Chapter 6: Radiobiology

NPRE441:Principles of Radiation Protection

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Campus Instructional Facility

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Objective:

To familiarize the students with the basic principles of radiobiology.

Slides retrieved and adapted from:

- **Slide deck prepared by Dr. Elena Zannoni Spring 2023**
- **Slide deck NPRE441 Spring 2021 by Prof.L.J. Meng (UIUC, USA)**
- **Slide deck prepared in 2006 by Dr.E.B. Podgorsak (McGill University, Montreal)**
- **Slide deck prepared in 2015 by Dr.M. Cremonesi (IEO European Institute of Oncology, Milano, Italy)**
- **Slide deck prepared by Dr.E.Okuno (Institute of Physics of S. Paulo University, S. Paulo, Brazil)**

IAEA
International Atomic Energy Agency

環境省 Ministry of the Environment
Government of Japan

CHAPTER 6. TABLE OF CONTENTS
(classes April 3rd, 8th, 10th, 15th)

3. Type of radiation damage

Classification/ overview

A. Stochastic and deterministic (non-stochastic) effects
B. Somatic and genetic/hereditary effects
C. Acute vs late tissue or organ effects
D. Total body irradiation and Acute Radiation Syndrome
E. Equivalent and Effective Dose

Specific effects

F. Carcinogenesis (Risk models)
G. Cataractogenesis
H. Skin effects
I. Infertility
J. Fetal Irradiation

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Effects of radiation exposure depend on several factors

- Type of tissue exposed
- Volume of tissue exposed
- Type of radiation
- Dose per fraction
  - Late effects more impacted by dose per fraction
  - Early effects more impacted by total dose
- Dose rate

CHAPTER 6. TABLE OF CONTENTS
(classes April 3rd, 8th, 15th, ?)

3. Type of radiation damage

A. Stochastic and deterministic (non-stochastic) effects
B. Somatic and genetic/hereditary effects
C. Acute vs late tissue or organ effects
D. Total body irradiation and Acute Radiation Syndrome
E. Equivalent and Effective Dose
F. Carcinogenesis (Thyroid, leukemia) ← Stochastic
G. Cataractogenesis
H. Skin effects
I. Infertility ← Deterministic
J. Fetal Irradiation

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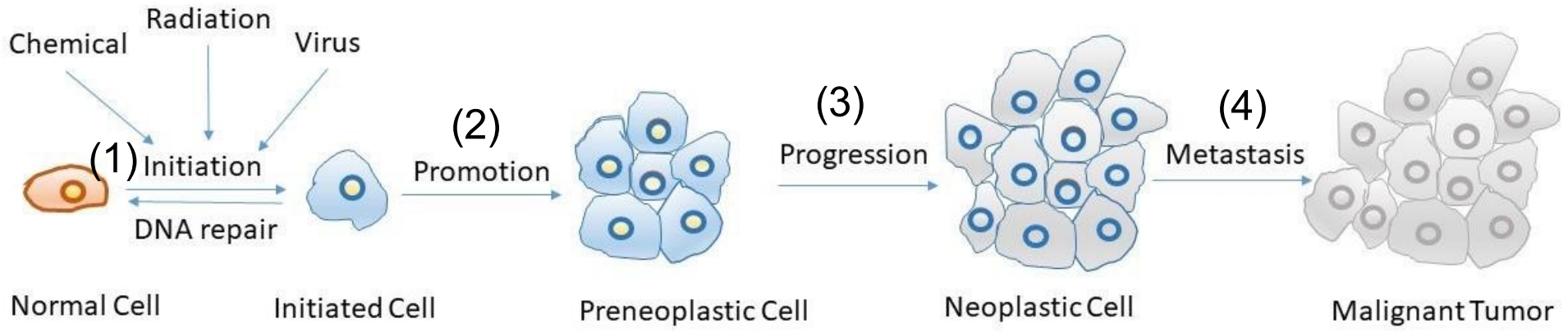
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis

- The development of cancer in tissues is assumed to be a multi-stage process that can be sub-divided into four phases:



CANCER

Martincorena, Iñigo et al. Cell, Volume 171, Issue 5, 1029 - 1041.e21
https://www.cell.com/cell/fulltext/S0092-8674(17)31136-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867417311364%3Fshowall%3Dtrue

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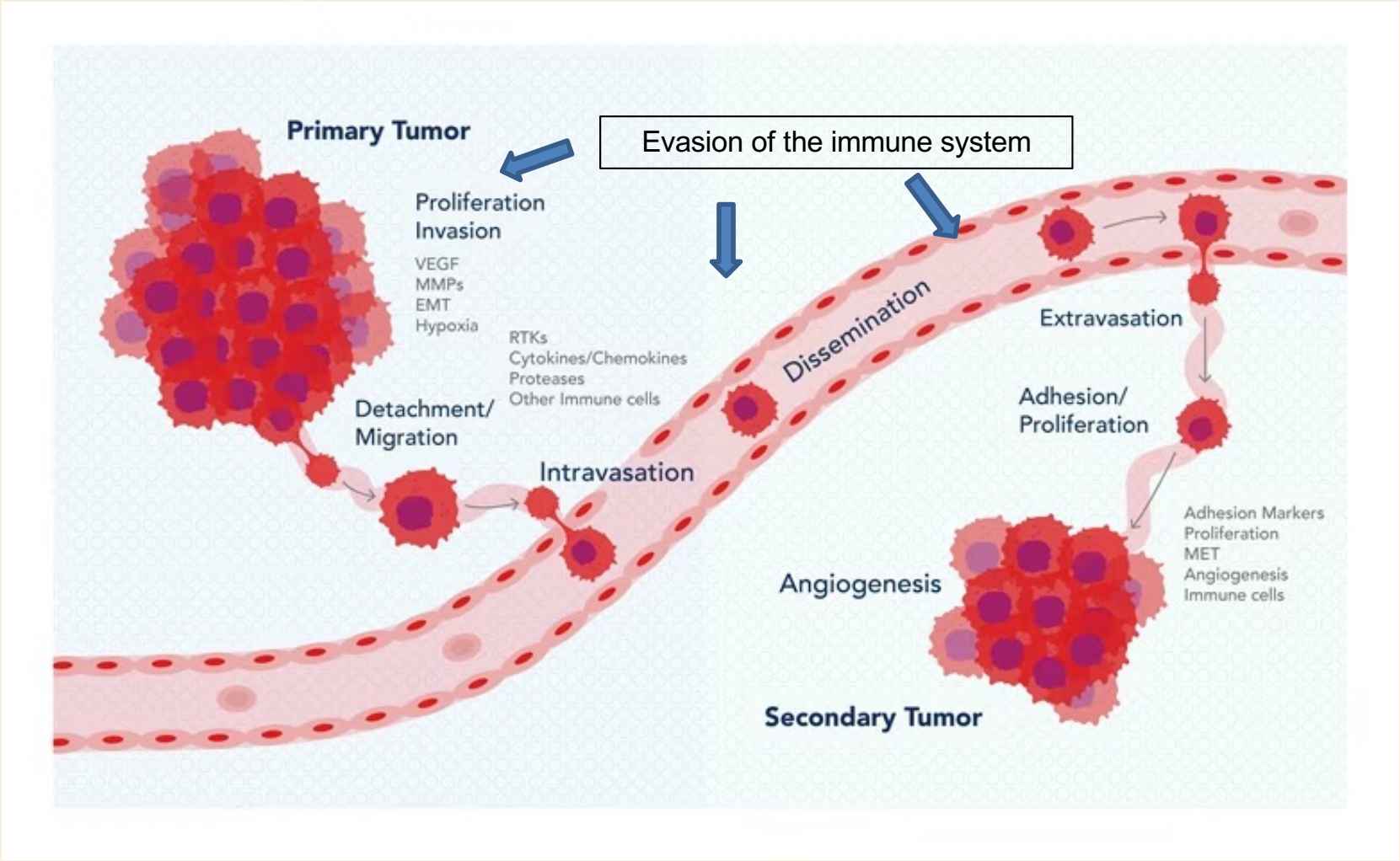
Metastatic cascade

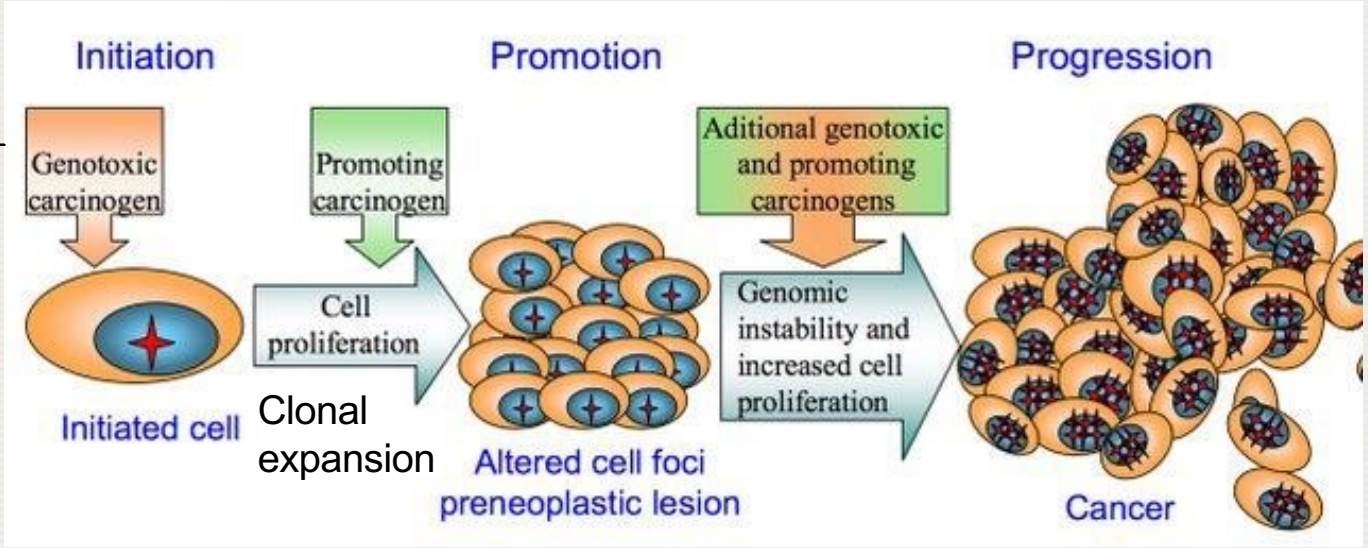


6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis

Neoplastic initiation leads to the irreversible potential of normal cells for neoplastic development by creating unlimited proliferative capacity

Endogenous (ROS)
Exogenous (smoke, radiation, smog)



- Further neoplastic development of initiated cells depends on promotional events (tumor promoters) which involves intercellular communication, e.g. by growth factors, hormones or environmental agents (alcohol, high estrogen, dietary fat, chronic irritation, UV, ect..) This results in the proliferation of the initiated pre-neoplastic cells in a semi-autonomous manner.

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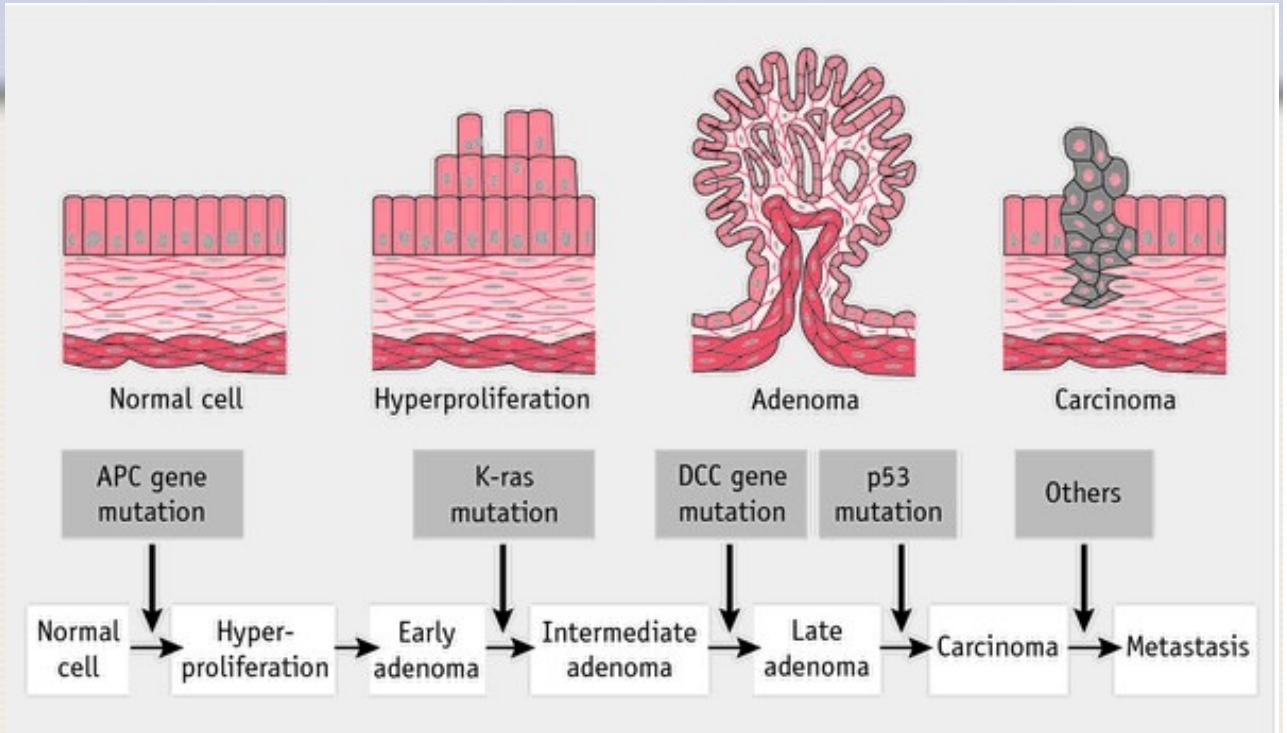
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis

Carcinoma is the most common type of cancer. It begins in the epithelial tissue of the skin, or in the tissue that lines internal organs, such as the liver or kidneys.



- During the process of conversion of the pre-neoplastic cells into fully malignant cells additional mutations in other genes are accumulated, probably facilitated by increasing loss of genomic stability
- The subsequent progression into an invasive cancer depends on still more mutations in the unstable genome

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6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis

Two classes of cancer-associated genes have been identified:

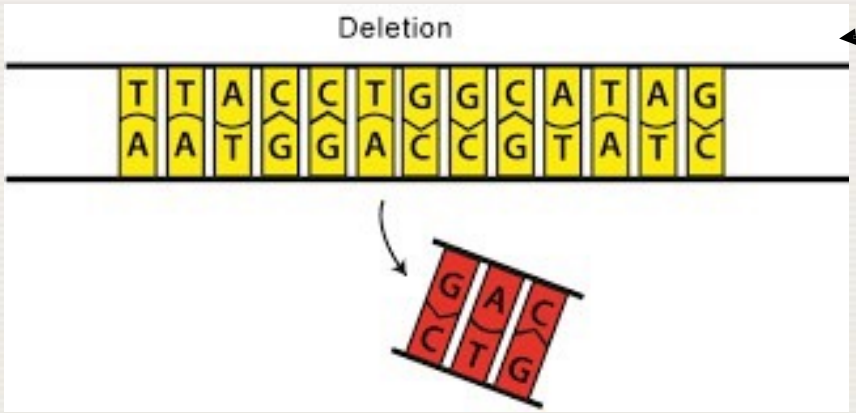
proto-oncogenes

Normal genes involved in growth regulation and result in an **increased rate of proliferation**

tumour suppressor genes

Genes involved in growth regulation of normal cells and that **prevent excessive cell proliferation**

Proto-oncogene mutations to oncogenes are thus classified as "gain-of-function" mutations



The critical mutation in these genes are "loss-of-function" mutations which may be the result of partial or complete loss of the gene structure, e.g. by **deletions.**

Since radiation-induced DNA damage preferentially causes deletions, it is generally assumed that the **inactivating mutation of tumour suppressor genes** is the most probable mechanism for the induction of cancer by radiation

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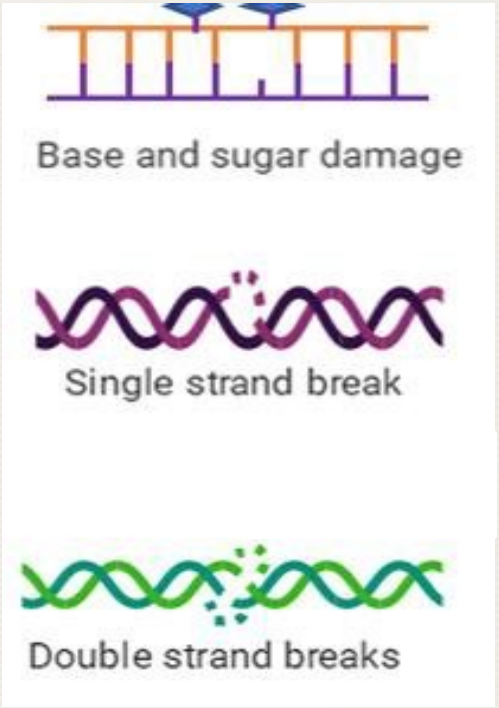
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis

- a single double strand break may, although with an extremely low probability, cause a deletion in a specific DNA sequence, e.g. of a tumour suppressor gene
- in principle, a single mutational event in a critical gene in a single target cell *in vivo* can create the potential for neoplastic development
- a single radiation track traversing the nucleus of an appropriate target cell has a finite probability of generating the specific damage of DNA that results in the initiating mutation
- This argument would strengthen the hypothesis that the risk of radiation induced cancer increases progressively with increasing dose, and there is **no lower threshold**



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Risks of Health Effects of Radiation

In order to evaluate the health effects of radiation on exposed populations or workers, the incidence or frequency of a certain effect (per unit of radiation dose) is studied in both the **exposed** and non exposed **control group** (incidence vs prevalence)

