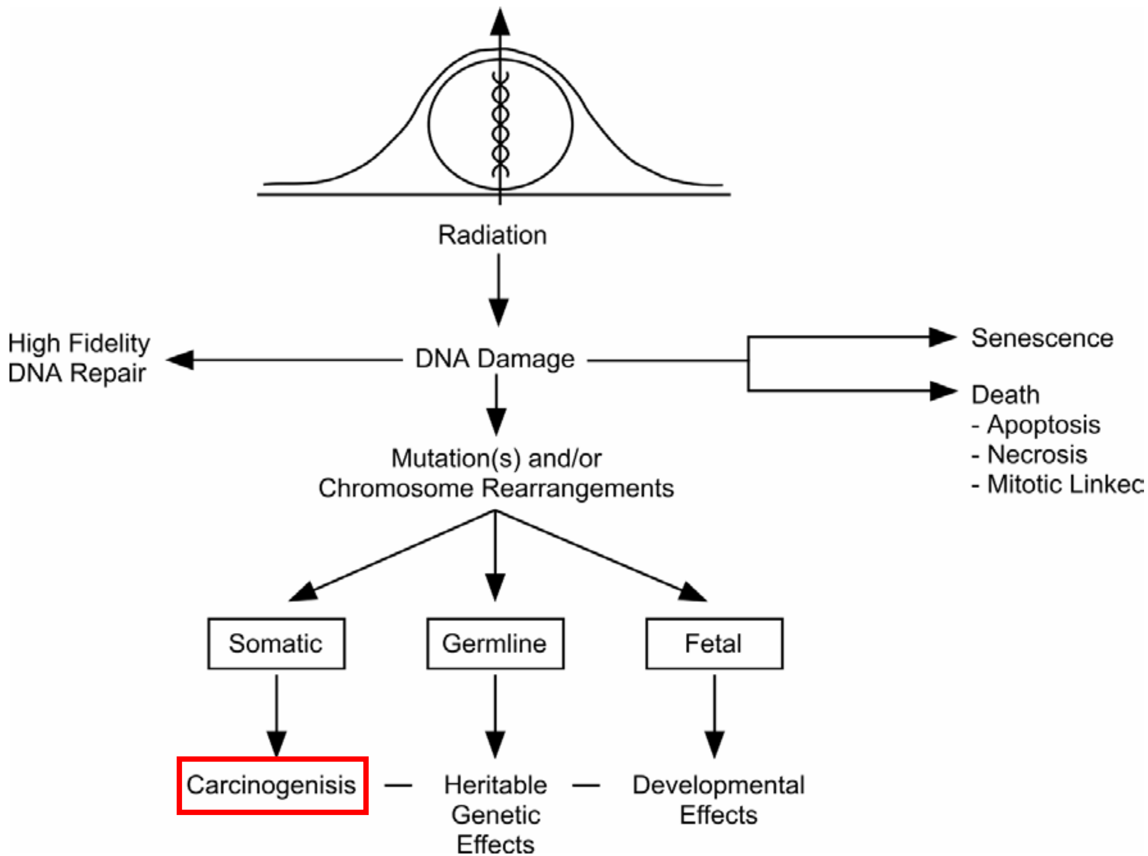
Chapter 10 – Radiation Carcinogenesis

11/4/2024

DNA as the Target



Outline

- **Tissue Reactions (Deterministic) and Stochastic Effects**
- Early Human Experience
- Recent Human Experience
- Common Radiation-Induced Cancer
- The Latent Period
- Risk Estimates
- Second Malignancies in Radiotherapy Patients
- Cancer Risks in Nuclear-Industry Workers and Radiologists
- Childhood Cancer After Radiation Exposure in Utero

ICRP Terminology of Radiation Damage

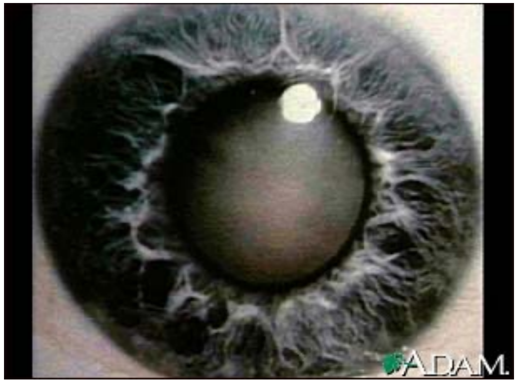
Radiation can produce two very different types of damage

Tissue Reaction	Stochastic Effect
Previously called “Deterministic Effect”	
Damage is due to cells being killed and removed from a tissue or organ	Effects were due to cells that are not killed but are changed or mutated in some way

Tissue Reaction (Deterministic Effect)

Consider **radiation-induced cataracts** as an example

Cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity



Tissue Reaction (Deterministic Effect)

It is well established that ionizing radiation may also cause cataract

- A minimum dose of 2 Gy is required to produce a cataract, i.e., there is a **threshold dose**
- Above the threshold dose, the **probability** of developing cataracts increases rapidly with the dose
- The **severity** of cataract also increases with dose

A tissue reaction (deterministic effect) has a threshold in dose, probability increases with the dose, and the severity of the effect is dose related random

Stochastic Effect

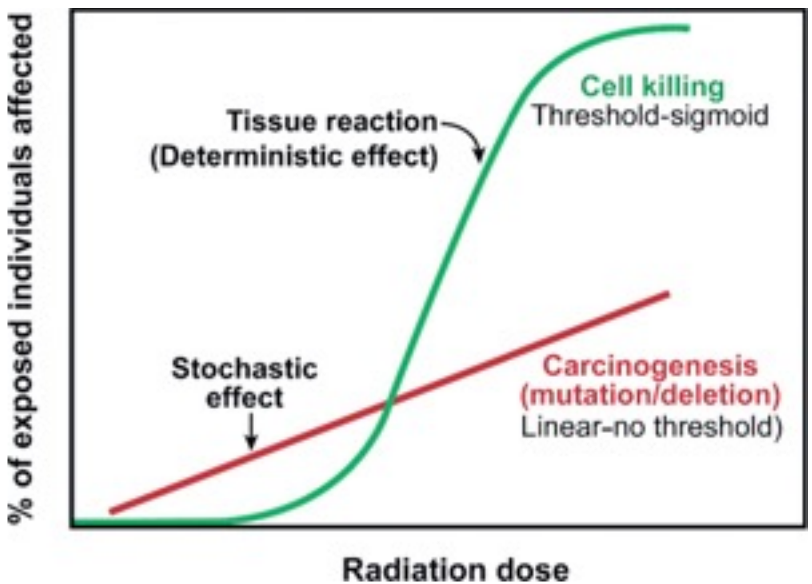
Consider **radiation carcinogenesis** as an example

- There is probably **no threshold dose**
- If somatic cells are exposed to radiation, the **probability** of cancer **increases** with dose
- The **severity** of the cancer is **independent** of dose

A **stochastic effect** has no threshold in dose, the probability of an effect increases with dose, but the severity of the effect is not dose related

Hereditary effect are also stochastic

Dose Response Relationship



Tissue Reaction

- Threshold-sigmoid
- Probability ↑ with dose
- Severity ↑ with dose

Stochastic Effect

- Linear (linear-quadratic)-
no threshold
- Probability ↑ with dose
- Severity not dose related

Threshold Dose

	Tissue Reaction (Deterministic Effect)	Stochastic Effect
Threshold dose	Yes	No
Mechanism	Most organs or tissues of the body are unaffected by the loss of a few cells; but if the number of cells lost is sufficiently large, there is loss of tissue function	A single photon could result in a single base change in a single cell, which is sufficient to cause cancer or hereditary defect

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Early Human Experience

- Examples include
  - Early radiation workers
  - Uranium miners
  - Radium dial painters
  - Patients administered thorotrast

Occupational exposure

- Largely anecdotal, NOT quantitative enough for risk estimates

Early Radiation Workers

- The “martyrs of radiology” – early radiologists and staff deliberately irradiated their hands to test the equipment and operated the x-ray tubes with no shielding
- Lost fingers to skin cancer and often lives

Early Radiation Workers

Early radiation workers' fingers and hands often develop cancer

Early radiologists tested their equipment by fluoroscoping their own hands

Dentists who held films in patients' mouths

Early Radiation Workers

Marie Curie and her daughter Irene

Both were thought to have died of leukemia as a consequence of radiation exposure they received during their experiments with radioactivity

Uranium Miners

- Pitchblende and uranium miners in Czechoslovakia, Sweden, Newfoundland and Colorado
- Exposed to radon gas which became deposited on particles of dust in the lungs
- The daughter products, often α particle emitters, caused lung cancers due to high-LET irradiation of the lung epithelium

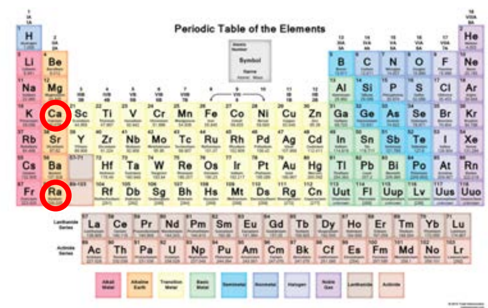
Pitchblende

http://www.britannica.com/EBchecked/topic/462007/pitchblende

- Amorphous, black, pitchy form of the crystalline uranium oxide mineral uraninite
- Containing 50–80 percent of Uranium
- Three chemical elements were first discovered in pitchblende: **uranium** by the German chemist Martin Klaproth in 1789, and **polonium** and **radium** by the French scientists Pierre and Marie Curie in 1898.
- Deposits, frequently in association with uraninite or with secondary uranium minerals, are known in Congo (Kinshasa); the Czech Republic; England; the Northwest Territories and Saskatchewan in Canada; and Arizona, Colorado, Montana, New Mexico, and Utah in the United States.

Radium Dial Painters

- Young women were taught to lick their brushes to keep them sharp when painting the dials of watches and clocks with luminous paint containing **radium**
- Radium is a bone seeker (like calcium), so it is deposited in the tips of growing bones



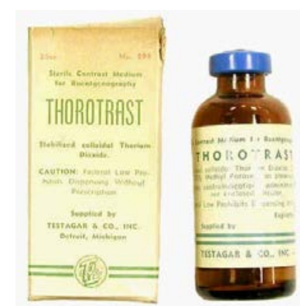
- About 10% developed bone or sinus cancers

Radium Dial Painters

Patients Administered Thorotrast

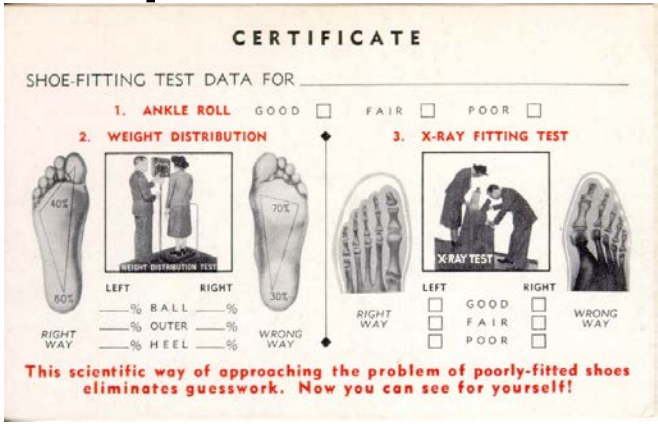
- Thorotrast, containing radioactive **thorium**, an α-emitter, was commonly used as a contrast agent (high Z) up until the 1960s

- Thorium deposited in the liver and caused liver cancers



Shoe Fitting Fluoroscope

Shoe-fitting fluoroscope



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Recent Human Experience

- Japanese atomic bomb survivors
- Nuclear fallout and accidents
- Ankylosing spondylitis therapy
- Children treated for enlarged thymus
- Children treated for tinea capitis
- Women given multiple fluoroscopies
- Women treated for postpartum mastitis

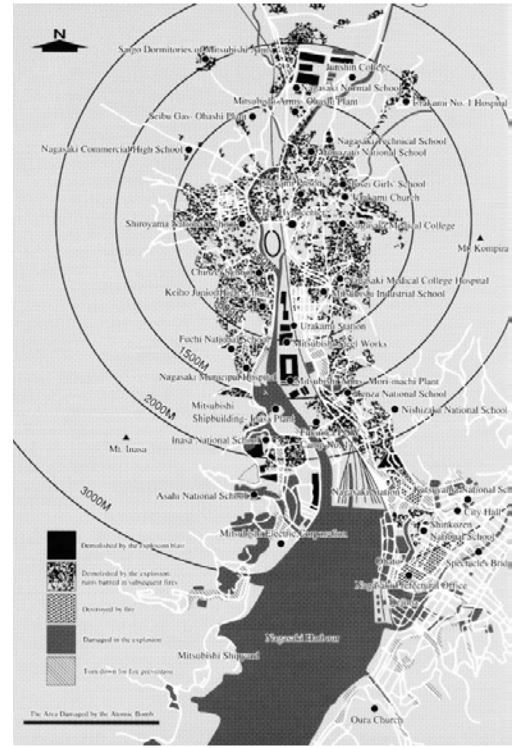
Dosimetry allows risk estimates

Atomic Bomb Survivors

- The Japanese survivors of the Hiroshima and Nagasaki atomic bombs are the most important group of individuals studied for the effects of radiation in whom doses could be estimated
- Over 120,000 survivors have been followed
- About 50,000 received doses in excess of 0.005 Sv
- To date, there has been ~ 22,000 cases of cancer, ~1,000 of which were considered to be caused by radiation

