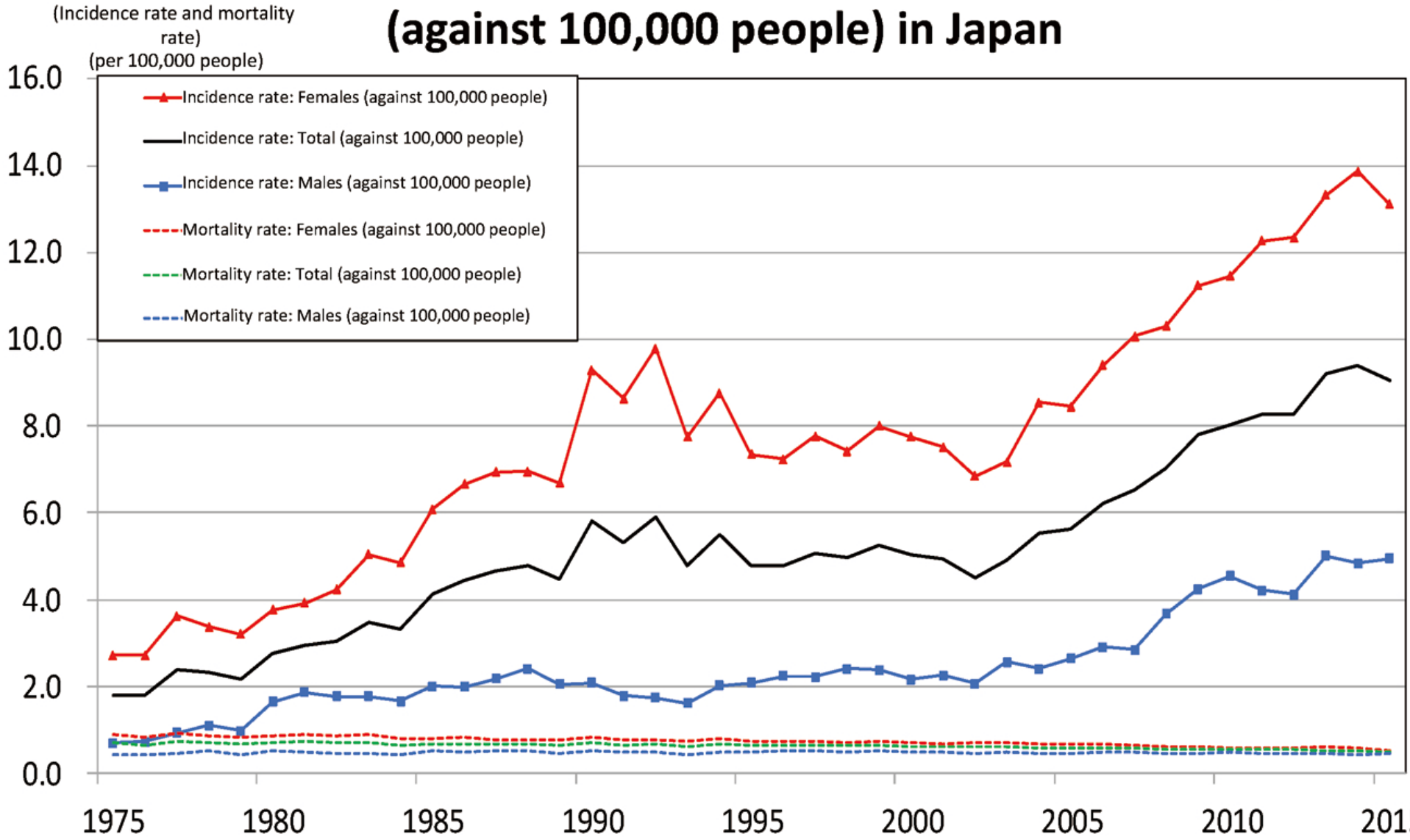
South Korea*2

*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

Incidence Rates of Thyroid Cancer: Japan

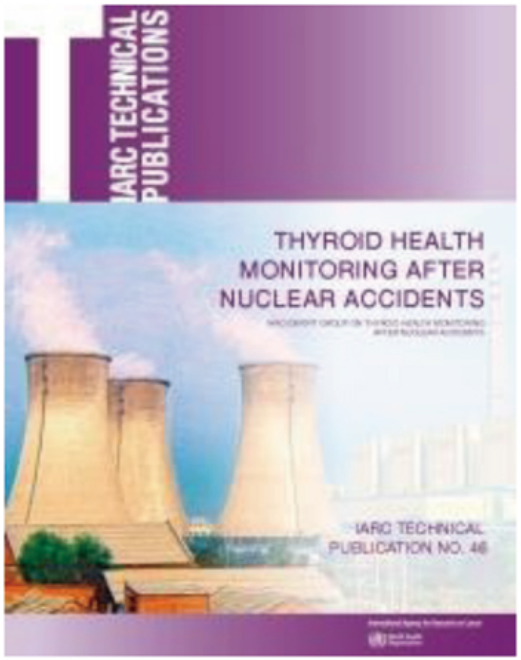
Annual changes in age-adjusted incidence rates and mortality rates (against 100,000 people) in Japan



Source: Prepared based on the "Cancer Registration and Statistics," Cancer Information Service, National Cancer Center Japan

Recommendations by the IARC Expert Group

- In September 2018, an international Expert Group convened by the International Agency for Research on Cancer (IARC) published the Report on Thyroid Health Monitoring after Nuclear Accidents.
- In order to present the principles upon conducting a thyroid ultrasound examination in the event of a nuclear accident, the report compiles the latest knowledge on epidemiology and clinical practice concerning thyroid cancer and provides the following two recommendations. Incidentally, the report does not intend to remark on or evaluate thyroid ultrasound examinations conducted so far after nuclear accidents in the past.



Recommendation 1

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

*1 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

Recommendation 2

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

*2 Those who were exposed in utero or during childhood or adolescence (younger than 19 years old) with a thyroid dose of 100-500 mGy or more

Source: Prepared based on the "Thyroid Health Monitoring after Nuclear Accidents" by the IARC (2018) and "Long-term strategies for thyroid health monitoring after nuclear accidents - A summary of IARC Technical Publication No. 46" by the IARC (2018) (translated into Japanese: http://www.env.go.jp/chemi/rhm/post_132.html)

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) Jpn. 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)

