Carcinogenic & Hereditary Effects of Radiation

Dr Rakesh Kapoor MD, MAMS, FICRO

Professor & Head Unit II
Department of Radiotherapy and Clinical Oncology, Tertiary Cancer Center, PGIMER
Chairman, Indian College Of Radiation Oncology.
Founder Director, HBCH & RC Punjab. (Unit of T.M.C, Mumbai) DAE, (GOI)
Ex. Head: Department of Biostatistics, P.G.I.M.E.R
Ex. Additional Medical Superintendent, P.G.I.M.E.R

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Radiation

- Radiation is energy that moves from one place to another in a form that can be described as waves or particles.
- We are exposed to radiation in our everyday life.
- Some of the most familiar sources of radiation include the sun, microwave ovens in our kitchens and the radios we listen to in our cars. Most of this radiation carries no risk to our health. But some does.
- In general, radiation has lower risk at lower doses but can be associated with higher risks at higher doses.

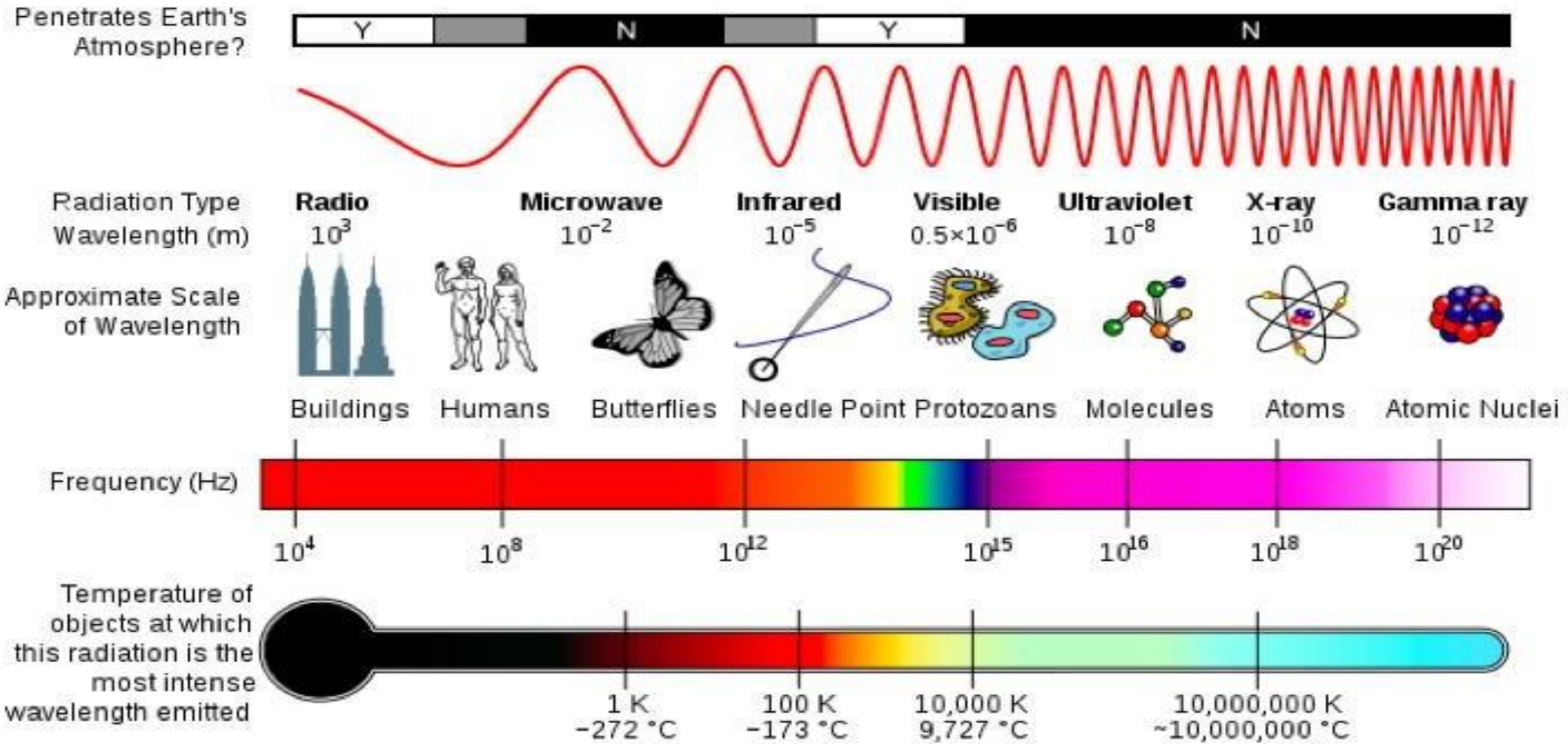
Types of Radiation

Ionizing radiation:

- α particles (2 protons and 2 neutrons) - β particles (electron equivalent)
- Neutrons
- Gamma rays
- X-rays

Non-ionizing radiation:

- Microwaves
- Visible light
- Radio waves and TV waves
- UV radiation (except shortest wavelengths)


Penetrates Earth's Atmosphere?
Y
N
Y
N
Radiation Type
Wavelength (m)
Approximate Scale of Wavelength
Radio
10^{3}
Microwave
10^{-2}
Infrared
10^{-5}
Visible
0.5×10^{-6}
Ultraviolet
10^{-8}
X-ray
10^{-10}
Gamma ray
10^{-12}
Buildings
Humans
Butterflies
Needle Point Protozoans
Molecules
Atoms
Atomic Nuclei
Frequency (Hz)
10^{4}
10^{8}
10^{12}
10^{15}
10^{16}
10^{18}
10^{20}
Temperature of objects at which this radiation is the most intense wavelength emitted
1 K
−272 °C
100 K
−173 °C
10,000 K
9,727 °C
10,000,000 K
~10,000,000 °C

Units & Doses

Absorbed dose (D):

The energy imparted per unit mass by ionizing radiation to matter at a specific point.

Gy: The SI unit of absorbed dose is Joule per kilogram (J kg-1). The special name for this unit is Gray (Gy).

Rad: The previously used special unit of absorbed dose, the rad, was defined to be an energy absorption of 100 ergs/gram.
Therefore, 1 Gy = 100 rad.

Units & Doses

Activity:

Units and doses

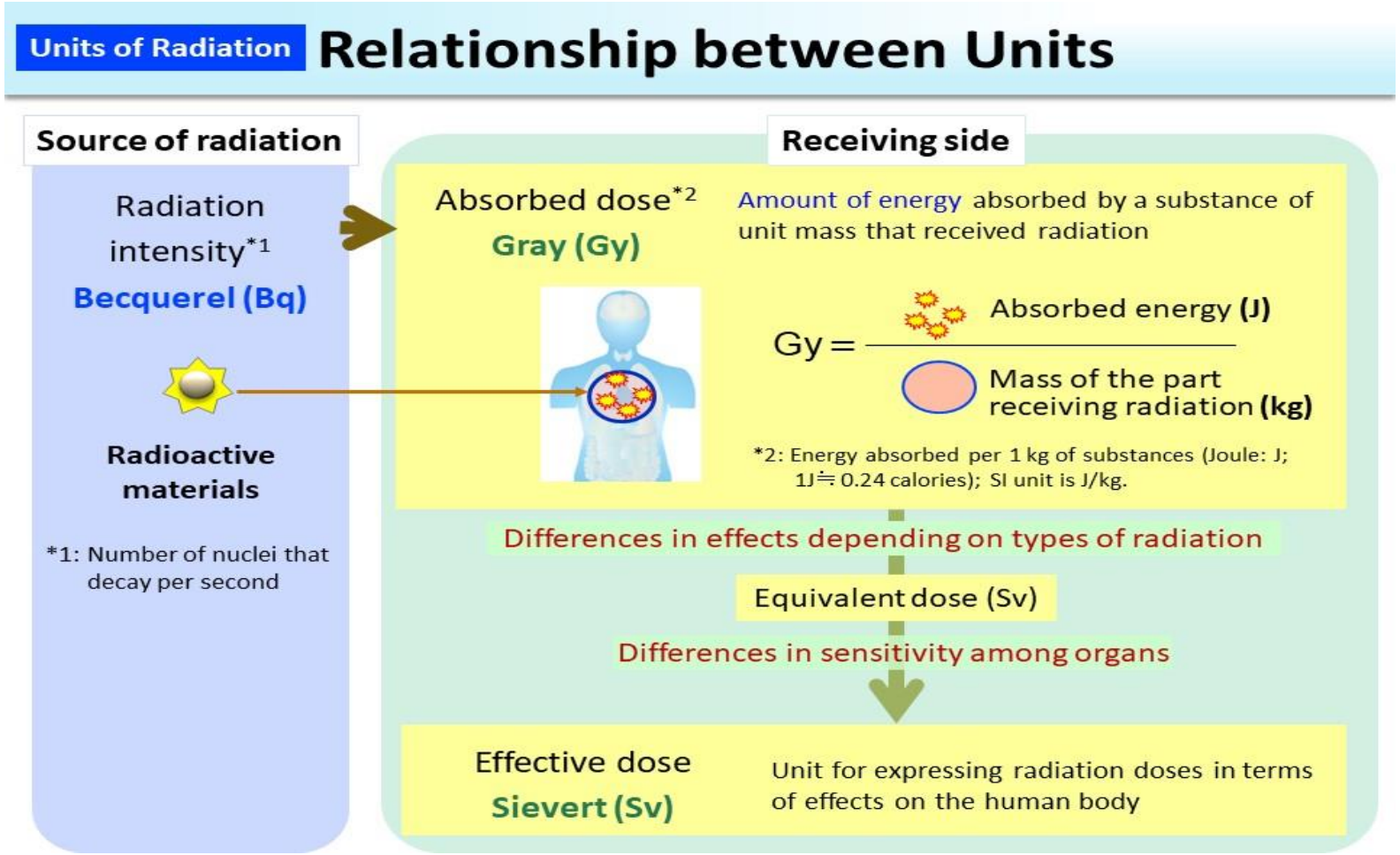
Quantity of a radionuclide which describes the rate at which decays occur in an amount of a radionuclide.

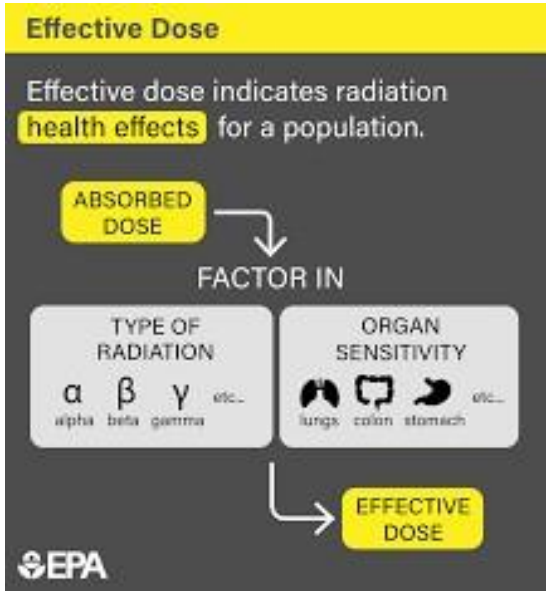
The SI unit of radioactivity is the becquerel (Bq), which replaced the old unit, the curie (Ci).

Becquerel (Bq): One becquerel corresponds to 1 disintegration of a radionuclide per second.

Curie (Ci): Old unit of radioactivity, corresponding to 3.7 x 1010 radioactive disintegrations per second

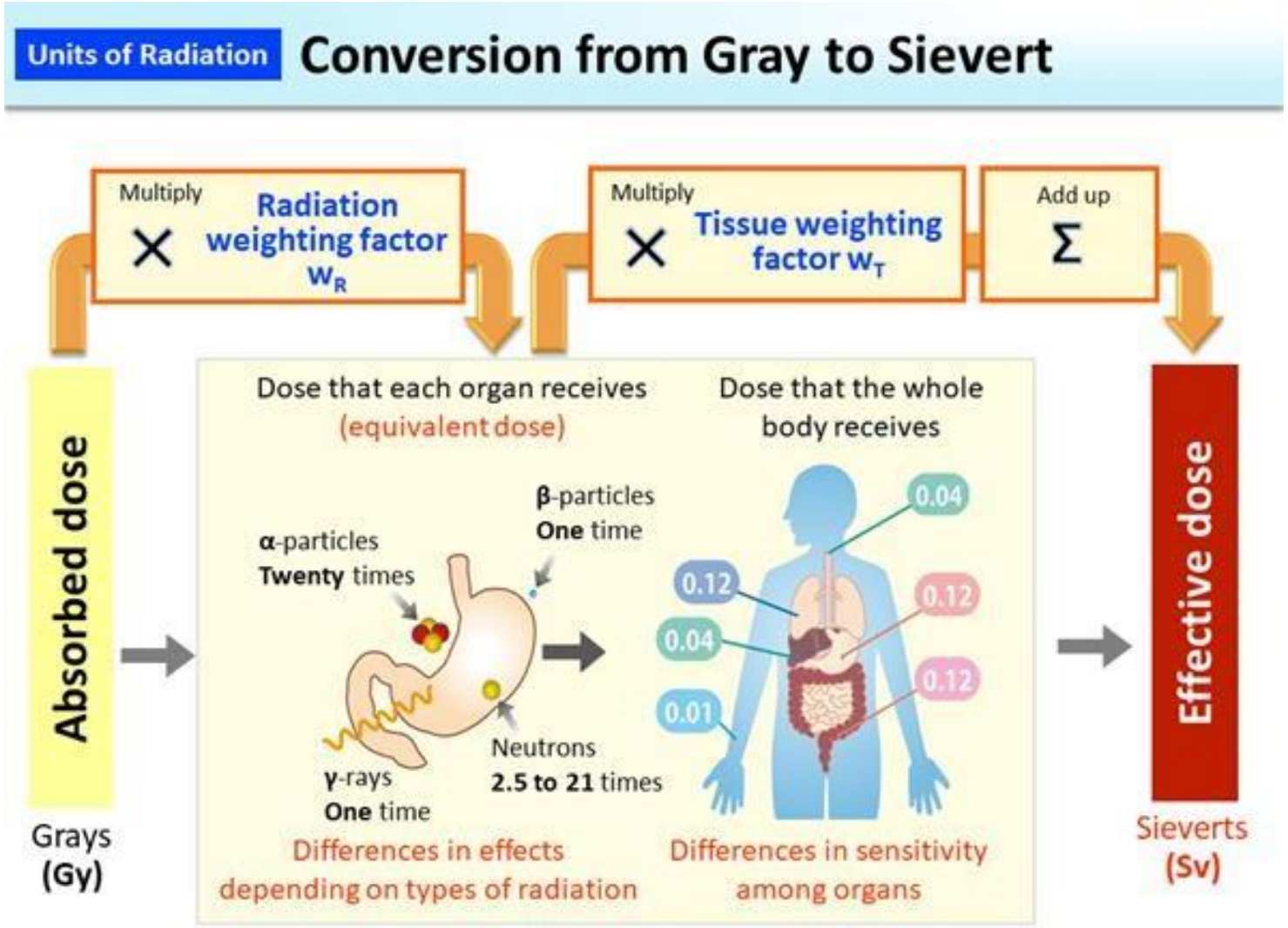
Units & Doses





WF varies with type of radiation

Photons and electrons, WF= 1.
Protons, WF= 2.
Neutrons, WF varies, up to 20.
Heavy ions, WF= 20.



