The biological effects of ionizing radiation

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CERN Academic Training Lectures

27th, 28th and 29th May 2008

The biological effects of ionizing radiation

First lecture

- - Ionizing radiations and radiations units
- - Exposure to natural background radiation
- - Exposures by medical usage of radiation
- - Biological effects (cellular damage, genomic instability, bystander effects and adaptive response, dose response as function of radiation quality, dose fractionation and dose rates effects).

Second lecture

- - Biological effects (some particular effects, tissue reactions: skin, intestine, blood, testis, ovary, fetus. Hereditary effects. Lethal doses. Stochastic effects)
- - Health effects of ionizing radiations on short and long terms, from high and low doses (Hiroshima and Nagasaki).

Third lecture

- - Health effects of ionizing radiations on short and long terms, from high and low doses (Chernobyl, radiologists, radon exposures, nuclear workers.)
- - Risk estimate from epidemiological data
- - Radiation limits and ICRP recommendation
- - Future research on radiation effects.

Mice male germ cells particularity

- Effect for type B spermatogonia lethality was the same if dose was delivered in hours, minutes or nano-seconds (Bianchi et al.1972)

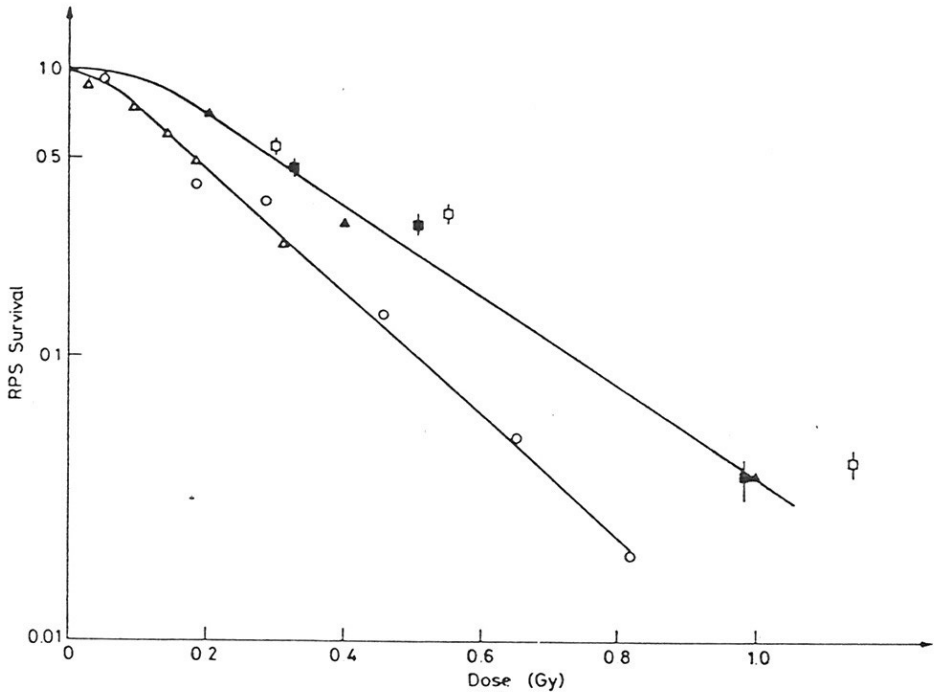
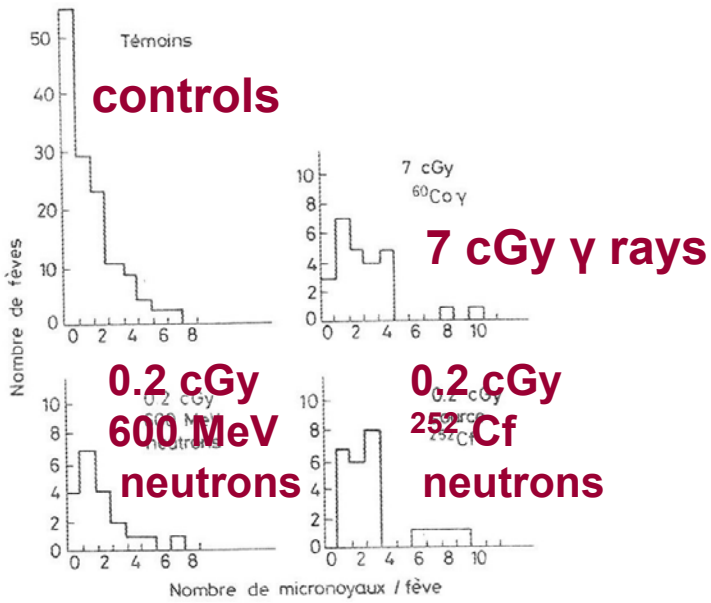