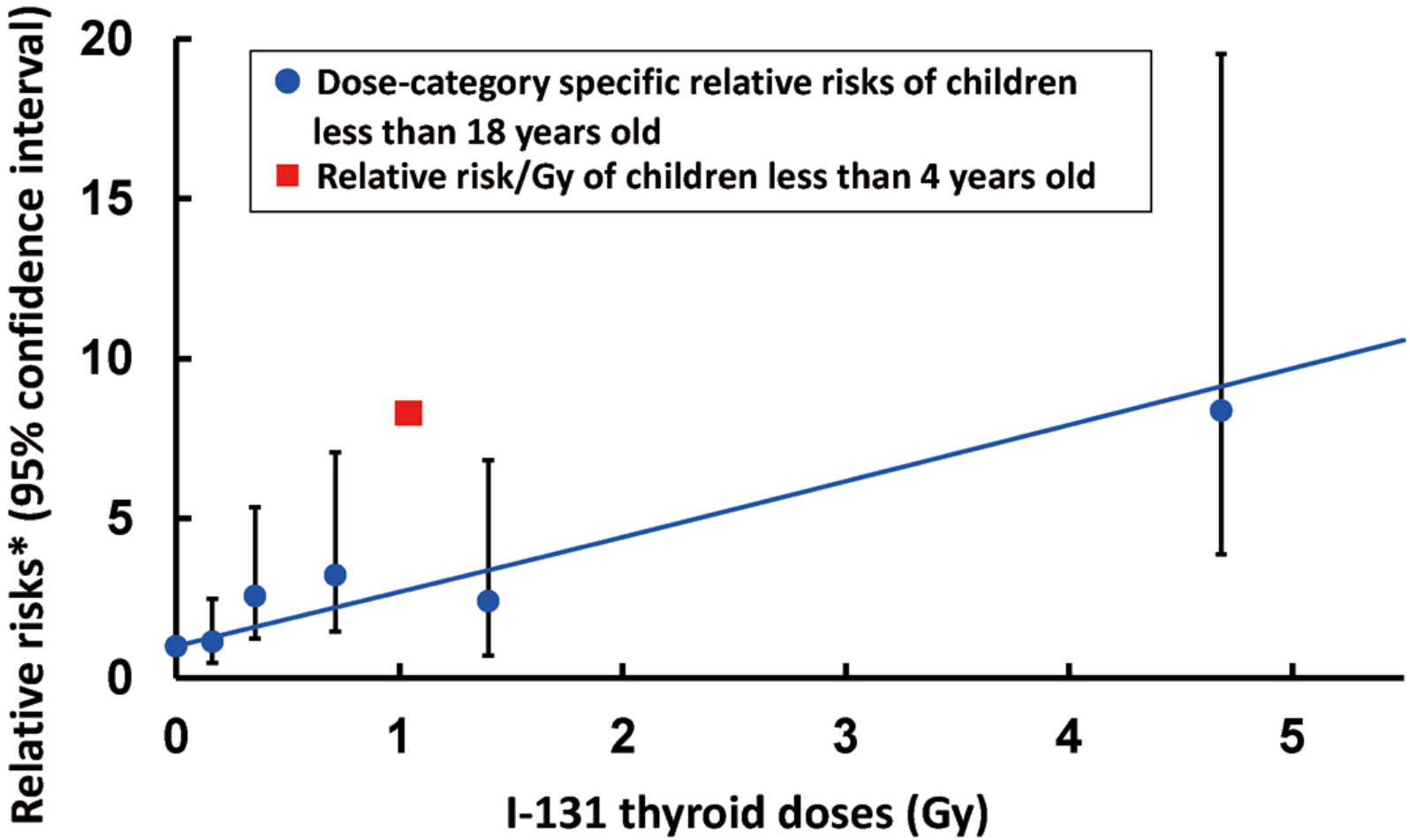
- When the thyroid exposure dose is 1,000 mSv, the probability of developing thyroid cancer increases
  - by 0.58% to 1.39% for females and by 0.18% to 0.34% for males**.

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

    ** There are multiple methods to calculate probability increases. Both for females and males, the lowest values are estimated using a method called the EAR model and the highest values are estimated using a method called the ERR model.

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.

Relationship between Thyroid Cancer and Doses
- Chernobyl NPS 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.

Thyroid Cancer and Iodine Intake
- Chernobyl NPS 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.