Risks

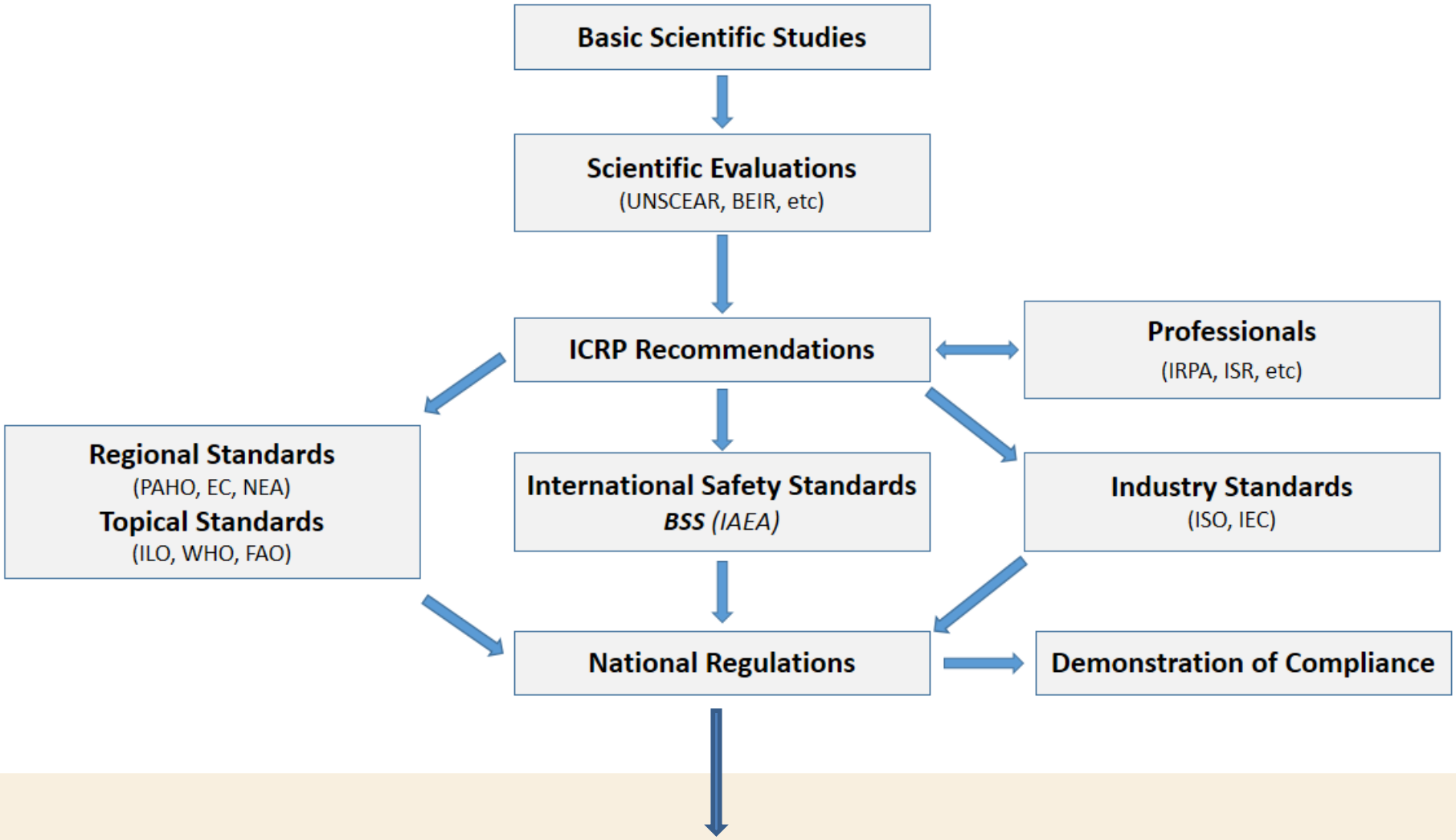
- The magnitude of the influence of damage
- The possibility of any damage (probability)
- The combination of the magnitude of the influence and the possibility (probability)

Quantitatively expressed **probability**, not focused on the actual existence of damage (deterministic effect)

Quick aside - Abbreviations

- **BEIR** = Biologic Effects of Ionizing Radiation
  - National Academy of Sciences (National Research Council)
    - Independent, non-profit
  - Reports issued every ~3-10 years, last one (VII) in 2006
- **UNSCEAR** = United Nations Scientific Committee on the Effects of Atomic Radiation
  - Established in 1955 by the UN
  - Issues periodic public reports about sources of radiation
  - 28 reports between 1958 and 2017
  - Committee meets annually (scientists from 21 states)
- **IAEA** = International Atomic Energy Agency
  - Founded in 1957 by the UN (HQ in Vienna, Austria)
  - Governs the peaceful use of nuclear energy, safeguards against military use, and monitors radiation safety

International Policy Relationships for Radiological Protection

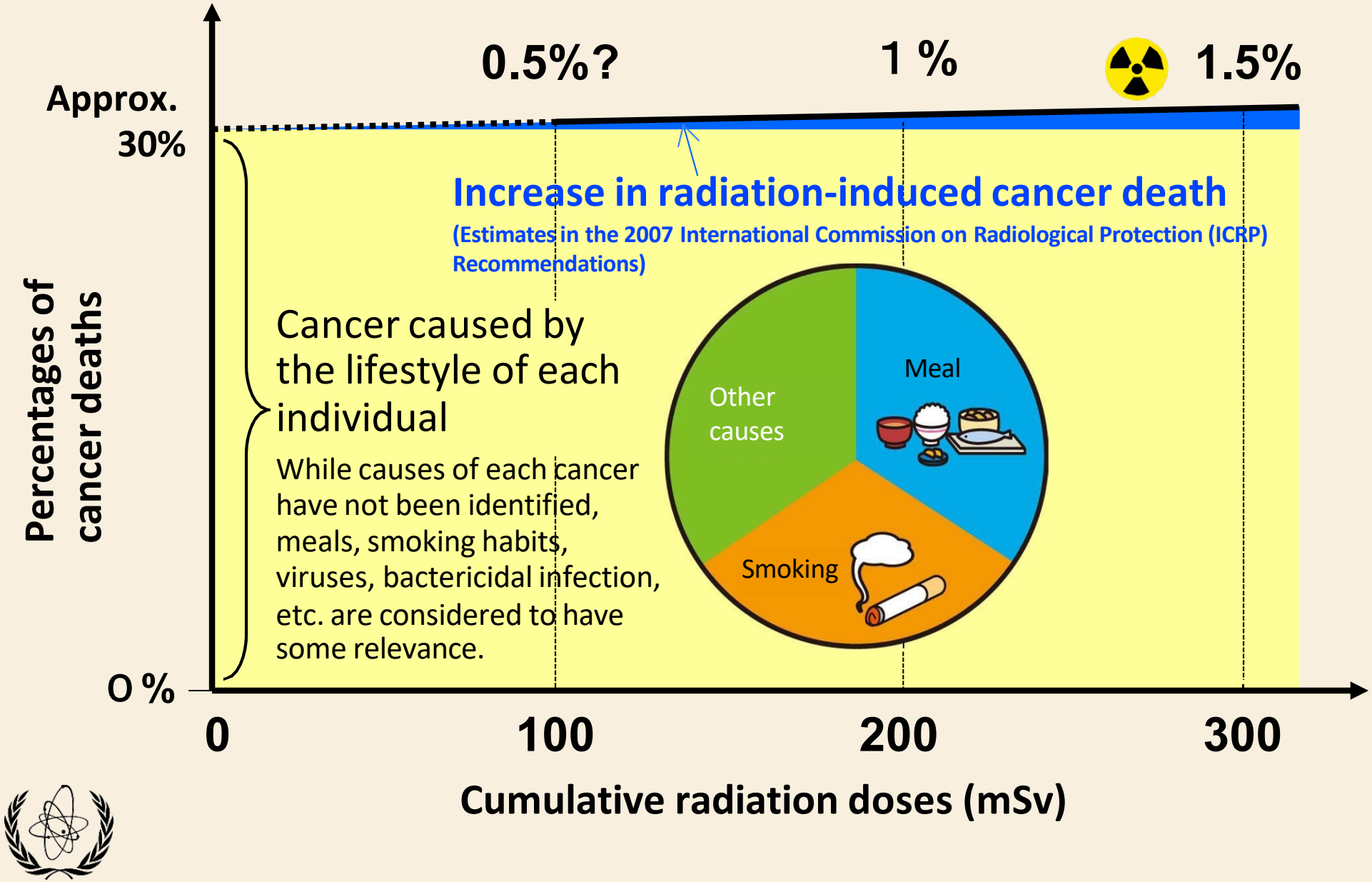


National: Nuclear Regulatory Commission (NRC)

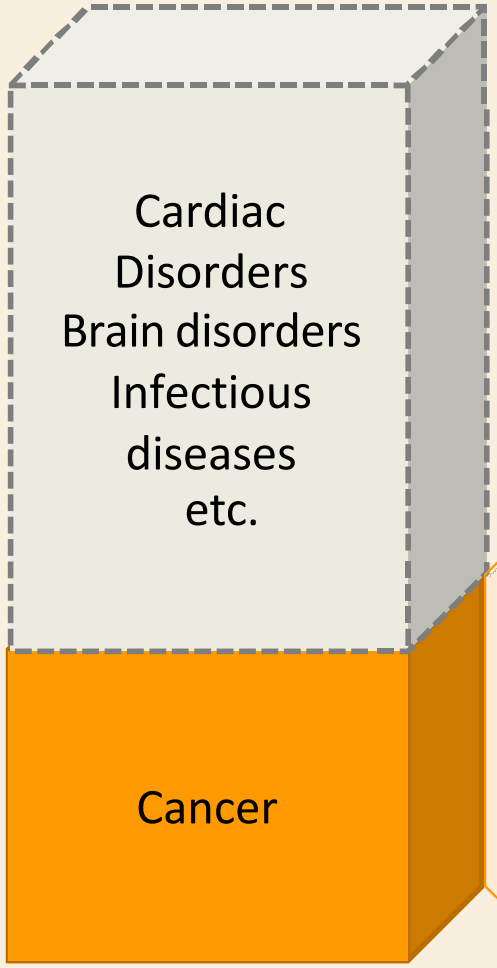
State: Illinois Emergency Management Association (IEMA)

Risks

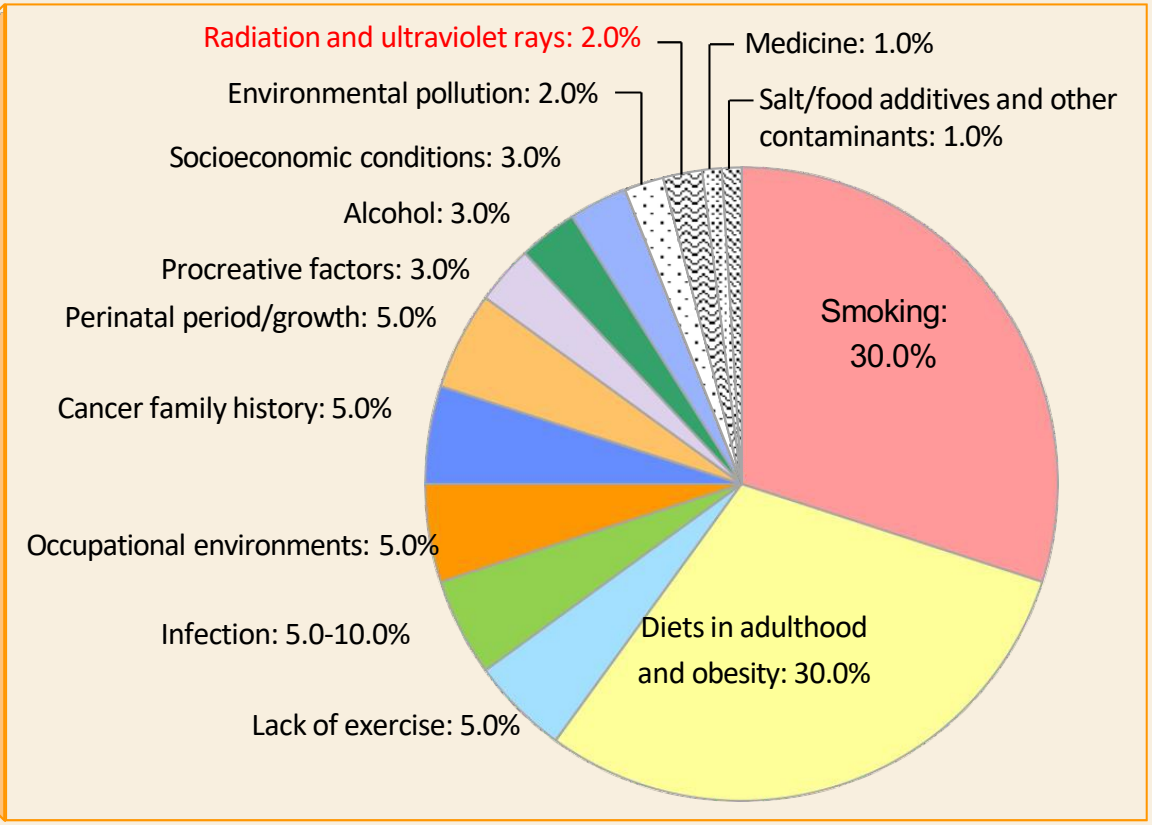
Risks of Cancer Death from Low-Dose Exposure



Factors Associated with Carcinogenesis



Factors associated with human cancer



Source: Prepared based on Cancer Causes Control 1996.7.S55-S58

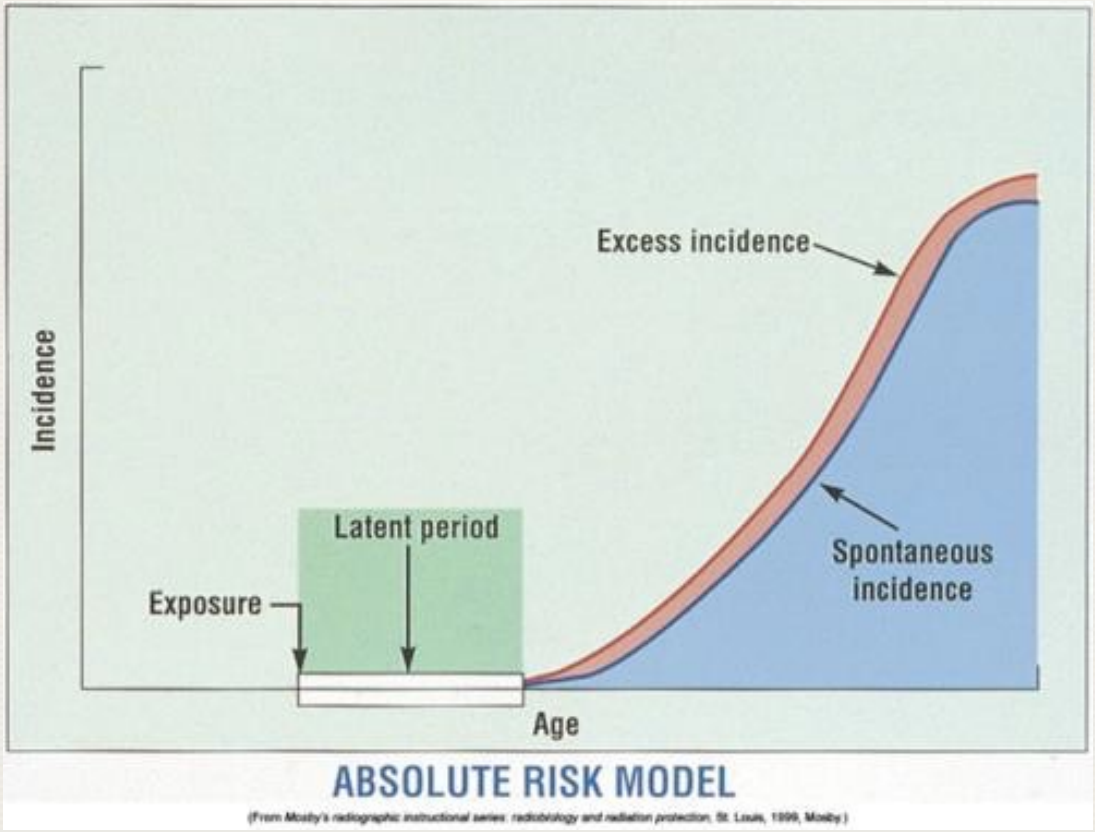
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis: risk models

For assessing the risk of radiation-induced cancer in humans two conceptually different models are used:

absolute-risk

- This model assumes that radiation induces cancers **over and above the natural incidence and unrelated to it (addition of a constant factor)**
- After the latency period has passed, the cancer risk returns to “spontaneous” levels



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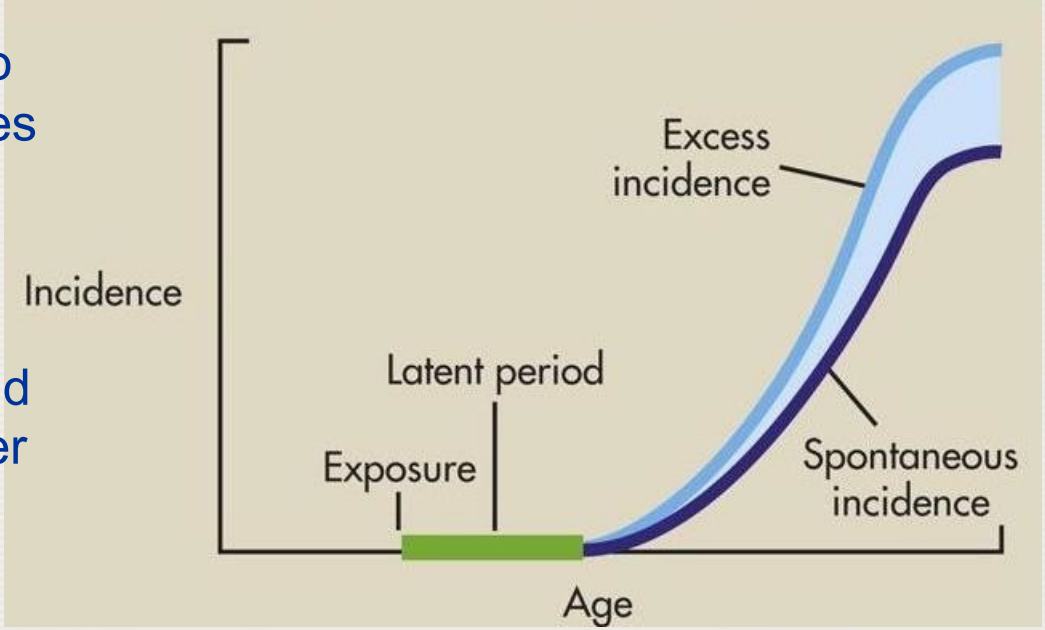
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis: risk models

For assessing the risk of radiation-induced cancer in humans two conceptually different models are used:

relative-risk

- This model assumes that the effect is to increase the natural incidence at all ages subsequent to exposure by a **given factor**
- Because the natural or spontaneous cancer incidence rises significantly in old age, this model predicts a larger number of radiation-induced cancers in old age
- This model is favoured by the **BEIR** committee estimating risks after radiation exposure



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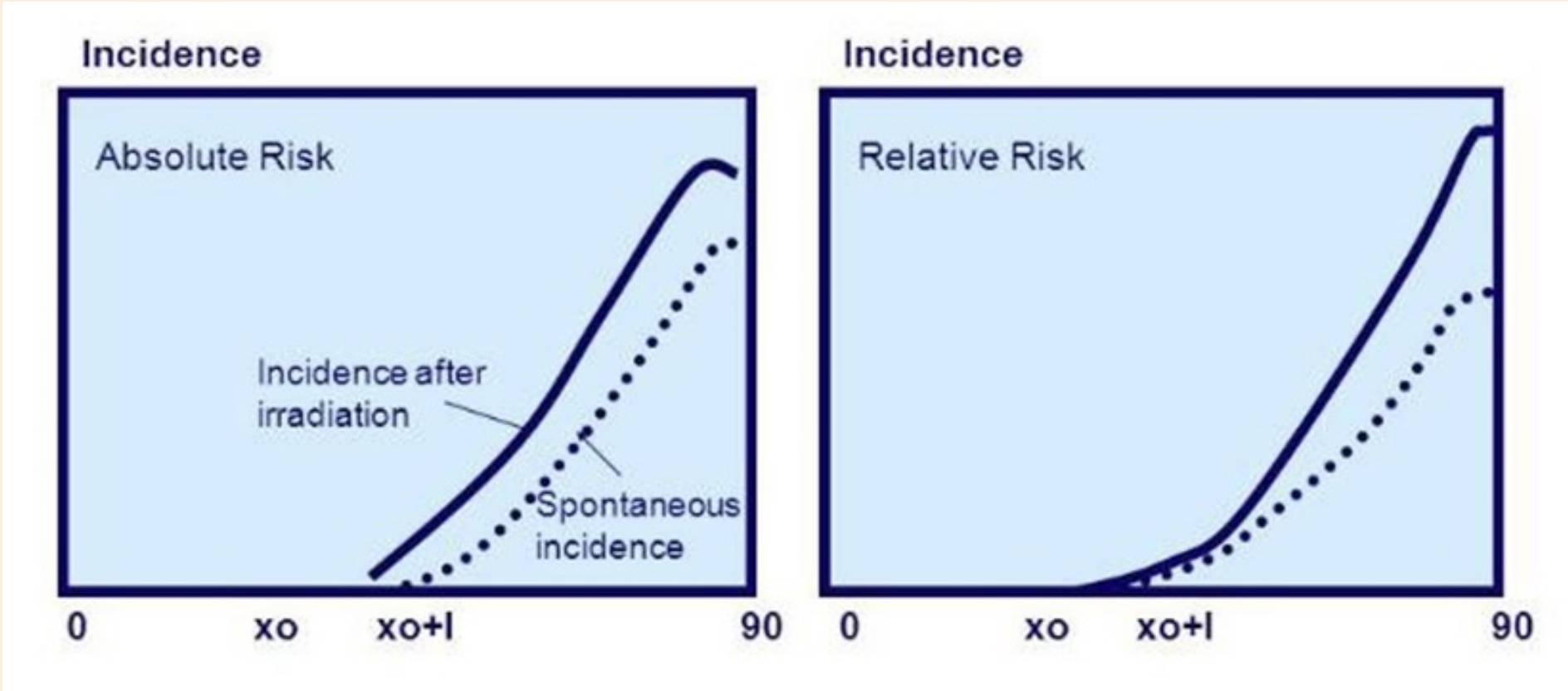
BEIR (National Academy of Sciences, Biological Effects of Ionizing Radiation)


Incidence
Absolute Risk
Incidence after irradiation
Spontaneous incidence
0
xo
xo+l
90
Incidence
Relative Risk
0
xo
xo+l
90

Risks

Carcinogenesis: risk models

Factors	Incidence		Total
	Yes	No	
Exposed group	A	B	A+B
Non-exposed group	C	D	C+D

How many times factor exposure would increase the incidence of an individual:

$$\text{Relative risk (RR)} = \frac{\text{Incidence risk among an exposed group}}{\text{Incidence risk among a non-exposed group}} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$$

Relative risk larger than 1 represents that risks have increased due to factor exposure.