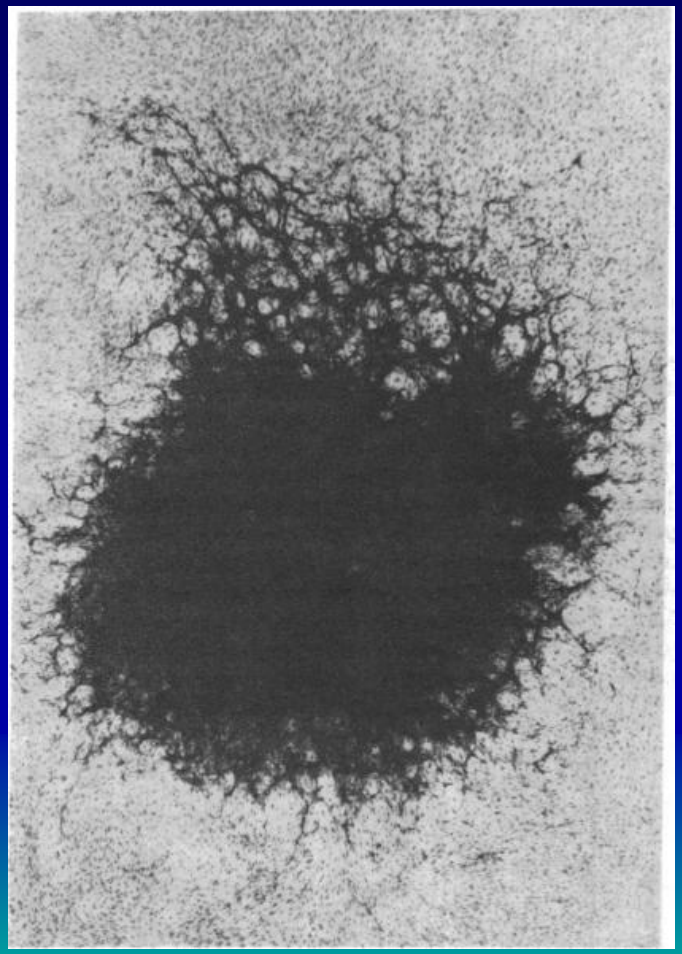
Fig. 7.17 Type B spermatogonial survival in animals killed 46 hours after irradiation, determined by counting RPS in tubules in stage VII. (Bianchi et al 1972)
△, X-rays 0.027 Gy/min ▲, Pulsed electrons 2 × 10^6 Gy min □, X-rays 0.4 Gy min
○, X-rays 0.045 Gy/min ■, Pulsed electrons 2 × 10^5 Gy/min

Micronuclei in bean roots after 200 mGy Cf irradiations (50% γ contamination) or 600 MeV Neutrons



From Bianchi M. 1981

Oncogenic transformation in vitro



From Miller R.C. et al. 1979

Oncogenic transformation for low doses of neutrons

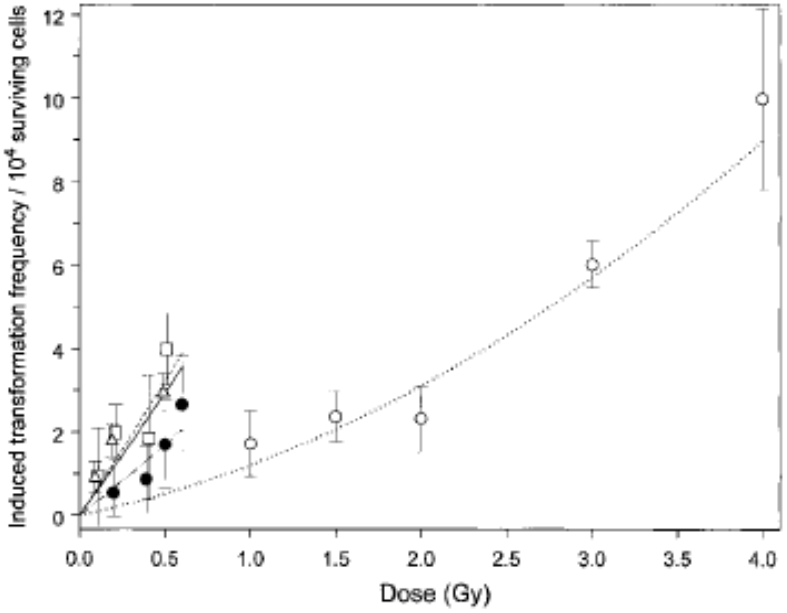


Figure 4. Induced oncogenic transformation frequency (with 95% confidence limits) as a function of radiation dose for C3H10T½ cells exposed to 350 keV monoenergetic neutrons (△, dashed curve), neutrons with a dose-averaged energy of 70 keV (□, solid curve) or 40 keV (●, dot-dash curve) and 250 kVp X-rays (○, dotted curve); curves refer to fits of the data to equation 1, with controls (the parameter b in equation 1) subtracted out.