Exposure of a Group of Evacuees
- Chernobyl NPS Accident -

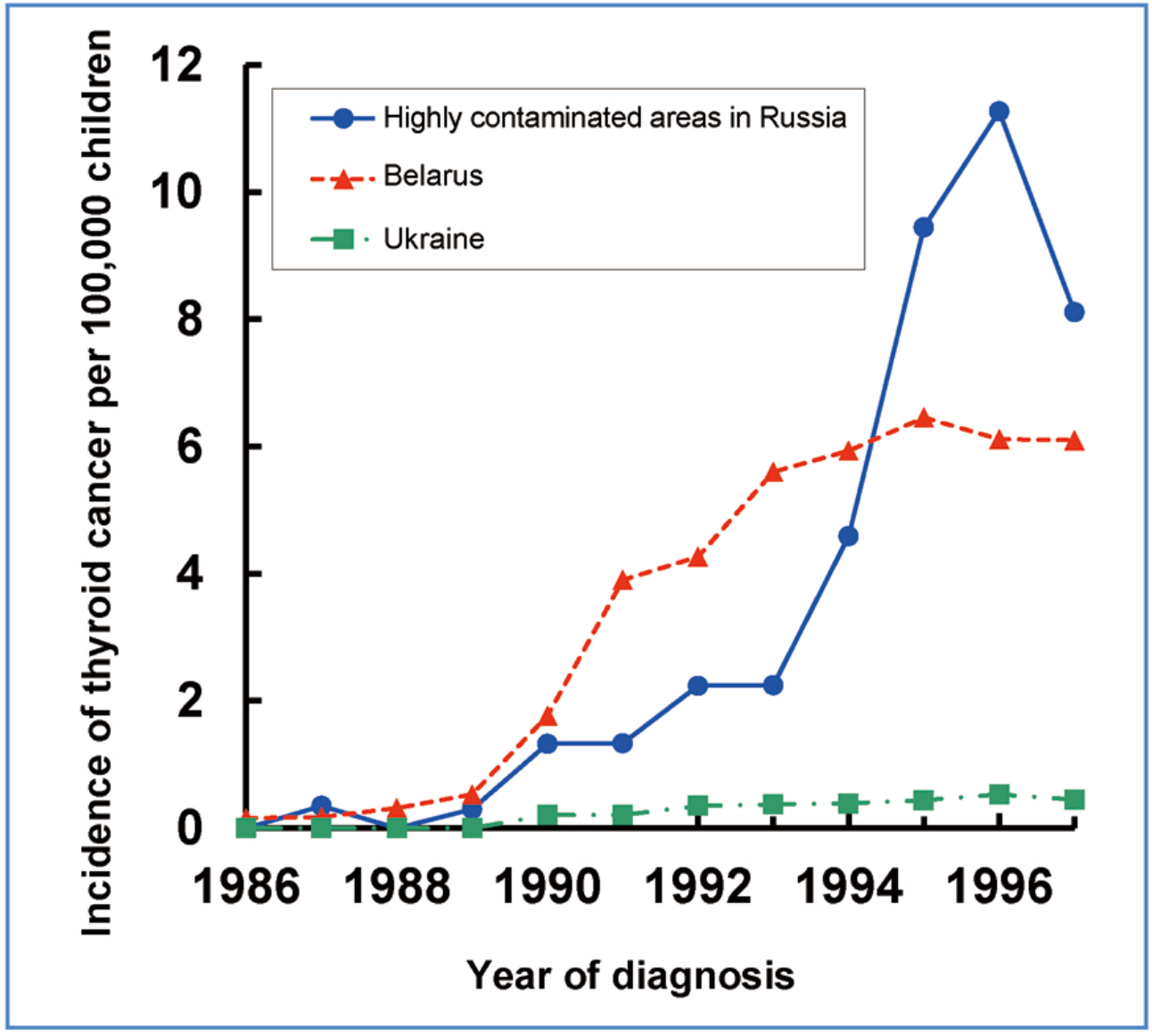
Countries	Number of people (1,000 people)	Average effective dose (mSv)		Average thyroid dose (mGy)
		External exposure	Internal exposure (in organs other than the thyroid)	
Belarus	25	30	6	1,100
Russia	0.19	25	10	440
Ukraine	90	20	10	330

mSv: millisieverts mGy: milligrays

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

Time of Developing Childhood Thyroid Cancer
- Chernobyl NPS Accident -

Childhood thyroid cancer (Chernobyl NPS 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

