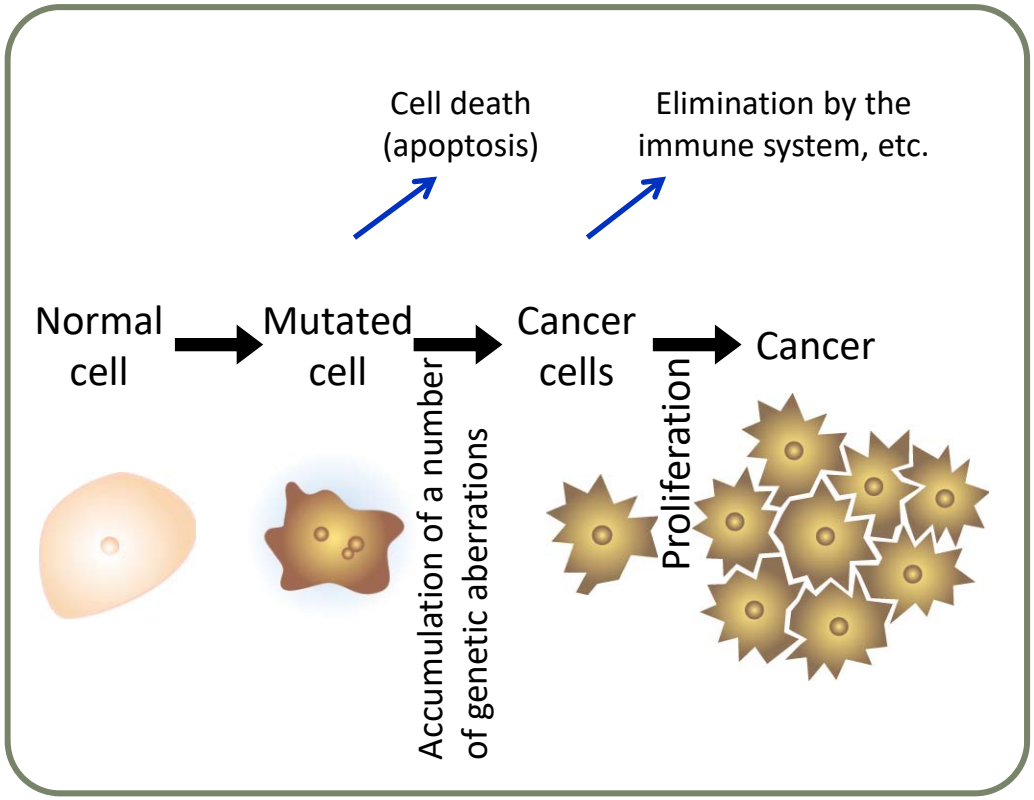
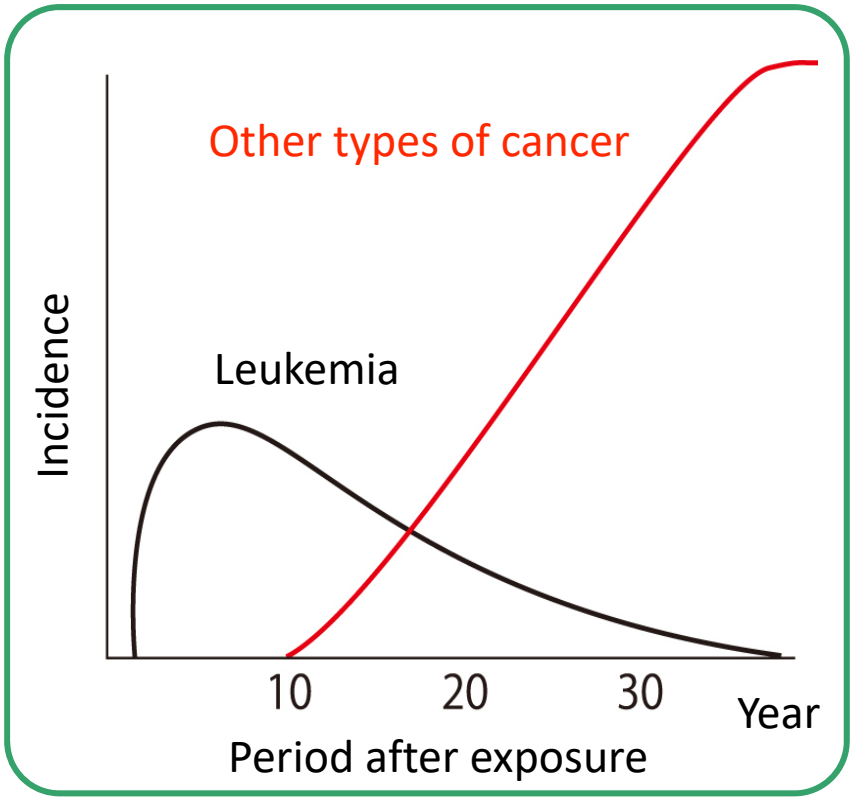
Mechanism of Carcinogenesis



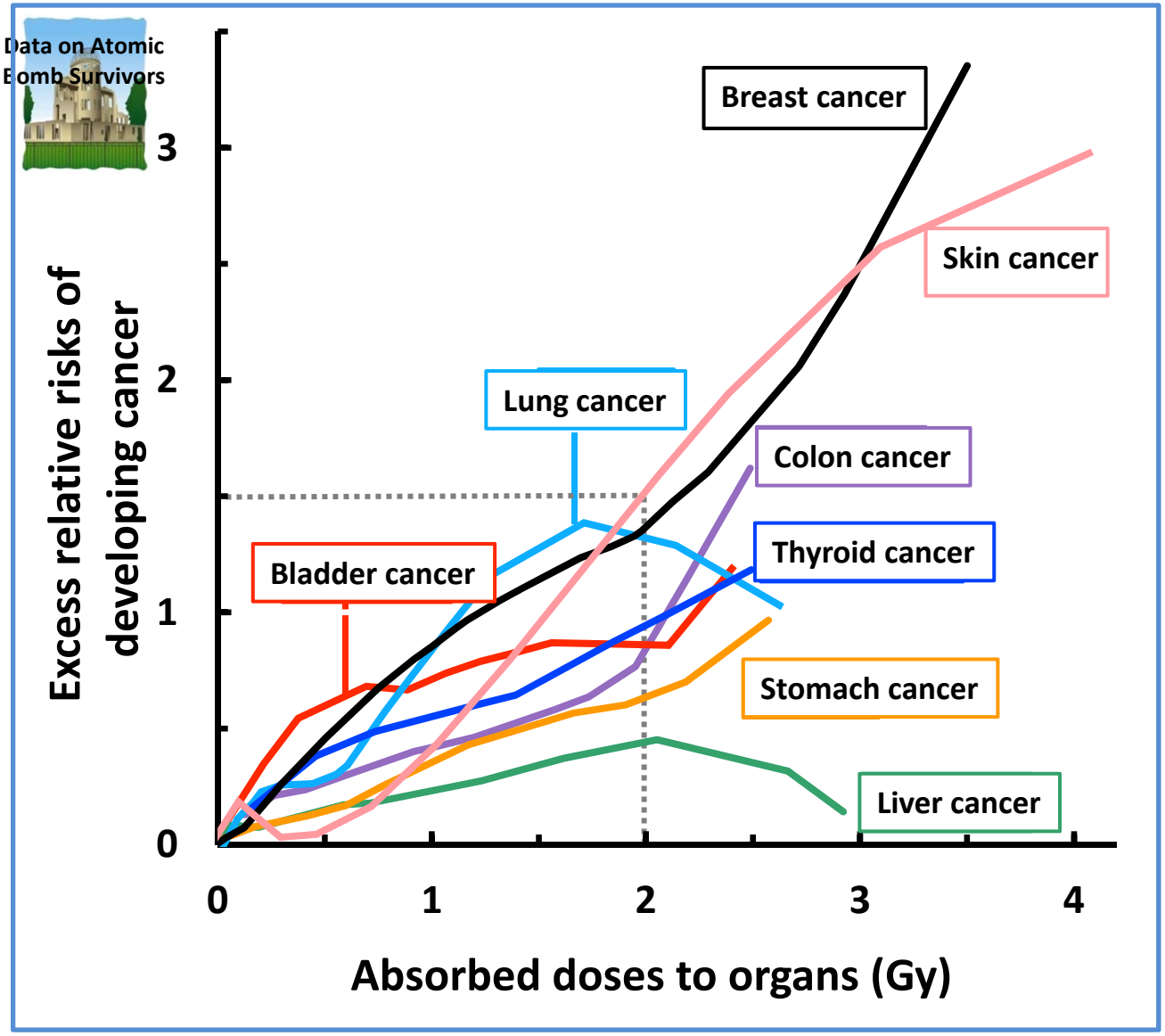


- Radiation is only one of various factors that induce cancer.

- 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$_{WT}$*
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.

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.

