

Timing of onset of symptoms correlates with the lifespan of the functional cells.

Early Effects: stem cells are the “target”

- Effects occur in a few days to weeks
- Rapidly dividing cell populations
- Examples: skin epidermis, gastrointestinal tract, hematopoietic system
- Damage can be repaired. Stem cells repopulate rapidly.

Late Effects:

- Effects occur in months to years.
- Slowly proliferating tissues: lung, kidney, liver, CNS
- Damage never repaired completely
- Vascular damage or mature functional cells as the “target”?

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Chronic effects of radiation exposure

Cells not killed, but damaged.....

- **Cataract formation**
- **Genetic (hereditary) effects**
- **Effects on the fetus**
- **Carcinogenic effects (cancer)**

Human Radiation Exposure Data

Japanese A-bomb survivors

- 93,000 survivors
- 27,000 non-exposed comparable individuals as controls
- Location at the time of the blast must be accounted for in the dosimetry.

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RERF: Radiation Effects Research
Foundation

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Joint US-Japan research foundation
following all of the survivors for
life.

www.rerf.or.jp

Hereditary Effects: effects on the offspring

- Radiation does not produce “new mutations”.
- Radiation increases the incidence of mutations that occur spontaneously in the population.

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TABLE 11.2. *Doubling Dose (Gametic) in the Offspring of Survivors of the Atomic-Bomb Attacks on Hiroshima and Nagasaki*

Genetic Indicator	Doubling Dose, Sv
Untoward pregnancy outcome	0.69
Childhood mortality	1.47
Sex chromosome aneuploidy	2.52
Simple average	1.56

Adapted from Schull WJ, Otake M, Neal JV: Genetic effects of the atomic bomb: A reappraisal. *Science* 213:1220–1227, 1981, with permission.

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Doubling dose: increases the natural background frequency by a factor of 2.

Background mutation rate ~ 1-6%

Radiation-induced risk of hereditary disorder estimated at $0.6 \times 10^{-2}/\text{Sv}/\text{per person}$

Dose rate effect data from the “Mega mouse” Experiments at Oak Ridge National Laboratory.

Fetal Effects

- Lethal effects
- Malformations
- Growth disturbances

Principal factors

- Dose
- Gestation age at time of irradiation

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Data from rats given 200 rads at various time post-fertilization.

Japanese atomic bomb survivors irradiated *in utero*.

Growth retardation: height, weight and head diameter

Mental retardation: observed in children irradiated at 8-15 weeks (only) of pregnancy.

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Effects observed at doses as low as 0.06 Gy.

Cataracts: any detectable change in the normally transparent lens of the eye.

Deterministic response

- Cells are produced by mitosis in the germination zone (GZ) of the epithelium.
- Differentiate into lens fibers in the meridional rows (MR).
- Cells in the central zone (CZ) do not normally divide.

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- No blood supply.
- No mechanism for removal of dead or damaged cells.
- Abnormal fibers migrate towards the posterior pole, the beginning of a cataract.
- Single doses > 2 Gy will cause cataracts.
- Fractionation and low dose rate increase the threshold to 4-5 Gy.

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Studies of Mortality of Atomic Bomb Survivors. Report 13: Solid Cancer and Noncancer Disease Mortality: 1950–1997

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Estimation of risk from radiation exposure

Excess risk: the excess cases of a particular health effect associated with exposure to radiation. Excess risk can be described in various ways:

- **Absolute Risk:** the difference in the rate of occurrence of a particular health effect in an exposed population and an equivalent population with no radiation exposure. (units: excess number of cases per person-year-sievert).
- **Relative Risk:** the ratio of the rates in exposed and unexposed populations (dimensionless)
- **Excess Relative Risk (ERR):** the ratio of the rate difference to the rate in an unexposed population (N.B., $ERR = \text{relative risk} - 1$)

Excess risks depend on:

- radiation dose
- age at exposure
- time since exposure
- current age
- gender

Risk estimates are usually reported for a specific dose (often 1 gray or 1 sievert).