Nagasaki Bomb

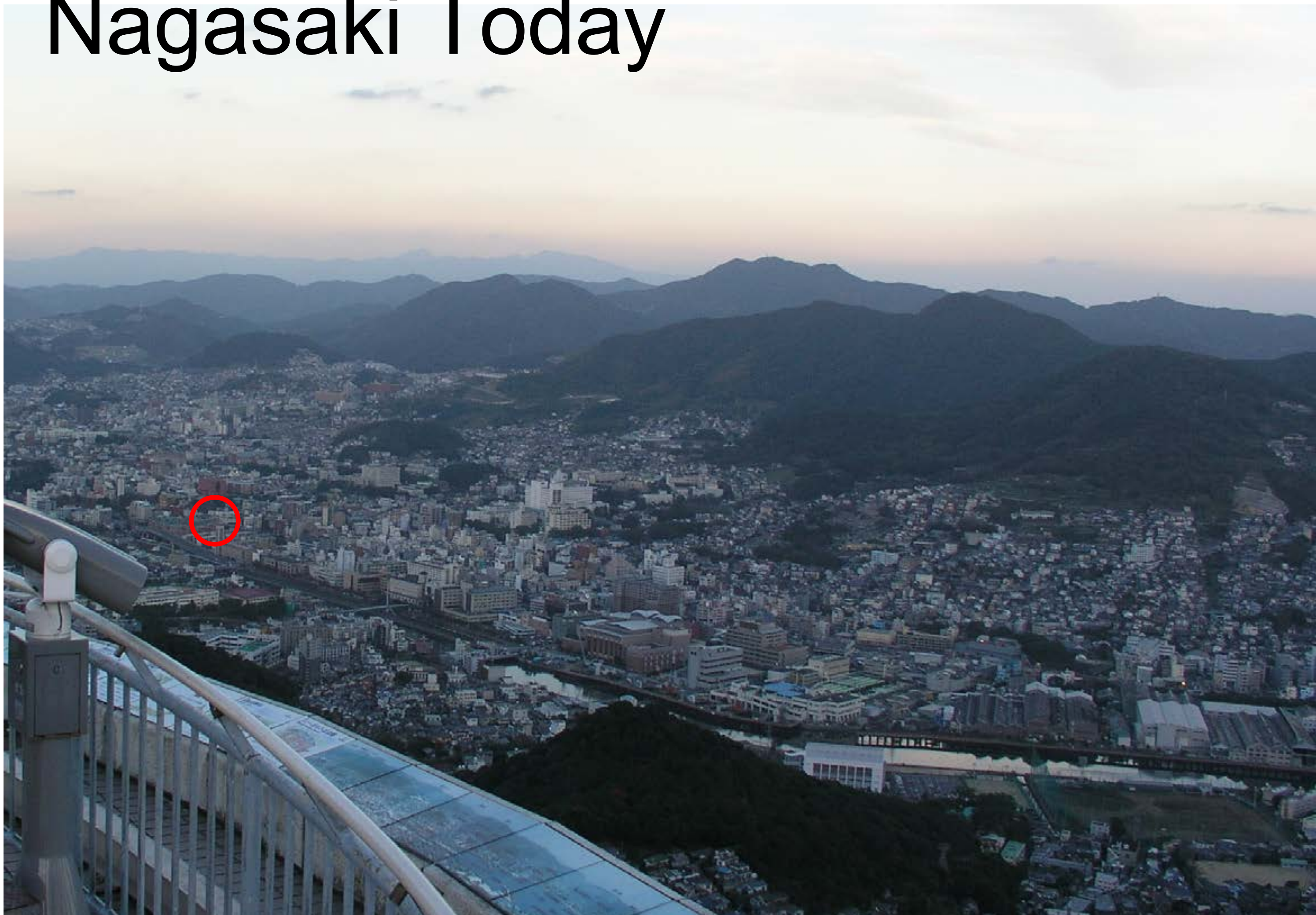
Gamma emitter with few neutrons



Map of Nagasaki and epicenter of bomb

Nagasaki Bomb

Nagasaki Today



Hiroshima Bomb

Mixture of neutrons and gamma rays; not tested before → dosimetry based on computer simulation

Hiroshima chamber of Commerce - before 1945

Hiroshima Bomb

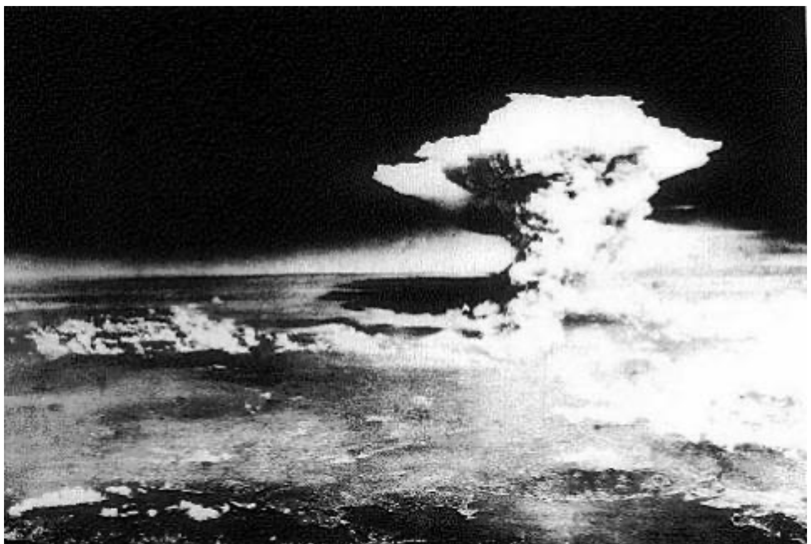
Hiroshima immediately after the bomb

The A-bomb Dome today

Fallout Victims

- Nuclear weapon testing in the Pacific in the 1950s
- Due to a wind shift, fallout fell on Marshall Islands
- Due to I-131 in the fallout and subsequent ingestion, 100% of young children developed thyroid tumors
- It is estimated that the average dose to thyroids was about 15 Gy

Fallout Victims



March 1, 1954

Project 4.1

Fallout Victims

Project 4.1 was the designation for a medical study conducted by the United States of those residents of the Marshall Islands exposed to radioactive fallout from the March 1, 1954, Castle Bravo nuclear test

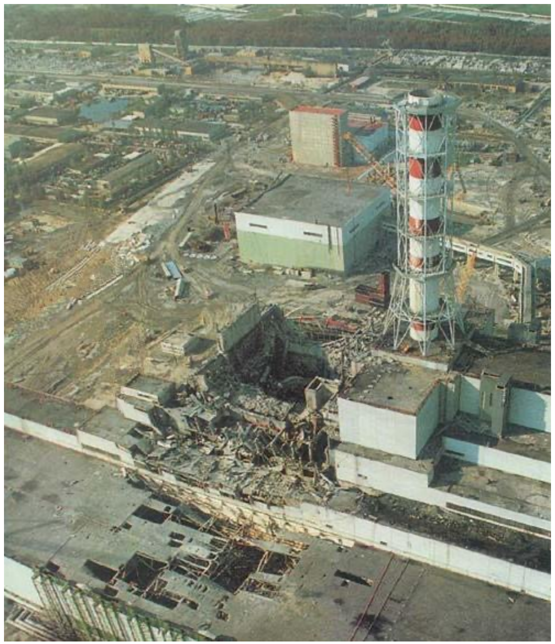
As a Department of Energy Committee writing on the human radiation experiments wrote, "It appears to have been almost immediately apparent to the AEC and the Joint Task Force running the Castle series that research on radiation effects could be done in conjunction with the medical treatment of the exposed populations." The DOE report also concluded that "The dual purpose of what is now a DOE medical program has led to a view by the Marshallese that they were being used as 'guinea pigs' in a 'radiation experiment.'"

Chernobyl Accident

- The Chernobyl nuclear reactor accident occurred on 4/26/1986 was the worst nuclear power plant accident in history
- 400x more fallout was released than had been by the atomic bombing of Hiroshima
- Large areas in Ukraine, Belarus, and Russia were badly contaminated, resulting in evacuation and resettlement of over 336,000 people

Chernobyl Disaster

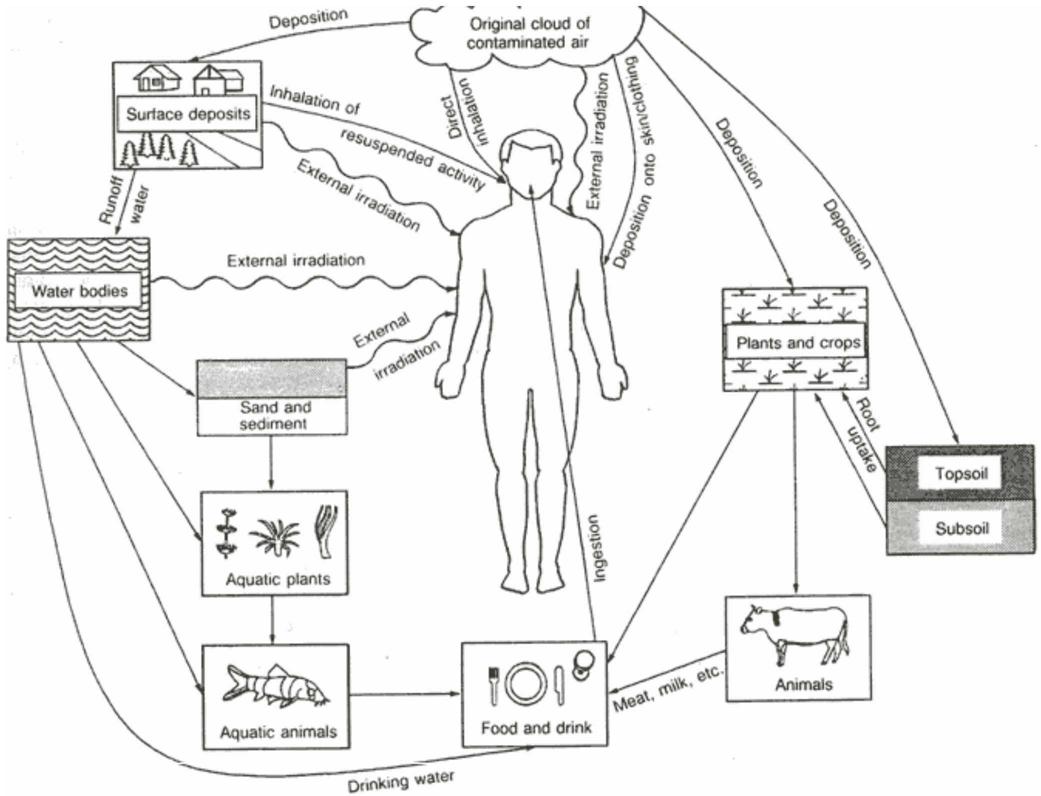
Areas Affected



Nuclear reactor

On April 26, 1986, at 01:23:44 a.m. reactor number four at the Chernobyl plant exploded. Further explosions and the resulting fire sent a plume of highly radioactive fallout into the atmosphere and over an extensive geographical area.

Chernobyl Disaster



Pathways to Contamination following Chernobyl

Results of the Chernobyl Accident

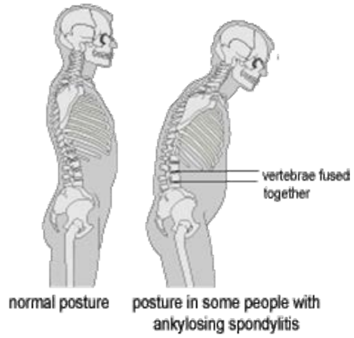
- 28 people died of Acute Radiation Syndrome; 19 more died later (1987-2005)
- Evironmental problems: The accident released 10^{18} Becquerel of radioactive material
- Psychological trauma

Chernobyl Disaster

- It is still too early to determine the extent of cancer induction in people exposed at or near Chernobyl
- Thyroid cancer in children skyrocketed to nearly 7,000 cases in Belarus, Russia, and Ukraine by 2005
- The 2005 report prepared by the Chernobyl Forum, attributed 56 direct deaths (47 accident workers, and 9 children with thyroid cancer), and estimated that there may be 4,000 extra cancer deaths among the approximately 600,000 most highly exposed people
- 3 years later, the UN committee on atomic radiation abandoned the linear no-threshold model for predicting Chernobyl cancer deaths because of "unacceptable uncertainties"
- Critics such as Greenpeace responded with new predictions of 93,000 cancer deaths caused by Chernobyl

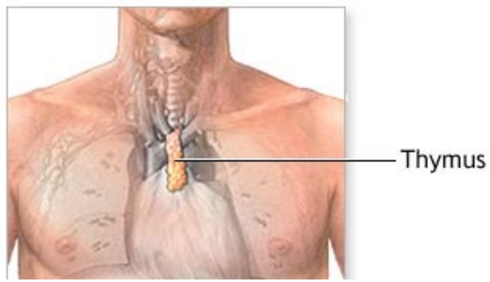
Ankylosing Spondylitis Therapy Patients

- Between 1935 and 1944, about 14,000 patients suffering this arthritic condition of the spine were treated with external beam radiotherapy or injections of Ra-224
- A small fraction of these developed leukemia or bone cancer attributed to their radiation exposure
- One of the largest bodies of data on radiation-induced leukemia with good dosimetry



Children Treated for Enlarged Thymus

- Children were treated by teletherapy to known doses
- Increased incidence of thyroid cancer was observed
- In females, an increase in breast cancer has also been suggested



Children Treated for Tinea Captis

- Children were epilated by irradiation of the scalp using X-rays
- Major studies made of children in Israel and New York City
- In Israel, a significant increase in thyroid, brain, salivary gland, and skin cancer, as well as leukemia has been observed

Patients treated for tinea captis who later developed a cancer in the scalp

Children Treated for Tinea Captis

- A group of comparable children in NY show quite different results
- There were only 2 malignant thyroid tumors in addition to some benign tumors
- There is, however, an incidence of skin cancer around the face and scalp in those areas also subjected to sunlight
- The skin tumor arose only in white children, and there were no tumors in black children in the New York series

Question

For Children who, historically, were treated for tinea capitis using ionizing radiation, which of the following organs did NOT demonstrate an excess relative risk for a radiation-induced malignancy?