Absorbed dose
Energy imparted by radiation to standard mass of tissue
[unit Gray - Gy]

Equivalent dose
Absorbed dose weighted for the harm of different types of radiation
[unit Sivert - Sv]

Effective dose
Equivalent dose weighted for the harm of different tissues
[unit Sivert - Sv]

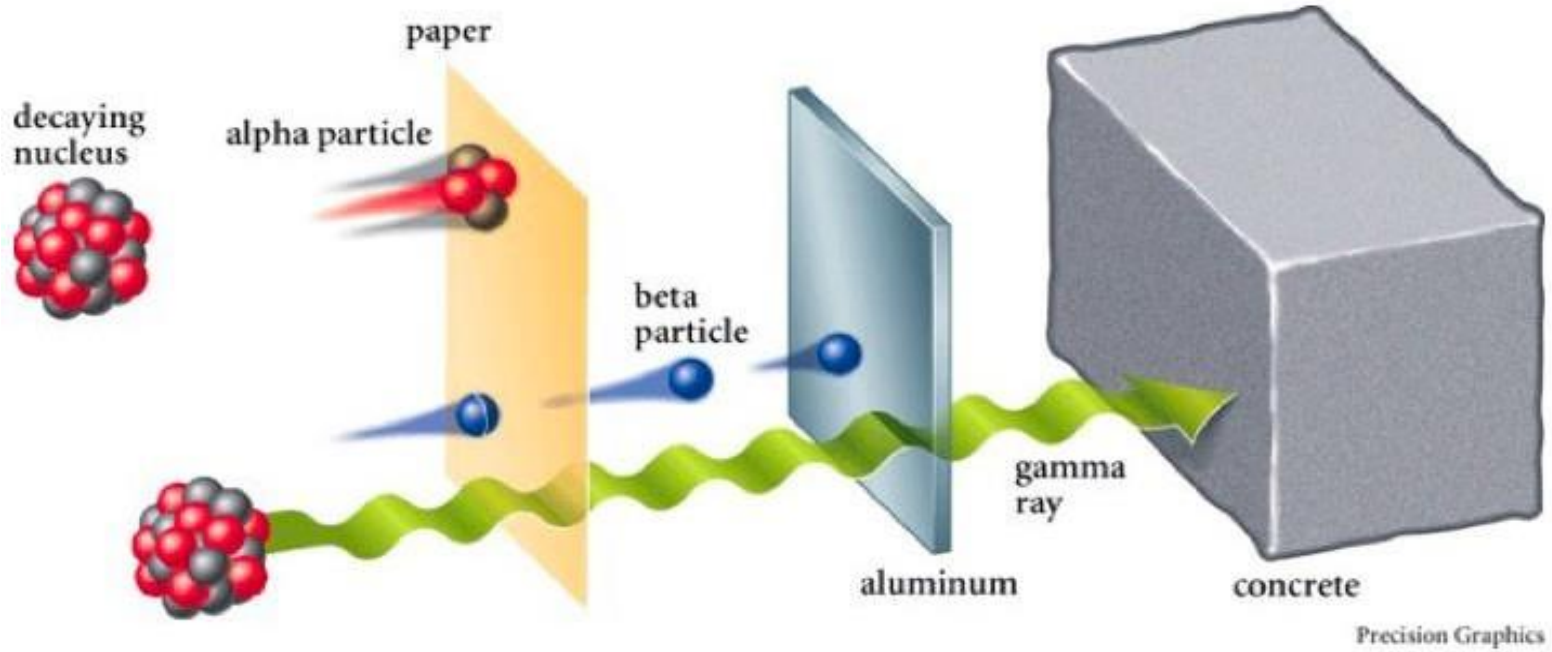
Linear Energy Transfer

The rate of energy loss or deposition along the track of an ionizing particle

- Loss of energy/unit distance traveled in matter
- Units = KeV/μm
- Varies depending of quality of radiation

x-ray or γ-ray: Sparsely Ionizing x x
β particle: x x x
Neutron: Densely Ionizing x x x x x
α particle: xxxxxx

The more sparsely ionizing, the more penetrating


paper
decaying nucleus
alpha particle
beta particle
gamma ray
aluminum
concrete
Precision Graphics

Effects of radiation

- **Acute Effect**
  - Occurs during standard 6-8 wks course
  - Depletes stem and progenitor cell pools
  - Severity of injury depends upon extent of cellular depletion and length of delay before new functional cells are released
  - Severity increases with dose and fractionation decreases severity allowing time for regeneration
- **Subacute Response**
  - Occurs few to several months after irradiation
  - Symptoms are usually reversible but sometimes may be severe to cause death
  - Mostly occurs during remodelling phase
  - Eg. somnolence after brain irradiation, subacute pneumonitis after lung irradiation
- **Late Response**
  - Occurs due to depletion of slowly proliferating cells that are lost at slow rate (eg. Renal tubular epithelium, oligodendrocytes, schwann cells, endothelium, fibroblasts)

Deterministic & Stochastic Effects

A **deterministic (non-random)** effect occurs after exceeding a threshold dose, and the severity of the effect correlates with the dose.
eg radiation induced skin erythema.

A **stochastic (random)** effect occurs randomly with a probability that is proportional to dose, and the severity of the effect is random.
eg Both secondary malignancies and heritable mutations are stochastic effects.

Effects on Human Body

Classification of Radiation Effects

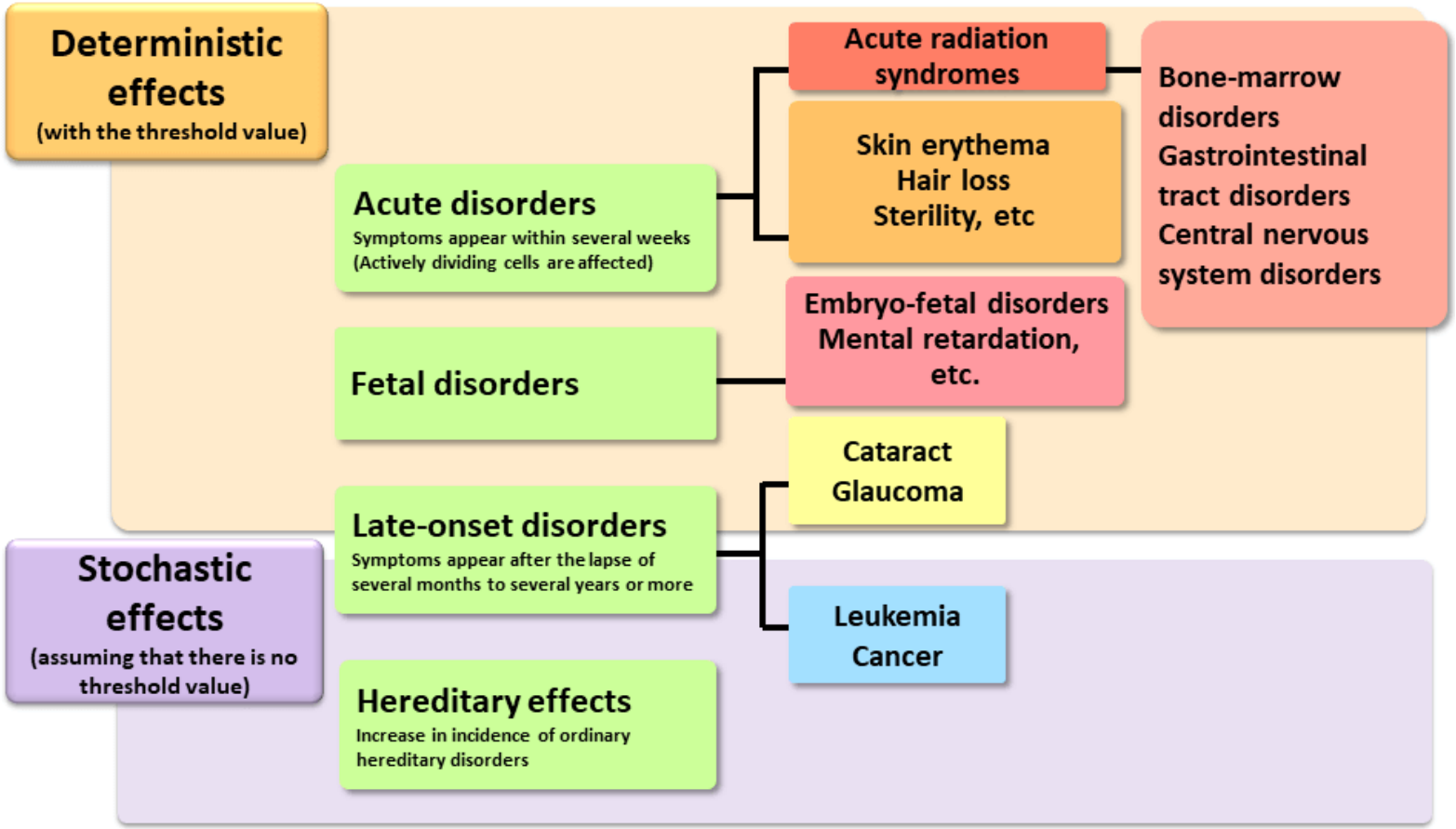
Categories of effects		Incubation period	e.g.	Mechanism of how radiation effects appear
	Physical effects	Within several weeks = Acute effects (early effects)	Acute radiation syndromes*1 Acute skin disease	Deterministic effects caused by cell deaths or cell degeneration*2 
		After the lapse of several months = Late effects	Abnormal fetal development (malformation)	
			Opacity of the lens	
			Cancer and leukemia	Stochastic effects due to mutation 
	Hereditary effects		Hereditary disorders	