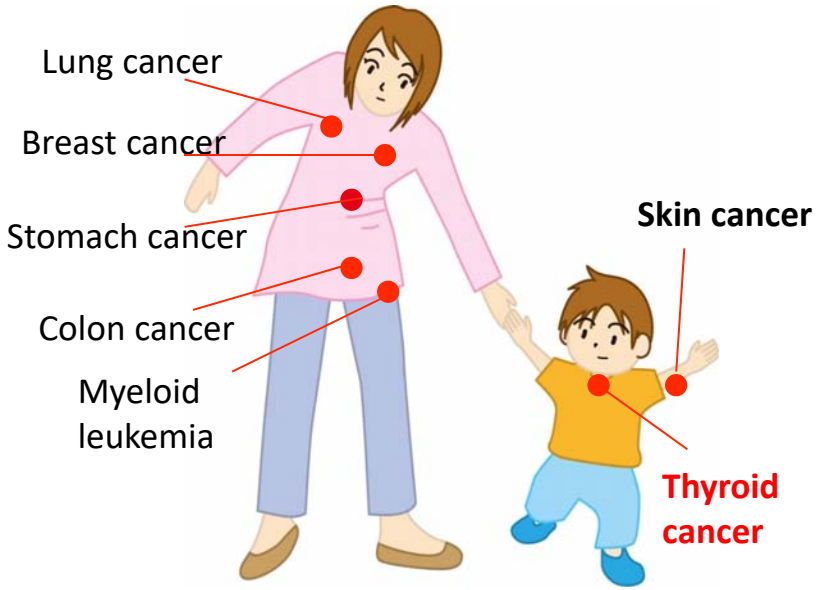
	Committed effective dose coefficients for I-131*1 (mSv/Bq)	Committed effective doses when having taken in 100 Bq of I-131 (mSv)	Equivalent doses to the thyroid when having taken in 100 Bq of I-131*2 (mSv)
3 month-old infants	**0.18**	**18**	**450**
1 year-old children	**0.18**	**18**	**450**
5 year-old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

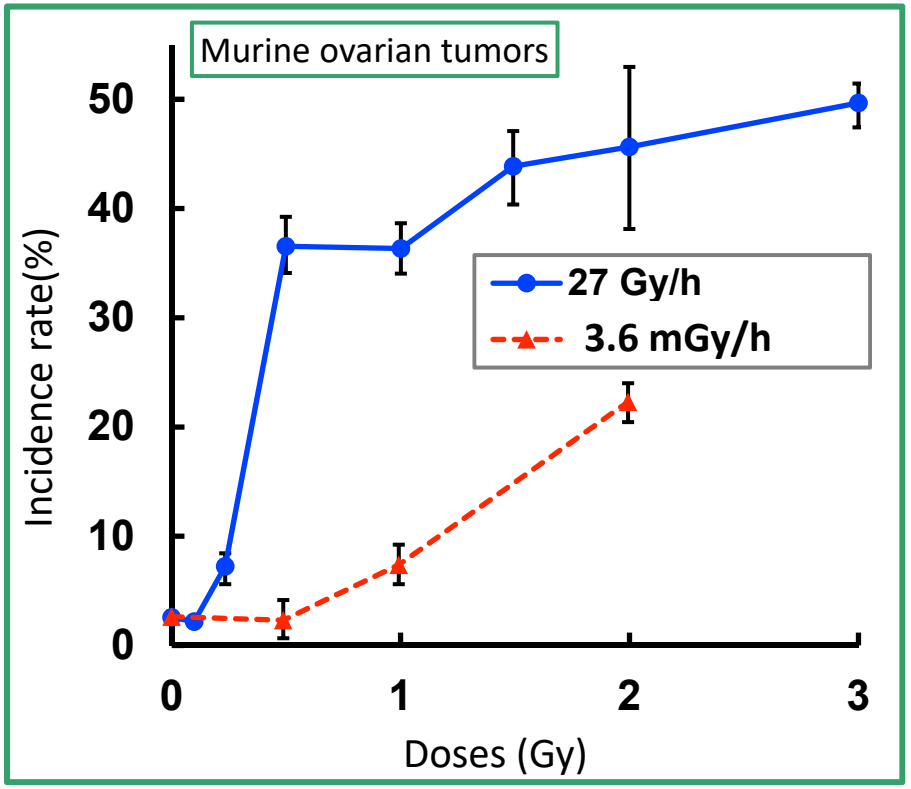
Risks of thyroid cancer and skin cancer are higher for children than for adults.

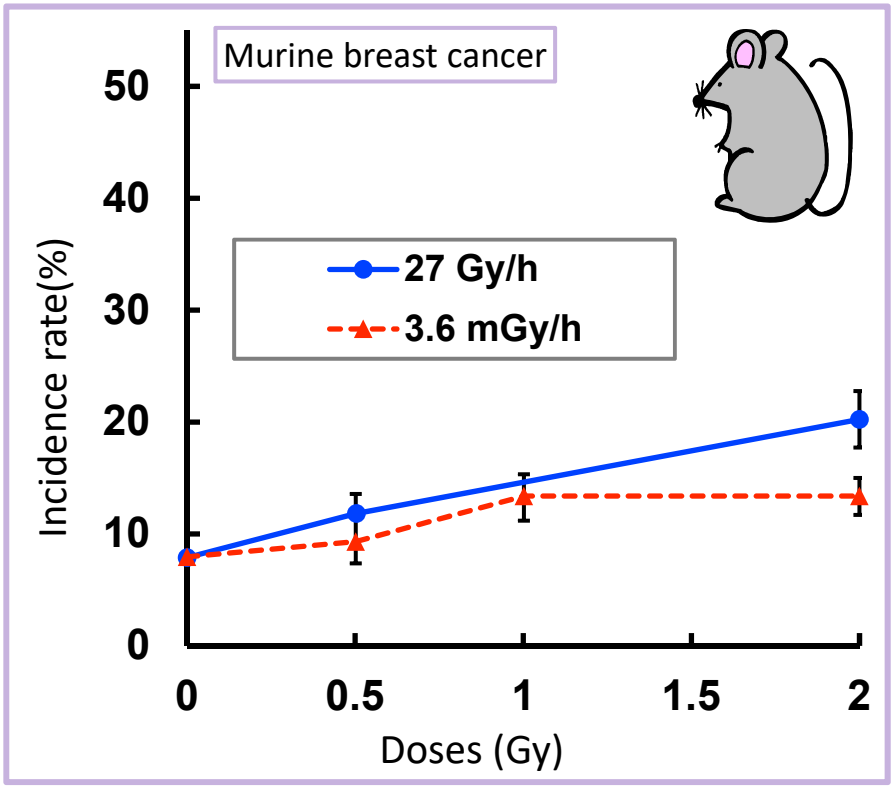
mSv/Bq: microsieverts/becquerel



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

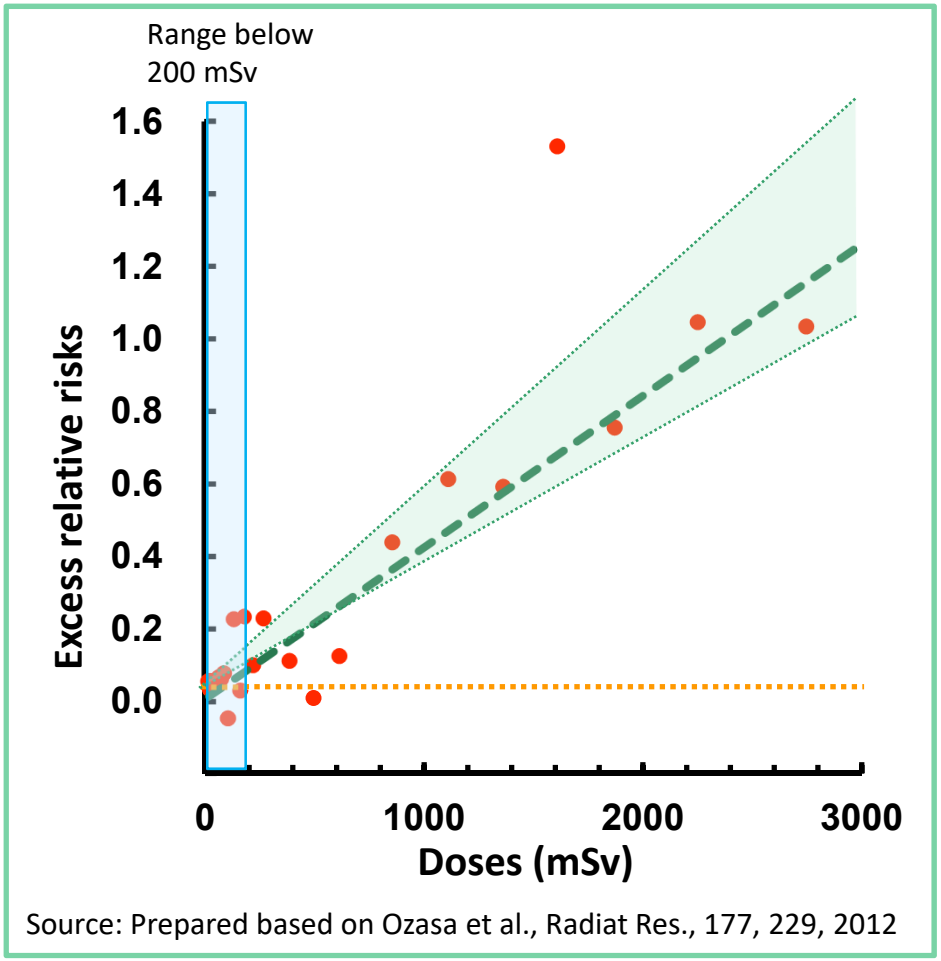
$$= \frac{\text{Risks of high-dose and high-dose-rate exposures}}{\text{Dose and dose-rate effectiveness factor}}$$

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

Cancer due to Acute External Exposure

Relationship between Solid Cancer Deaths and Doses

Deaths from solid cancer (results among atomic bomb survivors)