The value obtained by subtracting 1 from the relative risk is an excess relative risk, showing an increased amount of risks.

How many times factor exposure would increase the incidence rate of a group:

$$\text{Excess Absolute Risk (EAR)} = \text{Incidence risk among an exposed group} - \text{Incidence risk among a non-exposed group} = \frac{A}{A+B} - \frac{C}{C+D}$$

Risks

Risks of Cancer (Radiation)

Radiation doses (mSv)	Relative risks of cancer*
1,000 ~ 2,000	1.8 [estimated to be 1.5 times per 1,000 mSv]
500 ~ 1,000	1.4
200 ~ 500	1.19
100 ~ 200	1.08
Less than 100	Difficult to detect

Source: Website of the National Cancer Center Japan

* Risks of developing radiation-induced cancer are based on the data (solid cancers only) obtained from the analysis of instantaneous exposure due to the atomic bombing in Hiroshima and Nagasaki, and are not based on the observation of long-term exposure effects.
* 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.

Risks

Risks of Cancer (Life Habits)

Lifestyle factors	Relative risks of cancer
Smokers	1.6
Heavy drinking (450 g or more/week)*	1.6
Heavy drinking (300 to 449 g or more/week)*	1.4
Obese (BMI≧30)	1.22
Underweight (BMI<19)	1.29
Lack of exercise	1.15 ～ 1.19
High-salt foods	1.11 ～ 1.15
Lack of vegetable intake	1.06
Passive smoking (nonsmoking females)	1.02 ～ 1.03

* Alcohol consumption is in ethanol equivalent.

Source: Website of the National Cancer Center Japan

Cancer due to Acute External Exposure

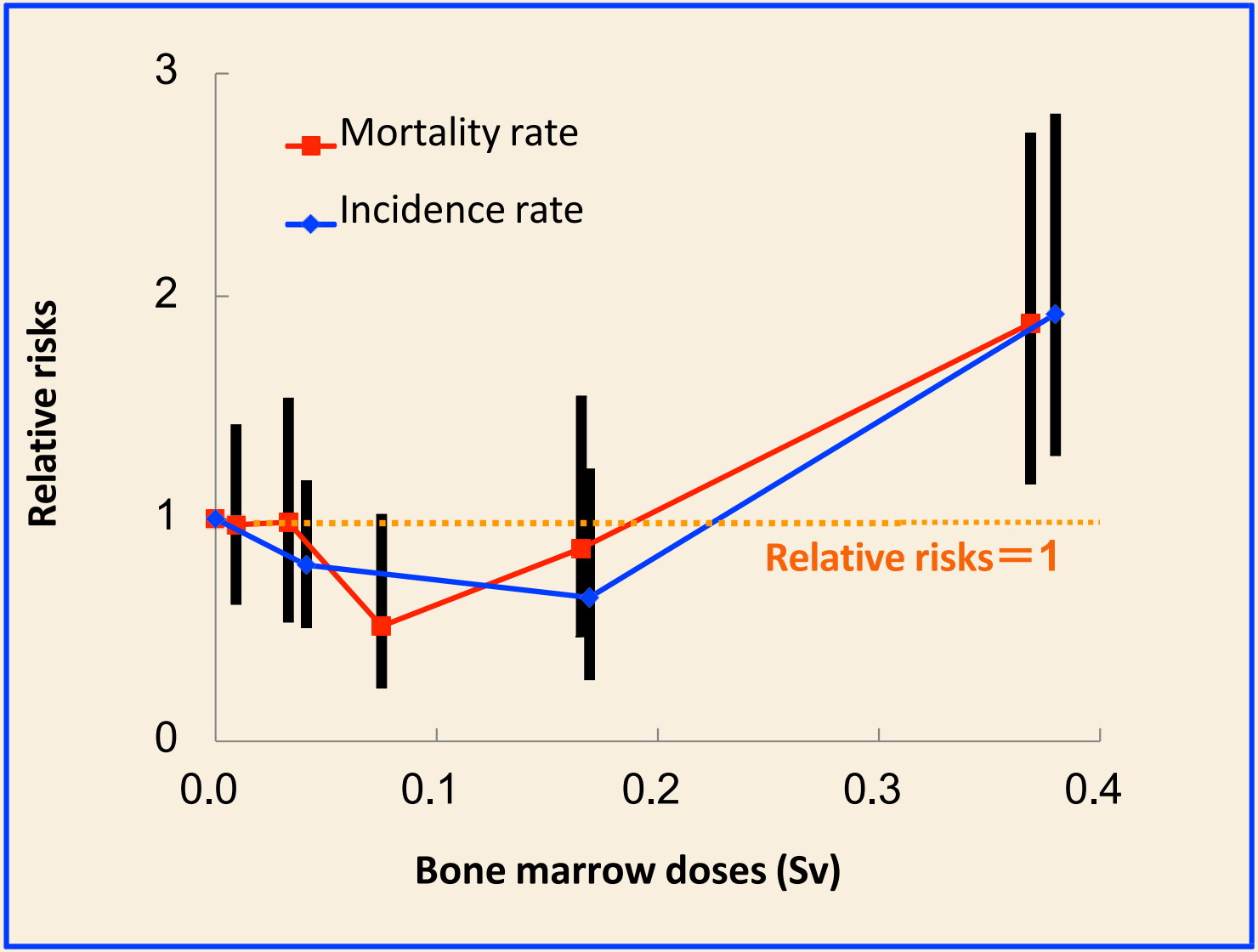
Risks of Developing Leukemia

Risks of developing leukemia among atomic bomb survivors

Incidence risk among an exposed group

$$RR = \frac{R_r}{R_0}$$

Incidence risk among the control group



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

Cancer due to Acute External Exposure

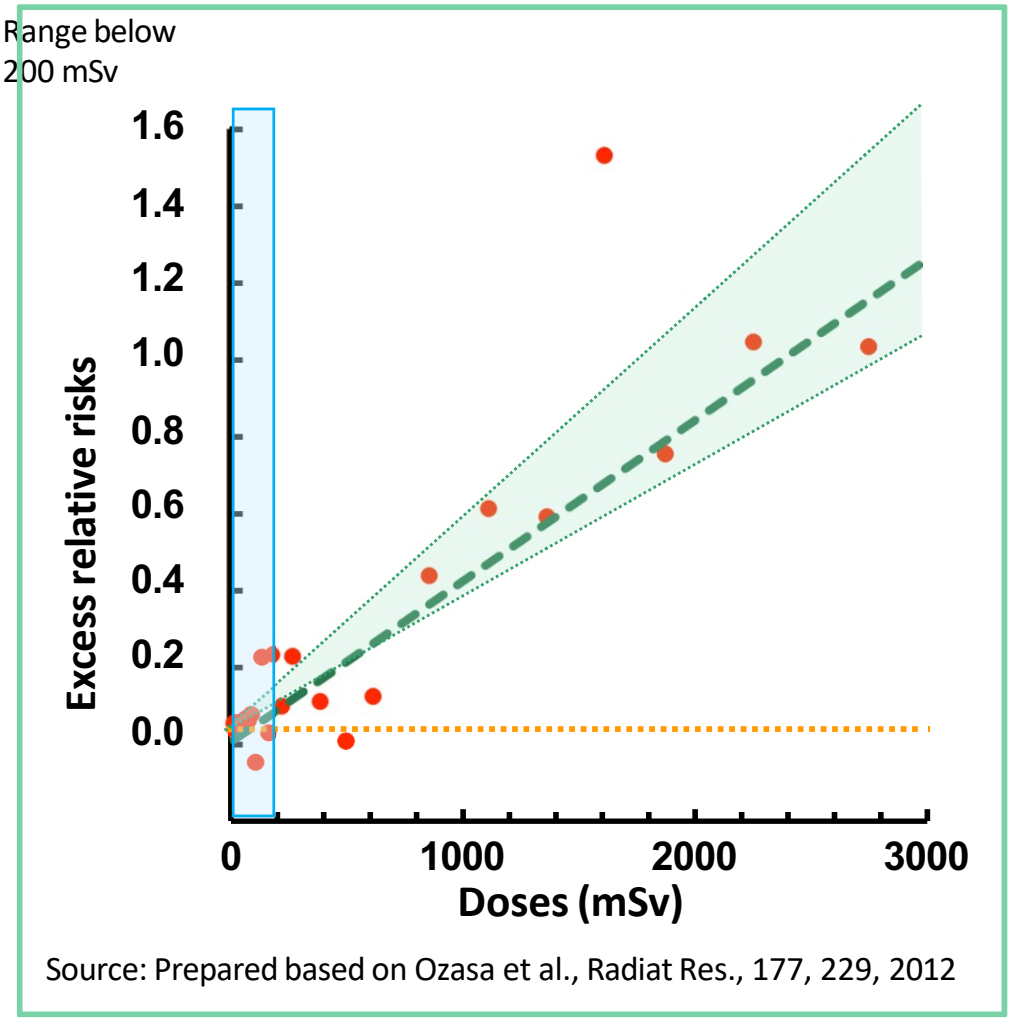
Relationship between Solid Cancer Deaths and Doses

Deaths from solid cancer (results among atomic bomb survivors)

Excess Relative Risk (ERR)

$$ERR = RR - 1$$

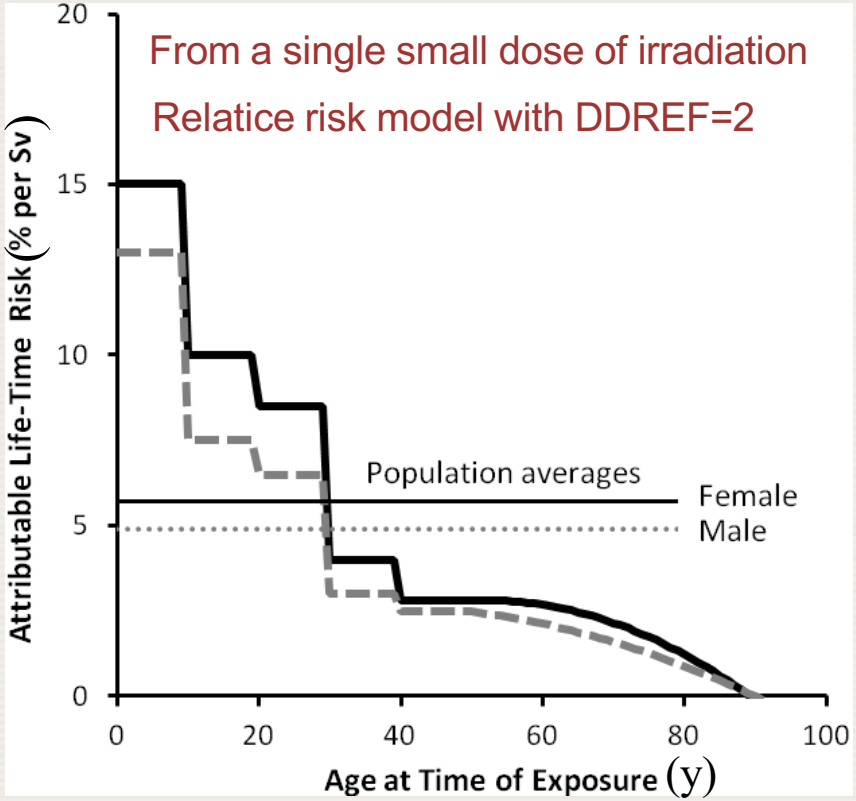
How cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people



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

6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis: risk models



Hall and Giaccia, 2006, adapted from ICRP: Recommendations. Annals of the ICRP Publication 60, Oxford, England, Pergamon Press, 1990

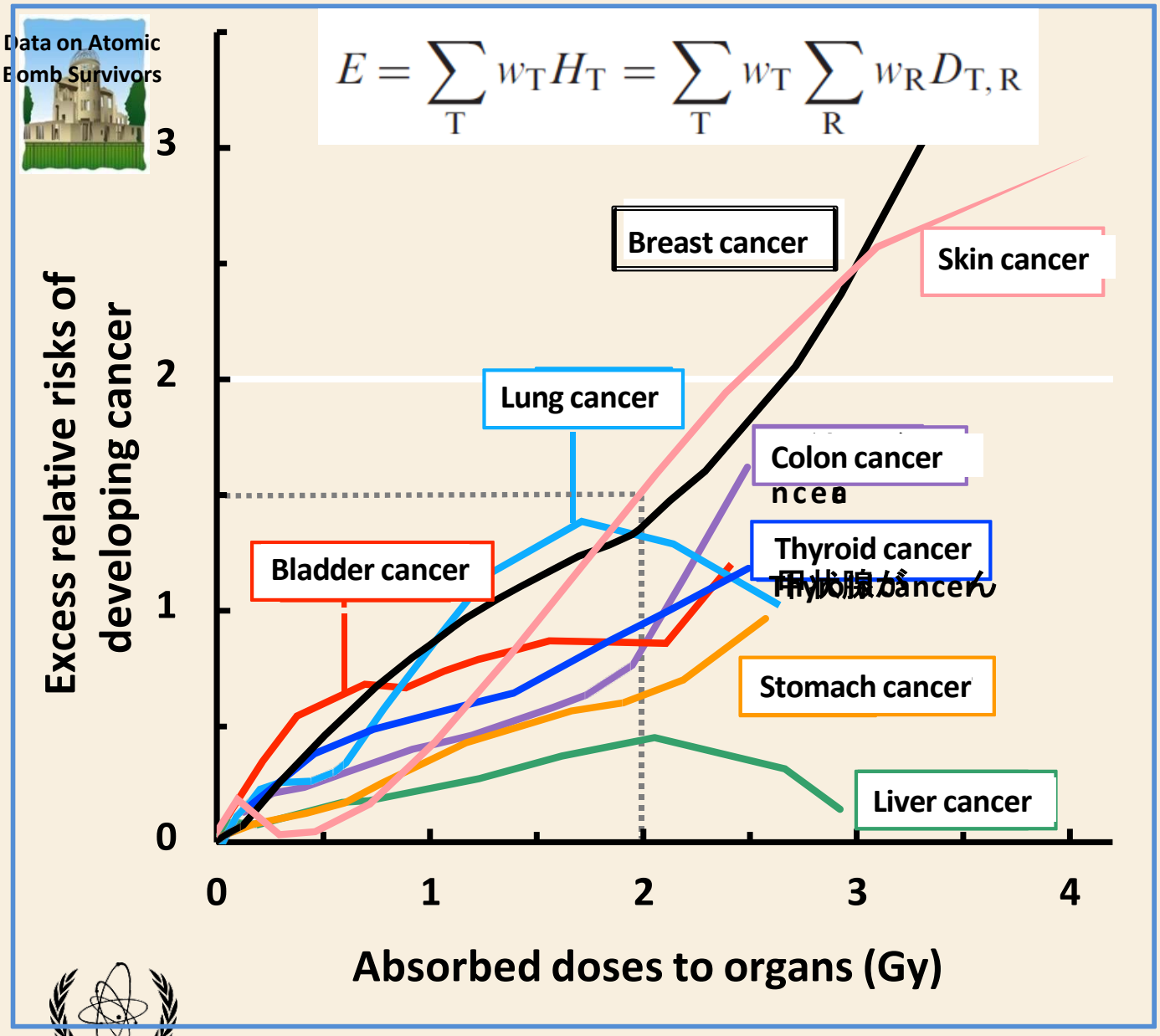
- There is ample evidence that cancer risk is dependent on:
  - ❑ the dose & dose rate
  - ❑ the age at exposure
  - ❑ (to a lesser extend) the gender
- In most cases, those exposed at an early age are more susceptible than those exposed at later times
- females are slightly more susceptible than males

Since not all radiation exposures concern the whole body but only a region or just a part of the body, tissue weighing factors (w_T) should be taken into account

$$E = \sum_T w_T H_T = \sum_T w_T \sum_R w_R D_{T,R}$$

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 due to Acute External Exposure

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

$$RR = \frac{R_r}{R_0}$$

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 and Leukemia

Difference in Radiosensitivity by Age

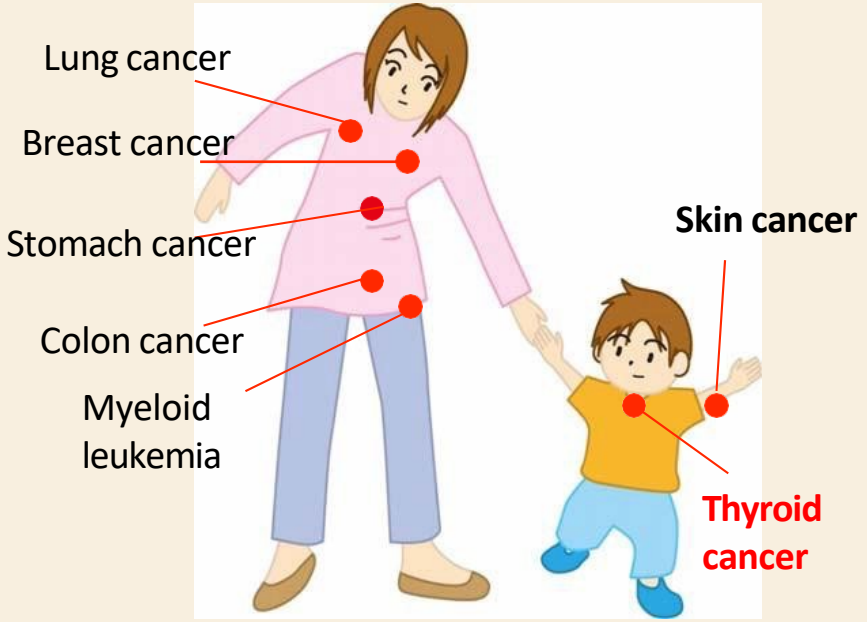
Children are NOT small adults.