*1: Major symptoms are vomiting within several hours after exposure, diarrhea continuing for several days to several weeks, decrease of the number of blood cells, bleeding, hair loss, transient male sterility, etc.
*2: Deterministic effects do not appear unless having been exposed to radiation exceeding a certain dose level.

Effects on Human Body

Types of 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).



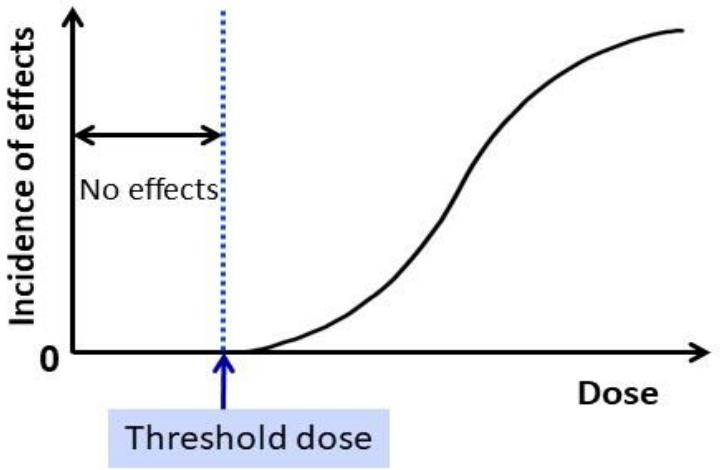
Effects on Human Body

Deterministic Effects and Stochastic Effects

Deterministic effects

(Hair loss, cataract, skin injury, etc.)

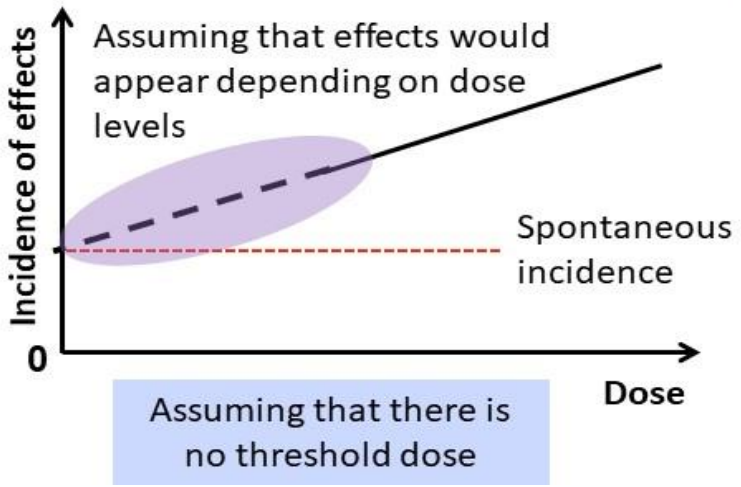
When a number of people were exposed to the same dose of radiation and certain symptoms appear in 1% of them, said dose is considered to be the threshold dose.
(2007 Recommendations of the International Commission on Radiological Protection (ICRP))



Stochastic effects

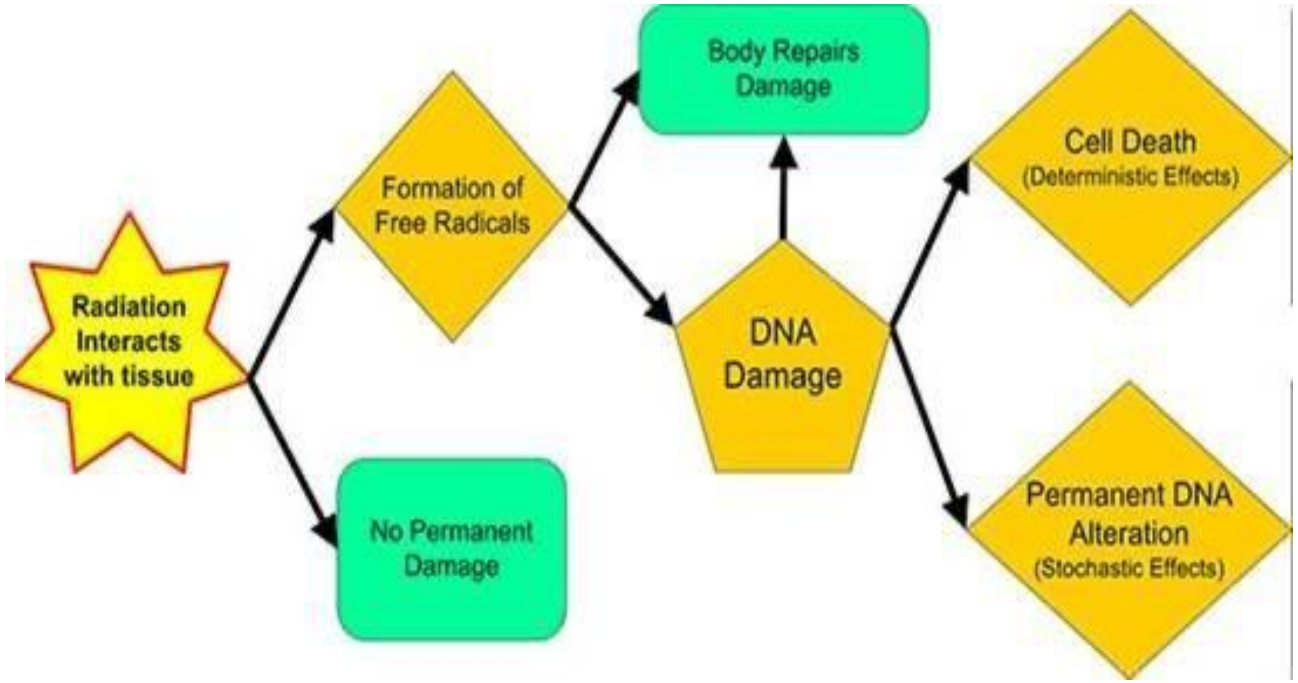
(Cancer, leukemia, hereditary effects, etc.)

Effects of radiation exposure under certain doses are not clear because effects of other cancer-promoting factors such as smoking and drinking habits are too large. However, the ICRP specifies the standards for radiological protection for such low-dose exposures, assuming that they may have some effects as well.