A. Brain
B. Thyroid
C. Pharynx
D. Bone Marrow
E. Breast

Women Given Multiple Fluoroscopies

- In sanitoria in Nova Scotia and Massachusetts, women were subjected to multiple fluoroscopies during pneumothorax treatment for tuberculosis (TB)
- Often, several hundred fluoroscopies were delivered at average doses of 0.04 – 0.2 Gy
- These patients were about 80% more likely to develop breast cancer in the exposed breast compared to their unexposed (control) breast

Pneumothorax for TB Treatment

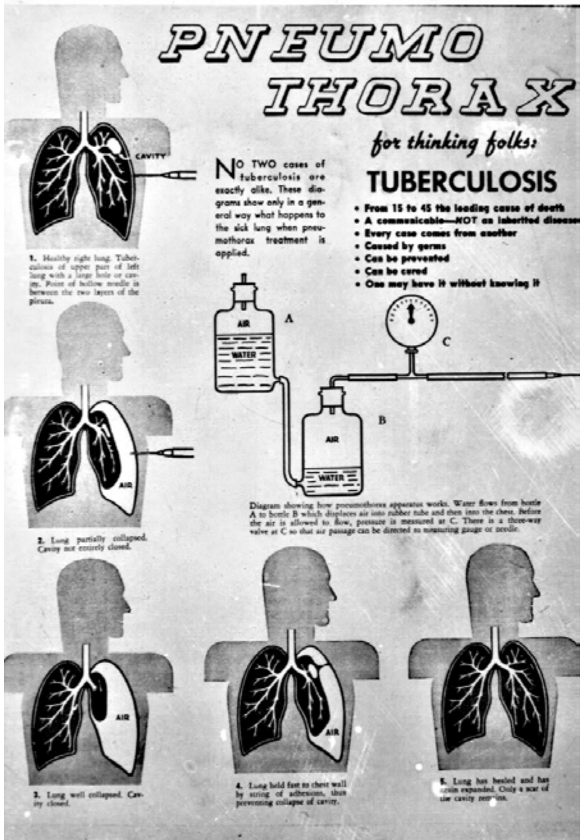
- In the 18th century, French physicians noticed that patients with tuberculosis who developed spontaneous pneumothoraces improved.
- By the late 19th century, Carlo Forlanini had developed a technique to induce pneumothorax, forcing nitrogen into the chest through a needle pleurocentesis, thus collapsing the lung in an attempt to close tuberculous cavities
- Artificial pneumothorax was independently developed as a treatment in the United States but did not gain widespread popularity there until several years later.
- Although the procedure was an important part of treatment until the introduction of effective antibiotics, tuberculosis remained such an overwhelming public health problem that it provided a powerful stimulus for continued surgical innovation.
- In this way, the treatment of tuberculosis really laid the foundations of modern thoracic surgery.

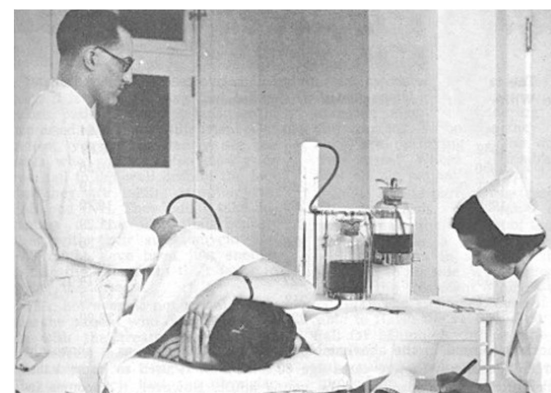
Pleurocentesis is performed while the patient is being monitored (circa 1930).

Creation of a pneumothorax: Ignoring physiologic principles, air (*luft*) is introduced into the chest (circa 1930).

http://www.cmaj.ca/content/182/2/179.full

Pneumothorax for TB Treatment





http://www.feltondesignanddata.com/cressontbsanatoriumremembered/id19.html

Women Treated for Postpartum Mastitis

- Patients were treated with 1-6 Gy
- An increased incidence of breast cancer has been observed

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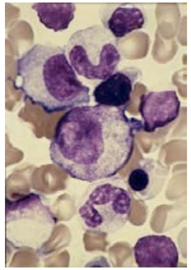
Radiation-Induced Cancer in Human Populations

- Under appropriate conditions, a malignancy can be induced in essentially all tissues of the body
- Most common examples are
  - Leukemia
  - Thyroid cancer
  - Breast cancer
  - Lung cancer
  - Bone cancer
  - Skin cancer

Leukemia

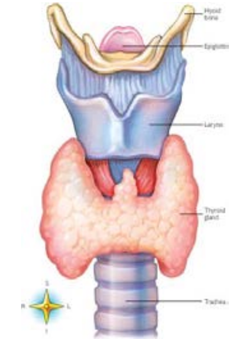


- Acute and chronic myeloid leukemia (AML & CML) account for the excess incidence observed in irradiated adults
- Children are most susceptible to radiation-induced acute lymphocytic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL) does not appear to be affected by radiation

Leukemia

- Leukemia was the first malignancy to be linked with radiation exposure in the A-bomb survivors
- Survivors of A-bomb and patients treated for ankylosing spondylitis were used for risk estimates
- Leukemic risks increased with dose up to ~ 3 Sv
- Linear-quadratic model (upward curvature) is better than linear function in relating the dose to leukemia risk
  - Risk per unit of dose at 1 Sv is ~ 3x greater than at 0.1 Sv

Thyroid Cancer



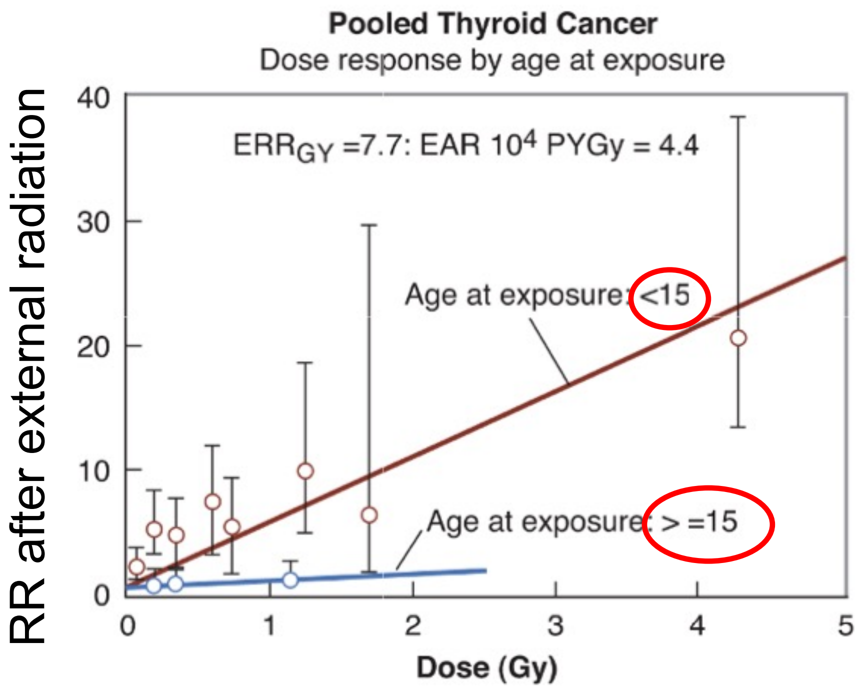
- Thyroid gland is highly sensitive to radiation carcinogenesis
- Fortunately, majority of induced cancer are well-differentiated, and highly curable
- Susceptibility is age-dependent – children are most susceptible
- ~ 7,000 cases of thyroid cancer were observed as a result of Chernobyl accident
  - Chernobyl is an area of low natural iodine levels

Thyroid Cancer

Figure 4. One major means by which fallout and nuclear debris are transferred through the atmosphere to people is via the production and consumption of dairy products. Fallout descends onto vegetation, which is eaten by dairy animals. The fallout passes into the animals' milk, which is prepared for human consumption. This pathway is the single largest means by which people in the U.S. were exposed to iodine-131 from fallout generated by nuclear weapons testing. (Figure adapted from the National Cancer Institute.)

- Increased risk in children beginning at 4 years after exposure; still has not dropped off in incidence, so risk may be higher for life
- Caused by I-131 in the milk and ≥90% was due to milk ingestion
- Could have been prevented by giving KI or avoid milk
- Increased incidence is also being observed in adults

Thyroid Cancer

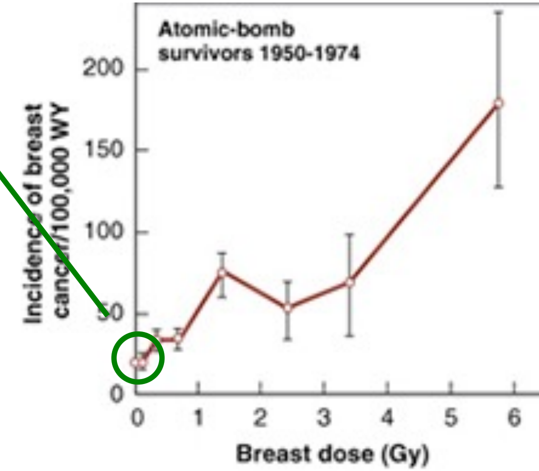


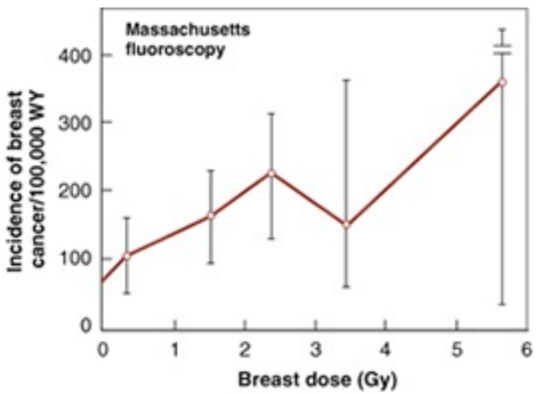
Note the importance of age at exposure

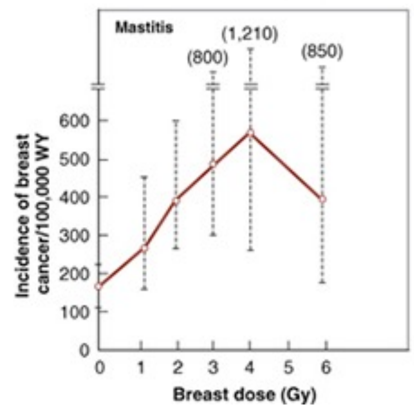
Pooled analysis of seven studies (external radiation)

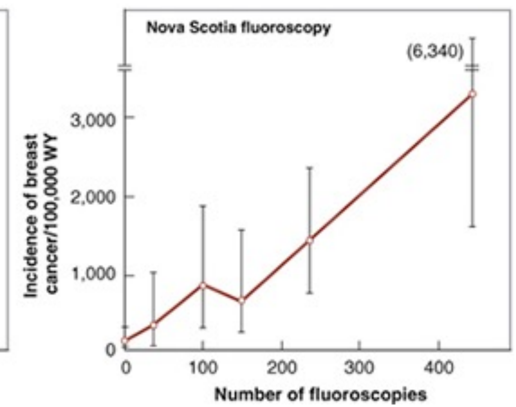
Breast Cancer

Note the natural low incidence of breast cancer in Japanese women



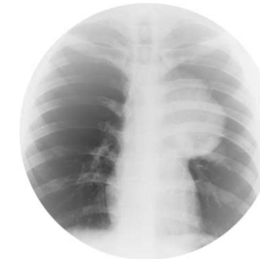






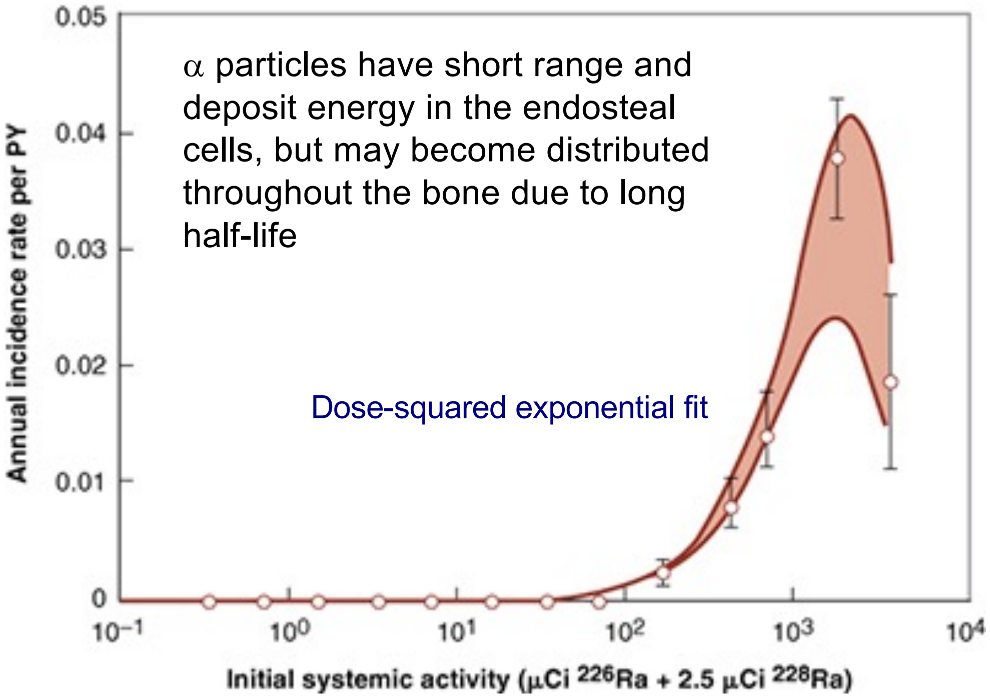
- Incidence rises with radiation dose
- The dose-response are reasonably well fitted by a straight line

Lung Cancer



- Many carcinogens can cause lung cancer
- There is a clear excess of lung cancers among workers in uranium, non-uranium, and the fluorspar mines
- However, it is difficult to separate the contributory effect of radon and cigarette smoking
- There is also evidence of an excess lung cancer from domestic radon exposure
- It is estimated that 10% of the lung cancer deaths in the US are due to domestic radon exposure

Bone Cancer



Bone Sarcoma incidence as a function of Ra ingested in female dial painters

Note that no tumors occurred at doses below 5 Gy → sarcomas are induced only after doses large enough to cause tissue damage and therefore to stimulate cell proliferation?