	Effective dose coefficients for I-131*1 (mSv/Bq)	**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: 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

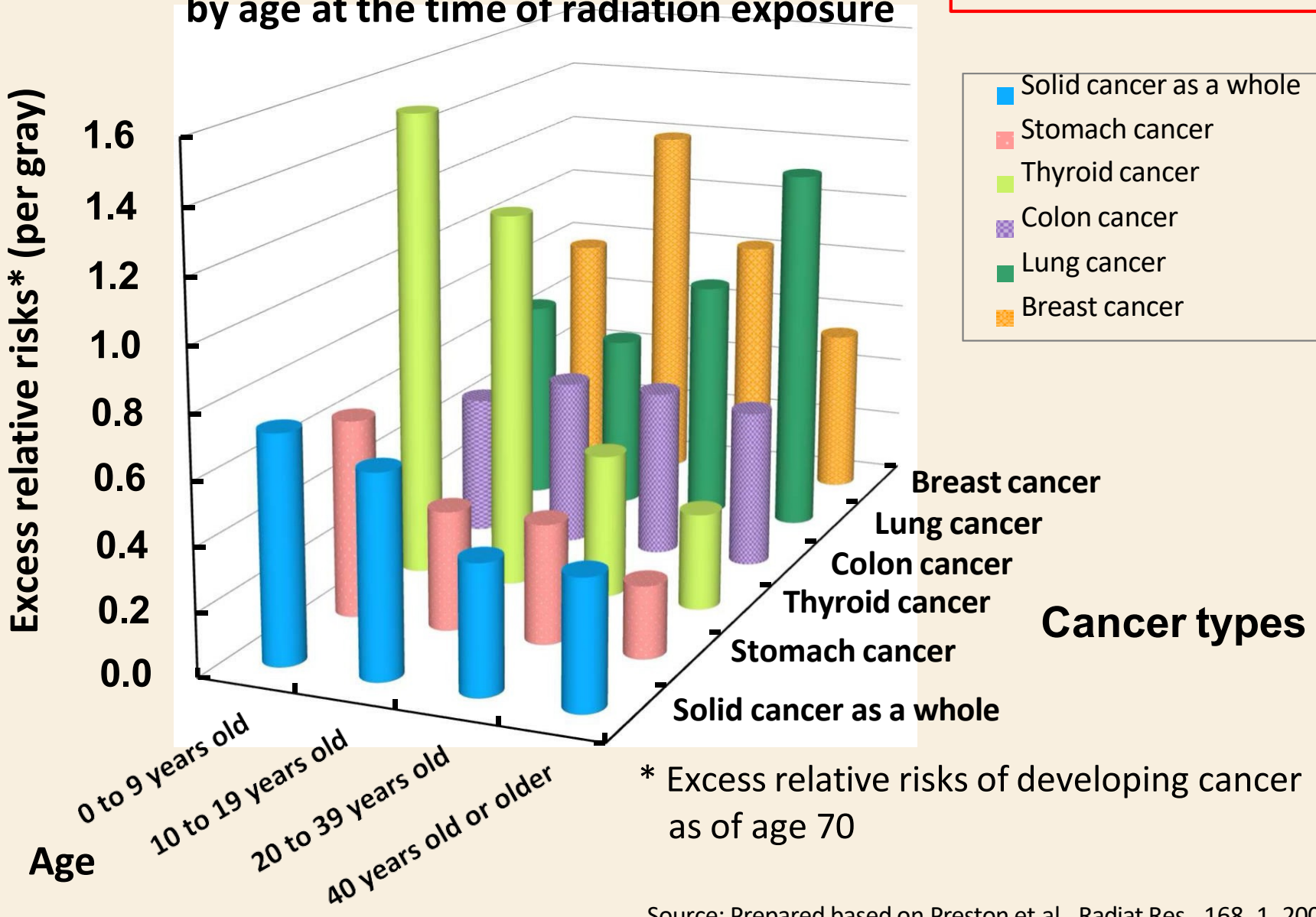
Cancer due to Acute External Exposure

Ages at the Time of Radiation Exposure and Cancer Types

Data on Atomic Bomb Survivors

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

$$ERR = RR - 1$$



* Excess relative risks of developing cancer as of age 70

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

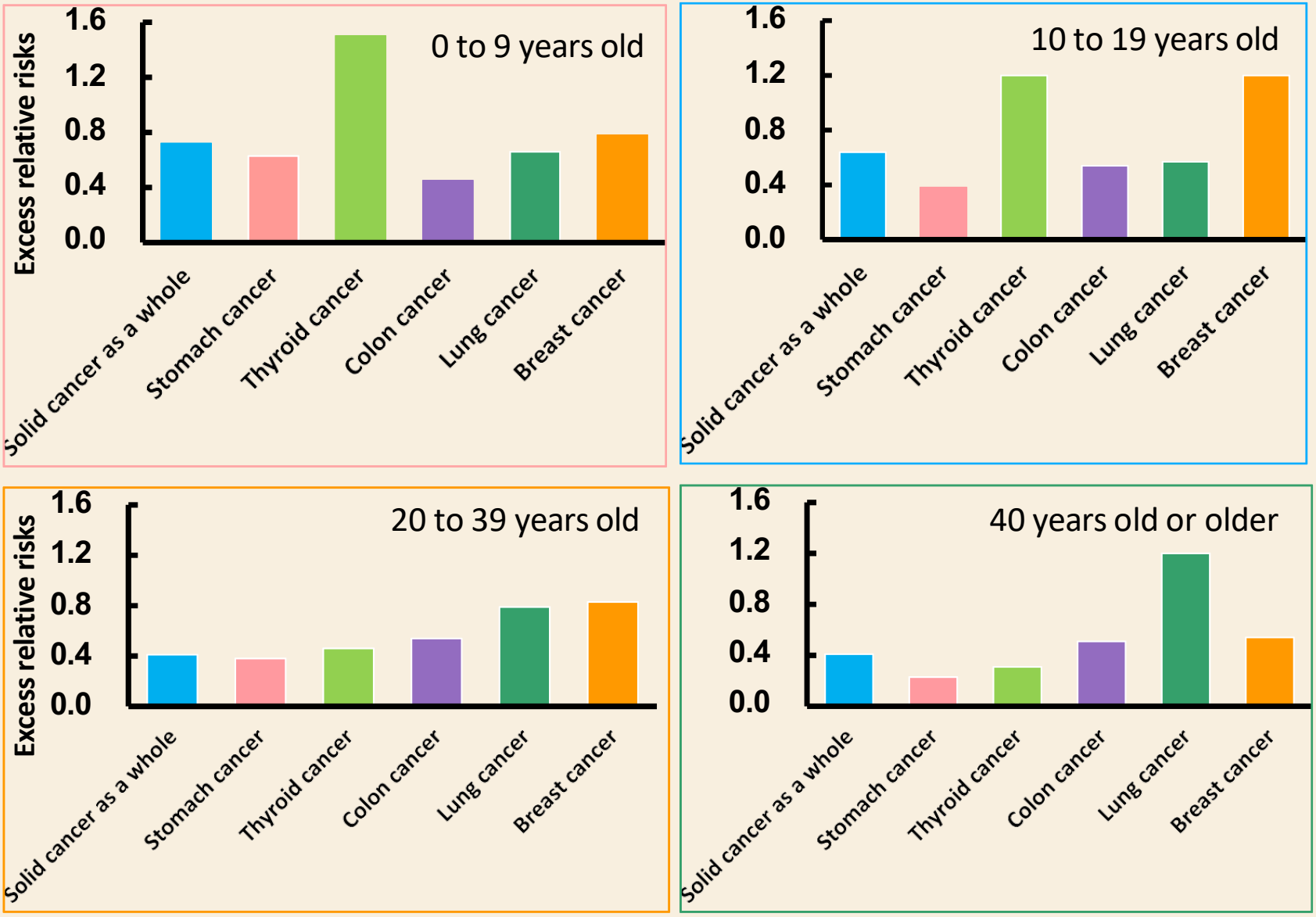
Cancer due to Acute External Exposure

Oncogenic Risks by Age at the Time of Radiation Exposure

Data on Atomic Bomb Survivors

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

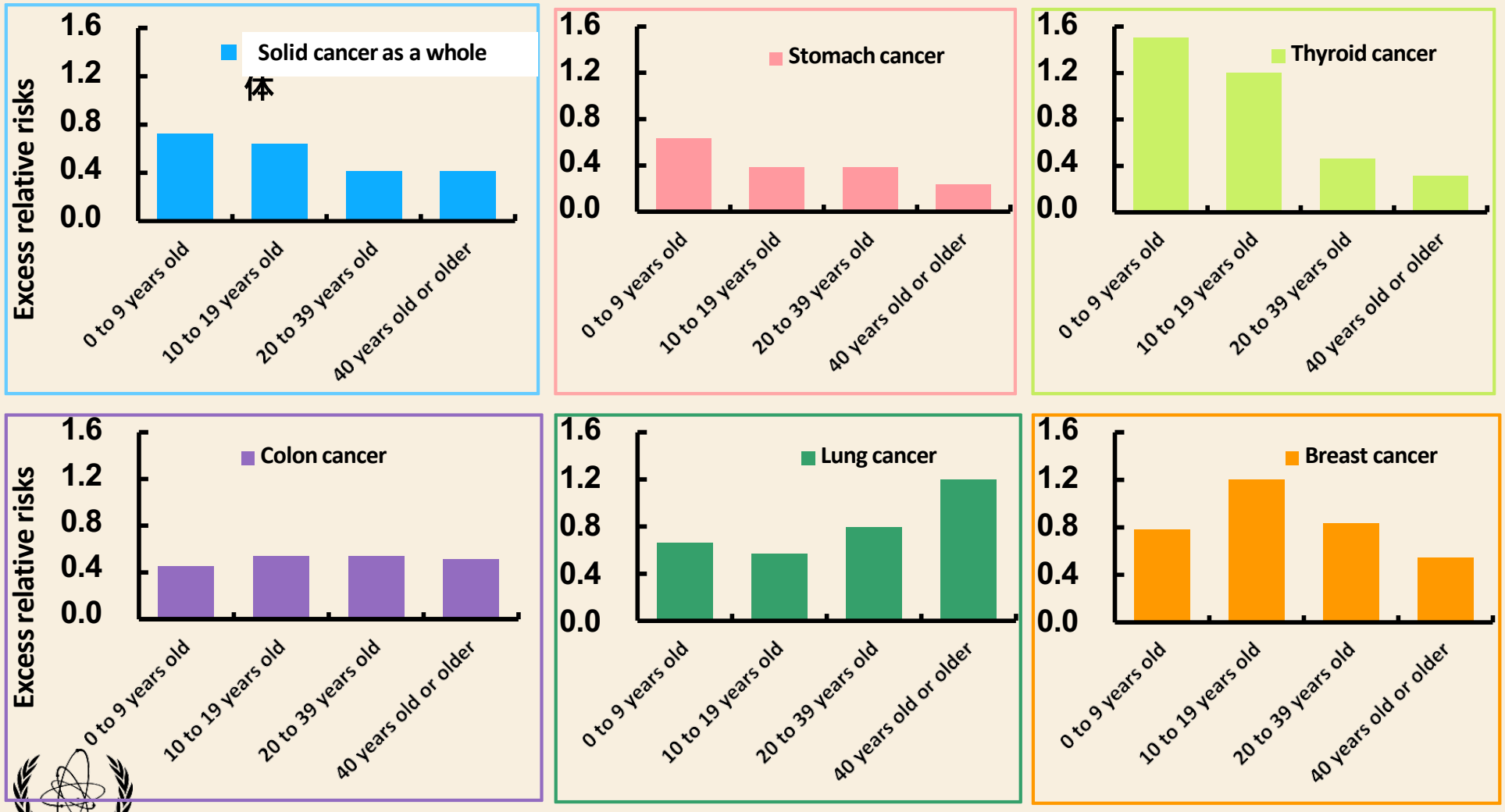
Cancer due to Acute External Exposure

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

Data on Atomic Bomb Survivors

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

6.3 CARCINOGENESIS (STOCHASTIC)

F. Lifetime attributable risk of cancer incidence from BEIR VII, (2006)

Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy

males	age of exposure (y)				
	5	15	30	50	70
Stomach	65	46	28	25	14
Colon	285	204	125	113	65
Liver	50	36	22	19	8
Lung	261	180	105	101	65
Prostate	80	57	35	33	14
Bladder	177	127	79	76	47
Other	672	394	198	140	57
Thyroid	76	33	9	1	0.1
All solid	1667	1076	602	507	270
Leukemia	149	105	84	84	73
All cancers	1816	1182	686	591	343

females	age of exposure (y)				
	5	15	30	50	70
Stomach	85	61	36	32	19
Colon	187	134	82	73	45
Liver	23	16	10	9	5
Lung	608	417	242	230	147
Breast	914	553	253	70	12
Uterus	42	30	18	13	5
Ovary	87	60	34	25	11
Bladder	180	129	79	74	47
Other	719	409	207	148	68
Thyroid	419	178	41	4	0.3
All solid	3265	1988	1002	678	358
Leukemia	112	76	63	62	51
All cancers	3377	2064	1065	740	409

These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a DDREF of 1.5, except for leukemia, which is based on a linear-quadratic model

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6.3 CARCINOGENESIS (STOCHASTIC)

F. Lifetime attributable risk of cancer mortality from BEIR VII, (2006)

Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy

males	age of exposure (y)				
	5	15	30	50	70
Stomach	34	25	16	13	8
Colon	139	99	61	57	36
Liver	37	27	16	14	8
Lung	264	182	107	104	71
Prostate	15	10	7	7	7
Bladder	38	27	17	17	15
Other	255	162	94	77	36
All solid	781	533	317	289	181
Leukemia	71	70	64	71	69
All cancers	852	603	381	360	250

females	age of exposure (y)				
	5	15	30	50	70
Stomach	48	34	21	19	13
Colon	86	62	38	35	25
Liver	20	14	9	8	5
Lung	534	367	213	204	140
Breast	214	130	61	19	5
Uterus	10	7	4	3	2
Ovary	47	34	20	18	10
Bladder	51	36	23	22	19
Other	287	179	103	86	47
All solid	1295	862	491	415	265
Leukemia	52	52	51	54	52
All cancers	1347	914	542	469	317

These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a DDREF of 1.5, except for leukemia, which is based on a linear-quadratic model

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6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis: risk models

Comparisons of:

- **Japanese data of A-bomb survivors**
- **experiments with animal models**
- **epidemiological studies including { multiple medical and chronic exposures**

have demonstrated that the risk calculated in proportion of the dose differs.

Both BEIR and UNSCEAR committees considered that there is a dose-rate effect for low energy transfer radiation:

Fewer malignancies are induced if a given dose is spread out over a period of time at low dose rate than if it is delivered in an acute exposure

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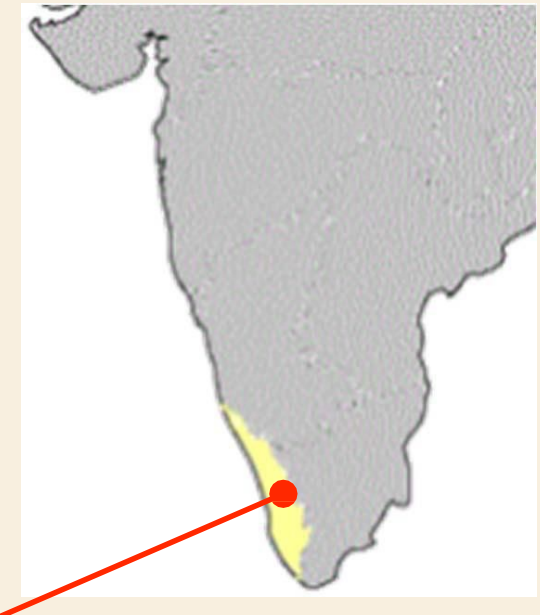
Carcinogenesis due to Chronic Exposure

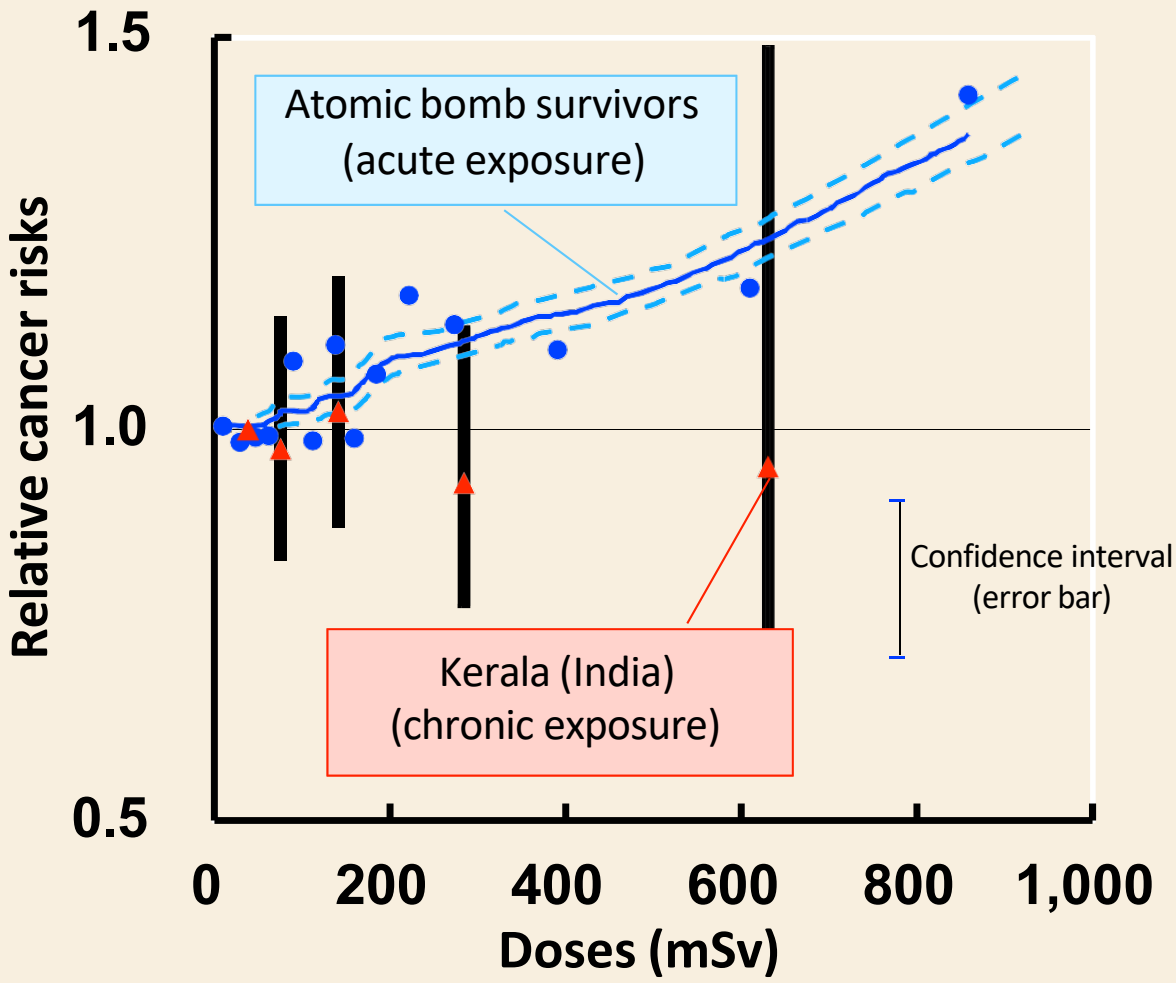
Effects of Long-Term Low-Dose Exposure

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

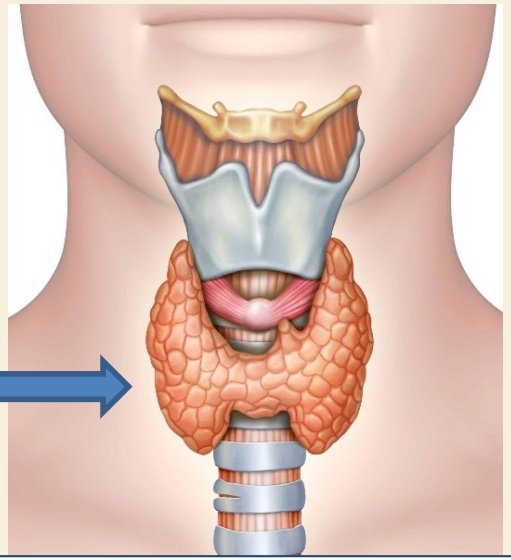


msv: millisieverts

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
(Chronic metabolism)