Causes of Radiation Induced Cancer

- **Radon**
- **Medical**
- **Occupational**
- **Accidental**



Radon

- Radioactive, colourless, odourless, tasteless gas.
- Responsible for the worldwide majority of the mean public exposure to ionizing radiation.
- Often the single largest contributor to an individual's background radiation dose, and is the most variable from location to location.
- Radon gas from natural sources can accumulate in buildings, especially in confined areas such as attics, and basements.
- Increased chances of lung cancer and others

Medical Imaging

- Contributes almost as much radiation dose to the public as natural background radiation

- Growing use of CT, esp 3D-CT: responsible for half the medical imaging dose

- Radiopharmaceuticals
- Radiotherapy treatment

Occupational

- ICRP recommendations: most regulators permit nuclear energy workers to receive up to 20 times more radiation dose than is permitted for the general public.
- Higher doses are usually permitted when responding to an emergency.
- Astronauts on long missions are at higher risk of cancer.

- **Some occupations are exposed to radiation without being classed as nuclear energy workers.**

  Airline crews: cosmic radiation because of reduced atmospheric shielding at altitude.

  Mine workers: exposures to radon, especially in uranium mines.

  Working in a granite building, is likely to receive a dose from natural uranium in the granite.

It was known early after the discovery of radiation that it could cause cancer

Both Marie Curie (the discoverer of radium) and her daughter Irene died of leukemia - probably due to their radiation exposures

Occupational exposure:
Bone cancer developed in the “radium dial painters”

Accidental

Chernobyl: 100 million curies (4 exabecquerels) of radioactive material leaked (1996)

^{131}I released were initially the most dangerous. Due to their short half-lives of 5 and 8 days they have now decayed, leaving the more long-lived ^{137}Cs (with a half-life of 30.07 years) and ^{90}Sr (with a half-life of 28.78 years) as main dangers.

Explosions and partial meltdowns at the Fukushima I Nuclear Power Plant in Japan (2011)

Tokaimura nuclear accidents of 1997 and 1999.

The 1997 accident was far less fatal than the 1999 accident. The 1999 nuclear accident was caused by two faulty technicians who, in their desire to speed up the process of converting uranium hexafluoride to enriched uranium dioxide, resulted in a critical mass

The satellite Transit 5BN-3 accident.

The satellite had a SNAP-3 radioisotope thermoelectric generator (RTG) with approximately 1 kilogram of Plutonium-238 on board when on April 21, 1964 it burned up and re-entered the atmosphere

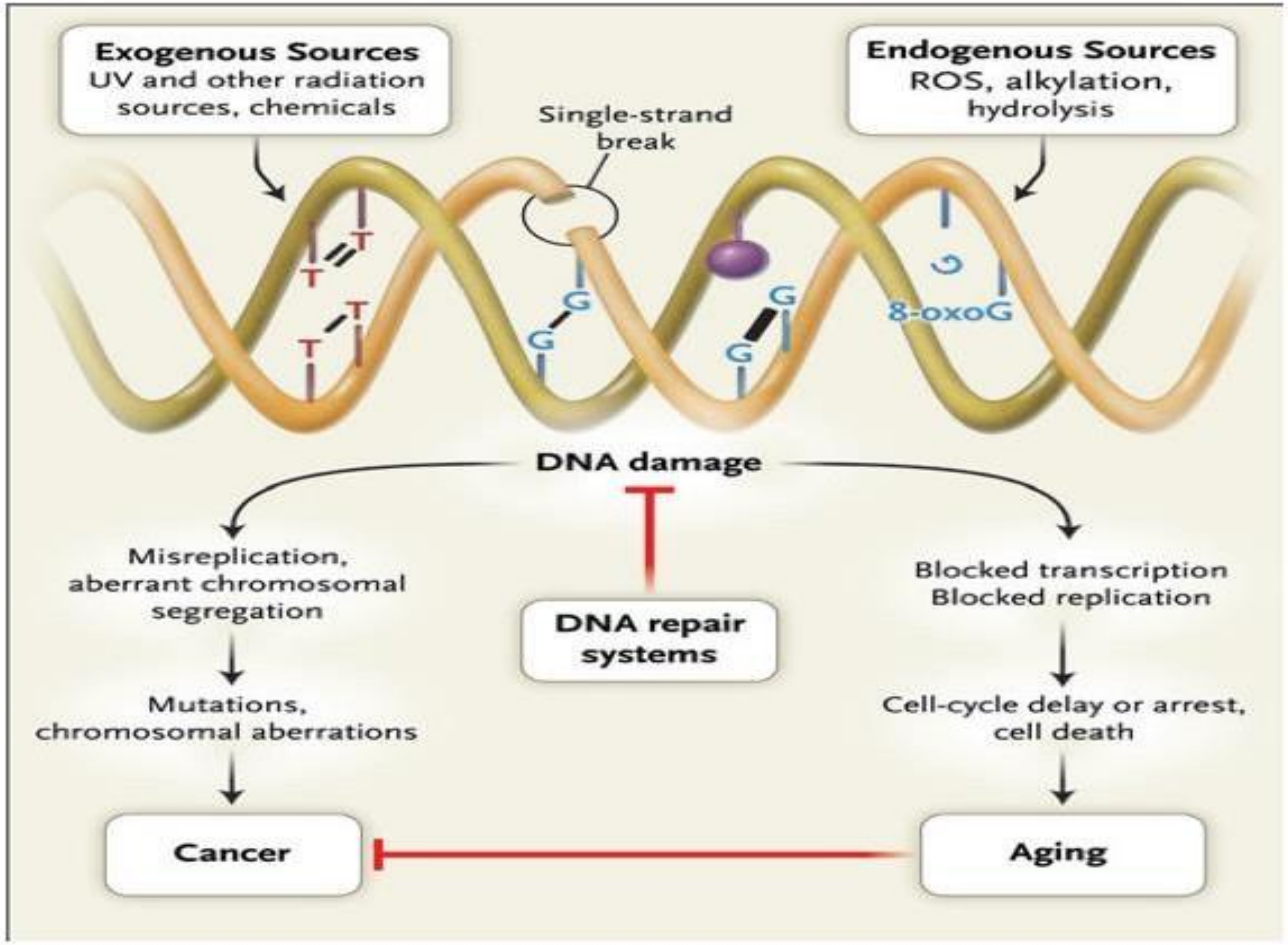
Early Cases of Human Experience

- Skin cancer in early x-ray workers
- Lung cancer in underground uranium miners in Saxony and Colorado
- Bone cancer in radium dial painters
- Liver cancer in thorotrast patients (use of thorium dioxide as radiocontrast agent in medical radiography in 30s-40s

Later Cases of Human Experience

- Hiroshima/Nagasaki survivors
- Radiation treatment of Anklyosing Spondylitis patients
- Elevated incidence of leukemia in early radiologists
- Thyroid cancer from treatment for enlarged thymus
- Thyroid and other cancers for treatment of tinea capitis by radiation
- Breast cancer due to frequent chest X-Ray fluoroscopy in tuberculosis patients between 1925 to 1954

DNA Damage & Repair



X.rays or ionizing radiation induces DSBs in the chromosomes. DSBs causes sticky ends, which can join with any other sticky ends.

1) Rejoin to original configurations
2) The breaks fails to rejoin causing deletion
3) Broken ends may join other sticky ends

Mechanism of Carcinogenesis

- Ionizing radiation causes double-strand breaks, leading to chromosomal aberrations, mutations, and genomic instability.

- Radiation-induced mutations are typically **large-scale** deletions, duplications, translocations, or other chromosomal aberrations, or aneuploidy.