Age at the time of exposure is an important factor in the development of bone cancer

Skin Cancer

- Squamous cell and basal cell carcinomas are most frequently observed
- Used to be an occupational disease for radiation workers
- Radiation-induced skin cancers are diagnosed readily and treated at an early stage

Comparative Susceptibility*

High	Moderate	Low	Very Low or Absent
▪ Bone marrow (leukemia other than CLL) ▪ Breast ▪ Salivary glands ▪ Thyroid (more common in female)	▪ Bladder ▪ Colon ▪ Stomach ▪ Liver ▪ Lung ▪ Ovary ▪ Skin	▪ Bone ▪ Brain ▪ Connective tissue ▪ Kidney ▪ Larynx ▪ Nasal sinuses	▪ Cervix ▪ CLL ▪ Oral cavity ▪ Esophagus ▪ Melanoma ▪ Prostate ▪ Uterus ▪ Pancreas ▪ Rectum ▪ Gallbladder ▪ Hodgkin's lymphoma ▪ Lymphatic system & myeloma ▪ Testes ▪ Muscle

*Based on % increases in background incidence/unit dose

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- Nonneoplastic Disease and Radiation

The Latent Period

Message Received: 3 days ago

Rashidi, Armin, MD → Yuan, Jianling, MD

Hi Jianling,
Remember this patient? Hodgkin with bulky mediastinal mass and vanishing bile ducts. Her liver function is remarkably better after chest RT and I am considering ABVD on Friday. Two questions:
1. She developed an SCC of her skin over the right SC area. The timeline doesn't fit radiation-related, what do you think?
2. What does your literature suggest for risk of radiation recall (pneumonitis) with chemo this far out from RT? I suspect her lungs were at least partially in the field?
Thank you,
Armin

10/15/2018

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FINAL DIAGNOSIS:
Skin, right lateral neck:
- Features consistent with squamous cell carcinoma, well differentiated,
extending to the deep margin - (see
comment)
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3960 cGy in 22 fractions
Completed 8/10/2018

- **Latent period** is the time interval between irradiation and the appearance of a malignancy
- Leukemia typically has a shorter latent period compare to solid tumors

The Latent Period – Leukemia

- For the A-bomb survivors, the incidence of leukemia began to appear after 2 years, and reached a peak by 5-7 years
- Most cases occurred in the first 15 years
- An **excess relative risk (**ERR) still existed even 40 years after exposure

The Latent Period – Solid Cancers

- For solid cancers, the latent period for A-bomb survivors has ranged from 10 to over 60 years
- Recent data from Chernobyl seems to indicate an even shorter minimum latent period for thyroid cancer in children exposed to ^{131}I in fallout, may be as short as 5 years

Age at Expression

- One should not view the latency as a *fixed* time interval
- **"Age at expression"** – regardless of the age at the time of exposure, radiation-induced solid tumors tend to be expressed later in life, at the same time as spontaneous tumors of the same type
- This suggests that although radiation may initiate the carcinogenic process at a young age, additional steps are required later in life
- Fixed time interval has been replaced by a combination of "age at exposure" and "time since exposure"

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- Cancer Risk in Irradiated Fetus

Committees Concerned with Risk Estimates

- UNSCEAR – United Nations Scientific Committee on the Effects of Atomic Radiation
- BEIR – Committee on the Biologic Effects of Ionizing Radiation
- Both are "scholarly" committees – under no obligation to draw conclusion if data are not available

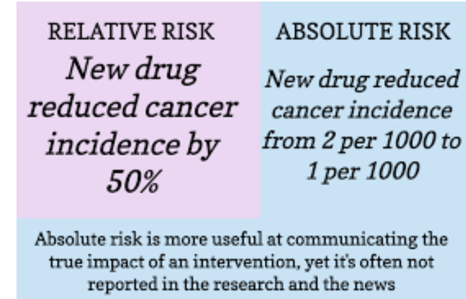
Committees Concerned with Radiation Protection

- ICRP – International Commission on Radiological Protection
- NCRP – National Council on Radiological Protection and Measurements
- Must make recommendations whether or not adequate data are available

Risk Estimates

- To use available human data to estimate risks as a function of dose, it is necessary to fit the data into a model
- Data obtained at relatively high doses must be extrapolated to the low doses of public health concern
- Estimates must be projected into the future
- Data pertaining to the Japanese must be transferred to other populations

Risk Models



Absolute Risk Model

Assumes that the excess risk from radiation ***adds to*** the underlying risk by an increment dependent on the dose but independent of the underlying natural risk

Relative Risk Model

Assumes that the effect of radiation is to increase the natural incidence **at all ages** subsequent to exposure ***by a given factor***; if the excess equals the baseline risk, the relative risk (RR) is 2

Model Favored by the BEIR

- The BEIR III committee preferred the absolute risk model, whereas the BEIR V committee used the relative risk model exclusively
- BIER VII (2006) favored **Time-dependent relative risk model** – the excess incidence of cancer was assumed to be a function of
  - Dose
  - Square of the dose
  - Age at exposure
  - Time since exposure
  - Gender – e.g. for breast cancer

Quantitative Risk Estimates

- Despite a diverse collection of data for cancer in humans from medical sources, both BEIR and UNSCEAR elected to base their risk estimates almost entirely of the A-bomb attacks on Hiroshima and Nagasaki

Hiroshima

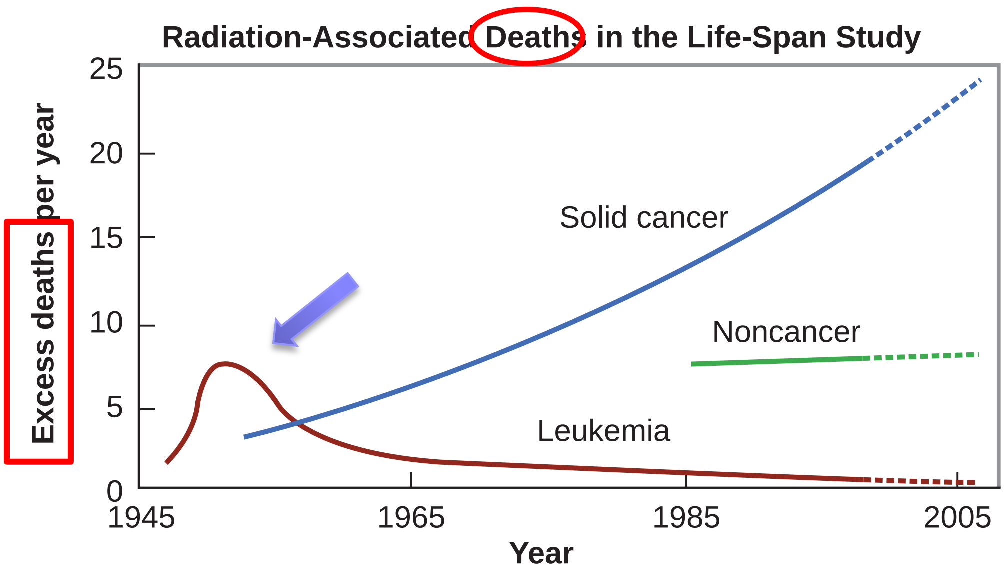
Nagasaki

Radiation Effects Research Foundation

RERF A-Bomb Cohorts

Cohort	Size	Objective
Life Span Study	120,000	Allows an estimates of cancer incidence and mortality
In-Utero Cohort	3,600	Allows estimates of malformation, growth retardation, microcephaly, mental retardation
Children of Exposed Individuals (F1)	77,000	Allows estimate of heritable effects

Radiation-Associated Deaths in the Life-Span Study

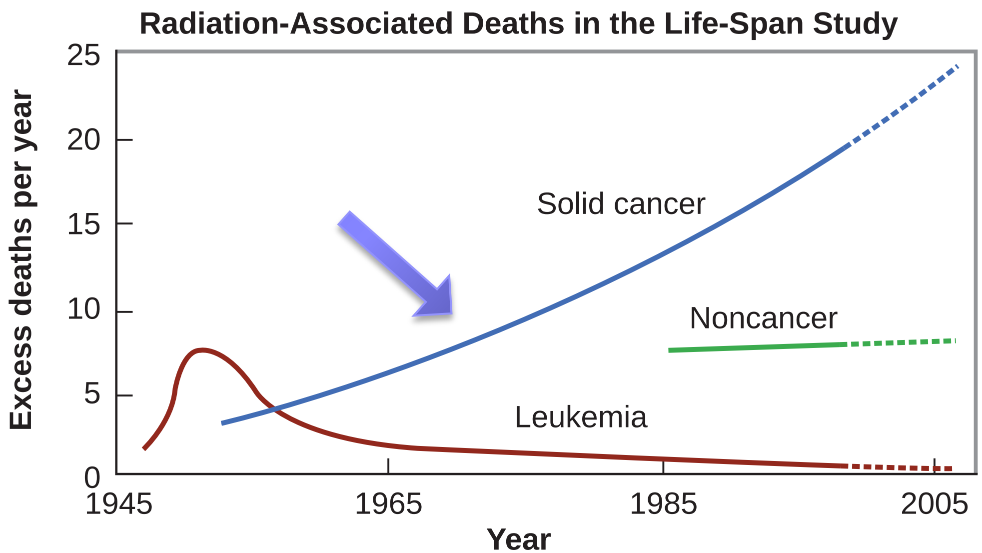


Leukemia

- Has the highest relative risk (RR) of any malignancy
- Leukemia deaths peaked at 5 to 7 yrs after exposure, then falls rapidly
- Risk may differ based on age at exposure

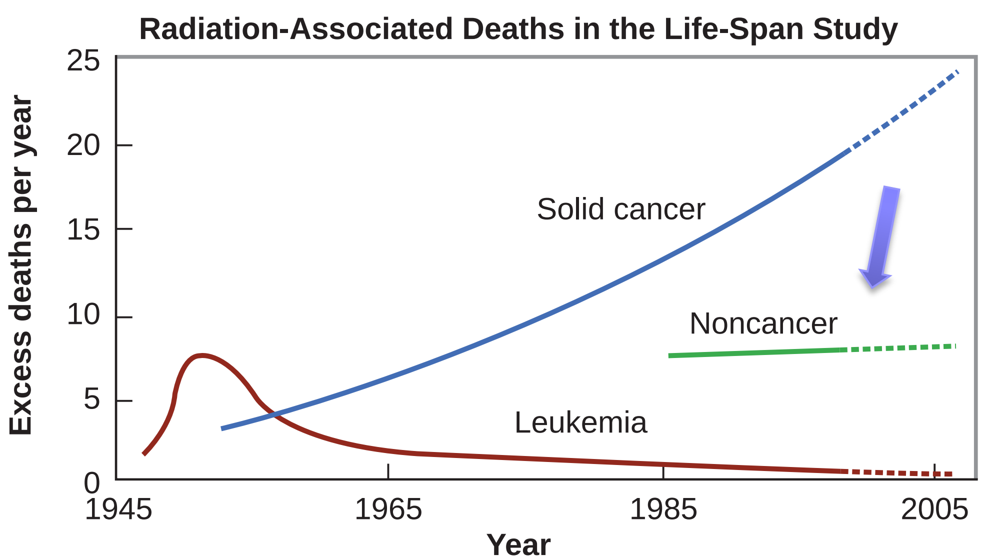
Radiation-Associated Deaths in the Life-Span Study

Solid Tumor



- Excess solid tumor did not appear for several years, but have continued to increase up to the present time
- Incidence is about 6:1 compared to leukemia death

Radiation-Associated Deaths in the Life-Span Study



Non-cancer Deaths

- By 1990, there was evidence for the induction of non-cancer effects
- Effects include heart disease, stroke, digestive disorder, and respiratory disease
- Unclear if there is a threshold – may require dose > 1 Sv
- Mechanism unclear