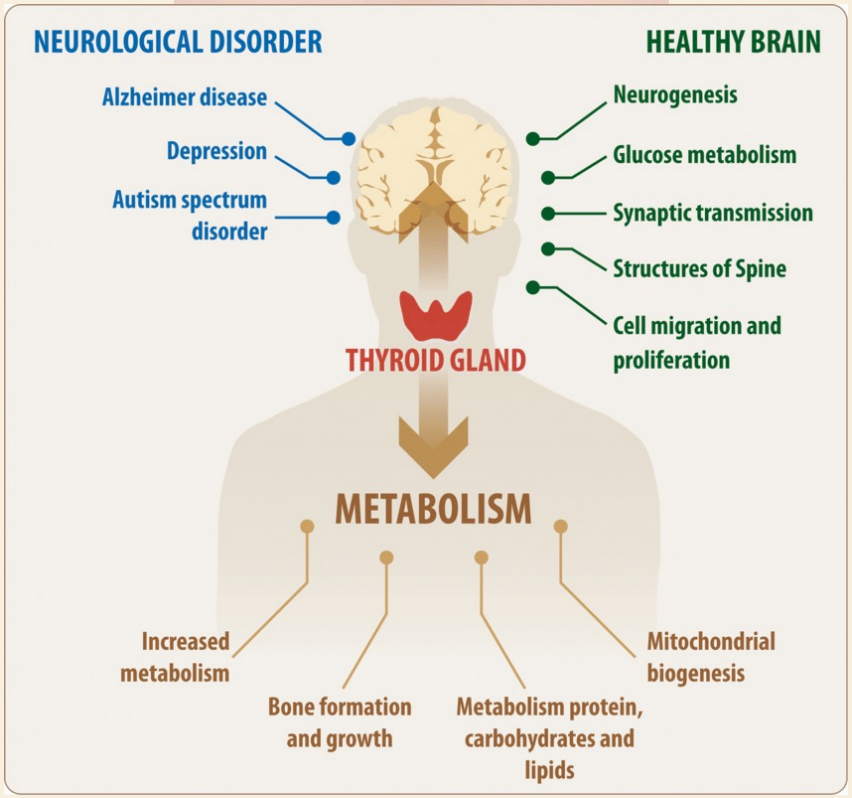
The thyroid is located in the lower center of the neck (below the Adam's apple).

- The thyroid takes in dietary **iodine**, produces thyroid hormones, and secretes them into the blood.
- Iodine = Raw material of thyroid hormones
- Iodine intake Dietary Reference Intakes 2015:

  Estimated average requirement: 0.095 mg

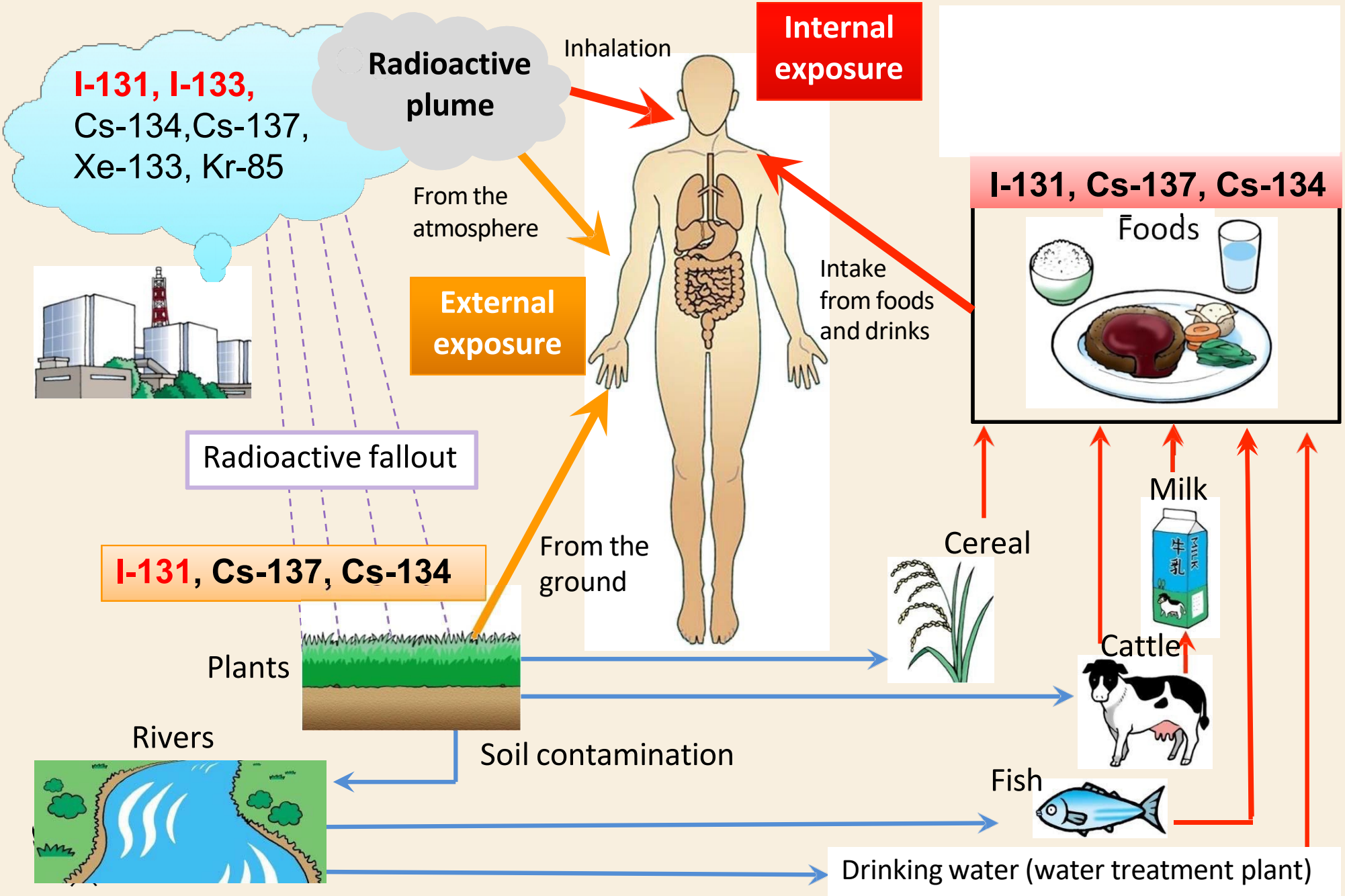
  Recommended intake: 0.13 mg

Actions of thyroid hormones



Nuclear Disaster

Effects of Reactor Accidents



Basic Information on Thyroid

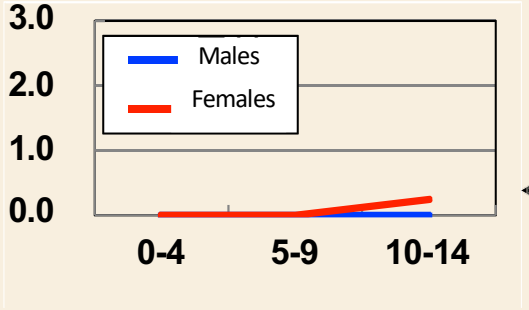
Characteristics of Thyroid Cancer

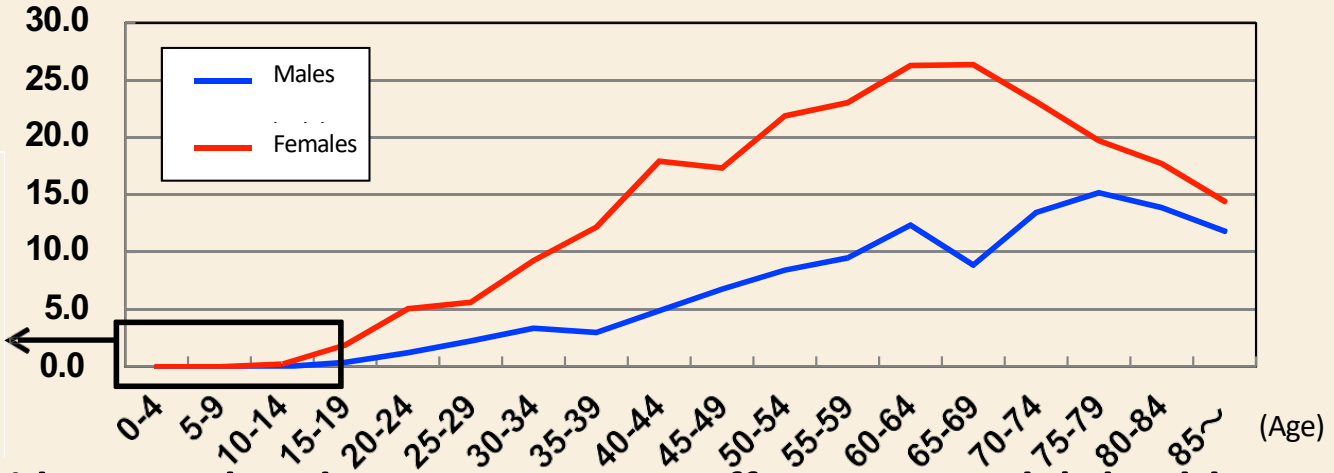
- **The incidence rate of thyroid cancer is higher for females** (estimated age-adjusted incidence rate (nationwide) (against 100,000 people), 2010).

  ⇒**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.





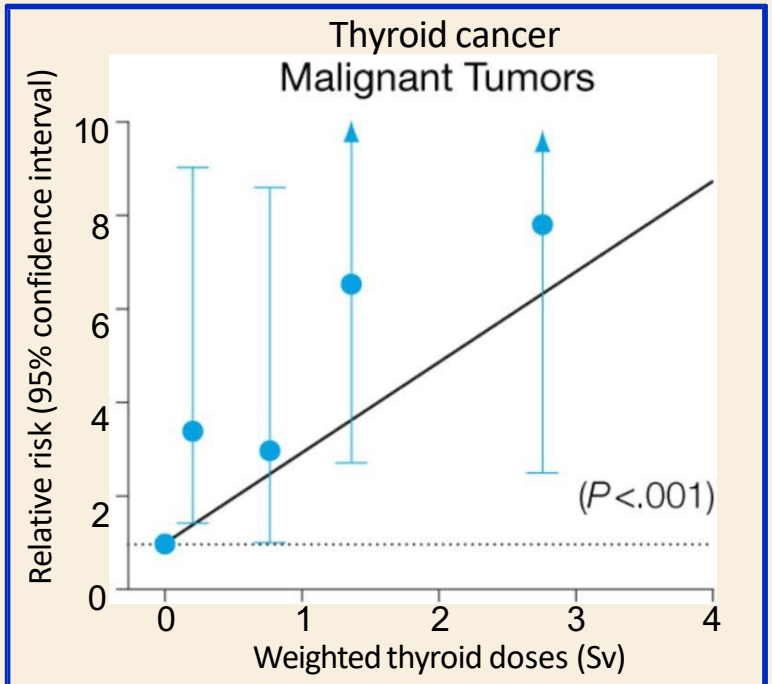
- **There is also occult thyroid cancer that does not exert any effects on people's health throughout their lifetime.**
- **In many cases, prognosis after surgery is good** (crude cancer mortality rate by organ/tissue (against 100,000 people), 2010).

	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)

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.

Quick aside - statistics

Calculating the Odds Ratio (OR)

	Disease (Case)	No Disease (Control)
Exposed	A	B
Unexposed	C	D

$$OR = \frac{\text{Odds that a case was exposed } (A/C)}{\text{Odds that a control was exposed } (B/D)} = \frac{AD}{BC}$$

	Outcome: Yes	Outcome: No
Predictor: Yes	A	B
Predictor: No	C	D

$$RR = \frac{(A/(A+B))}{(C/(C+D))}$$

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Relative Risk = Probability of Getting Disease if exposed / Probability of Getting disease if not exposed

Relative Risk = Probability of Outcome if on drug / Probability of Outcome if on placebo

Odds Ratio = Odds that the diseased were exposed / Odds the controls were exposed

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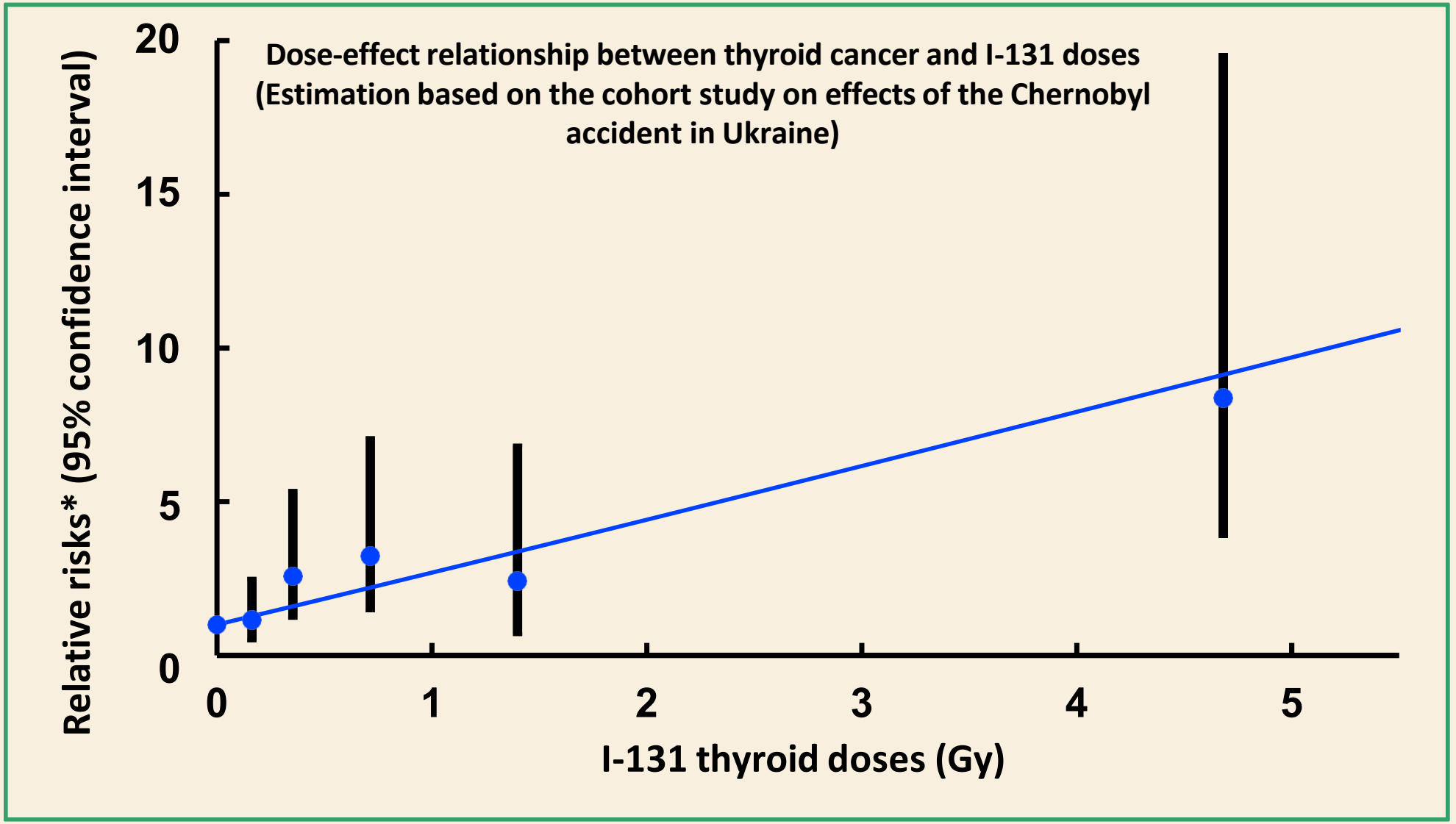
Basic Information on Thyroid

Relationship between Thyroid Cancer and Doses - Chernobyl Accident -



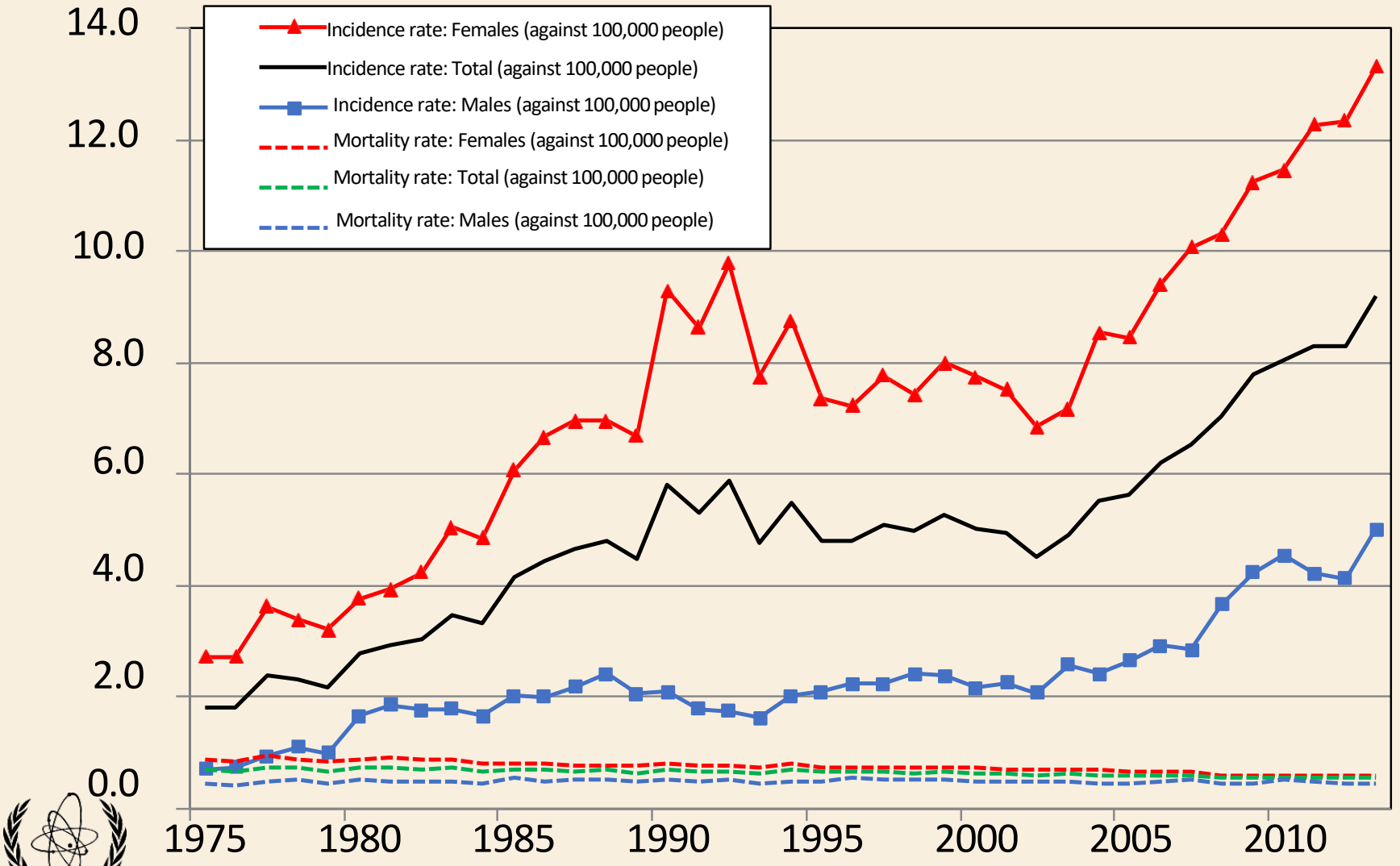
Source: Prepared based on Brenner et al., Environ Health Perspect 119, 933, 2011

* **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.