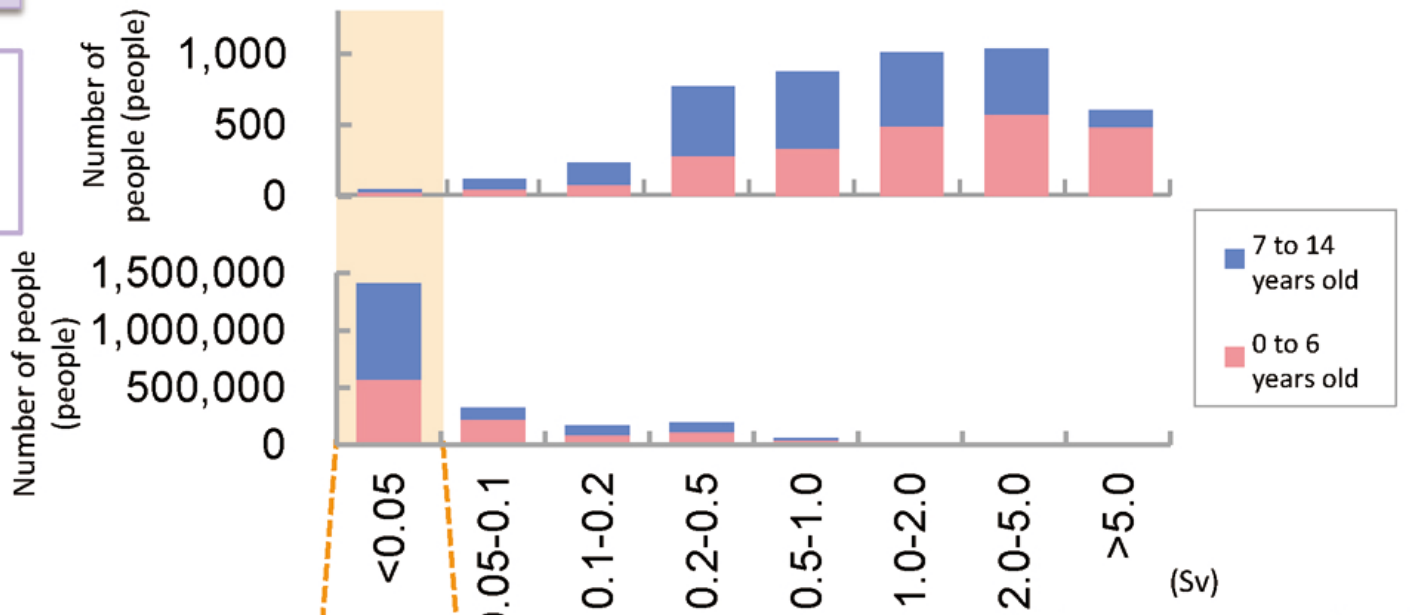
Comparison between the Chernobyl NPS Accident and the TEPCO's Fukushima Daiichi NPS Accident (Thyroid Doses)

Children's thyroid exposure doses

Chernobyl NPS Accident

A group of people who evacuated in Belarus in 1986

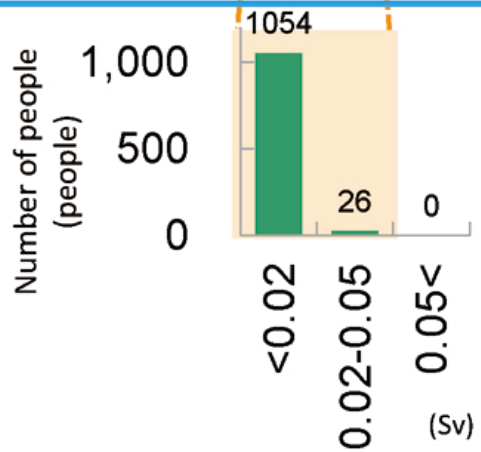
All people in Belarus (excluding evacuees)



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

Accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS

* This data is based on a survey targeting a limited group of residents and does not reflect the overall circumstances.