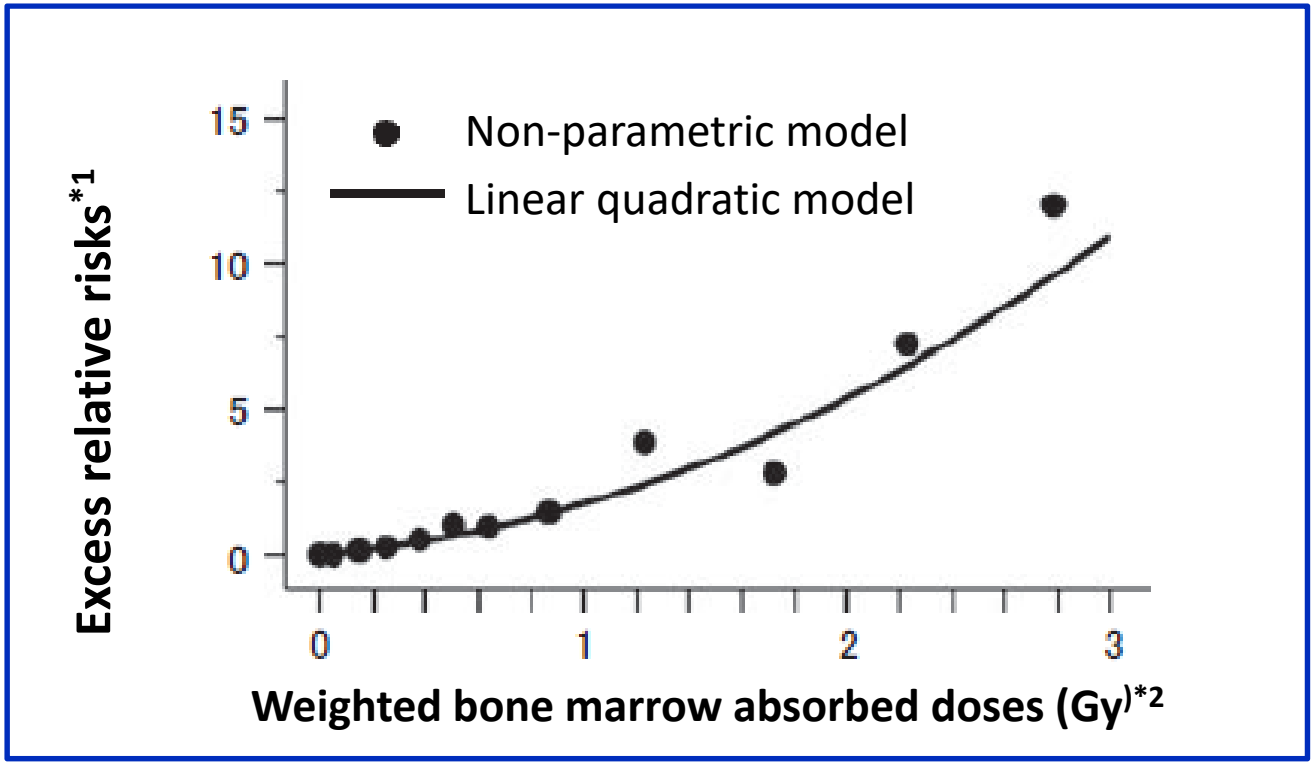
Source: Prepared based on Ozasa et al., Radiat Res., 177, 229, 2012

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

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

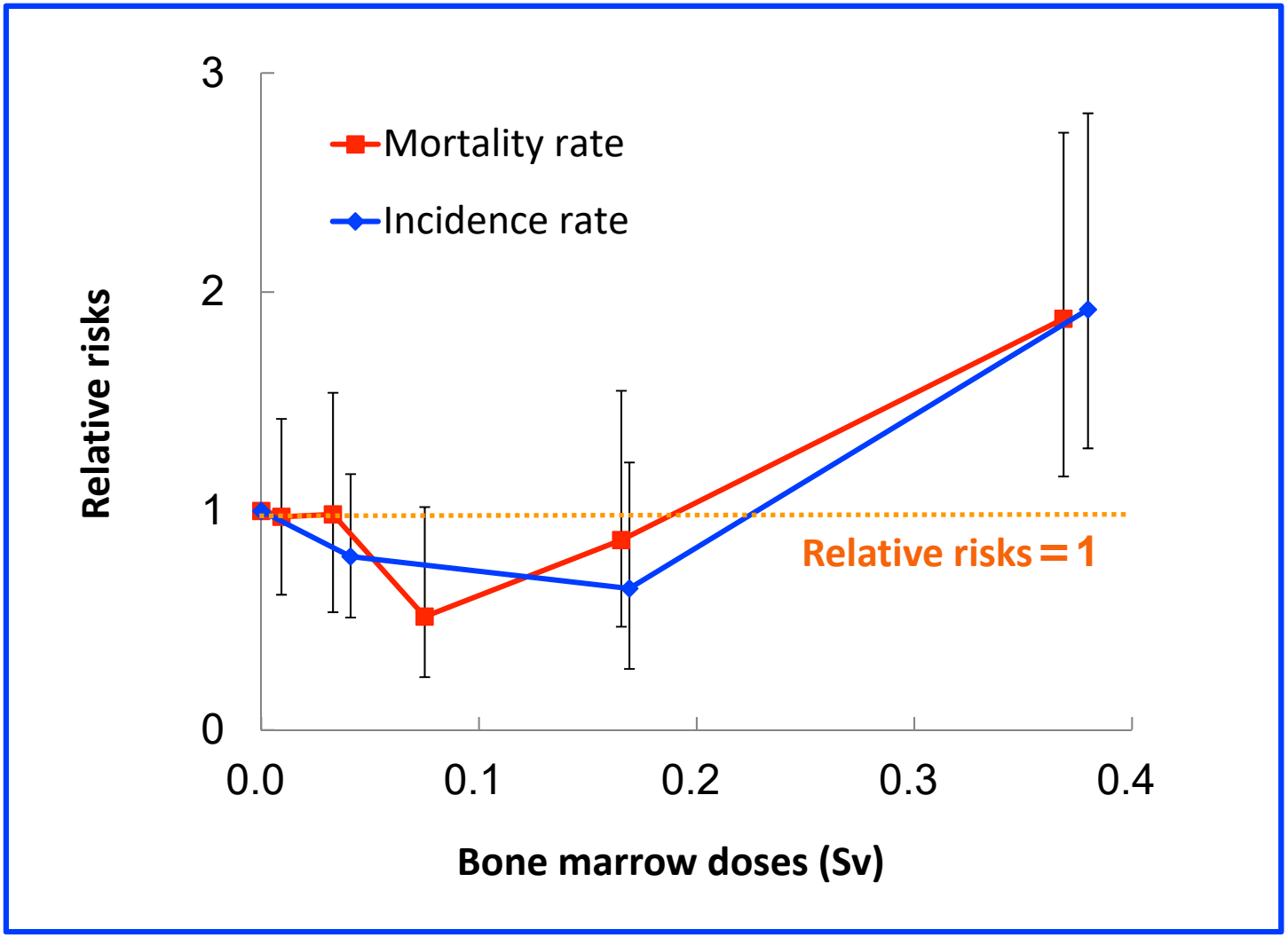
*2: In the case of leukemia, weighted bone marrow doses (sum of 10 times the neutron doses and total amount of γ-rays) are used.

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)

Cancer due to Acute External Exposure

Risks of Developing Leukemia

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

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:

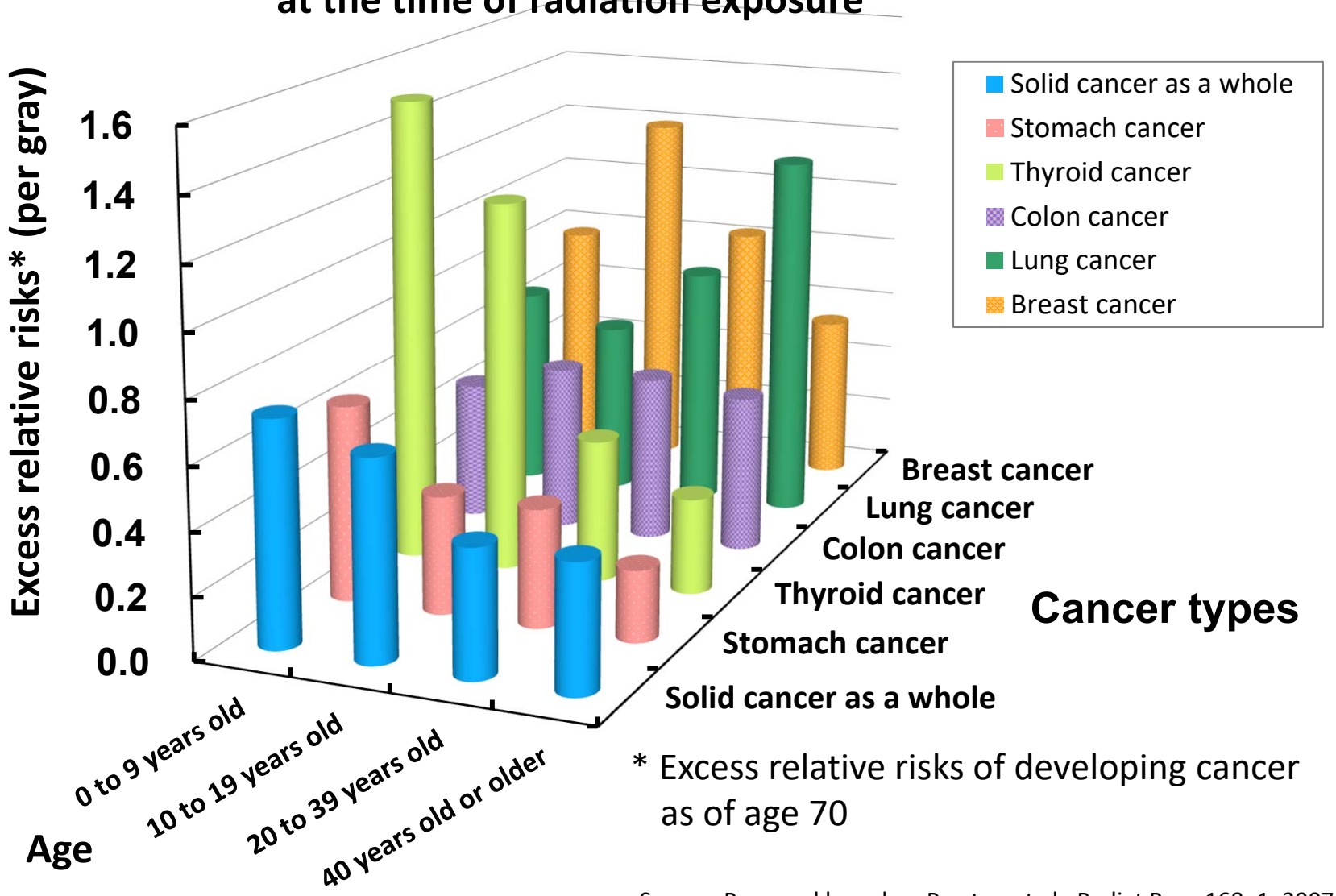
・Preston DL et al., Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. Radiat Res., 2003 Oct; 160(4):381-407