Basic Information on Thyroid

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

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
Unadministered	2.5 (0.8-6.0)	9.8 (4.6-19.8)
Administered	0.1 (-0.3-2.6)	2.3 (0.0-9.6)

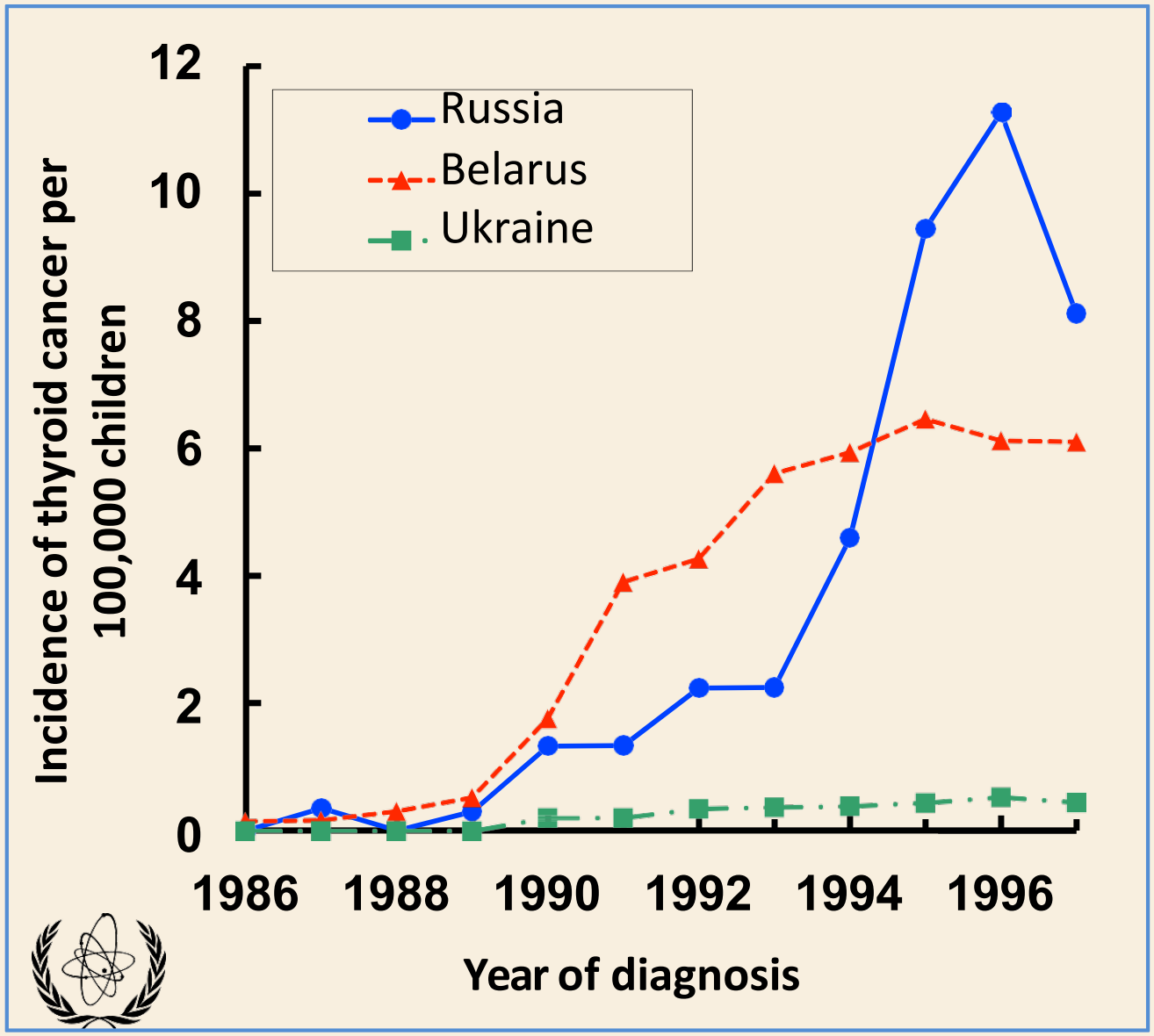
Source: Cardis et al., JNCI, 97, 724, 2005

* 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.

Basic Information on Thyroid
Thyroid Exposure

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

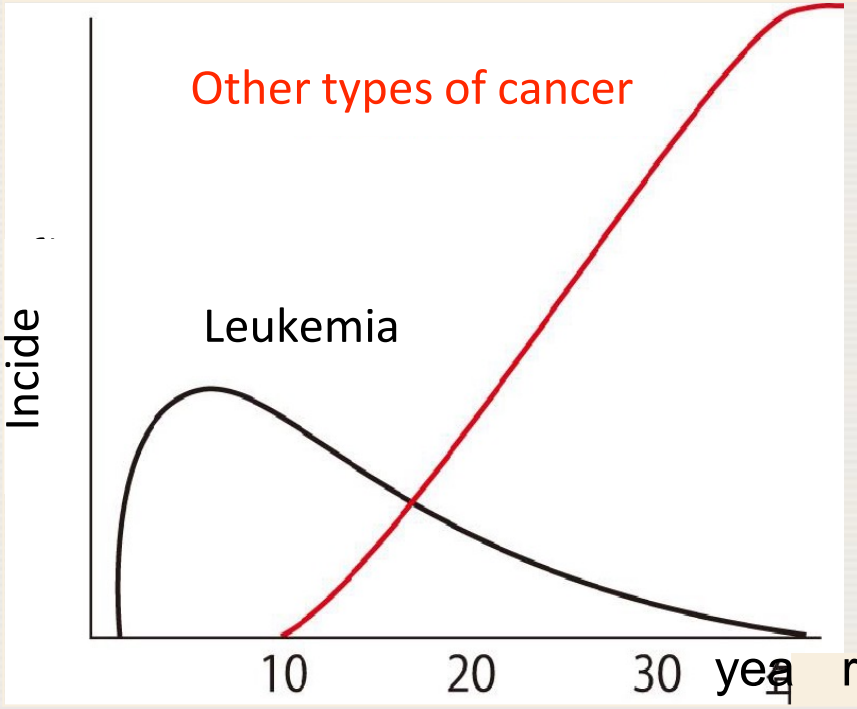
6.3 TYPE OF RADIATION DAMAGE

F. Carcinogenesis: risk models

Facts About Radiation-Induced Cancer:

- **Single exposure can be enough** to elevate cancer incidence several years later
- There is **no radiounique cancer**
- Breast, bone marrow, and thyroid are **especially radiosensitive**
- The most **prominent radiogenic tumor** is leukemia
- Solid tumors have a latent period of 10 years
- Leukemia's latent period is thought to be about 2-5 years

- **Age of irradiated individual is most important factor**
- Percentage increase in cancer incidence varies between organs and types of cancers



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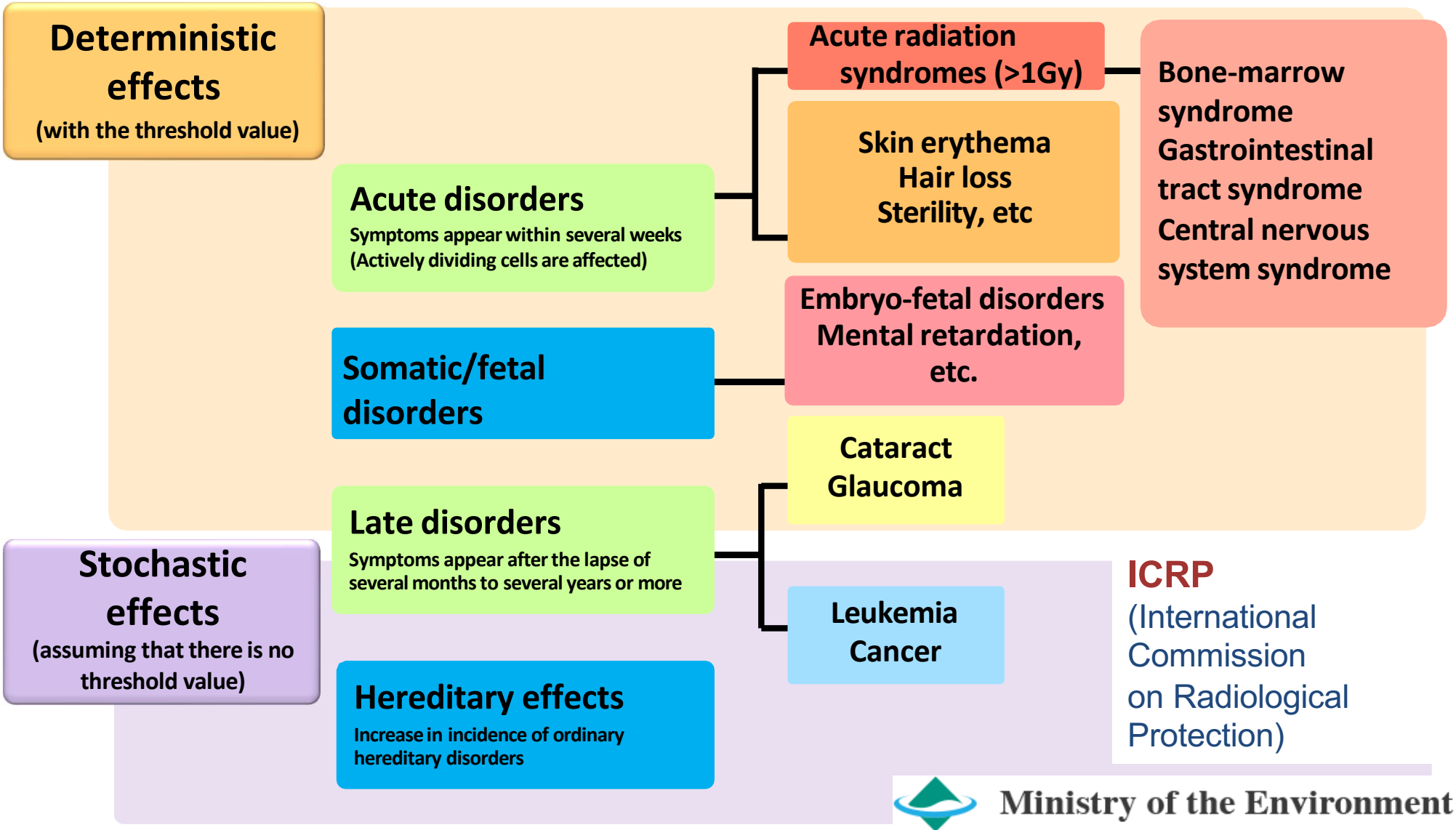
Types of Irradiation Effects

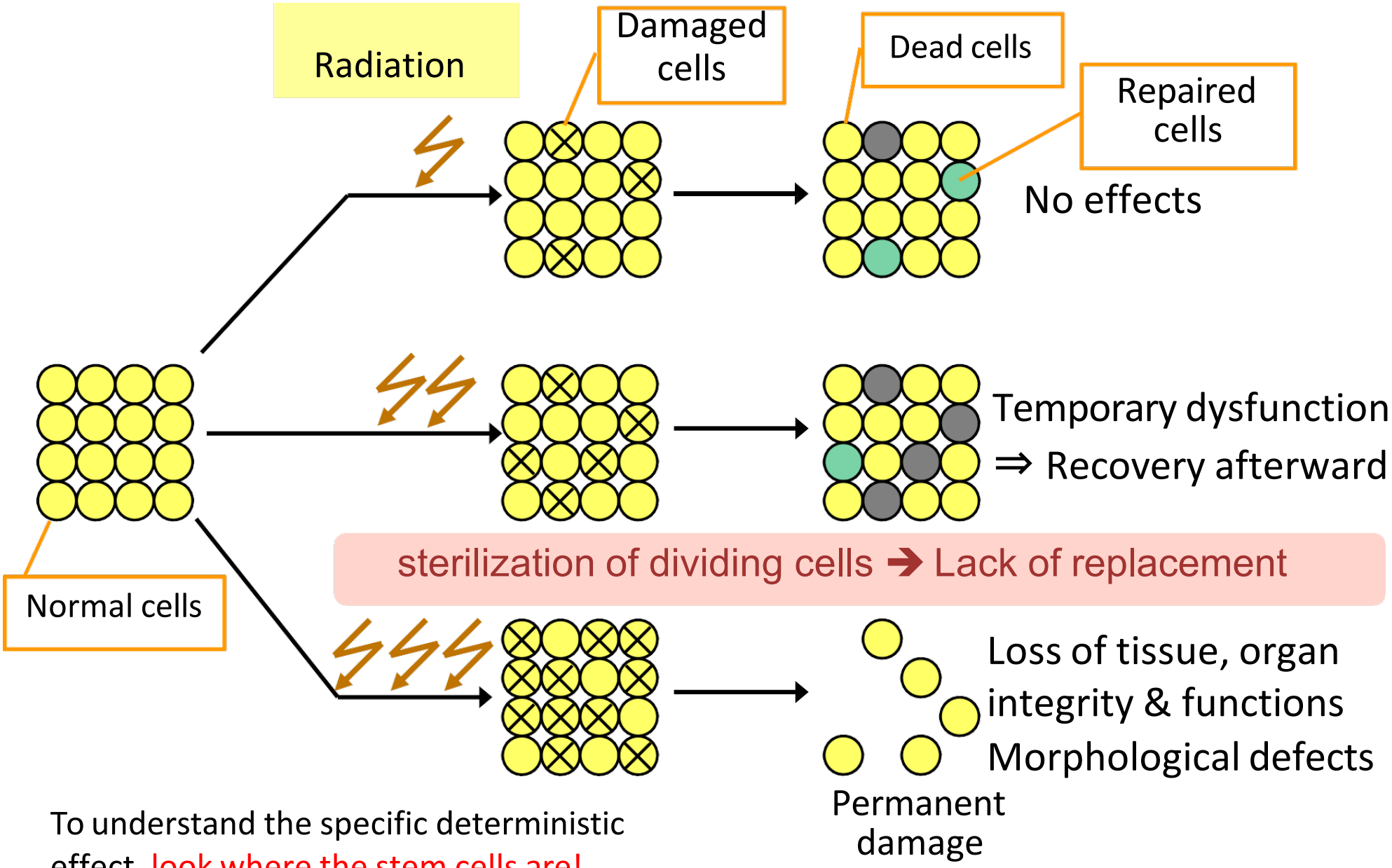
► Consideration is to be given to whether any health effects arise after radiation exposure and what effects, if any, the amount of radiation, parts exposed to radiation (whole-body exposure or local exposure), and exposure modes (acute, chronic or fractionated exposure).



ICRP
(International Commission on Radiological Protection)

Ministry of the Environment
Government of Japan
環境省

Deterministic Effects

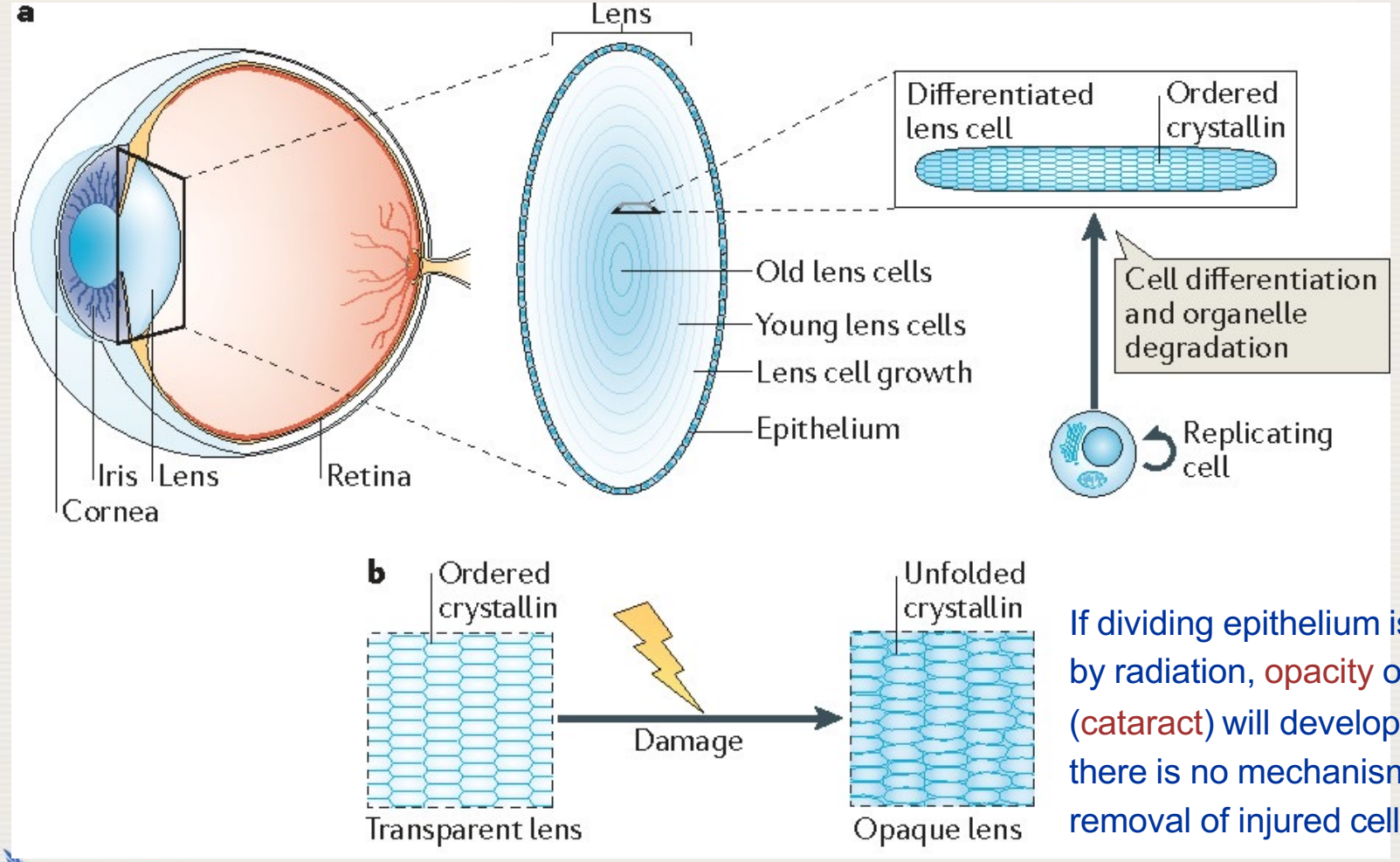


To understand the specific deterministic effect, look where the stem cells are!