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Estimates based on a model that accounts for age at exposure and gender.
The vertical dotted line represents no excess risk.
The solid vertical line represents the excess relative risk for all cancers.

Cancer deaths between 1950 and 1990 among Life Span Study - Survivors with significant exposures (> 0.005 Sv)

Dose Range	Number of Cancer Deaths	Estimated Excess Deaths	Attributable Fraction (excess lifetime risk)
0.005-0.2 Sv	3391	63	2% (=100 x 63/3391)
0.2 – 0.5 Sv	646	76	12%
0.5 – 1 Sv	342	79	23%
> 1 Sv	308	121	39%
All	4687	339	7%

Excess Lifetime Risk

- Based on observed cancer incidence to date
- Depends on dose, age at exposure, sex.

Lifetime cancer risks for atomic bomb survivors who received an acute dose of 0.2 Sv

Age at exposure (years)	Excess lifetime risk	Background lifetime risk	Excess relative risk (ERR)
MEN			
10	0.03	0.26	12% (= 100 x 0.03/0.26)
30	0.02	0.28	7%
50	0.01	0.18	6%
WOMEN			
10	0.05	0.19	26%
30	0.03	0.20	15%
50	0.01	0.15	7%

(Data from <http://www.rerf.or.jp>)

Numbers of cancer deaths by cancer type and strength of evidence for a radiation effect

SITE	TOTAL DEATHS	ESTIMATED EXCESS	EVIDENCE FOR EFFECT
Stomach	2529	65	strong
Lung	939	67	strong
Liver	753	30	strong
Uterus	476	9	moderate
Colon	347	23	strong
Rectum	298	7	weak
Pancreas	297	3	weak
Esophagus	234	14	strong
Gallbladder	228	12	moderate
F. Breast	211	37	strong
Ovary	120	10	strong
Bladder	118	10	strong
Prostate	80	2	weak
Bone	32	3	moderate
Other solid	948	47	strong
Lymphoma	162	1	weak
Myeloma	51	6	strong

- Statistical significance may vary, but excess risks are seen for all types of cancer.
- Supports the notion that radiation increases the risk for ALL types of cancer.

Radiation in Medicine: therapy and diagnosis

- a) thyroid cancer: 1930s and 1940s use of x-rays to shrink enlarged thymus in children.
- b) Ringworm of the scalp: 1940s and 1950s x rays used to cause temporary hair loss (several Gy), treat hair follicles more effectively. Increases in thyroid cancer, leukemia, brain tumors (10,000 patients in Israel, 2215 in New York).
- c) In Britain, ~14,000 patients with a congenital spinal cord problem known as ankylosing spondylitis were irradiated to relieve pain. Increased incidence of leukemia.
- d) Female tuberculosis patients undergoing repeated fluoroscopy procedures showed an increase in breast cancer.

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Radium dial painters

- Practice continued up to 1925. Ingestion of ^{226}Ra (bone seeker) caused an increased incidence of bone cancer.
- At autopsy, bone was analyzed for radium content.
- Note, that there appears to be a threshold below which no effects are seen.

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What are the risks from low-doses of radiation?

All human data are relatively high dose and delivered at high dose rates.....

.....and extrapolated down to the low dose region at low dose rates.

This is a source of significant and continuing controversy.

Risk Estimation Models

- **linear no-threshold**
- **threshold**
- **linear-quadratic**

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The choice of model, and the estimated risk, has serious implications for radiation protection.

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Data from high dose rate exposures is extrapolated to low doses and low dose rates.

Low dose rate exposure is significantly less damaging.

Is there a 4th curve??

Hormesis

a term coined to describe the behavior of an agent that is lethal at high doses but *beneficial* at low doses.

(e.g., nickel, chromium, hormones, ultraviolet light)

The radiation effects paradigm:

- Radiation exposure is harmful.
- Radiation exposure is harmful at all doses.
- There are no effects at low doses that cannot be predicted from the effects at high-dose levels.

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