・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

Cancer due to Acute External Exposure

Ages at the Time of Radiation Exposure and Cancer Types

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



* Excess relative risks of developing cancer as of age 70

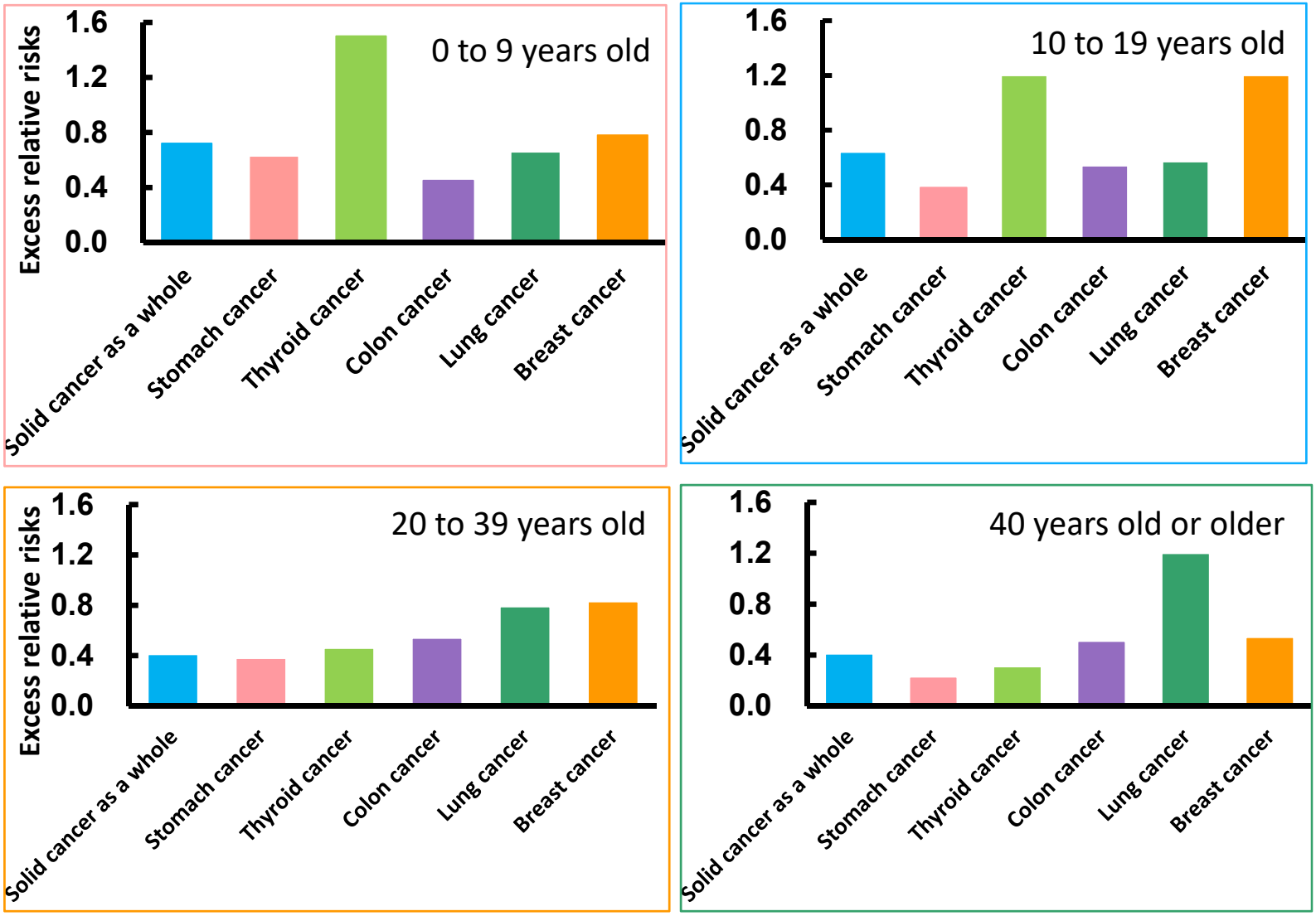
Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

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)



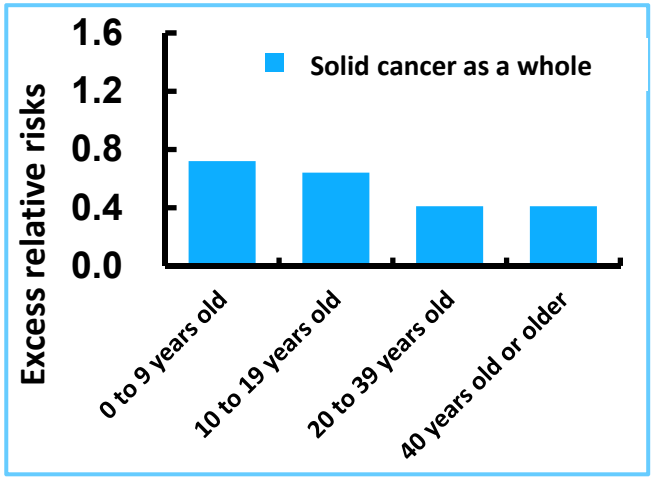
Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

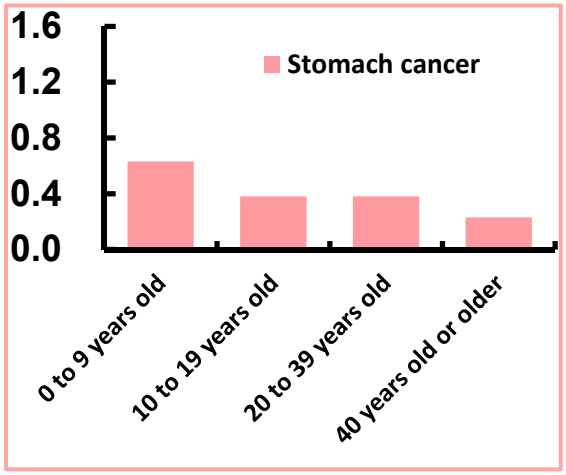
Cancer due to Acute External Exposure

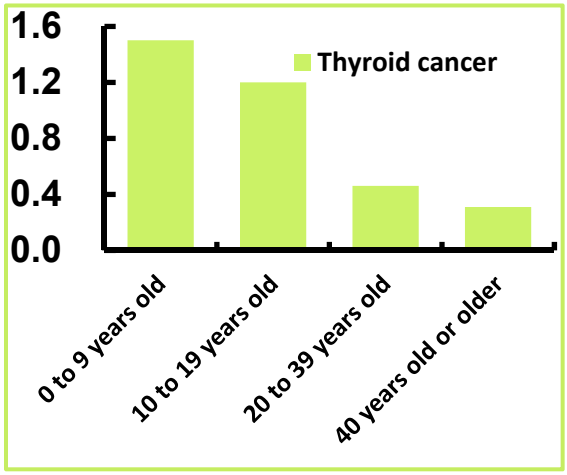
Ages at the Time of Radiation Exposure and Risks by Type of Cancer

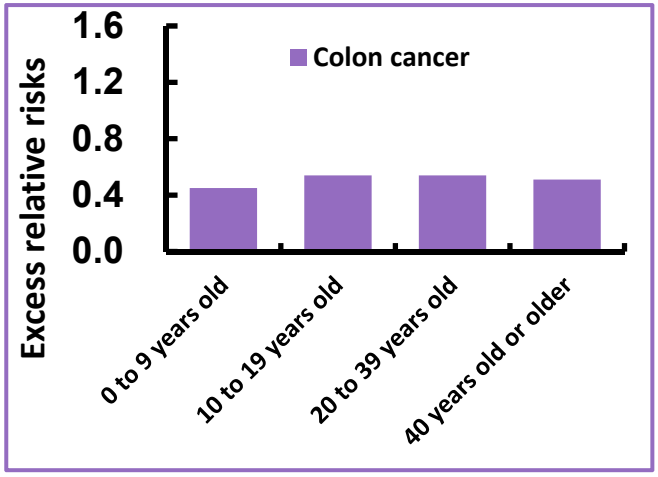
Excess relative risks of developing cancer by age for each type of cancer

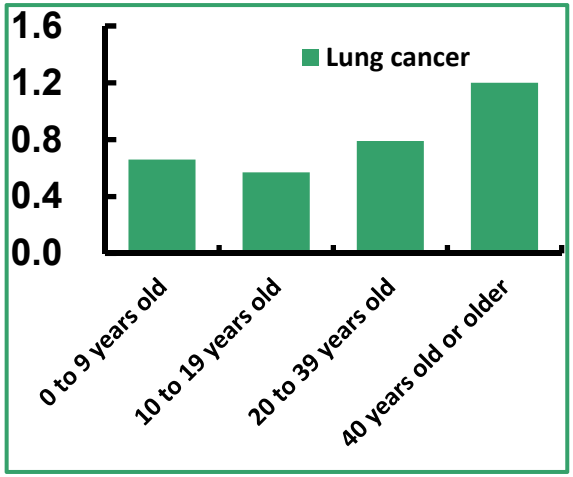
* Excess relative risks of developing cancer as of age 70 (per gray)