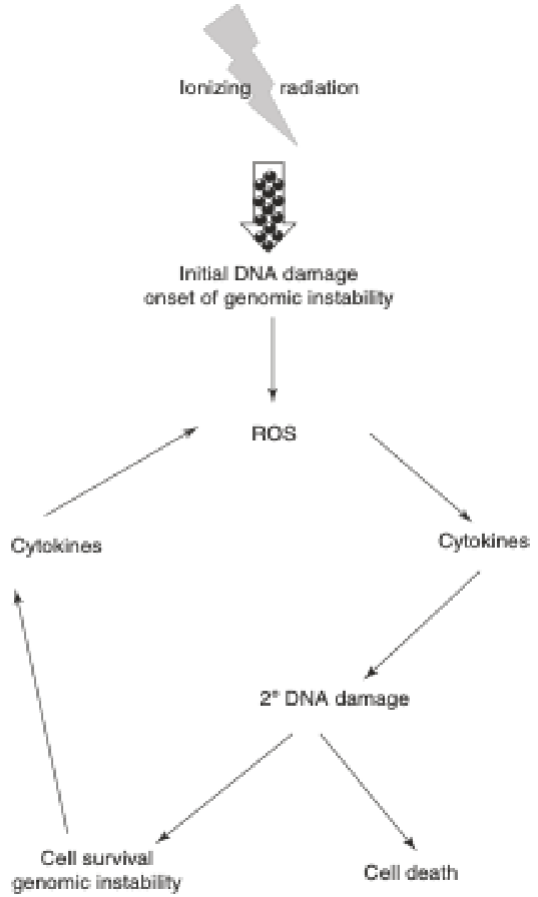
- Radiation can also cause **point mutations** (single-nucleotide polymorphisms, transitions, transversions, frameshifts, micro-deletions, or insertions).
  - All of the above changes are considered ***genetic alterations***.

- Ionizing radiation can also induce changes in gene promoter methylation. These are considered ***epigenetic alterations***.

Mechanism of Carcinogenesis

Sporadic and radiation-induced carcinogenesis involves activation of oncogenes and loss of tumor suppressor genes.

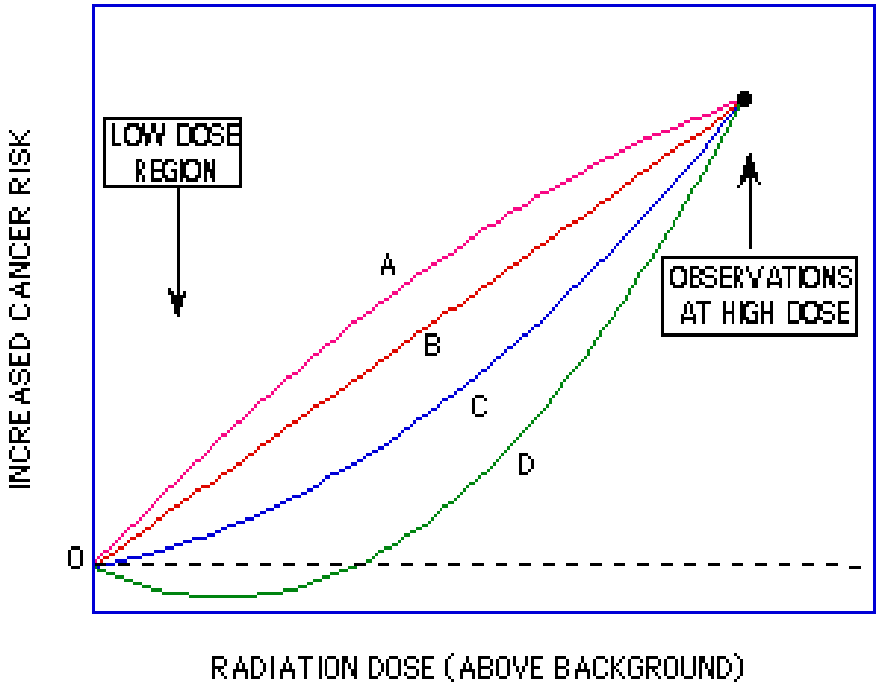
- Oncogenes can be activated or overexpressed by both genetic and epigenetic mechanisms.
- Tumor suppressor genes can be deleted or silenced by both genetic and epigenetic mechanisms.
- These genetic and epigenetic changes can be delayed and caused by radiation induced genomic instability driven by ROS and cytokine cycles (TNF-α and TGF-β, etc.) over many years



Dose Response to Radiation Induced Cancers

The linear no-threshold (LNT) model assumes a direct linear relationship between dose and carcinogenesis.

- This is in contrast to dose–response models that have a threshold beneath which radiation carcinogenesis does not occur.
- Radiation hormesis models hypothesize that extremely low doses of radiation may actually be beneficial
- The current human evidence is insufficient to either prove or disprove the existence of a threshold.
- The **LNT** model is the most conservative approach, so it is used for radiation protection purposes.



Different assumptions on the extrapolation of the cancer risk vs. radiation dose to low-dose levels, given a known risk at a high dose:
(A) supra-linearity, **(B)** linear
(C) linear-quadratic, **(D)** hormesis

Radiation Protection Organizations

- The **Biological Effects of Ionizing Radiation (BEIR)** Committee is an academic committee devoted to the basic science behind radiation protection.

- The **United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)** is a reporting and regulatory agency.

- The **International Commission on Radiation Protection (ICRP)** is an advisory agency.

- The **National Council on Radiation Protection and Measurements (NCRP)** is a US council chartered by the US Congress that advises and publishes reports and recommendations.

Absolute & Relative Risk of Carcinogenesis

- Approximately, **40%** of all humans will suffer a malignancy at some point in their lifetime.

- For the vast majority of people exposed to radiation, the absolute risk of a **radiation-induced malignancy** is much smaller than the absolute risk of **sporadic malignancies**.

- The **BEIR** and **ICRP** models of radiation carcinogenesis assume that radiation is a **relative** modifier of malignancy.
  - That is, radiation multiplies the frequency of malignancy by a dose- and age-dependent factor.
  - This model implies that radiation-induced malignancies are likely to have an age and site distribution similar to sporadic malignancies, whether or not that is true.

ICRP Carcinogenesis Risk Estimates

- Carcinogenesis risk estimates derived from Japanese nuclear bomb survivors

- The dose and dose-rate effectiveness factor (**DDREF**) corrects for the decreased biological effectiveness of low-LET, low dose, and low dose rate irradiation.

  - **Low DDREF exposures** are defined as **low-LET** radiation with a dose rate less than **0.1 Gy/h**, or total dose less than **0.2 Gy** at any dose rate.
  - **High DDREF exposures** are **high-LET** radiation, or dose greater than **0.2 Gy** and dose rate over **0.1 Gy/h**.

ICRP Carcinogenesis Risk Estimates

- For the purposes of carcinogenesis, we should use **effective dose (Sv)**. This is an equivalent dose weighted for volume of tissue irradiated.

- According to **ICRP 60**, the total risk of radiation-induced malignancies is:

  - **10%/ Sv** for entire population and **high DDREF**.
  - **8%/ Sv** for working population (children excluded) and **high DDREF**.
  - **5%/ Sv** for entire population and **low DDREF**.
  - **4%/ Sv** for working population and **low DDREF**.

- The **ICRP** numbers are widely used to estimate the risk of secondary malignancies from diagnostic studies, airline screening X-rays, nuclear accidents, etc

Carcinogenic Risk and Age, Gender, and Time

Compared to the whole population, an individual patient may have more or less risk of carcinogenesis based on several factors:

Age: Children are much more susceptible to radiation-induced malignancy.
– **Children < 5yo** are ~**3×** more susceptible than the population average, or ~ **10×** more susceptible than older adults.

Gender: Women are more susceptible to radiation-induced malignancy because of breast cancer.

Time: Radiation-induced malignancies occur years to decades after irradiation.

A patient with a short life expectancy is very unlikely to develop a radiation- induced malignancy.

Cahan's Criteria, Cahan et al, 1948

- **The modified Cahan's criteria for diagnosis of RIM (Radiation Induced Malignancy)**

1. A RIM must have arisen in an irradiated field.
2. A sufficient latent period, preferably longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy.
3. The treated tumor and alleged induced tumor must have been biopsied. The two tumors must be of different histology.
4. The tissue in which the alleged induced tumor arose must have been normal (i.e., metabolically and genetically normal) prior to the radiation exposure.