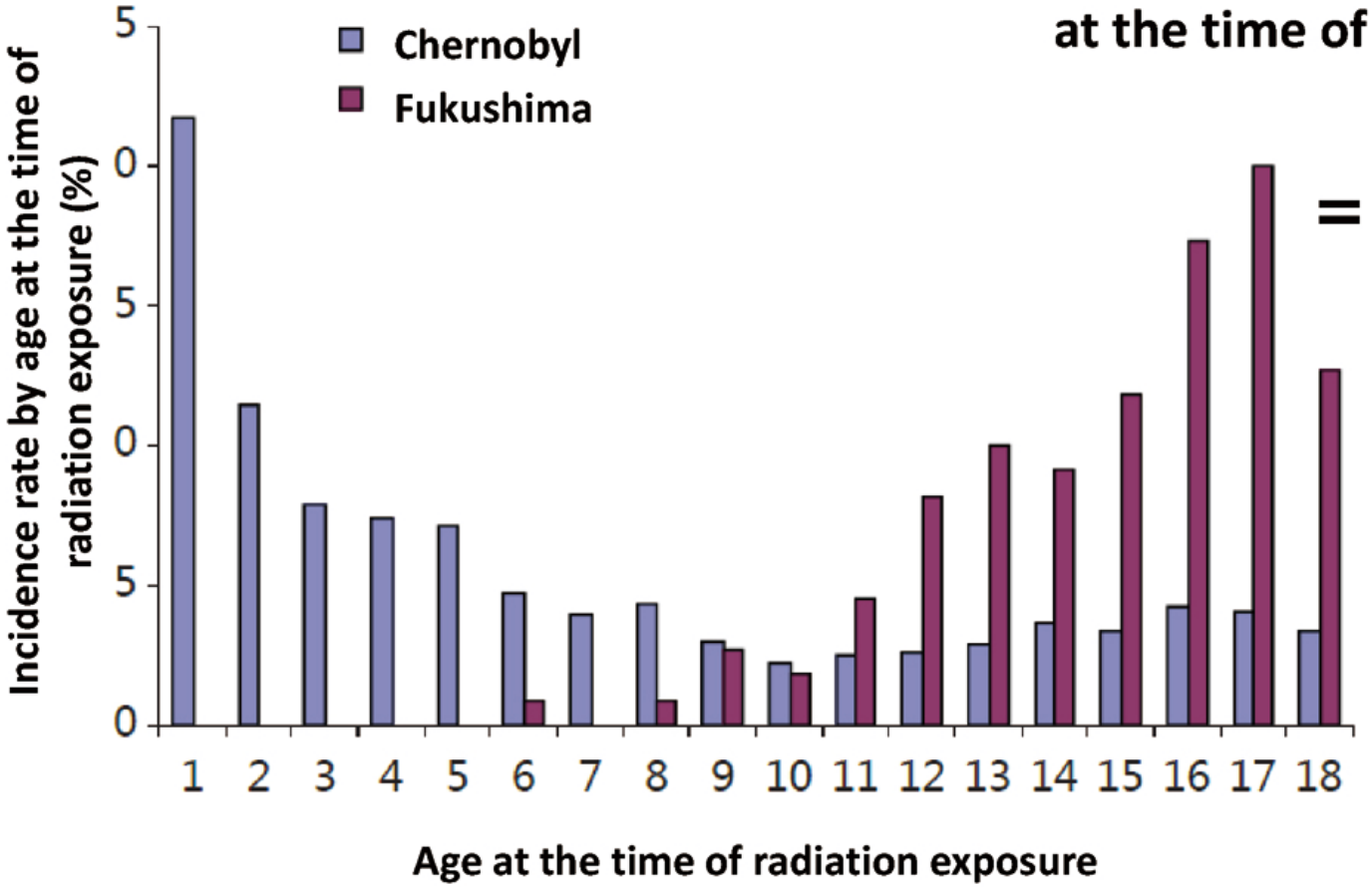


Calculation method
For comparison, the "Results of the Simple Thyroid Screening for Children" contained in the "Outline of Children's Simple Measurement Test Results" (August 17, 2011; Team in Charge of Assisting the Lives of Disaster Victims (Medical Team)) is rearranged using "screening level of 0.2 μSv/h (equivalent to 100 mSv of thyroid dose equivalent for 1-year-old children)" (May 12, 2011; Nuclear Safety Commission of Japan) (Gy = Sv)
Source: "Safety of Fukushima-produced Foods," Nuclear Disaster Expert Group
Judging from the measurement method and ambient dose rates at the relevant locations, the detection limit is set at around 0.02 Sv.

Comparison between the Chernobyl NPS Accident and the TEPCO's Fukushima Daiichi NPS Accident (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 (%)

$$= \frac{\text{Number of incidence for each age}}{\text{Total number of incidence of thyroid cancer}}$$

(Fukushima: Diagnosed as malignant or suspected)

Source: Prepared based on Williams D, Eur Thyroid J 2015; 4: 164–173

Evaluation of the Interim Report on Thyroid Cancer Compiled by the Expert Meeting on Health Management After the TEPCO's Fukushima Daiichi NPS Accident

The Expert Meeting* compiled the Interim Report (December 2014), wherein it considered the following points concerning the thyroid cancer cases found through the Preliminary Baseline Survey 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 NPS Accident.

ii) In the case of the Chernobyl NPS 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 Preliminary Baseline Survey in Fukushima.

iii) Increases in thyroid cancer cases after the Chernobyl NPS 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 Preliminary Baseline Survey 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)