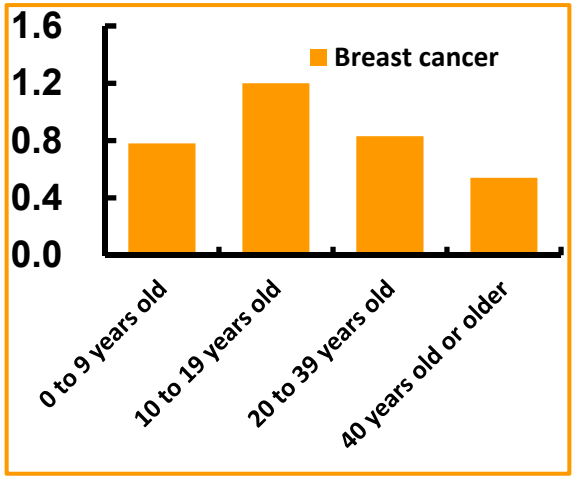








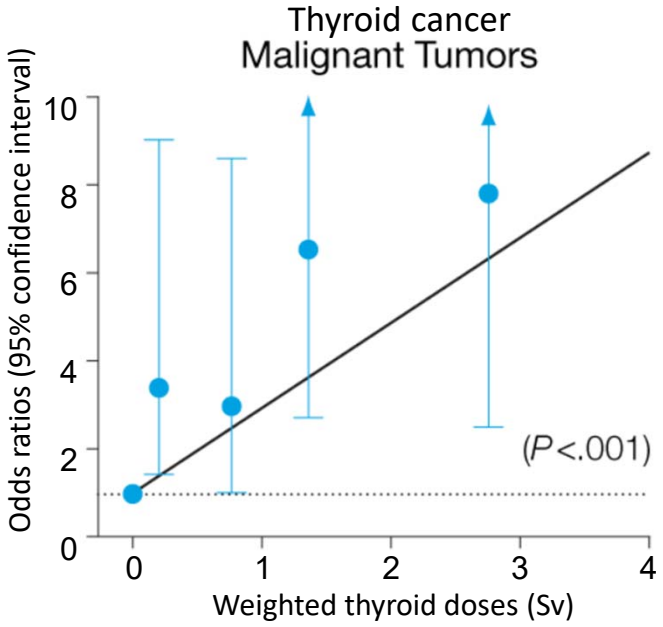




Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

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.

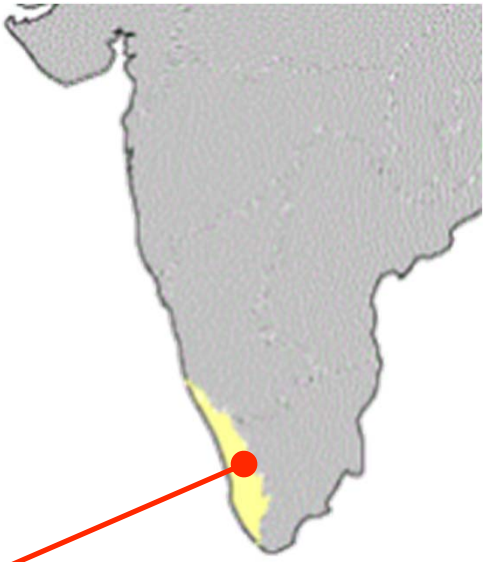
Odds of p / Odds of q = p / (1-p) ÷ q / (1-q)

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

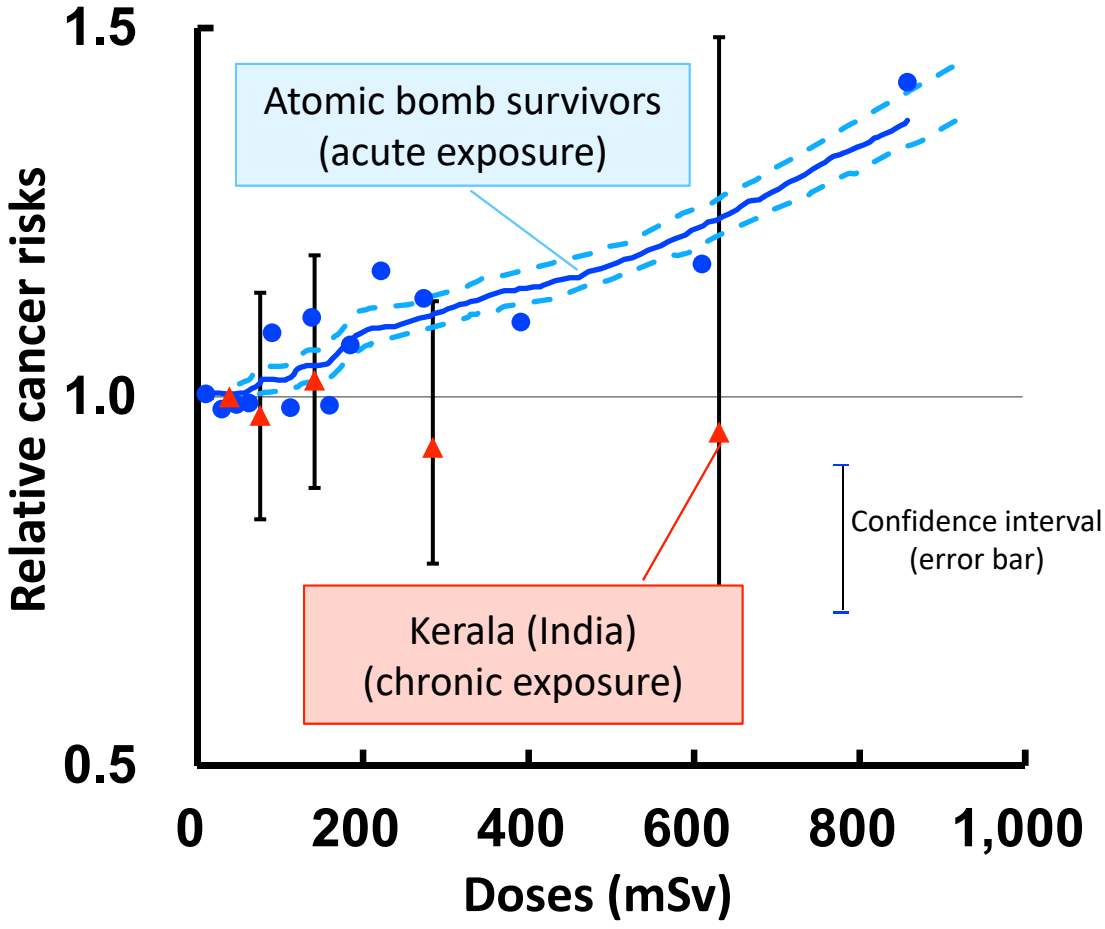
Carcinogenesis due to Chronic Exposure

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

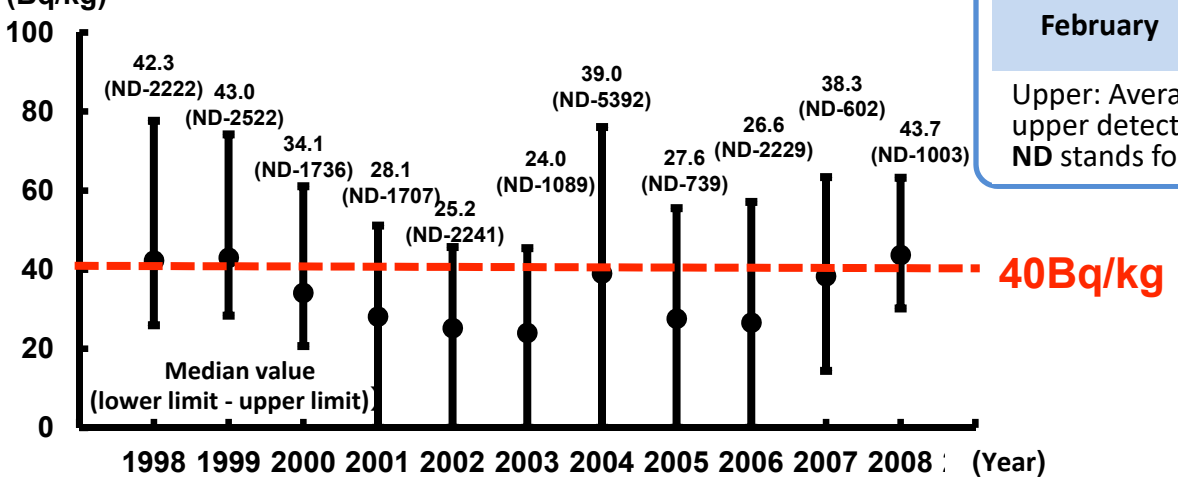
Basic Information on Thyroid
Thyroid Exposure

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.



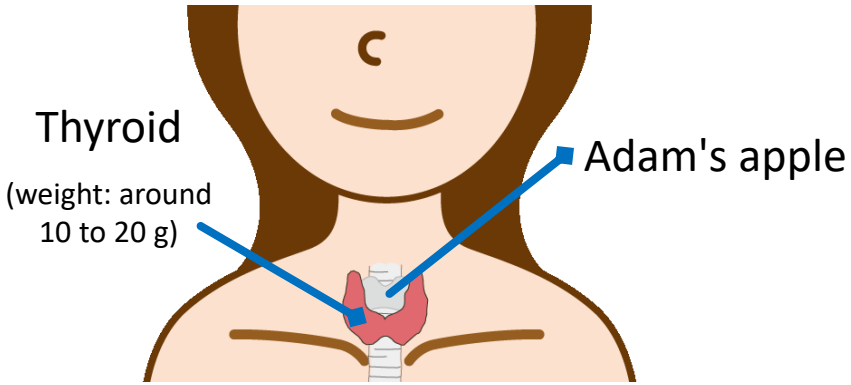
The annual internal exposure of 40 Bq/kg was detected in the Bryansk State from 1998 to 2008.