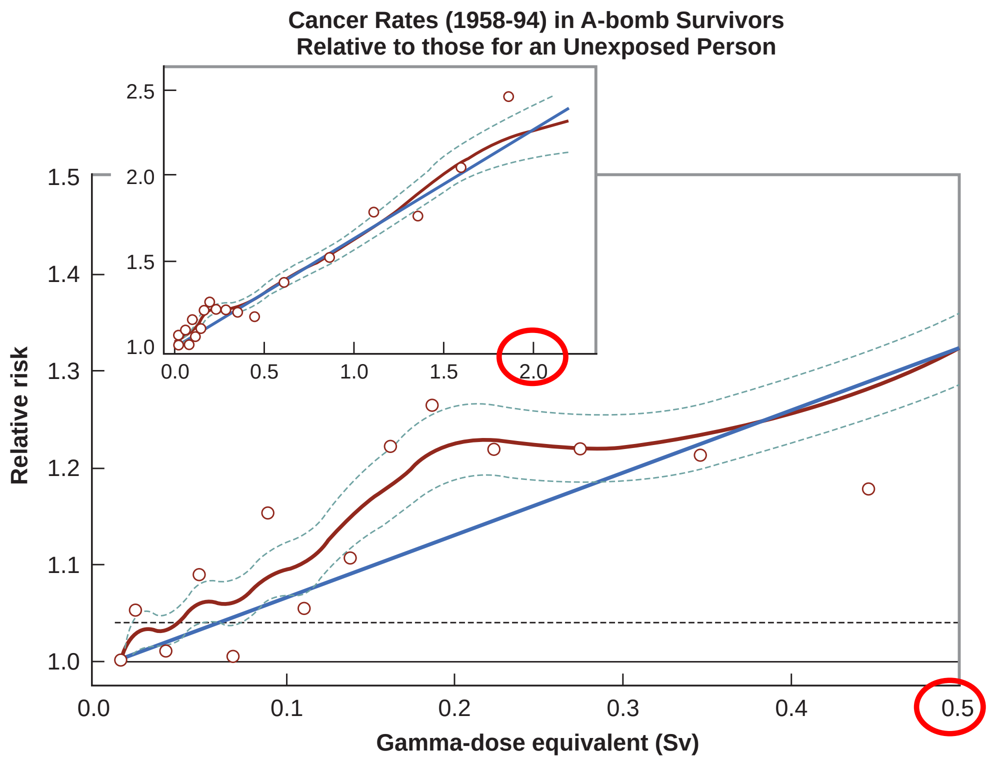
Solid Cancer Incidence Raw Data

Dose, Sv	# Subjects	Solid Cancers	Estimated Excess
Beyond > 3,000 m	25,427	3,994	0
< 0.005 Sv within < 3,000m	35,545	5,603	3
0.005 – 0.1	27,789	4,406	81
0.1 – 0.2	5,527	968	75
0.2 – 0.5	5,935	1,144	179
0.5 – 1	3,173	688	206
1 – 2	1,647	460	196
2-4	564	185	111
Total	**105,427**	**17,448**	**853**

(1958-1998)

- Note that there is a relatively paucity of data
- Note that excess cases caused by radiation are few compared with naturally occurring malignancies

Estimated Relative Risk



The RR is a linear function of dose up to ~ 2 Sv

Over the **low-dose range** (0-0.5 Sv), there is a suggestion that the risks are slightly higher than the linear extrapolation from higher doses

Dose and Dose-Rate Effectiveness Factor (DDREF)

- The Japanese data relate only to high doses and high dose rates
- Both the UNSCEAR and BEIR committees considered that there is a **dose-rate effect** for low LET radiations
- 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

Dose and Dose-rate Effective Factor

The **DDREF** is defined as the factor by which radiation cancer risks observed after large acute doses should be reduced when the radiation at low dose rate or in as a series of small dose fractions

- Animal data indicated a dose rate effect for radiation induced cancers up to a factor of 10, but there is far too little human data for such estimate
- For purpose of radiation protection, the ICRP recommends that high dose rate be reduced by a factor of **2** for risk estimates at doses below **0.2 Gy** or dose rate below **0.1 Gy/h**

Note that **BEIR VII** Committee uses a value of 1.5 for its own risk estimations

ICRP Summary Risk Estimates

TABLE 10.4. *International Commission on Radiological Protection Summary of Risks of Cancer Lethality by Radiation*

	High Dose High Dose Rate	Low Dose Low Dose Rate
Working population	8×10^{-2} per Sv	4×10^{-2} per Sv
Whole population	10×10^{-2} per Sv	5×10^{-2} per Sv

~ 8% of people exposed to 1 Sv would die from a radiation-induced cancer.

DDREF = 2

The value for the whole population are a little higher because of the sensitivity of the young

BEIR VII Estimate

TABLE 10.4. *International Commission on Radiological Protection Summary of Risks of Cancer Lethality by Radiation*

	High Dose High Dose Rate	Low Dose Low Dose Rate
Working population	8×10^{-2} per Sv	4×10^{-2} per Sv
Whole population	10×10^{-2} per Sv	5×10^{-2} per Sv

All solid cancers in all age groups

Note that these are absolute risk

Population Average Cancer Risk Percent per Sievert

	Cancer Incidence	Cancer Mortality
Male	8.6%/Sv	4.6%/Sv
Female	12.8%/Sv	6.2%/Sv
Combined	10.8%/Sv	5.4%/Sv

National Research Council (2006) *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.* The National Academies Press, Washington, DC.

True or False

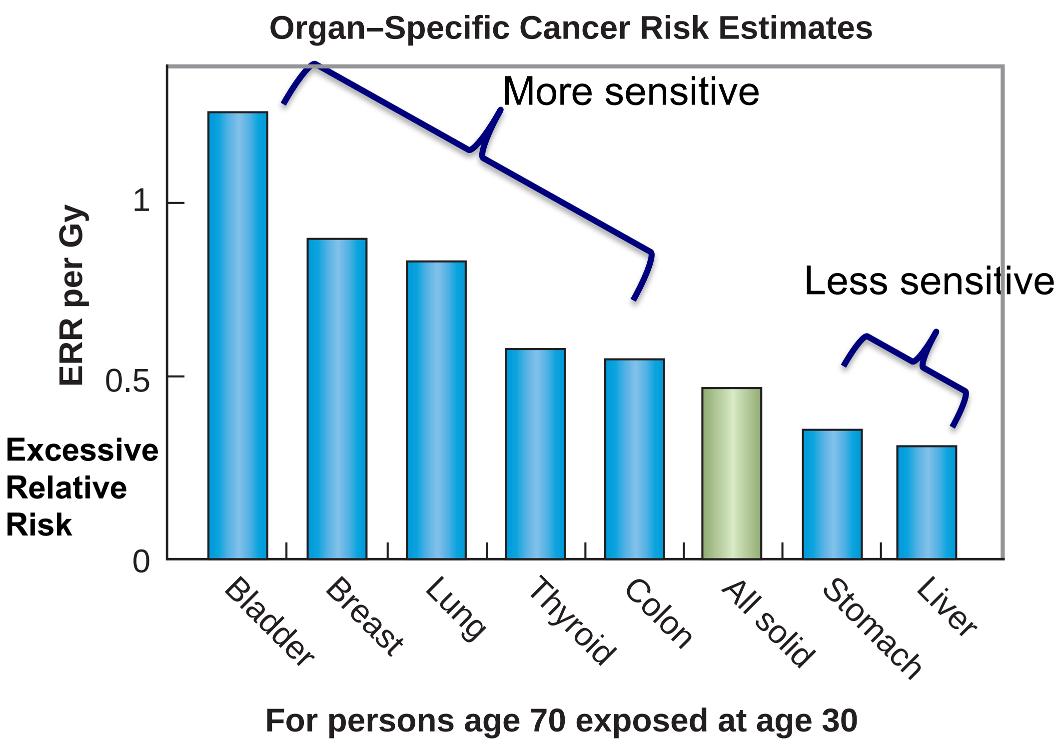
Based on the BEIR VII estimates, human exposure to ionizing radiation accounts for lifetime excess cancer risk (both fatal and non-fatal) of ~ 5% per 100 mSv.

False

	Cancer Incidence	Cancer Mortality
Male	8.6%/Sv	4.6%/Sv
Female	12.8%/Sv	6.2%/Sv
Combined	10.8%/Sv	5.4%/Sv

~ 1% per 100 mSv

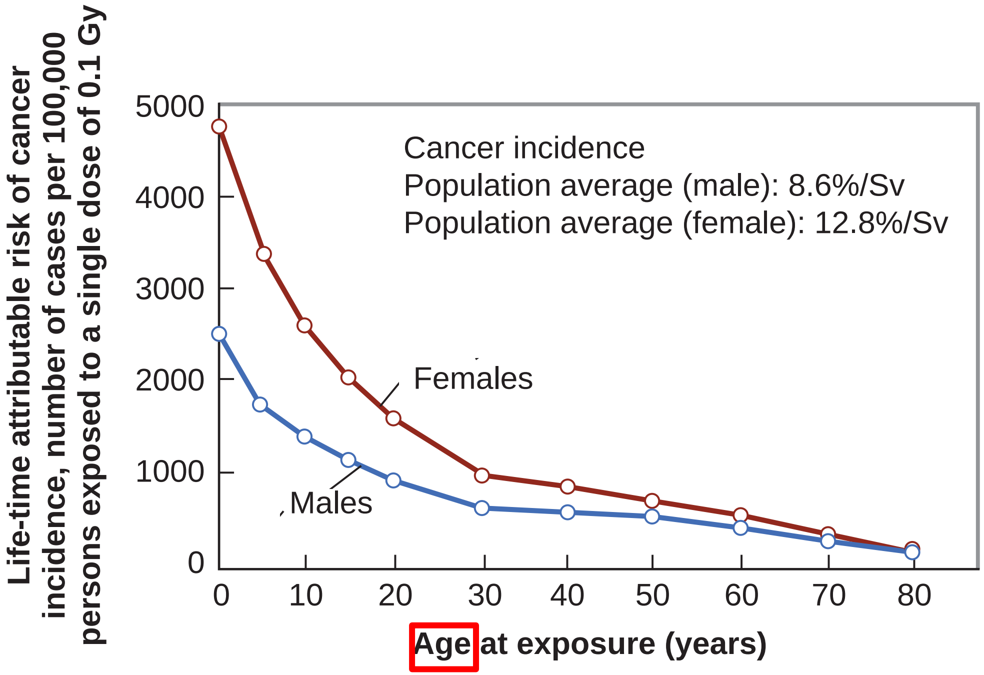
Organ-Specific Cancer Risk



These data may be used to calculate cancer risks from diagnostic or therapeutic procedures where only a specific area of the body is irradiated

Age Effect

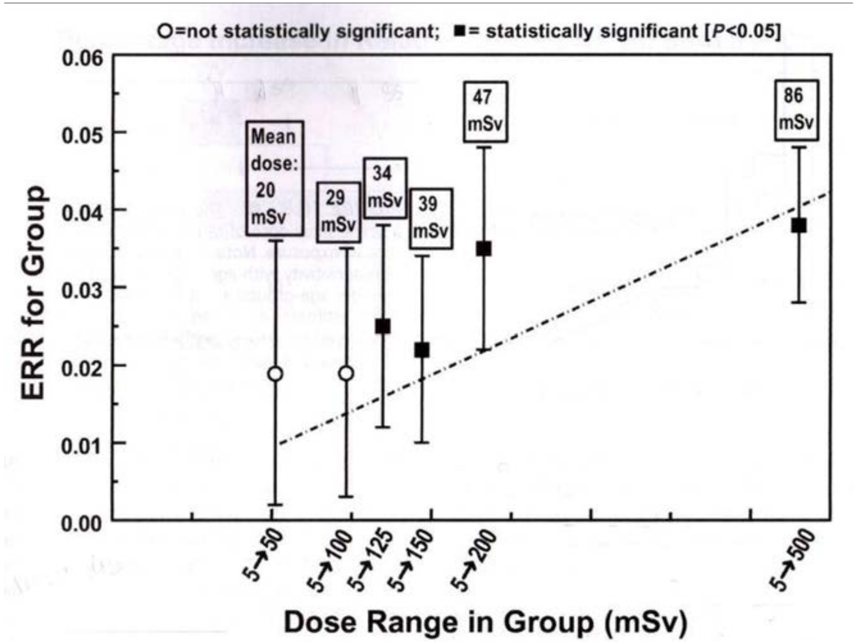
- Children and young adults are much more susceptible to radiation-induced cancer
- Females are more susceptible (breast)



Exceptions to the age effect

- Leukemia – constant
- Lung cancer – ↑ in middle age

Lowest Dose to Induce Cancer



Note the large error bars

Survivors were grouped according to the maximum dose received (up to 0.5 Sv)

30,000 A-Bomb survivors were exposed to 5-100 mSv

In this population, there is a small but statistically significant increased cancer risk (updated)

Carcinogenesis is a stochastic effect

Outline

- Deterministic and Stochastic Effects
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- Recent Human Experience
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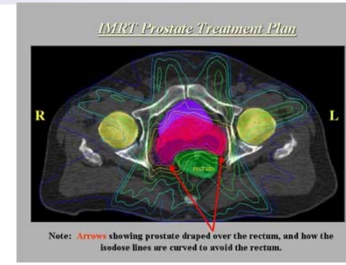
- The Latent Period
- Risk Estimates
- **Second Malignancies in Radiotherapy Patients**
- Cancer Risks in Nuclear-Industry Workers and Radiologists
- Childhood Cancer After Radiation Exposure in Utero