Category of Effects of Exposure to Low Doses of Radiation

Three general categories:

- **Genetic**: Effect is suffered by the offspring of the individual exposed

- **Somatic**: Effect is primarily suffered by the individual exposed. Since cancer is the primary result, also called **Carcinogenic effect**.

- **In-utero**: not a genetic consequence

  : effect suffered by a developing embryo/fetus is seen after birth

  : A special type of somatic effect, since the embryo/fetus is the one exposed to radiation

Genetic Effects

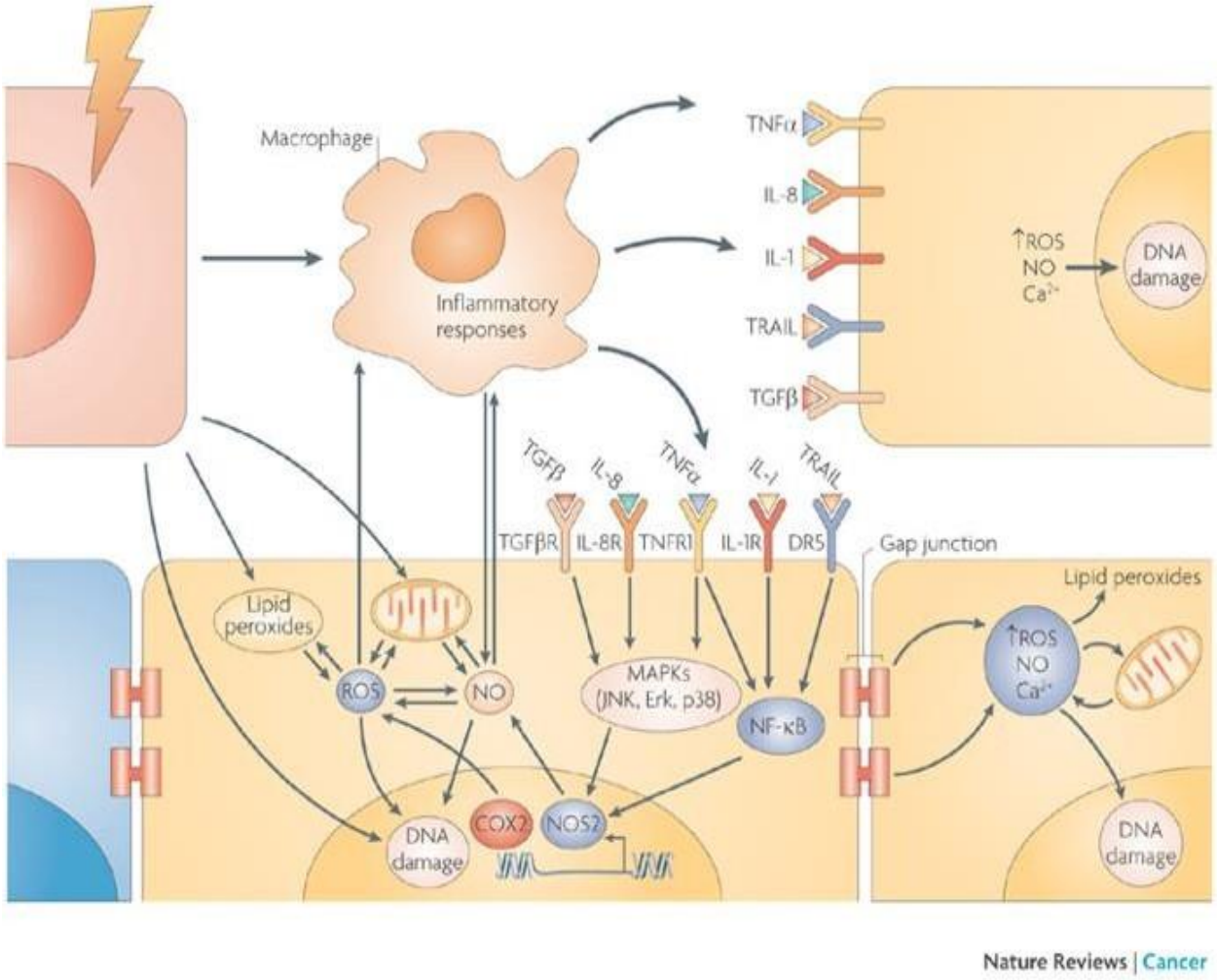
- Mutation of very specific cells, sperm or egg cells

- Physical mutagenic agent: Radiation
- Chemical mutagenic agent: Tar
- Biological mutagenic agent: Virus

- Radiation increases the spontaneous mutation rate, but does not produce any new mutation

- **Not all mutations would be lethal/ harmful but it is prudent to assume that all mutations are bad, and thus, by UNSRC regulation (10 CFR Part 20), radiation exposure SHALL be held to the absolute minimum or As Low As Reasonably Achievable (ALARA)**

Bystander Effect



- Genetic alterations can occur in cells that receive no direct radiation exposure

- Damage signals transmitted from neighbouring irradiated cells

Hereditary Effects of Radiation

- **Effects to be observed in offspring born after one or both parents had been irradiated prior to conception**
- **Radiation exposure does not induce new types of mutations in the germ cells but increase the incidence of spontaneous mutations**
- **Descendents of Hiroshima and Nagasaki survivors were studied**
- **A cohort of 31,150 children born to parents who were within 2 km of the hypocenter at the time of the bombing was compared with a control cohort of 41,066 children**

But, no statistical abnormalities were detected

Hereditary Effects of Radiation

- In the absence of human data the estimation of hereditary effects are based on animal studies

- Risks to offspring following prenatal exposure:

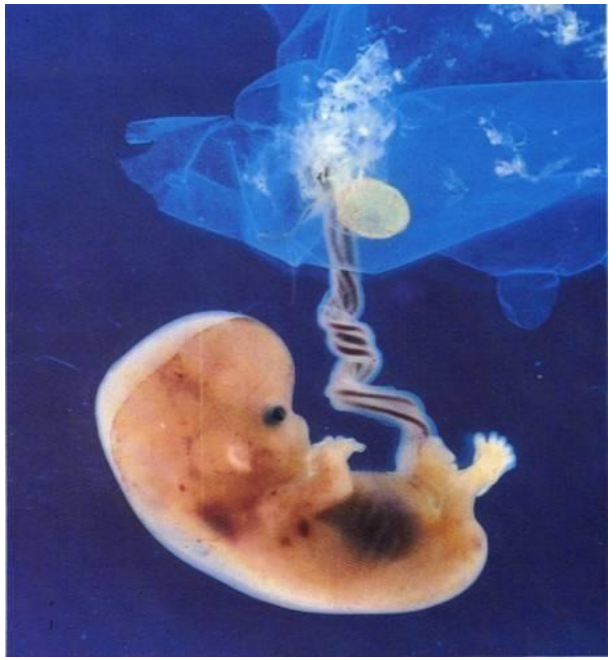
  Total risk = 0.0003 - 0.0005% per mGy to the first generation

  Constitutes 0.4-0.6% of baseline frequency

  (UNSCEAR 2001 Report Hereditary Effects of Radiation)

Typical Effects of Radiation on Embryo/ Fetus

1. Death of the embryo or fetus



2. Induction of:

Malformation

Growth Retardation

Functional Disturbance

Cancer

3. Factors influencing the probability of effects

Dose for embryo or fœtus

Gestation status at the time of exposure

A study of about 1,600 children exposed in-utero at Hiroshima and Nagasaki to various radiation doses and at various developmental stages:

Excess mental retardation was at a maximum between 8 and 15 weeks

Risk: 0.05% per mSv (8-15 weeks)

RADIATION-INDUCED SECOND CANCERS: THE IMPACT OF 3D-CRT AND IMRT

ERIC J. HALL, D.SC.* AND CHENG-SHIE WUU, PH.D.†

*Center for Radiological Research and †Department of Radiation Oncology, Columbia University, College of Physicians and Surgeons, New York, NY

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, pp. 83–88, 2003

By contrast, the move from 3D-CRT to intensity-modulated radiation therapy (IMRT) involves more fields, and the dose–volume histograms show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2 to 3, increasing the total body exposure, due to leakage radiation. Both factors will tend to increase the risk of second cancers. Altogether, IMRT is likely to almost double the incidence of second malignancies compared with conventional radiotherapy from about 1% to 1.75% for patients surviving 10 years. The numbers may be larger for longer survival (or for younger patients), but the ratio should remain the same.