Bq/kg: Becquerels per kilogram

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

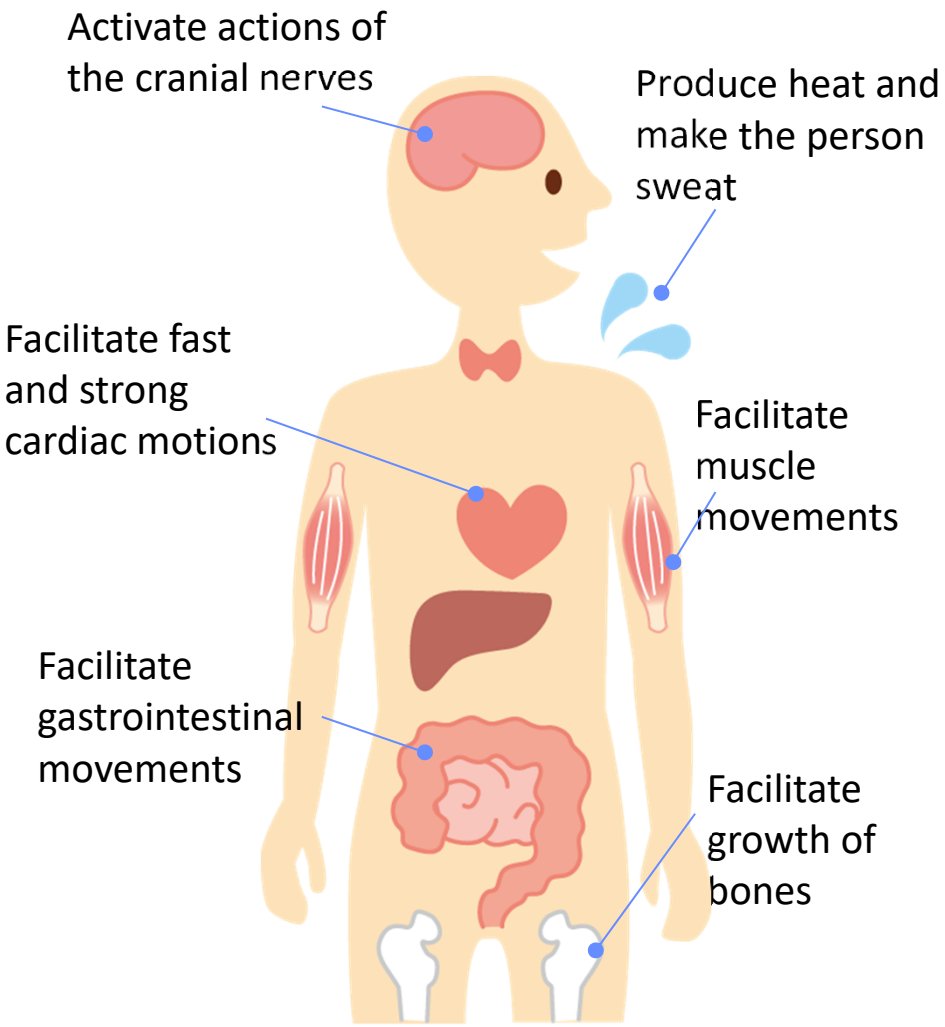
Basic Information on Thyroid

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.

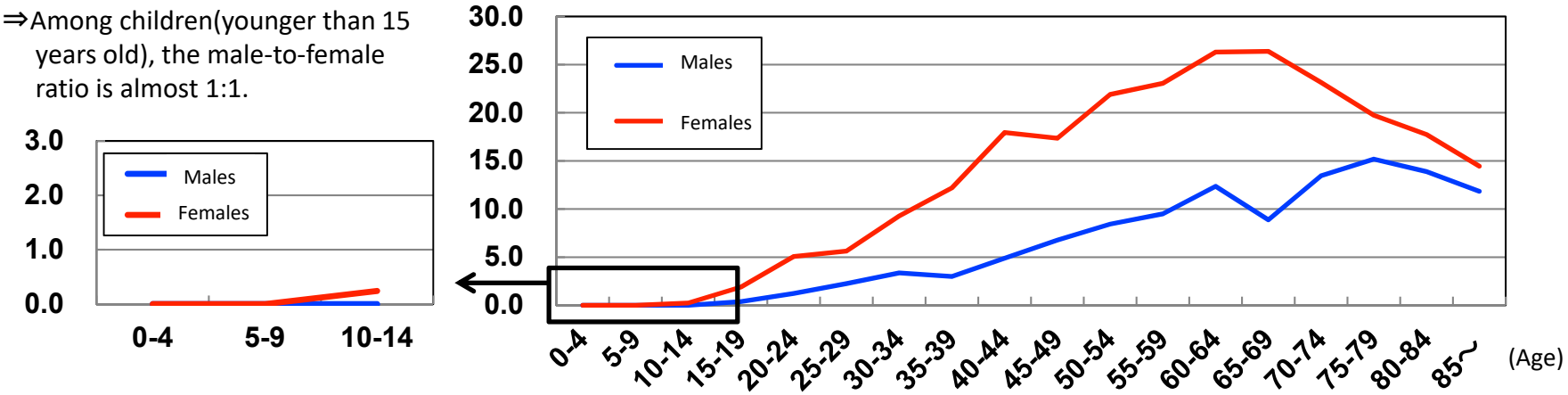
Characteristics of Thyroid Cancer

- **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.



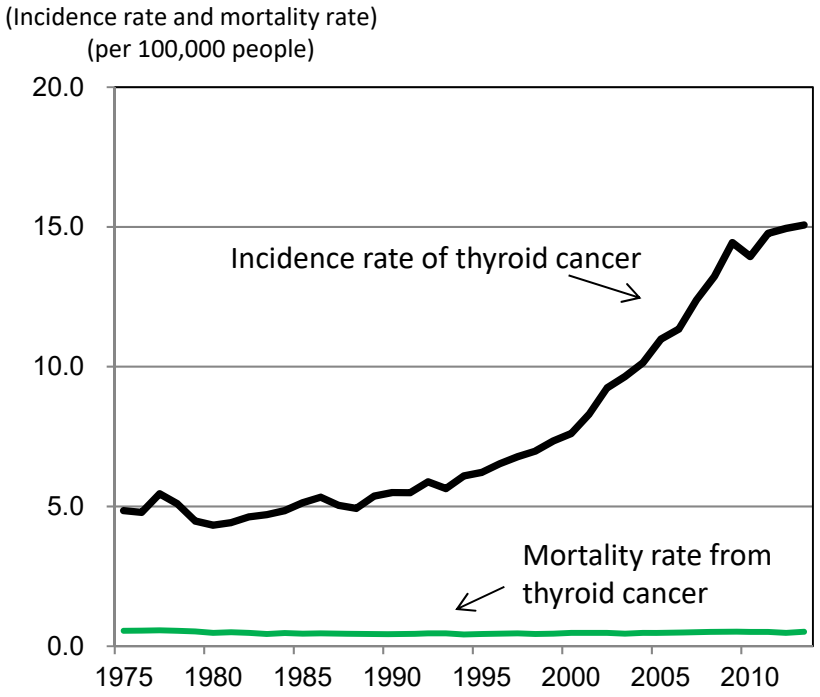
- **There is also occult thyroid cancer that does not exert any effects on people's health throughout their lifetime.**
- **In many cases, prognosis after surgery is good** (crude cancer mortality rate by organ/tissue (against 100,000 people), 2010).

	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

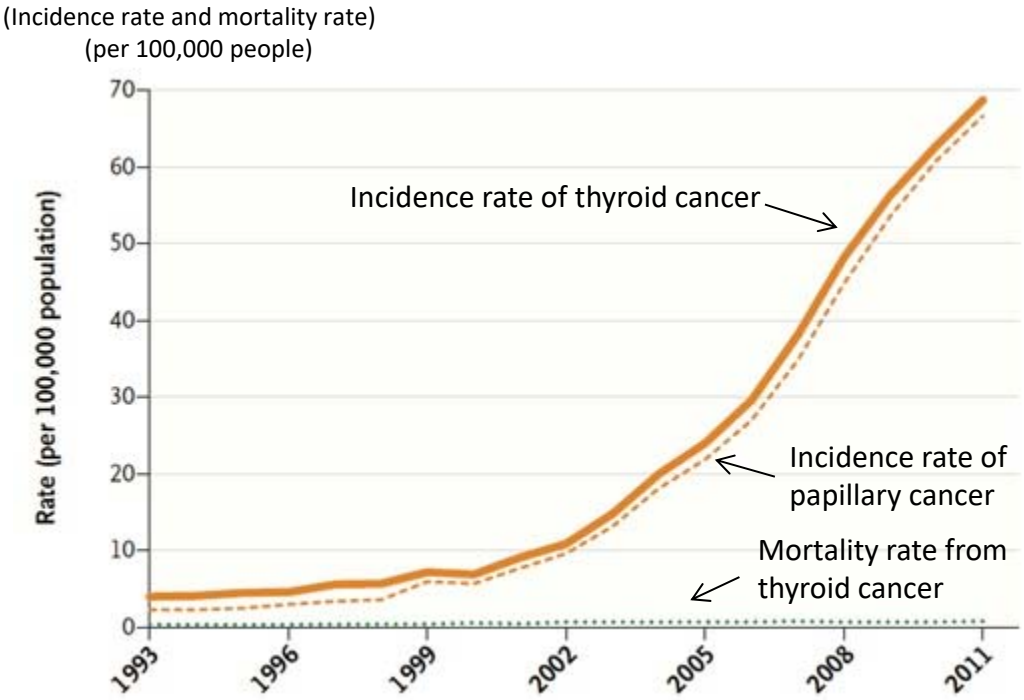
(Source: "Cancer Registration and Statistics," Cancer Information Service, National Cancer Center Japan)