Second Malignancies in Radiotherapy Patients

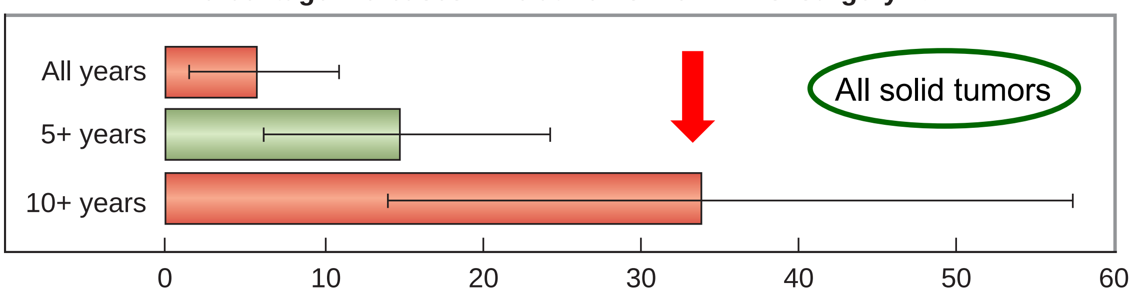
- Several large studies have shown that there is a small, but significant, risk of 2nd malignancies in cancer patients treated with radiation
- The confounding variable here is, of course, the "natural" risk of 2nd malignancies in cancer patients
- The major studies of special significance are
  - **Prostate cancer** patients treated by either surgery or radiation
  - Women treated for carcinoma of the **cervix**
  - **Hodgkin's lymphoma** survivor
  - **Brain tumor** induced by cranio-spinal irradiation in children

Prostate Cancer Patients



- Over 50,000 men treated with radiotherapy were compared with over 70,000 treated by surgery (SEER Database)
- There was no difference observed in the risk of leukemia but, after 10 years, the irradiated patients showed a relative increase of over 30% in solid cancers, and over 200% increase in sarcomas

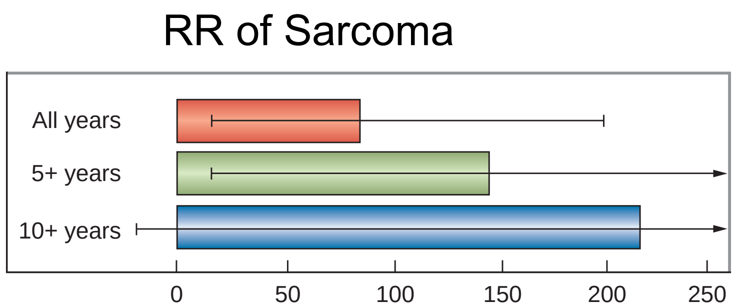
Percentage increases in relative risk for RT vs. surgery %

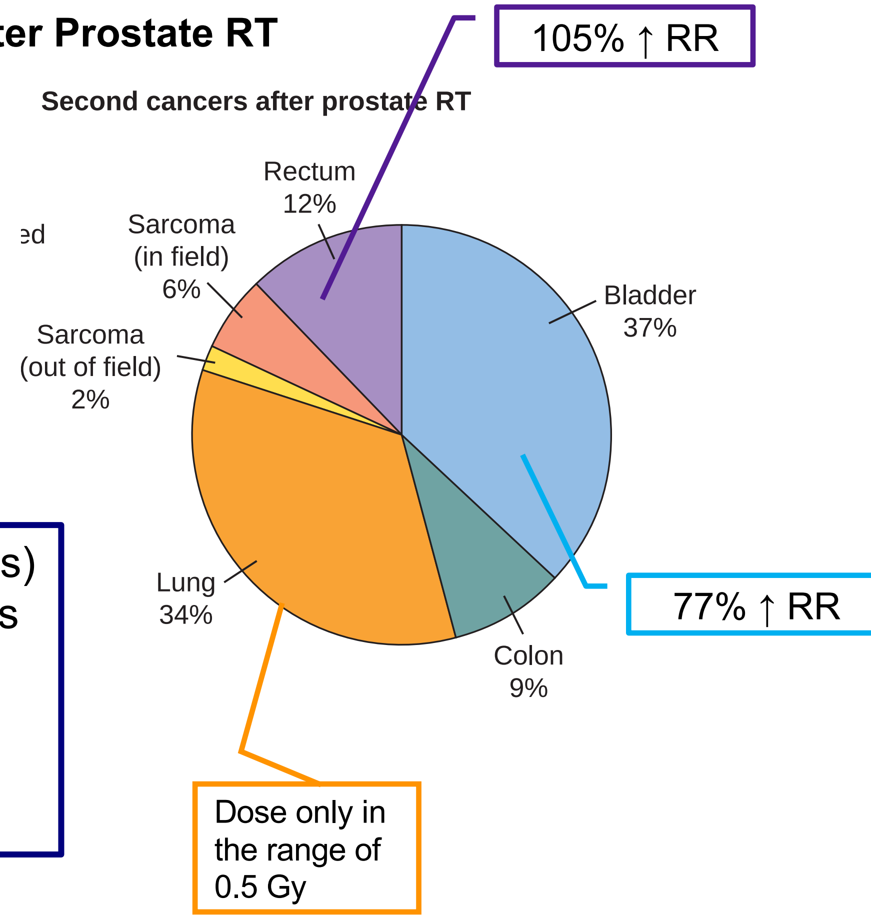


- RR ↑ with time post-treatment, and reached 34% after 10+ years
- The absolute risk was about 1 in 70 by 10 years posttreatment

Prostate Cancer Patients

Distribution of Second Cancer after Prostate RT

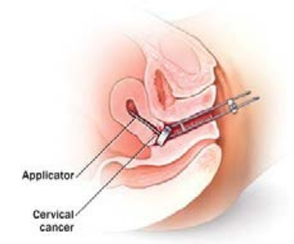




Carcinomas (originating in actively dividing cells) can be efficiently induced by relatively low doses of radiation

For **sarcoma** (mostly dormant), large radiation doses are needed to produce sufficient tissue damage to stimulate cellular renewal

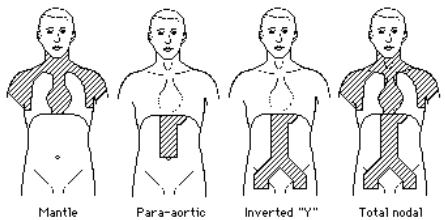
Cervical Cancer Patients



- About 150,000 patients were studied, comparing 2nd malignancy rates in patients treated with radiation vs. surgery
- An increase in cancers was observed for bladder (RR = 4.0), rectum, vagina and, possibly, bone (RR = 1.3), uterus, and cecum, as well as non-Hodgkin's lymphoma
- A steep dose-response curve was observed, with a 5-fold increase in 2nd cancer in tissues irradiated to doses > 150 Gy
- Risks were highest among long-term survivors and concentrated among women irradiated at relatively young ages

Hodgkin's Lymphoma Patients

- 2nd cancer is the leading cause of death in long-term survivors of HD
- The most prominent cancers are those of the breast in young women for whom the risk of breast cancer was as high as 60%
- For women over 30, the increased risk of breast cancer was only slight



Hodgkin's Lymphoma Patients

Medical resident only

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 24, 2015 VOL. 373 NO. 26

Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma

- 3,905 persons in Netherlands
- Treated for HL 1965-2000 (15-50 yo)
- 5 yrs of survival
- Median FU 19.1 yrs

Table 2. Standardized Incidence Ratios, Absolute Excess Risks, and 30-Year Cumulative Incidences of Selected Subsequent Malignant Neoplasms.*

Second Cancer or Cancer Site	ICD Code	No. of Patients	Standardized Incidence Ratio (95% CI)	Absolute Excess Risk *no./10,000 person-yr (95% CI)*	30-Yr Cumulative Incidence (95% CI)
Any cancer, excluding MDS†	—	884	4.6 (4.3 to 4.9)	121.8 (111.8 to 132.4)	32.5 (30.4 to 34.6)
Any solid cancer	C00–C80	757	4.2 (3.9 to 4.5)	100.5 (91.3 to 110.2)	28.5 (26.4 to 30.5)
Female breast‡	C50	183	4.7 (4.0 to 5.4)	54.3 (44.7 to 65.0)	16.6 (14.1 to 19.2)

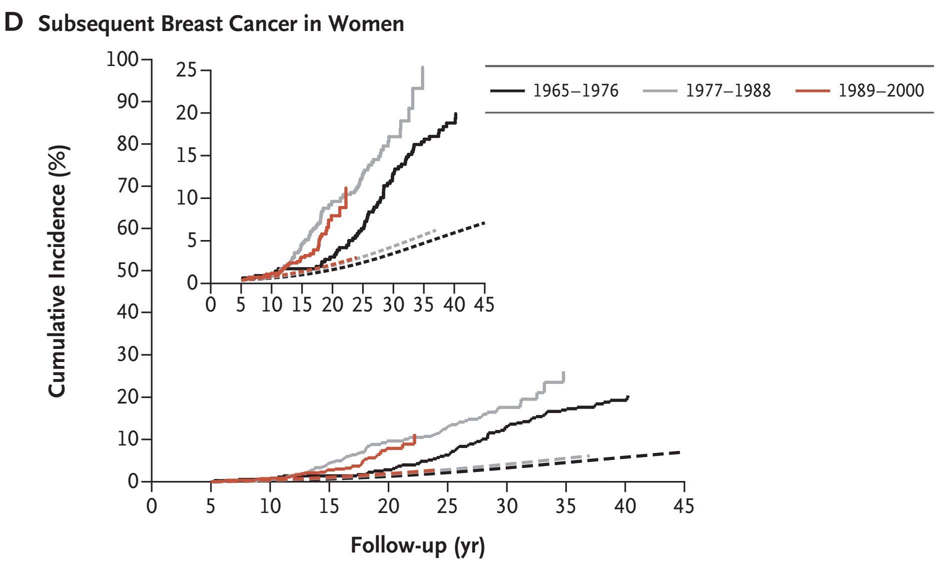
- The risk was still elevated 35 years or more after treatment
- Cumulative incidence of a 2nd cancer at 40 years was **48.5%**

The **standardized incidence ratio** (SIR) is a comparison of the incidence of second cancer observed in the study cohort with the expected incidence in the general population.

Hodgkin's Lymphoma Patients

Medical resident only

By Treatment Period

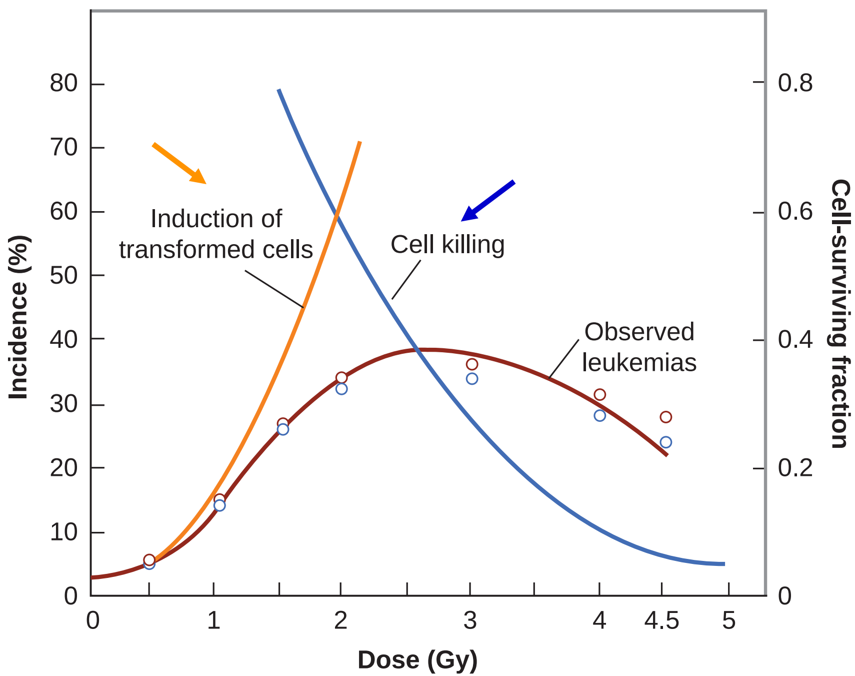


Solid lines represent the observed incidence, and dashed lines the expected incidence in the general population. The insets show the same data on enlarged y axes.