Second Cancers after Radiotherapy for Cervix Cancer *(Boice et al, 1985)*

Table 1. Second cancer risk in patients treated with radiation therapy for Ca cervix

	Relative risk
Tissues receiving several hundred Gy	
Ca bladder	4.5
Rectum	1.8
Vagina	2.7
?Bone	1.3
?Uterine corpus	1.3
?Cecum	1.5
Non-Hodgkin's lymphoma	2.5
Tissues receiving several Gy	
Ca stomach	2.1
Leukemia	2.0

Boice et al: JNCI: 74.955, 1985

Journal of Cancer Research and Therapeutics

ORIGINAL ARTICLE

Dosimetric risk estimates of radiationinduced malignancies after intensity modulated radiotherapy

Patil, Vijay M.; Kapoor, Rakesh; Chakraborty, Santam; Ghoshal, Sushmita; Oinam, Arun S.; Sharma, Suresh C.

Author Information

Journal of Cancer Research and Therapeutics 6(4):p 442-447, Oct–Dec 2010. | **DOI:** 10.4103/0973-1482.77082

OPEN

Abstract

Context:

The increasing popularity of intensity-modulated radiotherapy (IMRT) stems from its ability to generate a more conformal plan than hitherto possible with conventional planning. As a result, IMRT is in widespread use across diverse indications. However, the inherent nature of IMRT delivery makes it monitor unit inefficient and leads to increased normal tissue integral dose. This in turn may result in an increased risk of radiation-induced second malignancies.

Aim:

To calculate the risk of second malignancy post-IMRT.

Settings and Design:

Observational study in a tertiary care institute.

Materials and Methods:

Eighteen previously untreated patients with head and neck cancers (n = 10) and prostate cancer (n = 8) were selected. In these patients, selected infield organs around the planning target volume were contoured, *viz.* brain and thyroid in patients with head and neck cancer and bladder, rectum and small intestine in patients with carcinoma prostate. The estimates of radiation-induced malignancies in these organs and the whole of the body were derived using the concept of Organ Equivalent Dose.

Schneider's Formula:

- Organ equivalent dose (OED) in which any dose distribution in an organ is equivalent and corresponds to the same OED if it causes the same radiation-induced cancer incidence.
- For low doses, the OED is simply the average organ dose, since for these doses the dose–response function behaves linearly with dose.
- However, at high doses the OED is different, because cell killing becomes important.
- The basis for the OED model is the dose–response relationship for radiation-induced cancer for different organs.

For any given organ, the risk of occurrence of a second malignancy was given by the formula:

$$I = I_0 X\ OED_{CTorg} \qquad \text{(Equation - 1)}$$

where, I_0 is the irradiation-induced cancer risk from low-dose radiation exposure, expressed as the absolute excess risk per 10,000 patients/year/Gy from the UNSCEAR report (2000) on the epidemiological evaluation of radiation-induced second cancers.

The OED for a given organ was calculated from the CT data using the formula:

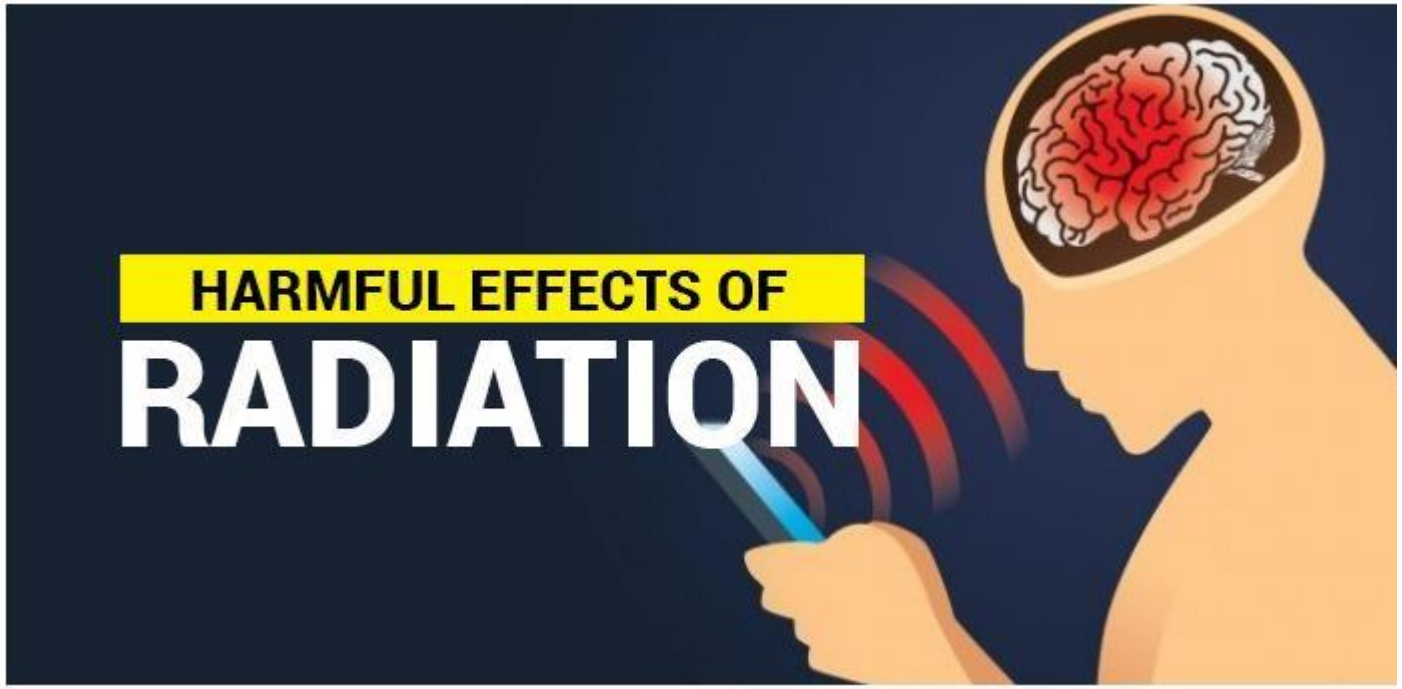
$$OED_{CTorg} = [\sum D_V X\ D^i_{CTorg} X\ (1 - e^{-(\delta DiCT)/\delta})] / V_{CT}$$

$$OED_{CTorg} = \frac{\sum D_v \times D^i_{CTorg} \times \left(1 - e^{\frac{-\ddot{a} \times D^i_{CT}}{\ddot{a}}}\right)}{V_{CT}} \qquad \text{(Equation-2)}$$

where, D_V is the volume corresponding to the dose D^i_{cTorg} for the specified organ obtained from the differential dose volume histogram, delta(δ) is the model parameter for the specified organ (Appendix 1) and V_{CT} is the volume of the concerned organ (ml).

Take Home

- Exposure to ionizing radiation is known to increase the future incidence of cancer, particularly leukemia.
- Mechanism by which this occurs is well understood, but quantitative models predicting the level of risk remain controversial.
- Most widely accepted model posits that the incidence of cancers due to ionizing radiation increases linearly with effective radiation dose at a rate of 5.5% per sievert;
- Natural background radiation is the most hazardous source of radiation to general public health, followed by medical imaging as a close second.
- The vast majority of non-invasive cancers are non-melanoma skin cancers caused by ultraviolet radiation (which lies on the boundary between ionizing and non-ionizing radiation).



Thank You