Incidence Rates of Thyroid Cancer: Overseas

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



America*1



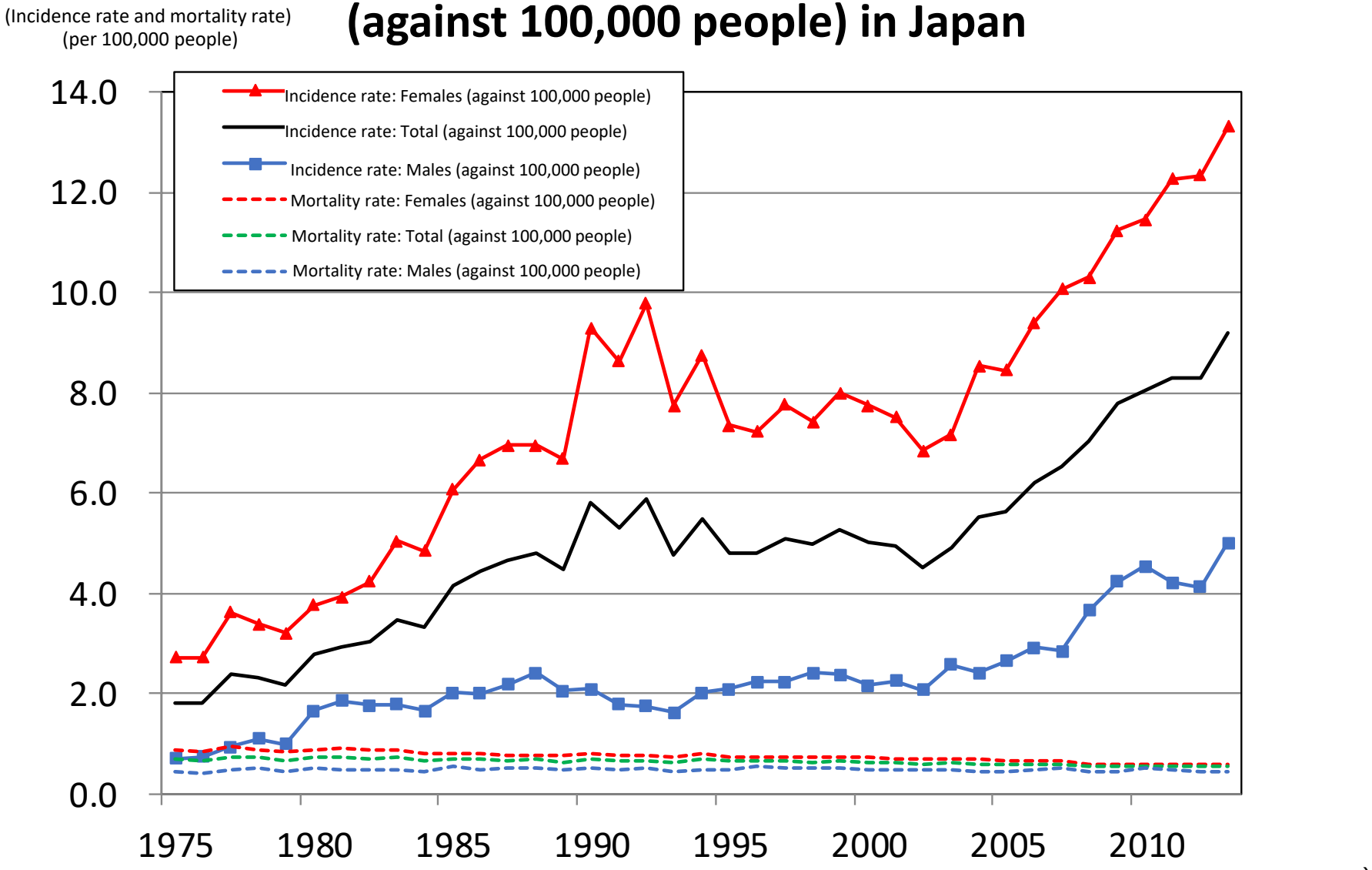
South Korea*2

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

Basic Information on Thyroid

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)

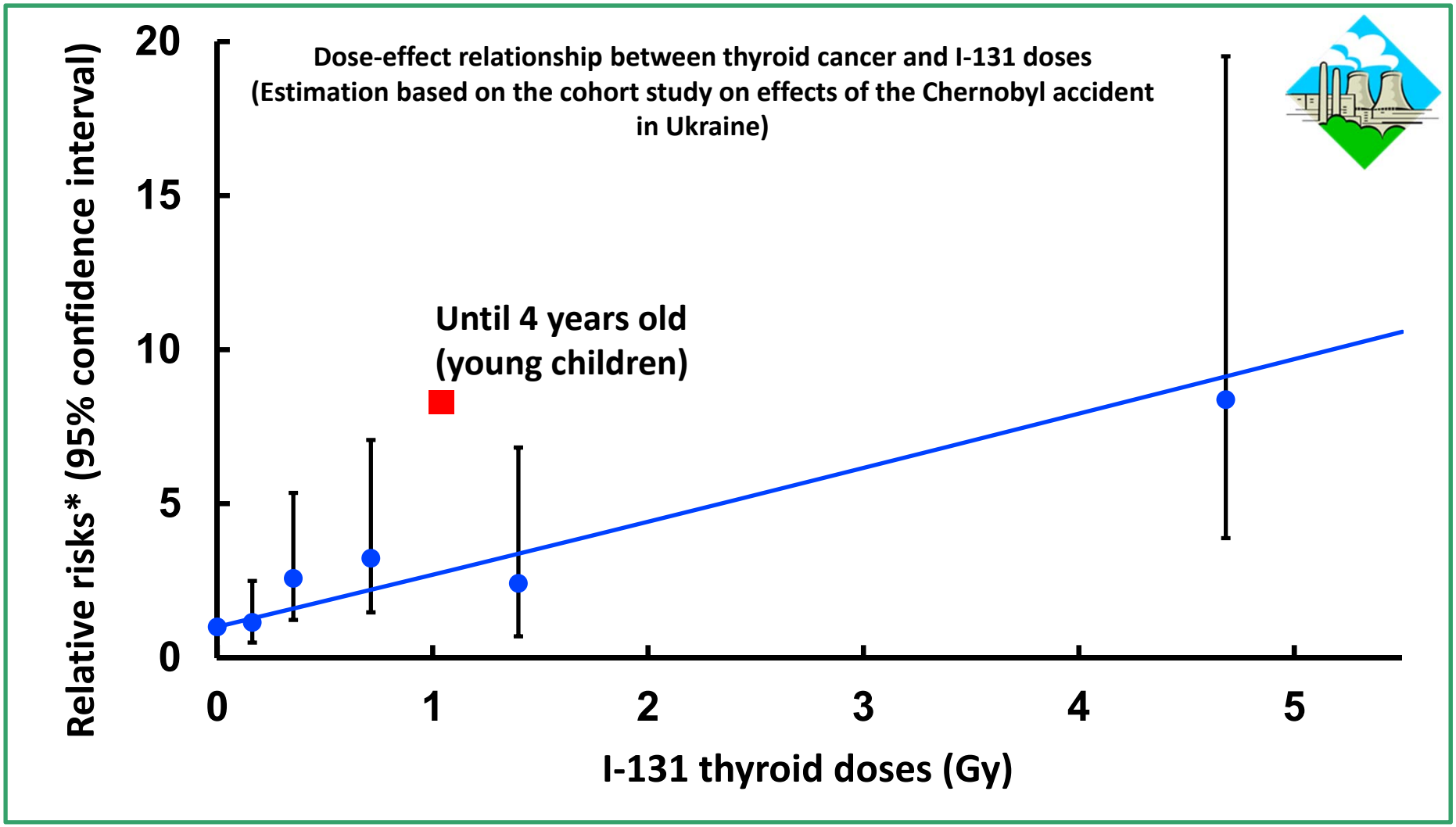
    * The probability that Japanese people develop cancer at least once during the lifetime, which was obtained based on the data on the number of cancer patients in Japan from 1975 to 1999
    (Kamo et al., Journal of Health and Welfare Statistics, Vol. 52, No. 6, June 2005)

- 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.

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.

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.