- The risk of breast cancer was lower among patients treated with supradiaphragmatic-field RT not including the axilla than among those exposed to mantle-field irradiation (HR 0.37)
- The risk was NOT lower among patients treated in the 1989–2000 study period than two earlier periods
- A cumulative procarbazine dose ≥4.3 g/m^2 (induces premature menopause) ⇔ a significantly ↓ risk of breast cancer (HR 0.57), but a ↑ risk of gastrointestinal cancer (HR 2.7)

Dose-Response Relationship at High Doses

Induction of leukemia in mice exposed to TBI



Gray attempted to explain the "bell-shaped" dose-response relationship for the induction of leukemia by the concurrent presence of 2 phenomenon

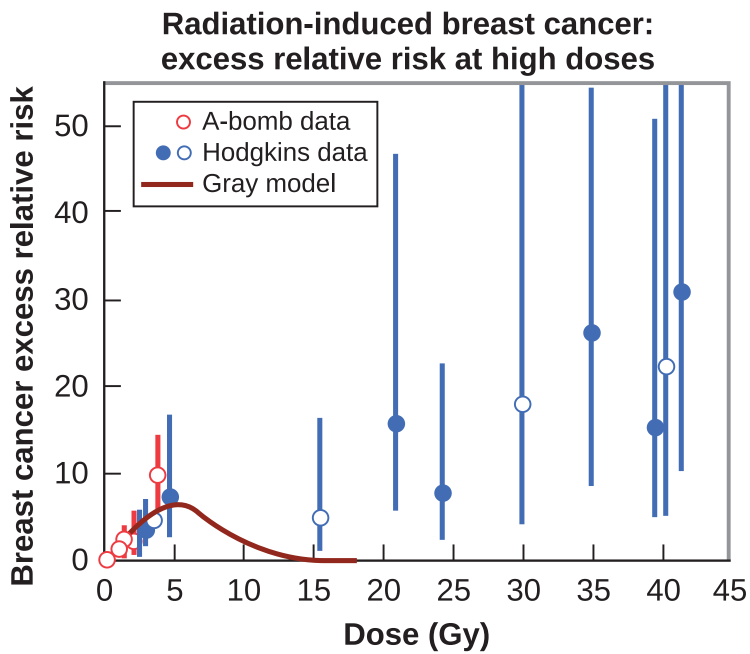
A dose-related ↑ in the proportion of transformed cells

A dose-related ↓ in the probability of transformed cells retaining reproductive integrity

It should be **NOT** assumed that this bell-shaped curve applies to radiation-induced carcinogenesis in general

Clinical Data – Radiation-Induced Breast Cancer

Breast cancer in Women treated for HD with Mantle field



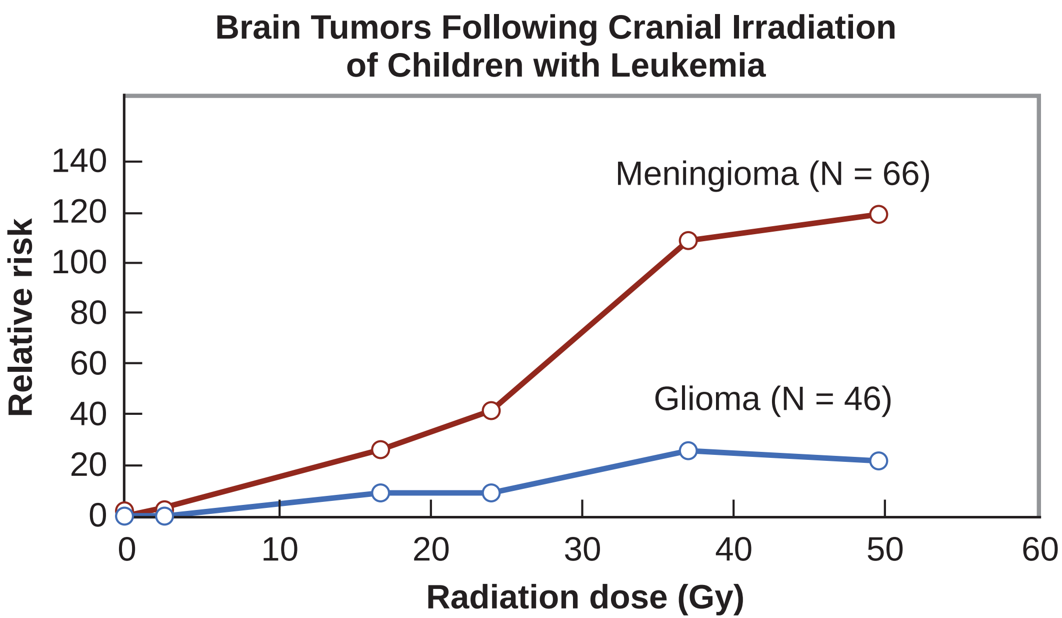
Fractionated Radiotherapy

Note that there was an increasing risk over the entire dose range

The authors speculated that cells initiated and transformed by radiation proliferate rapidly between daily dose fractions commonly used in radiotherapy

Clinical Data – Brain Tumor Induced by Cranial Irradiation

Childhood Cancer Survivor Study



Note again that the incidence of radiation-induced brain tumor does not fall at the high dose of fractionated therapy

How Do You Counsel Patients?

- The absolute risk of radiotherapy-induced 2nd malignancy is below or at 1% after radiotherapy of most adult cancers at 10 or 20 years later
- The risk of dying from uncontrolled disease is much higher

The answer is more guarded in pediatric population

Outline

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- Recent Human Experience
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- Childhood Cancer After Radiation Exposure in Utero

Cancer Risks in Nuclear-Industry Workers – IARC Study

400,000 nuclear workers from 15 countries who received **protracted exposures** to multiple low doses of radiation over many years

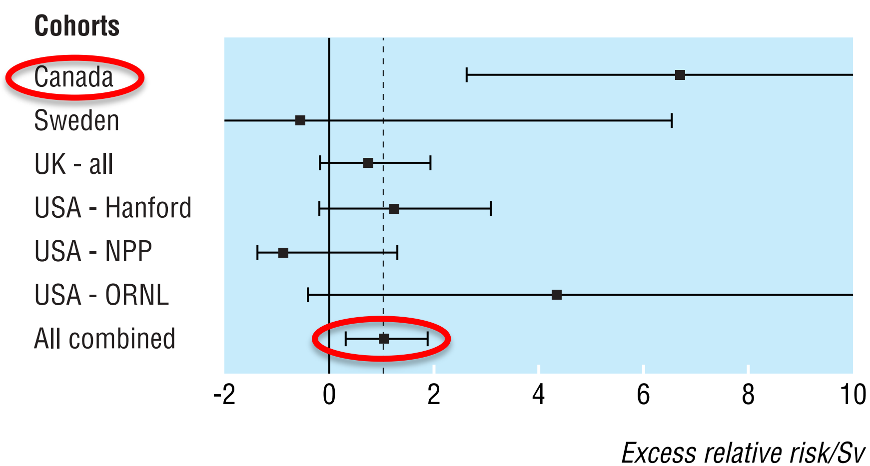


Fig 2 Excess relative risks per Sv for all cancer excluding leukaemia in cohorts with more than 100 deaths (NPP=nuclear power plants, ORNL=Oak Ridge National Laboratory)

There was a statistically significant excess of solid cancers for a mean dose of only 19.4 mSv

Caveats

- Data driven by the Canadian data (o/w would be NS)
- Lung cancer dominated the cancer spectrum (? Confounding by smoking)

The International Nuclear Workers Study (INWORKS)

Data from the 3 of the 15 nations (France, UK, US)
Monitored w/ personal dosimeters
FU up to 60 years after exposure

RR of Leukemia (ex CLL) & Lymphoma

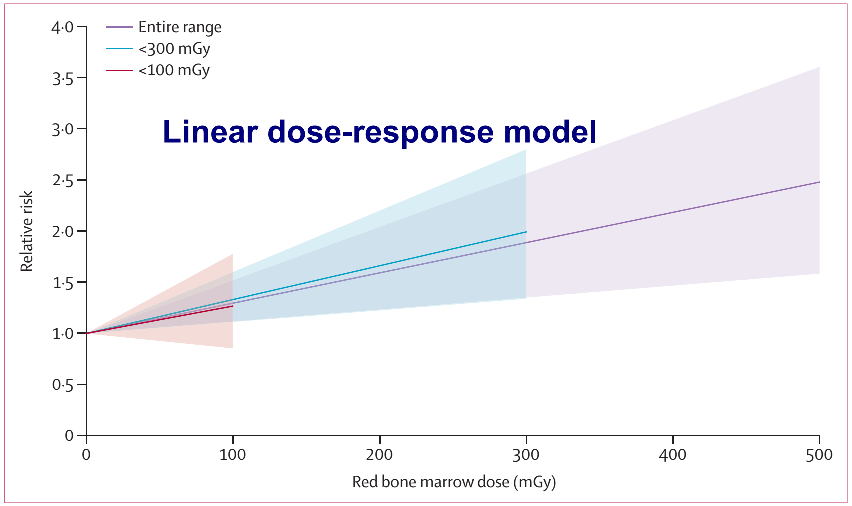


Figure: **Relative risk of leukaemia excluding chronic lymphocytic leukaemia associated with 2-year lagged cumulative red bone marrow dose**
The lines are the fitted linear dose–response model and the shading represents the 90% CIs.

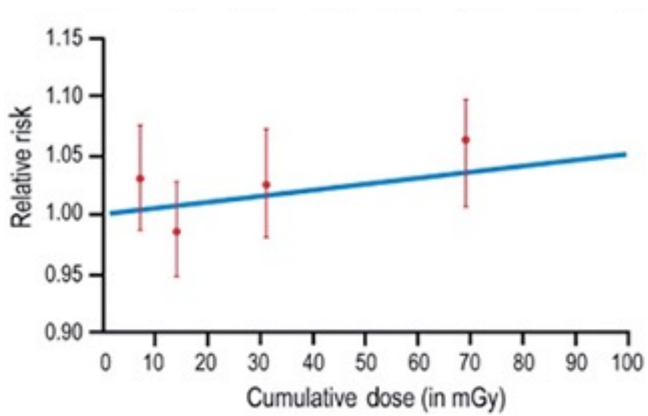
Excess relative risk (ERR) [chronic low dose exposure] similar to male atomic bomb survivors [acute exposure]

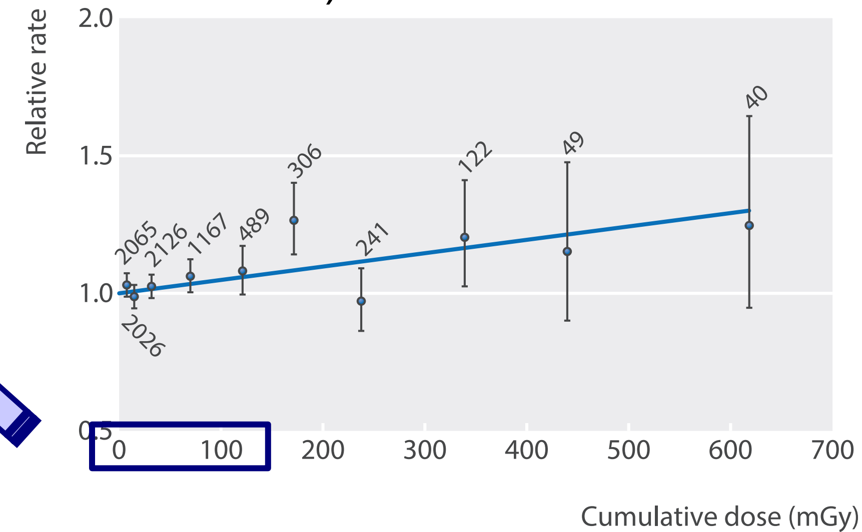
⇩

? DDREF for radiation carcinogenesis

INWORKS Study

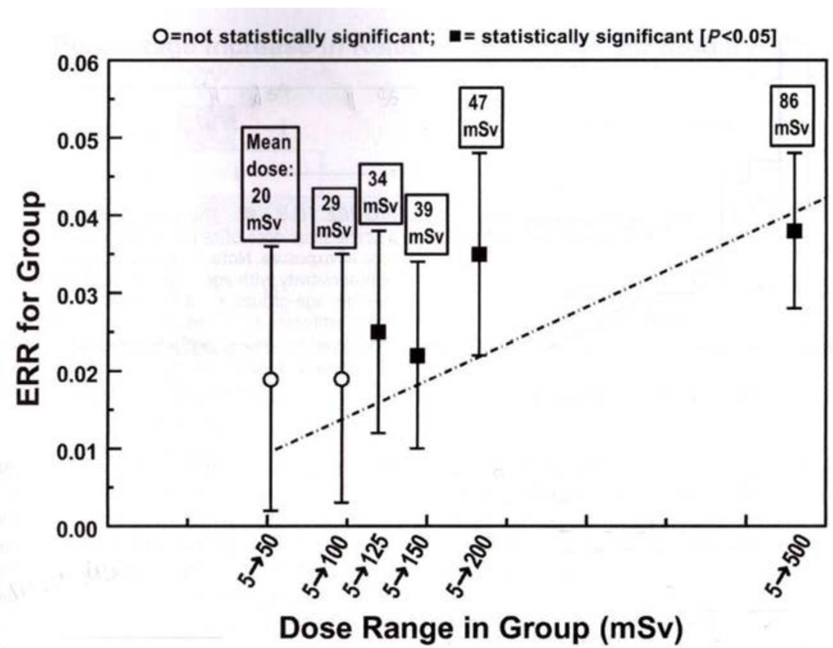
RR of Mortality from All Cancers (other than Leukemia)





- Risk increased by 48% per Gy
- The estimated association over 0-100 mGy is similar in magnitude to that obtained over the entire dose range
- Little indication of DDREF (in comparison with Japanese data)

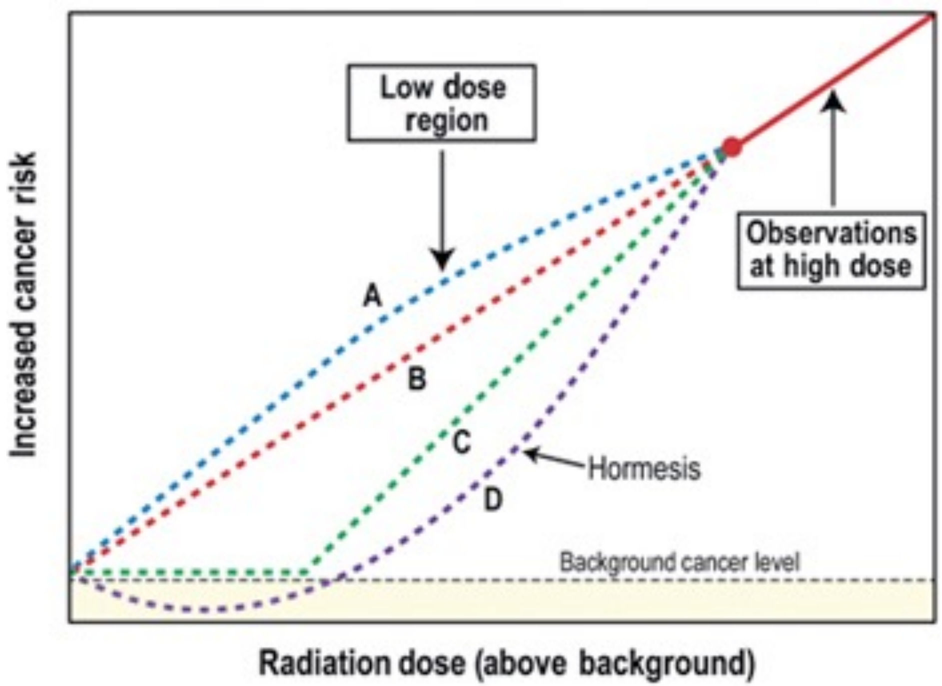
Extrapolating Cancer Risks from High to Low Doses