6.3.G TYPE OF RADIATION DAMAGE

Radiation-induced cataract formation

Lens of the eye are very sensitive to radiation. Threshold dose is **~0.5 Gy**, high doses of radiation (**>6 Gy**) lead to total blindness



If dividing epithelium is injured by radiation, opacity of the lens (cataract) will develop because there is no mechanism for removal of injured cells

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Fig.2 retrieved and adapted from Toyama, Brandon H. and Martin WHetzer. "Protein homeostasis: live long, won't prosper." *Nature Reviews Molecular Cell Biology* 14 (2012): 55-61.

6.3.G TYPE OF RADIATION DAMAGE

Radiation-induced cataract formation

- The lens of the eye contains transparent lens fibres and a small number of dividing cells limited to the pre-equatorial region of the epithelium within the lens capsule
- During life, the progeny of these mitotic cells differentiate into lens fibres and accrete at the equator
- It has been known for many years that the lens of the eye is very sensitive to radiation. Radiation even may lead to total blindness
- If dividing epithelium is injured by radiation, opacity (spots or cloudiness) of the lens (cataract) will develop because there is no mechanism for removal of injured cells and abnormal fibres

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6.3.G TYPE OF RADIATION DAMAGE

G. Radiation-induced cataract formation

Moderate doses of radiation can produce cataracts in a few individuals, with the incidence increasing to 100 % in individuals exposed to a single dose of **2 Gy or higher**

- The frequency of cataracts varies with exposure to:
  - chronic doses – lower frequency
  - acute doses – higher frequency
- The time period between exposure and the appearance of cataract might vary between about 6 months and 30 years. The radiation dose greatly influences the latent period
- The higher the dose is, the shorter the latent period
- Location within the lens can suggest etiology (what caused it)
- **Posterior pole (back) = likely due to radiation exposure**
- **Nuclear cataracts (center) = unlikely due to radiation exposure**

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(classes April 3rd, 8th, 15th, ?)

3. Type of radiation damage

A. Stochastic and deterministic (non-stochastic) effects
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D. Total body irradiation and Acute Radiation Syndrome
E. Equivalent and Effective Dose
F. Carcinogenesis (Risk models)
G. Cataractogenesis
H. Skin effects
I. Infertility
J. Fetal Irradiation

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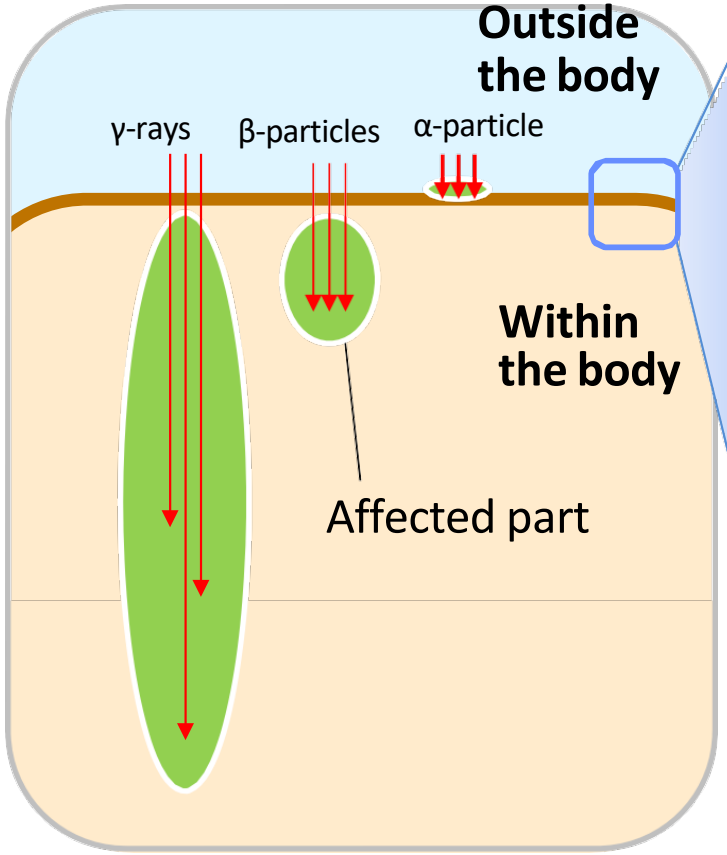
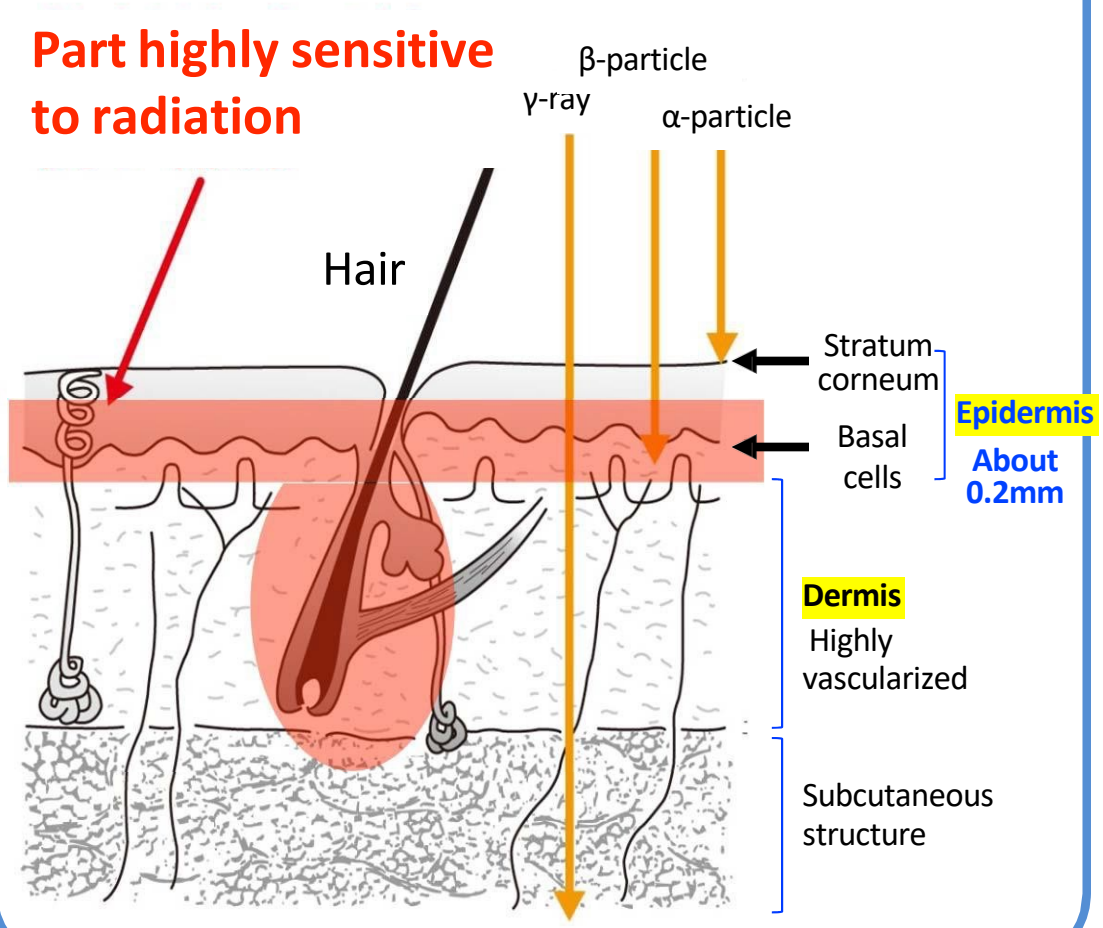
Exposure Routes

External Exposure and Skin



Skin structure:



6.3 TYPE OF RADIATION DAMAGE

H. Radiation-induced skin reaction

The skin consists of a :

relatively thin epidermis

- renews rapidly (15-30 days)

much thicker underlying dermis

- is highly vascularised
- contains
  - connective tissue
  - hair follicles
  - sweat glands
  - sebaceous glands
  - nerve endings

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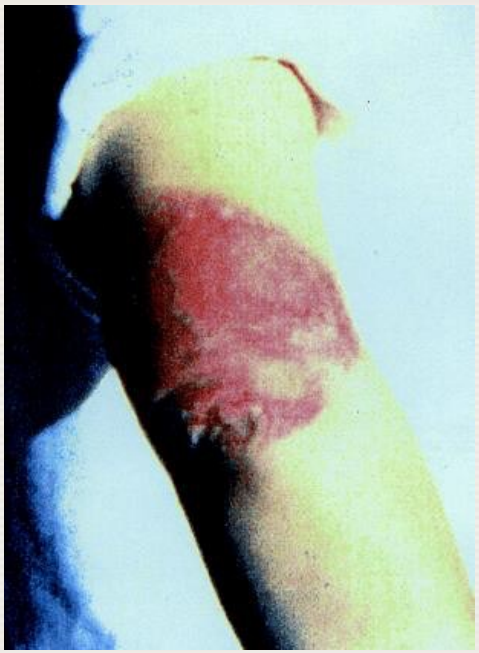
6.3 TYPE OF RADIATION DAMAGE

H. Radiation-induced skin reaction

- A wide-variety of expressions of radiation-induced skin effects have been described.
- Epilation (loss or removal of hair) may be present as an early effect.
- The most common is the erythema (reddening of the skin due to inflammation)



- early transient erythema similar to sunburn
- occurs within a few hours after irradiation
- reaches a peak value within 24 hours

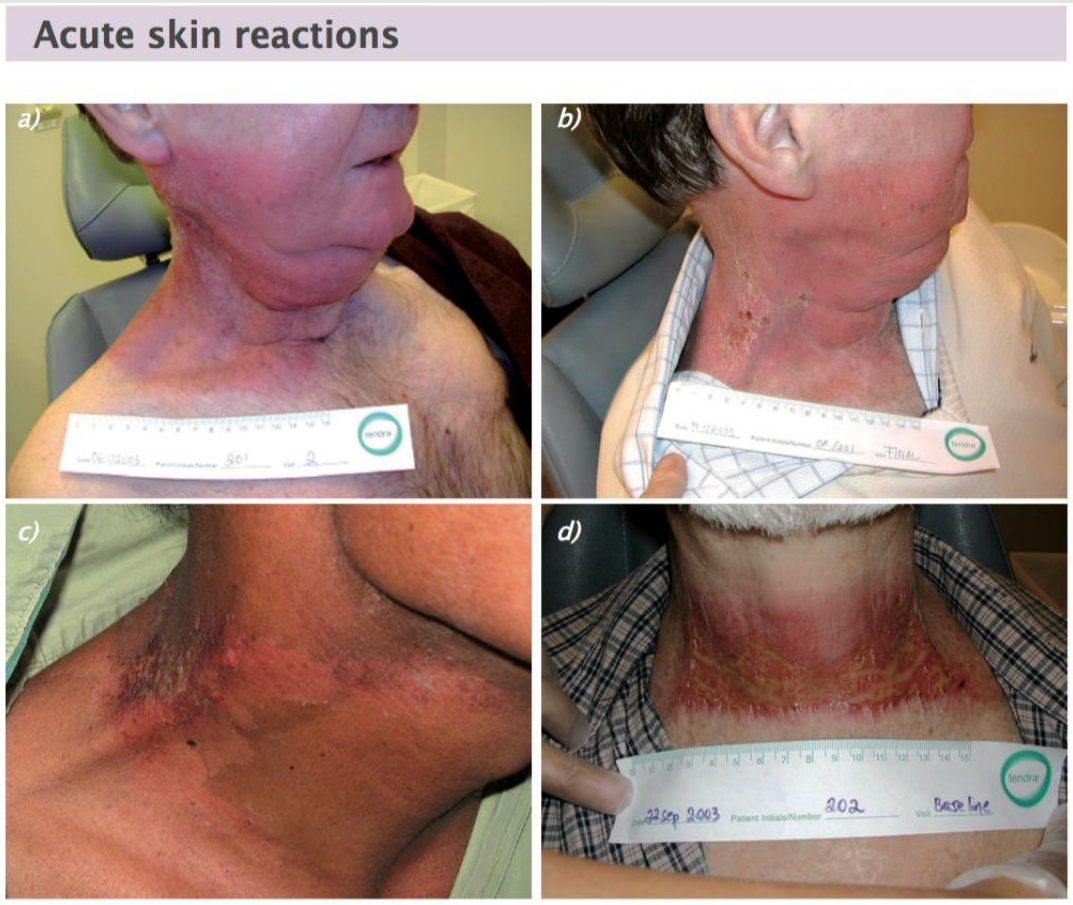
- Main severe erythema develops after a latent period of 8-10 days, mainly due to an inflammatory reaction of the skin
- It is bright red in colour, limited to the radiation field, and accompanied by a sensation of heat and itching

Demarcated erythema above right elbow at 3 weeks after radiofrequency cardiac catheter ablation (Koenig et al 2001)

https://www.iaea.org/resources/rpop/health-professionals/radiology/erythema

6.3 TYPE OF RADIATION DAMAGE

H. Radiation-induced skin reaction



- Transient erythema in human skin occurs after single doses **greater than 2 Gy**
- Main erythema occurs at doses **greater than about 7 Gy**
- Moist desquamation and ulceration occur after single doses of **15 to 20 Gy**

Acute radiation skin reactions start as erythema (a). If the reaction continues, dry desquamation occurs (b and c), which may be followed moist desquamation and ulceration (d). *Figures courtesy of Lena Sharp*

- After the desquamation reaches a peak value, recovery and regeneration of the epidermis will start from islands of surviving cells in the regenerating (basal) layer
- The recovery depends on the dose received and the volume (area) of skin irradiated

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6.3 TYPE OF RADIATION DAMAGE

H. Radiation-induced skin reaction

SKIN EFFECTS AFTER A SINGLE EXPOSURE (Wagner et al., 1994)

Effect	Acute exposure threshold (Gy)	Onset	Peak
Temporary epilation	3	~3 weeks	
Permanent epilation	7	~3 weeks	
Early transient	2	~ hours	~24 hours
Erythema			
Main erythema	6	~10 days	~2 weeks
Dry desquamation	10	~4 weeks	~5 weeks
Moist desquamation	15	~4 weeks	~5 weeks
Secondary ulceration	20	>6 weeks	
Late erythema	15	~6–10 weeks	
Dermal necrosis	18	>10 weeks	
Telangiectasia	12	> 52 weeks	

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G. Cataractogenesis
H. Skin effects
I. Infertility
J. Fetal Irradiation

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6.3 TYPE OF RADIATION DAMAGE

I. Infertility

The reproductive organs (gonads) of the human species are

- the testis (in males)
- the ovaries (in females)

in which the gametes are developed

- spermatozoa (in males)
- the ovum (in females)

Radiation exposure to the gonads may lead to:

1. Temporary or permanent sterility
2. Hereditary effects in the offspring of the exposed individuals, depending on the dose

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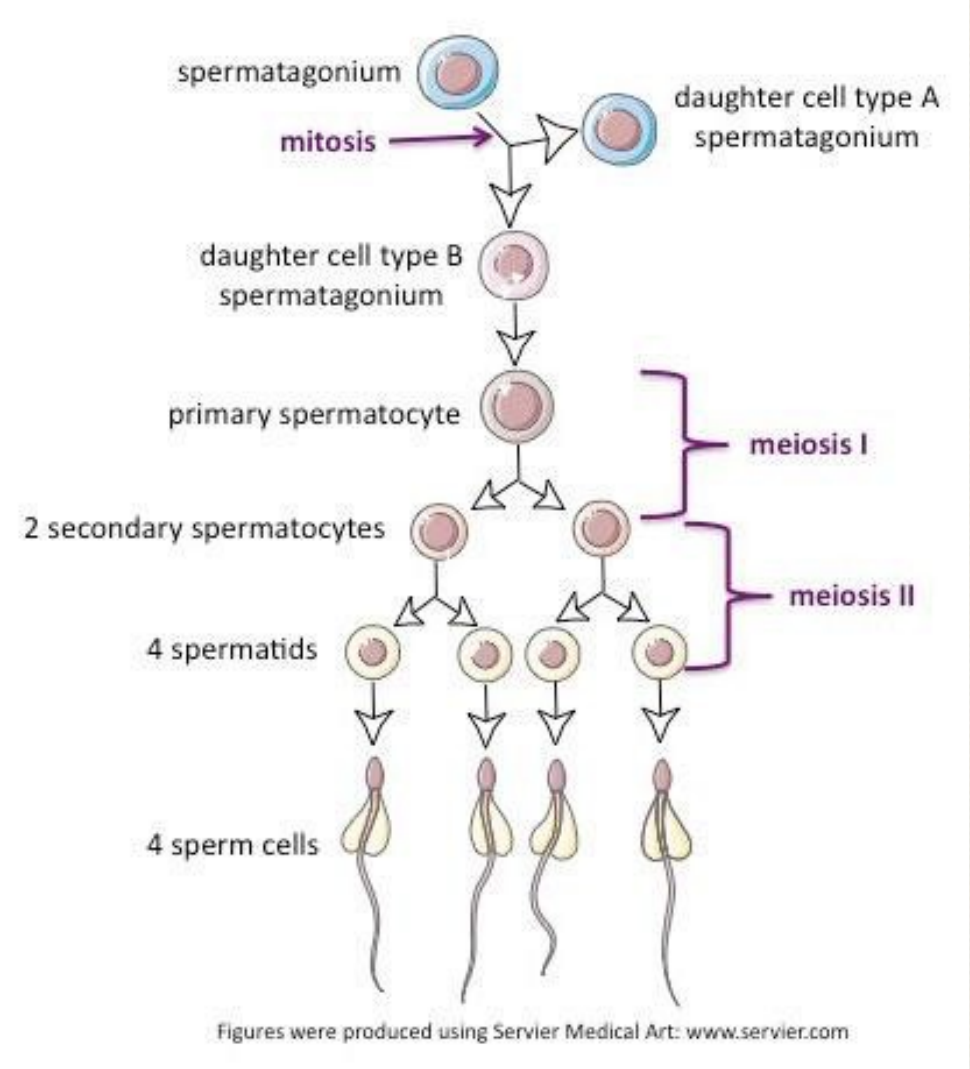
6.3 TYPE OF RADIATION DAMAGE