Exposure of a Group of Evacuees
- Chernobyl Accident -

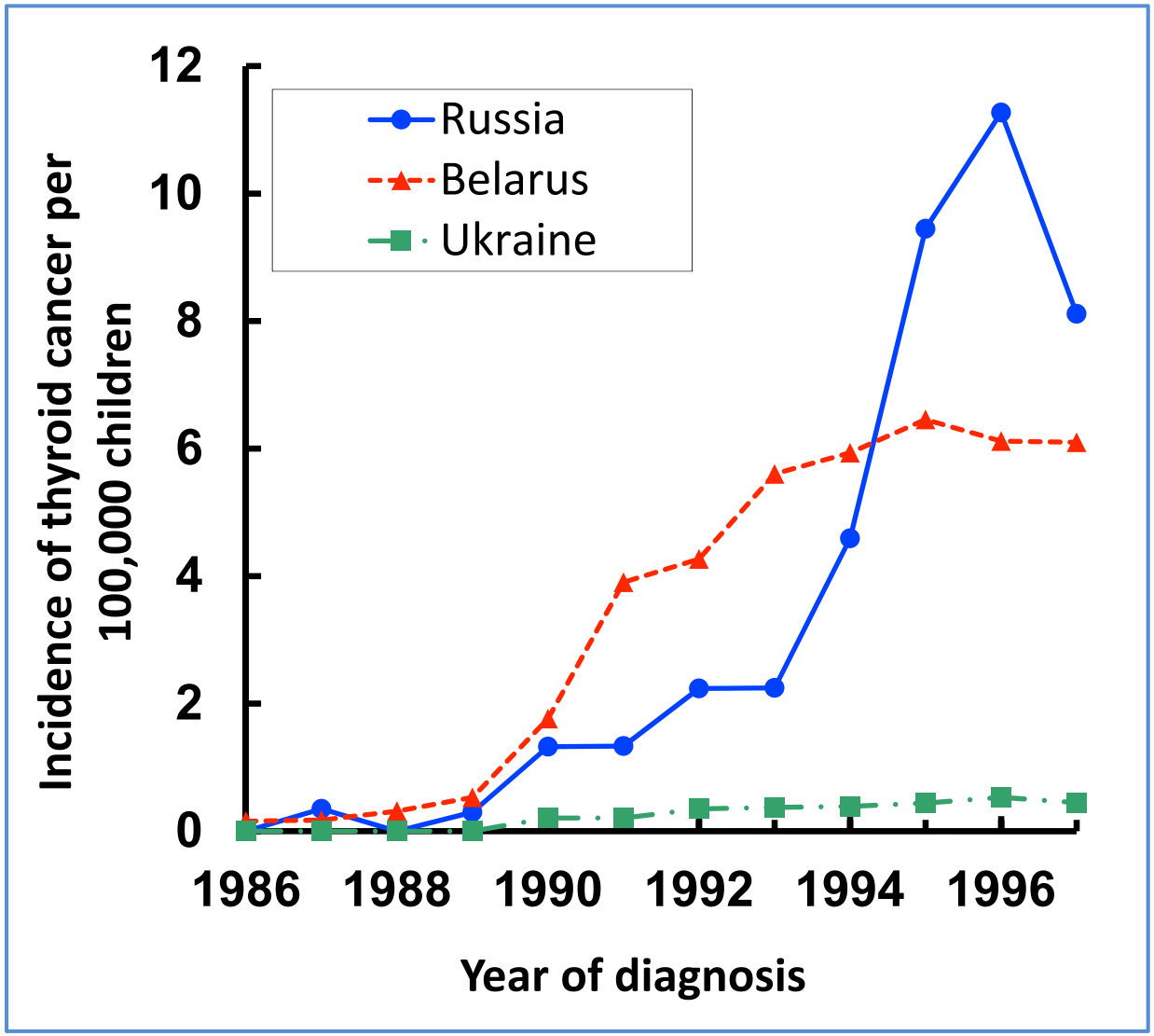
Countries	Number of people (1,000 people)	Average effective dose (mSv)		Average thyroid dose (mGy)
		External exposure	Internal exposure (in organs other than the thyroid)	
Belarus	25	30	6	1,100
Russia	0.19	25	10	440
Ukraine	90	20	10	330

mSv: millisieverts mGy: milligrays

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

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

Basic Information on Thyroid Thyroid Exposure

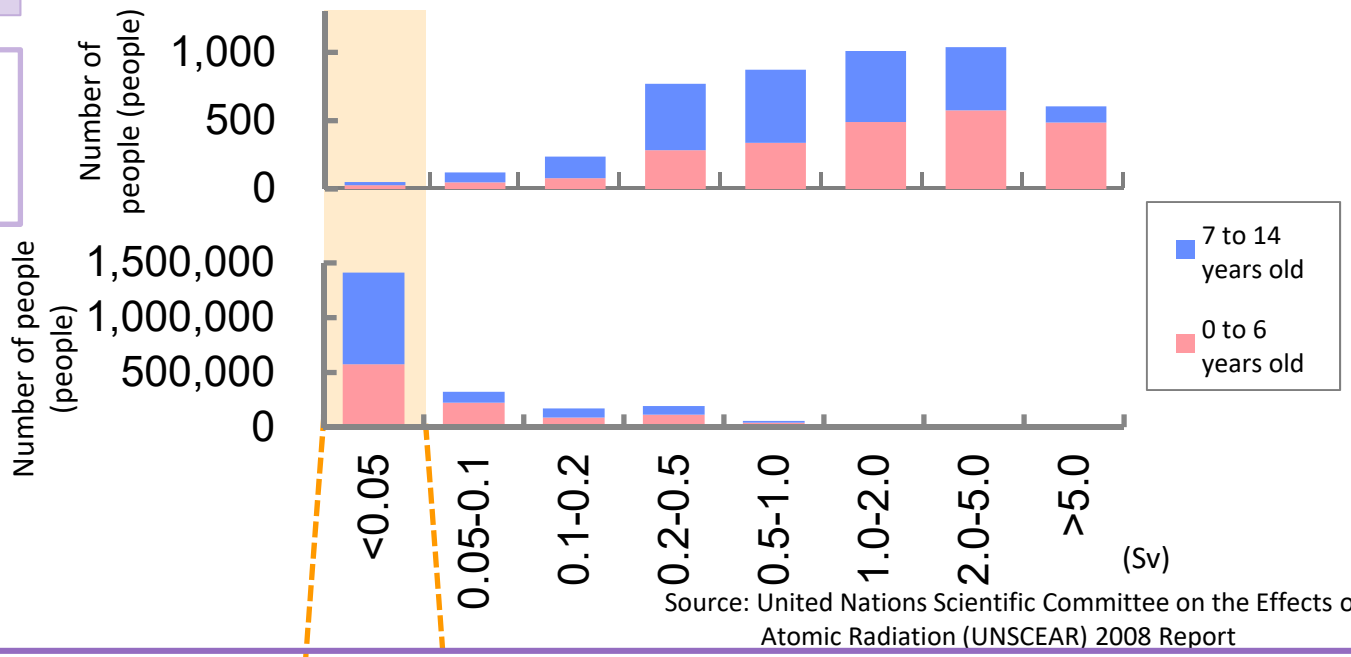
Comparison between the Chernobyl Accident and the Accident at Tokyo Electric Power Company (TEPCO)'s Fukushima Daiichi NPS (Thyroid Doses)

Children's thyroid exposure doses

Chernobyl accident

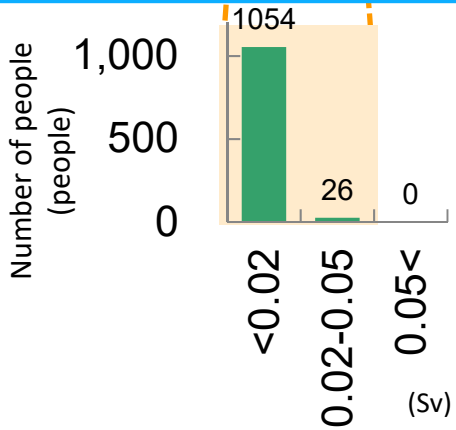
A group of people who evacuated in Belarus in 1986

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



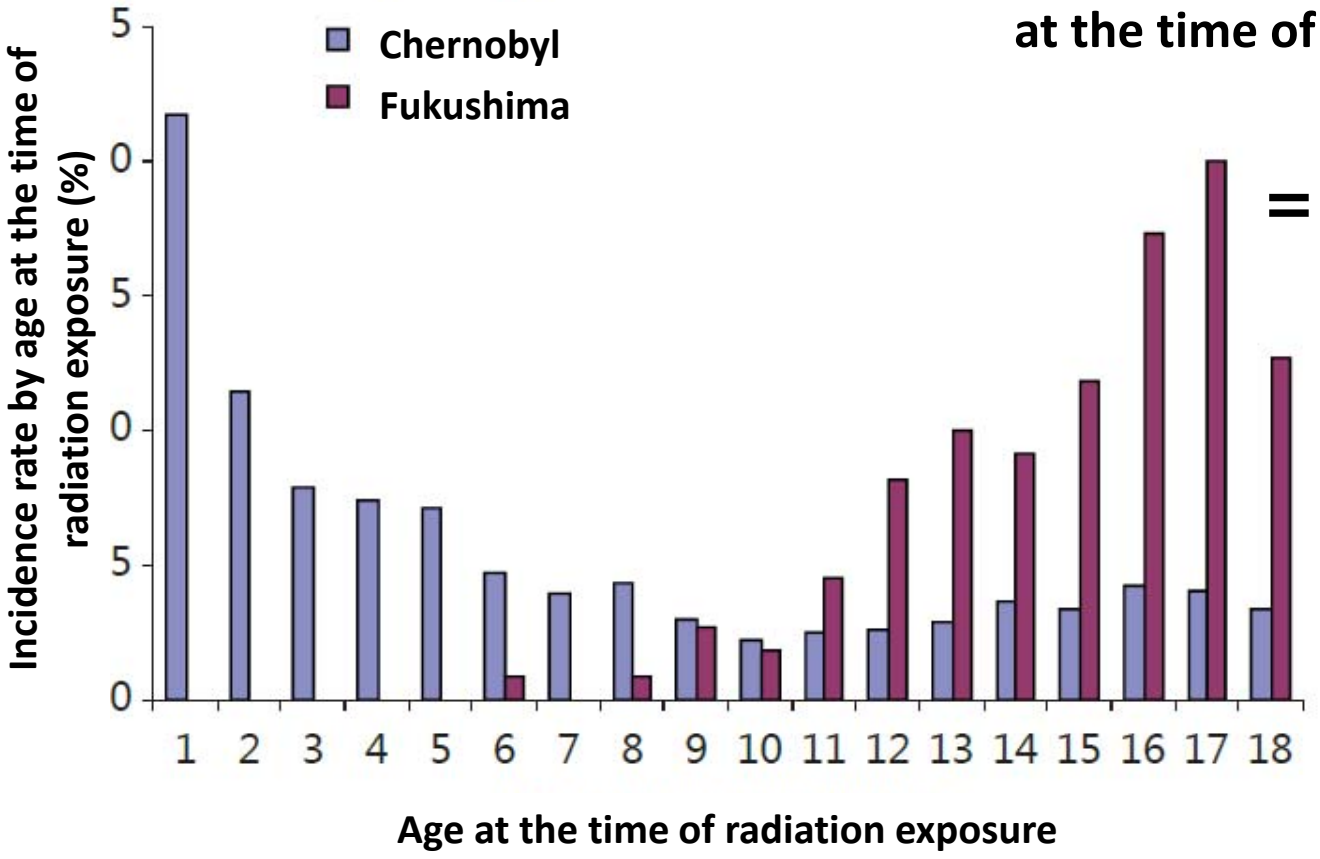
* This data is based on a survey targeting a limited group of residents and does not reflect the overall circumstances.

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 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 (%)

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

(Fukushima: Diagnosed as malignant or suspected)

Source: 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 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)