The A-bomb data has a large uncertainty at the low doses to which radiation workers are exposed

There has been a long-standing controversy of how best to extrapolate cancer risks from high doses to low doses

Extrapolating Cancer Risks from High to Low Doses



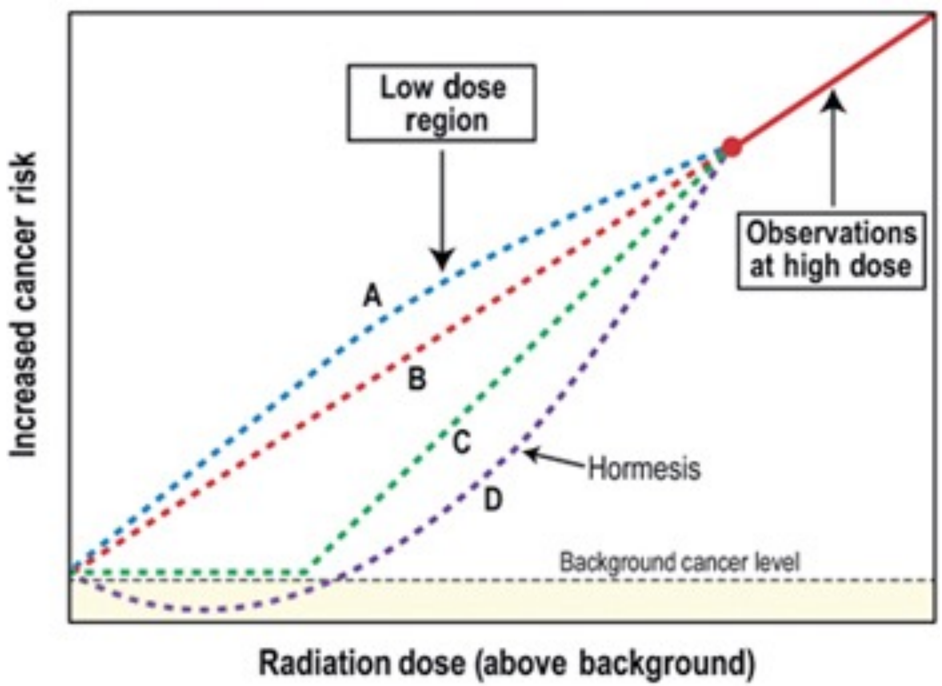
B – Linear no-threshold (LNT)

- Risks at low doses can be linearly extrapolated from high doses; no threshold
- Favored by BEIR, UNSCEAR, ICRP, NCRP
- Prudent and conservative assumption for radiation purpose

A

- Risks at low doses are higher than would be predicted from a linear extrapolation from high doses
- ? Consequence of bystander effect

Extrapolating Cancer Risks from High to Low Doses



C – Linear threshold

- There is a threshold, below which there are no deleterious effect of radiation

D – Radiation Hormesis

- Low levels of radiation are actually beneficial, activating repair mechanisms that protect against diseases
- Rejected by BEIR and UNSCARE

Mortality Patterns in Radiologists

Estimated annual doses 1 Gy per year!

Table 10.3 **Standard Mortality Ratios for All Causes of Death in British Radiologists, 1897-1997**

Years	Standard Mortality Ratio
1897-1920	1.75
1921-1935	1.24
1936-1954	1.12
1955-1979	0.71
All post-1920	1.04

- In early days, radiation risks to radiologists were large and easily demonstrable
- In more recent years, there is no sign of an excess mortality in radiologists
- At the same time there is no good evidence that low doses of radiation may be beneficial or can prolong life (when proper control was used)

Radiation Hormesis?

Experts say Trump's EPA is moving to loosen radiation limits

By ASSOCIATED PRESS / OCTOBER 2, 2018

A CT scan technician prepares for a patient at the Silver Cross Emergency Care Center in Homer Glen, Ill.

M. SPENCER GREEN/AP

WASHINGTON — The EPA is pursuing rule changes that experts say would weaken the way radiation exposure is regulated, turning to scientific outliers who argue that a bit of radiation damage is actually good for you — like a little bit of sunlight.

The government's current, decades-old guidance says that any exposure to harmful radiation is a cancer risk. And critics say the proposed change could lead to higher levels of exposure for workers at nuclear installations and oil and gas drilling sites, medical workers doing X-rays and CT scans, people living next to Superfund sites and any members of the public who one day might find themselves exposed to a radiation release.

The Trump administration already has targeted a range of other regulations on toxins and pollutants, including coal power plant emissions and car exhaust, that it sees as costly and burdensome for businesses. Supporters of the EPA's proposal argue the government's current model that there is no safe level of radiation — the so-called linear no-threshold model — forces unnecessary spending for handling exposure in accidents, at nuclear plants, in medical centers and at other sites.

Radiation Spa

THE WALL STREET JOURNAL.

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March 11, One Year On: Radium Hot Springs Still in Demand

By Eleanor Warnock
March 9, 2012 7:09 pm ET

PRINT   TEXT

Baths known as "radium hot springs" have existed in Japan for hundreds of years, their owners proclaiming the virtues of lightly radioactive radon gas as a way to clear skin, restore youth, and even, incongruous as it may sound, cure cancer.

Yama-no-yu: Japan's best radium hot spring.
Open-air bath set in a gorgeous strolling garden.

Come and enjoy an experience you won't find anywhere else. Izanro Iwasaki brings you the waters of Misasa Onsen, some of the world's finest radium hot springs, in 12 distinctive baths. Yama-no-yu, an open-air bath set in a gorgeous strolling garden, is divided into a left zone (Hidari-no-yu) and a right-hand zone (Migi-no-yu), which are designated as separate men's and women's bathing areas. The men's and women's bathing area's are switched over night, meaning you can enjoy one side in the evening, then the other side the next day.
A radium steam bath and drinking spring are also available, so not only can you soak in the soothing waters, you can also breathe in the vapors or drink the beneficial minerals of the radium waters. The distinctive feature of Misasa Onsen's waters is their "hormesis effect", which stimulates activity in the body's cells and leaves you feeling refreshed and invigorated.

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- **Childhood Cancer After Radiation Exposure in Utero**
- Nonneoplastic Disease and Radiation

Childhood Cancer after Radiation Exposure *In Utero*

- Stewart and Kneale reported an excess of leukemia and childhood cancer in children irradiated *in utero* as a consequence of diagnostic x-rays involving the pelvis of the mother
- An association between leukemia and x-rays *in utero* was confirmed in the United States

Childhood Cancer After Radiation Exposure *In Utero*

- Low-dose radiation of the fetus *in utero*, particularly in the last trimester, causes an increased risk of childhood malignancy
- An obstetric x-ray examination, even though the dose is only ~ 1 cGy, increases the RR of childhood cancer by 40%
- The excess absolute risk is ~ 6%/Gy

	Cancer Incidence	Cancer Mortality
Combined	10.8%/Sv	5.4%/Sv

Note that this is not too different from risk estimates derived from A-bomb survivors

Outline

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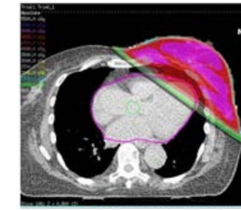
- **Nonneoplastic Disease and Radiation**

Risk of Cardiovascular Disease



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

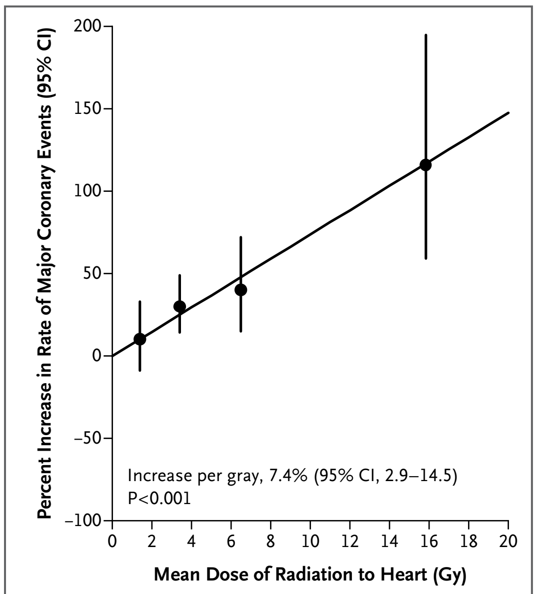


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Table. Patient-Averaged Mean Cardiac Doses and Estimated Patient-Averaged Lifetime Excess Risks of Major Coronary Events Associated With Contemporary Breast Cancer Radiotherapy

Treatment Side	Radiotherapy Position	Cardiac Dose, Mean (95% CI), Gy[a]	Excess Risk (95% CI), %[b]		
			Low Baseline Risk Patients[c]	Medium Baseline Risk Patients[c]	High Baseline Risk Patients[c]
Left	Supine	2.17 (1.36-2.98)	0.22 (0.08-0.36)	0.42 (0.14-0.70)	3.52 (1.47-5.85)
	Prone	1.03 (0.87-1.19)	0.09 (0.05-0.13)	0.17 (0.09-0.25)	1.31 (0.86-1.86)
Right	Supine	0.62 (0.54-0.71)	0.05 (0.03-0.07)	0.10 (0.06-0.14)	0.79 (0.57-1.06)
	Prone	0.64 (0.56-0.72)	0.06 (0.03-0.08)	0.11 (0.05-0.16)	0.84 (0.57-1.18)

- Cardiac doses from breast radiotherapy have generally decreased during recent decades
- Typical risks of major cardiac events associated with contemporary radiotherapy are lower than in earlier eras
- Estimated lifetime risks of major coronary events for patients who receive radiotherapy for breast cancer are now in the range from **0.05% to 3.5%**, with a typical value of 0.3% for a typical scenario

Review Questions

Question 1

What is the most common type of cancer identified in children who were in the vicinity of the Chernobyl nuclear power plant when it exploded in 1986?

A. Osteosarcoma
B. Leukemia
C. Thyroid Cancer
D. Glioma
E. Mesothelioma

Chernobyl Disaster

- It is still too early to determine the extent of cancer induction in people exposed at or near Chernobyl
- Thyroid cancer in children skyrocketed to nearly 7,000 cases in Belarus, Russia, and Ukraine by 2005
- The 2005 report prepared by the Chernobyl Forum, attributed 56 direct deaths (47 accident workers, and 9 children with thyroid cancer), and estimated that there may be 4,000 extra cancer deaths among the approximately 600,000 most highly exposed people
- 3 years later, the UN committee on atomic radiation abandoned the linear no-threshold model for predicting Chernobyl cancer deaths because of “unacceptable uncertainties”
- Critics such as Greenpeace responded with new predictions of 93,000 cancer deaths caused by Chernobyl

Question 2

Which of the following radiation-induced malignancies has the shortest median latent period?

A. Colorectal Cancer
B. Leukemia
C. Bone Sarcoma
D. Breast Cancer
E. Lung Cancer

The Latent Period – Leukemia

- For the A-bomb survivors, the incidence of leukemia began to appear after 2 years, and reached a peak by 5-7 years
- Most cases occurred in the first 15 years
- An **excess relative risk (**ERR) still existed even 40 years after exposure

The Latent Period – Solid Cancers

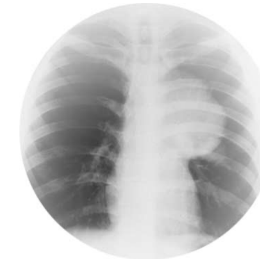
- For solid cancers, the latent period for A-bomb survivors has ranged from 10 to over 60 years
- Recent data from Chernobyl seems to indicate an even shorter minimum latent period for thyroid cancer in children exposed to ^{131}I in fallout, may be as short as 5 years

Question 3

The EPA estimates that the fraction of the total number of U.S. lung cancer deaths annually caused by indoor radon is approximately:

A. 0% for non-smokers
B. 0-0.1%
C. 1-2%
D. 10-20%
E. 40-60%

Lung Cancer



- Many carcinogens can cause lung cancer
- There is a clear excess of lung cancers among workers in uranium, non-uranium, and the fluorspar mines
- However, it is difficult to separate the contributory effect of radon and cigarette smoking
- There is also evidence of an excess lung cancer from domestic radon exposure
- It is estimated that 10% of the lung cancer deaths in the US are due to domestic radon exposure

EPA United States Environmental Protection Agency

World Health Organization's International Radon Project

(2009) The World Health Organization (WHO) says radon causes up to 15% of lung cancers worldwide. In an effort to reduce the rate of lung cancer around the world, the World Health Organization (WHO) launched an international radon project to help countries increase awareness, collect data and encourage action to reduce radon-related risks.

The U.S. EPA is one of several government agencies and countries supporting this initiative and is encouraged by WHO's attention to this important public health issue.

Question 4

Which one of the following conditions treated with radiation is associated with an increased incidence of leukemia?

A. Breast cancer
B. Ankylosing spondylitis
C. Cervical cancer
D. Brain tumors
E. Enlarged thymus

Ankylosing Spondylitis Therapy Patients

- Between 1935 and 1944, about 14,000 patients suffering this arthritic condition of the spine were treated with external beam radiotherapy or injections of Ra-224
- A small fraction of these developed leukemia or bone cancer attributed to their radiation exposure
- One of the largest bodies of data on radiation-induced leukemia with good dosimetry