I. Infertility

Spermatogenesis:

- Spermatogonial stem cells proliferate to spermatogonia (type A and B), and then differentiate into spermatocytes, (primary and secondary)
- The spermatocytes undergo meiosis to become spermatids. Without further cell divisions, the spermatids differentiate into sperm cells.
- The whole process takes approximately 74 days in humans



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6.3 TYPE OF RADIATION DAMAGE

I. Infertility

Effect of irradiation on Spermatogenesis:

The primary effect of radiation on the male reproductive system is:

- damage
- depopulation of the spermatogonia eventually resulting in depletion of mature sperm in the testis

- The sensitivity of germ cells to a given dose of radiation is strongly related to the stage they are in at the time they are irradiated
- Recovery of spermatogenesis will occur from the stem cell compartment when the exposure is below the sterilisation dose.
- Depending on the dose, recovery to pre-irradiation levels of sperm might take 2 to 3 months up to several years

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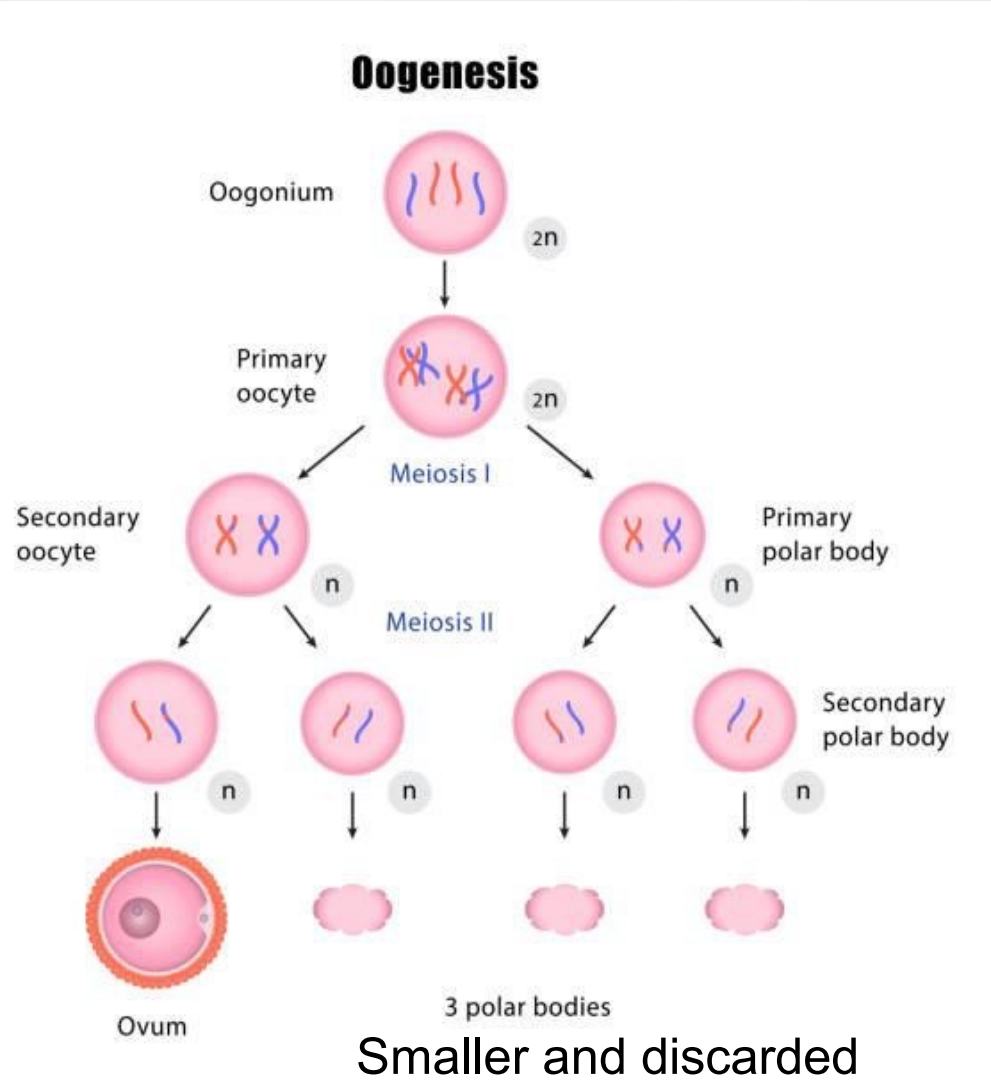
6.3 TYPE OF RADIATION DAMAGE

I. Infertility

Oogenesis:

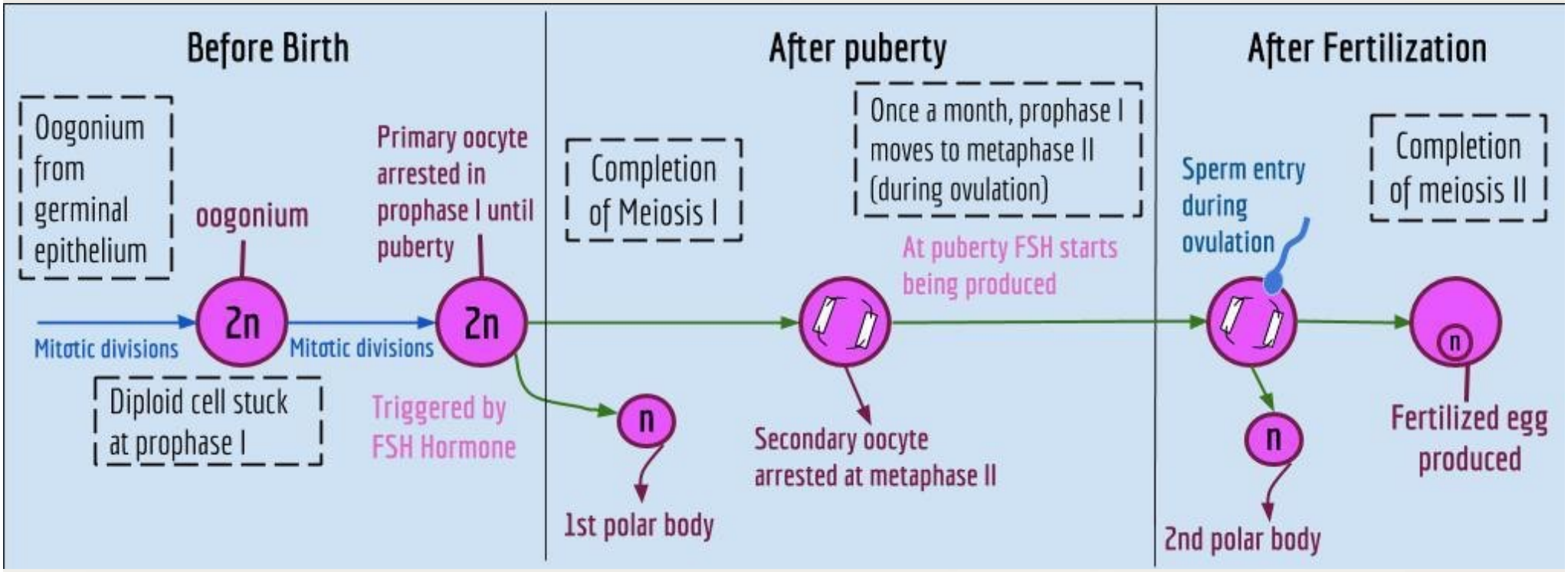
- The process in which primary oocytes develop into the ovum (egg cell)
- the female can only produce a limited number of egg cells since, after the foetal stage, oocytes no longer divide
- At birth a fixed number of oocytes are present and their number diminishes steadily with age
- Every month one mature egg cell (occasionally two or three) is released during the menstrual cycle



6.3 TYPE OF RADIATION DAMAGE

I. Infertility

Oogenesis



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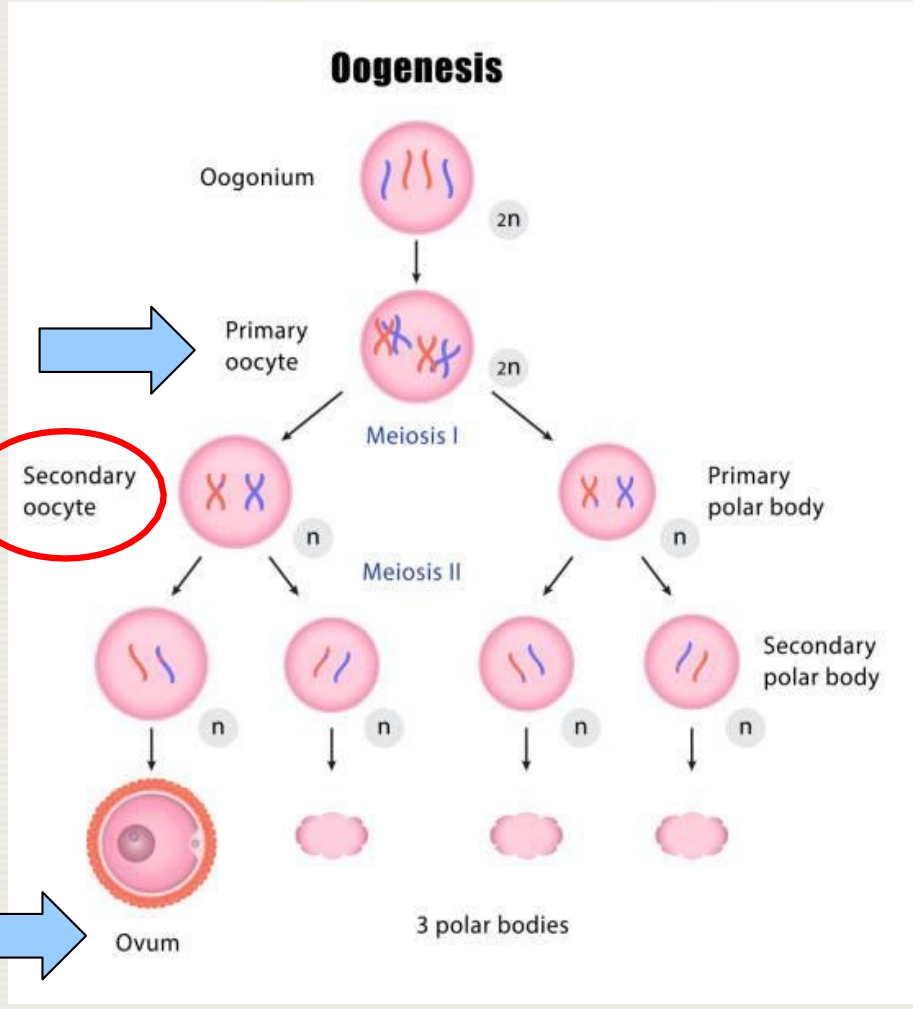
6.3 TYPE OF RADIATION DAMAGE

I. Infertility

Effect of irradiation on oogenesis:

- secondary oocytes are very sensitive to radiation
- The primary oocytes and the ovum are less sensitive
- In the case of radiation exposure of one or both of the ovaries it is recommended to delay a wanted pregnancy by at least 6 months



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6.3 TYPE OF RADIATION DAMAGE

I. Infertility

In males, a dose of

- 1.0 Gy leads to a temporary reduction in the number of spermatozoa
- 1.5 Gy leads to temporary sterility
- 2.0 Gy results in temporary sterility (for several years)
- **5.0 to 6.0 Gy** (acute) can produce permanent sterility

In females, a dose

- of 0.65 to 1.50 Gy will lead to a reduced fertility
- **greater than 6.0 Gy** produces permanent sterility

The “sterility” dose is smaller for older women who have fewer primary oocytes

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J. Fetal Irradiation

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6.3 TYPE OF RADIATION DAMAGE

J. Fetal irradiation

- Between conception and birth the foetus passes through three basic stages of development:
  - Pre-implantation (days 1 to 10).
  - Organogenesis (days 11 to 42).
  - Growth Stage or Fetal Period (days 43 to birth).
- Radiation is a known teratogen (i.e., causes birth defects).
- Effects of radiation on the fetus depend on two factors:
  - **Dose** to the fetus
  - **Stage of development** at the time of exposure
- Abortion to avoid the possibility of radiation induced congenital abnormalities should be considered only when the fetal dose has exceeded **0.10 Gy**. (ICRP- publication 84, studies on the Hiroshima children)

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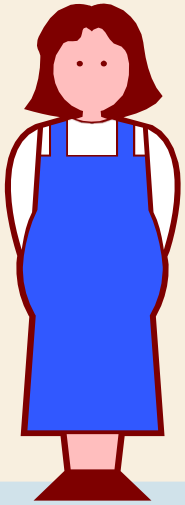
Effects on Fetuses

Deterministic Effects and Time Specificity



Period when important organs are formed
＝Period requiring careful attention to the use of drugs
＝Period when fetuses are vulnerable to radiation

Pre-implantation period
0 to 2 weeks after conception
Miscarriage (fetal death)

Organogenesis period
2 to 8 weeks after conception
Dysplasia (malformation, neonatal death)

Early fetal period
8 to 15 weeks after conception
Stunted growth or intellectual disability

Late fetal period
15 weeks after conception to delivery
Congenital defects, Cancer induction.

The threshold dose is 0.1 Gy or more

In the later stages of pregnancy, the threshold dose may be higher

* The time generally considered as two-week pregnancy is equivalent to zero weeks after conception.

6.3 TYPE OF RADIATION DAMAGE

J. Fetal irradiation

Embryos in the **pre-implantation stage** are very radiosensitive and radiation damage inevitably will lead to:

- death of the conceptus
- early spontaneous abortion

Those embryos, however, which survive this stage, develop normally

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6.3 TYPE OF RADIATION DAMAGE

J. Fetal irradiation

Radiation exposure during the period of major **organogenesis** will lead to the development of abnormalities, mostly related to the:

- central nervous system (brain defects and/or intellectual disability, formerly termed mental retardation)
- skeleton
- organ systems

- However, in most cases the damage to the fetus is too severe for survival, ultimately resulting in neonatal death
- During this period the developing brain is very sensitive to radiation

Irradiation during the **fetal period** (after week 8) results in an incidence of gross organ malformation abnormalities and intellectual disability (the risk of severe intellectual disability increases rapidly to a value of 40 % at 1 Gy)

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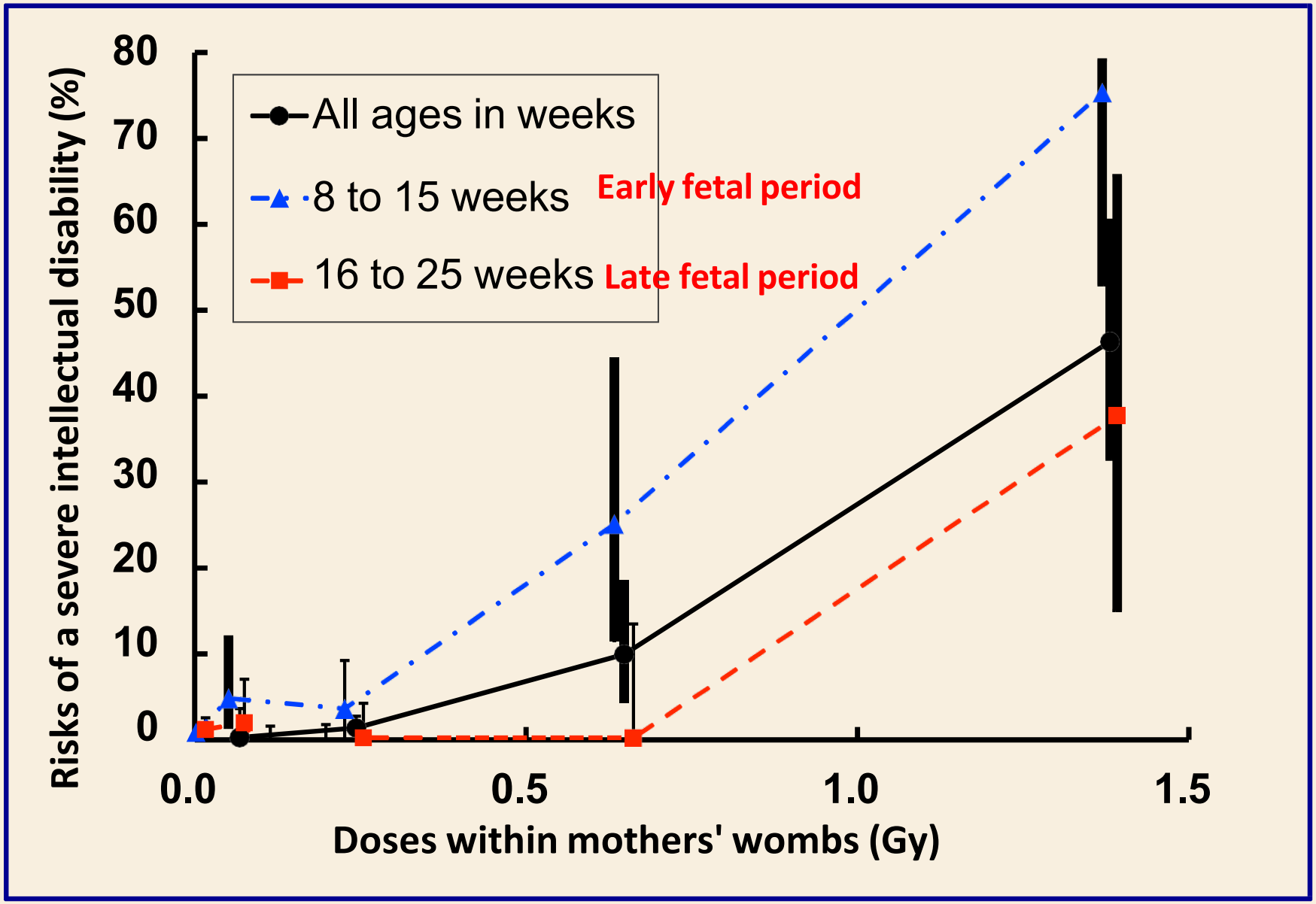
Effects on Fetuses

Intellectual disability

Data on Atomic Bomb Survivors



Source: Prepared based on "Physical and Mental Development of Children Exposed to Radiation in Their Mothers' Wombs" on the website of the Radiation Effects Research Foundation(https://www.rerf.or.jp/programs/roadmap/health_effects/uteroexp/physment/)

Effects on Fetuses

Effects on Children - Chernobyl Nuclear Accident -

Survey on children born from mothers who were pregnant at the time of the Chernobyl accident

Survey targets

(i) 138 children who were exposed to radiation in the womb and their parents(a group of children exposed to radiation in the womb: exposed group)

(ii) 122 children in non-contaminated regions in Belarus and their parents(control group: non-exposed group)

Children's mental development	When aged 6 to 7		When aged 10 to 11	
	(i) Exposed group	(ii) Control group	(i) Exposed group	(ii) Control group
Difficulty in speech	18.1%	8.2%	10.1%	3.3%
Disorder of emotion	20.3%	7.4%	18.1%	7.4%
IQ=70～79	15.9%	5.7%	10.1%	3.3%

○ A **significant difference in mental development** was observed between the exposed group and the control group, but there was **no correlation between exposed doses and intelligence quotients**.

○ There was correlation between parents' extreme anxiety and their **children's emotional disorders**.

It is accepted that radiation exposure during pregnancy does not directly affect intelligence quotients of fetuses and children after growth.

Source: Kolominsky Y et al., J Child Psychol Psychiatry, 40 (2): 299-305, 1999

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