Oncogenic transformation in alpha particles irradiated cells

(C3H 10T1/2)

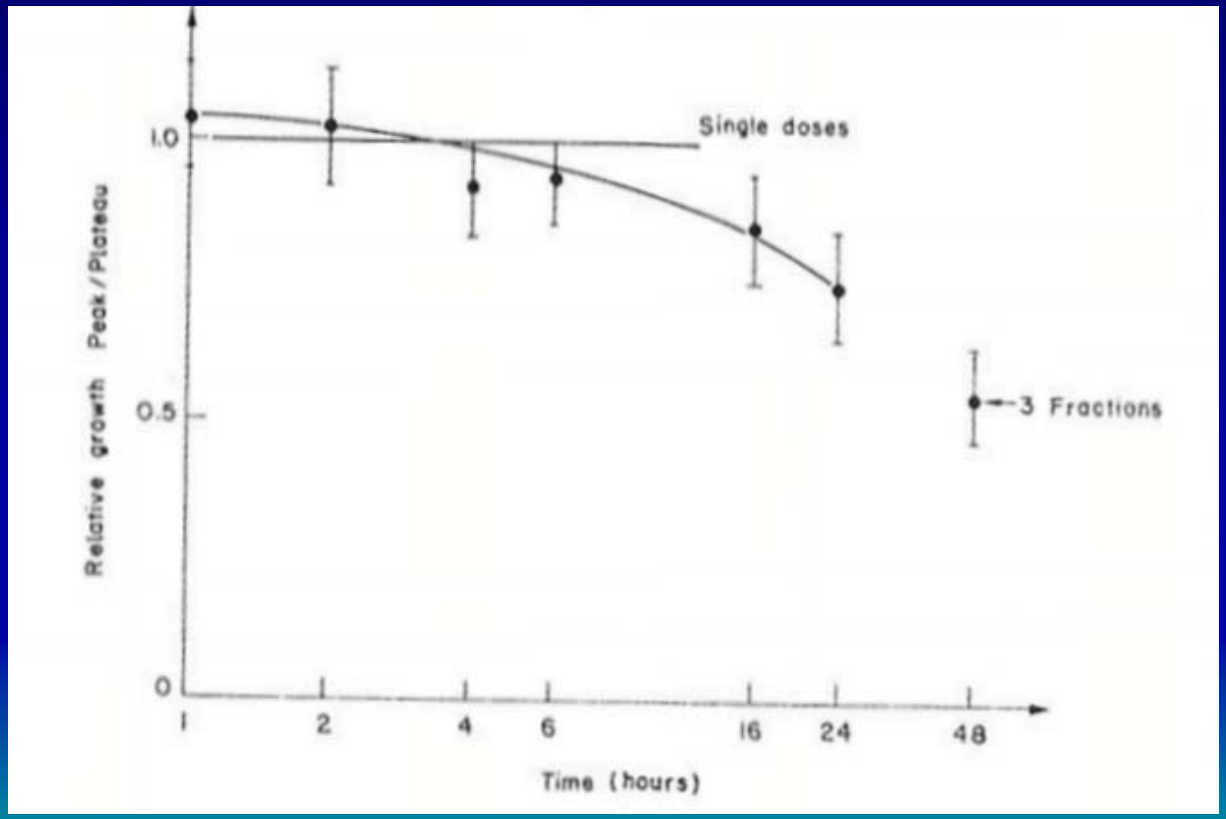
TABLE 1
Results from Microbeam Bystander Studies

Percentage of cells irradiated	Percentage of α particles traversing each irradiated cell	Clonogenic surviving fraction	Percentage of dishes exposed	Percentage of surviving cells exposed[a]	Percentage of transformed clones produced[b]	Transformation frequency/10⁴ surviving cells
0	0		26	9,600	0	0
10[c]	1[c]	0.98[c]	23[c]	8,500[c]	4[c]	4.7[c]
10[d]	1[d]	0.98[d]	85[d]	30,270[d]	7[d]	2.3[d]
10	2	0.95	27	10,000	7	7.0
10	4	0.89	25	9,000	7	7.8
10	8	0.75	18	8,500	9	10.6
0[e]	0		143	46,200	4	0.86
100[e]	1	0.83	105	42,700	5	1.2
100[e]	2	0.64	59	12,200	7	5.8
100[e]	4	0.41	18	6,600	5	7.6
100[e]	8	0.16	13	3,800	5	13.2

[a] Estimated, accounting for measured plating efficiency and clonogenic surviving fraction.
[b] No more than one transformed clone per dish was observed.
[c] Initial experiment only.
[d] Data combined from initial experiment and two subsequent repeats (see caveats in text).
[e] Data from ref. (*30*).

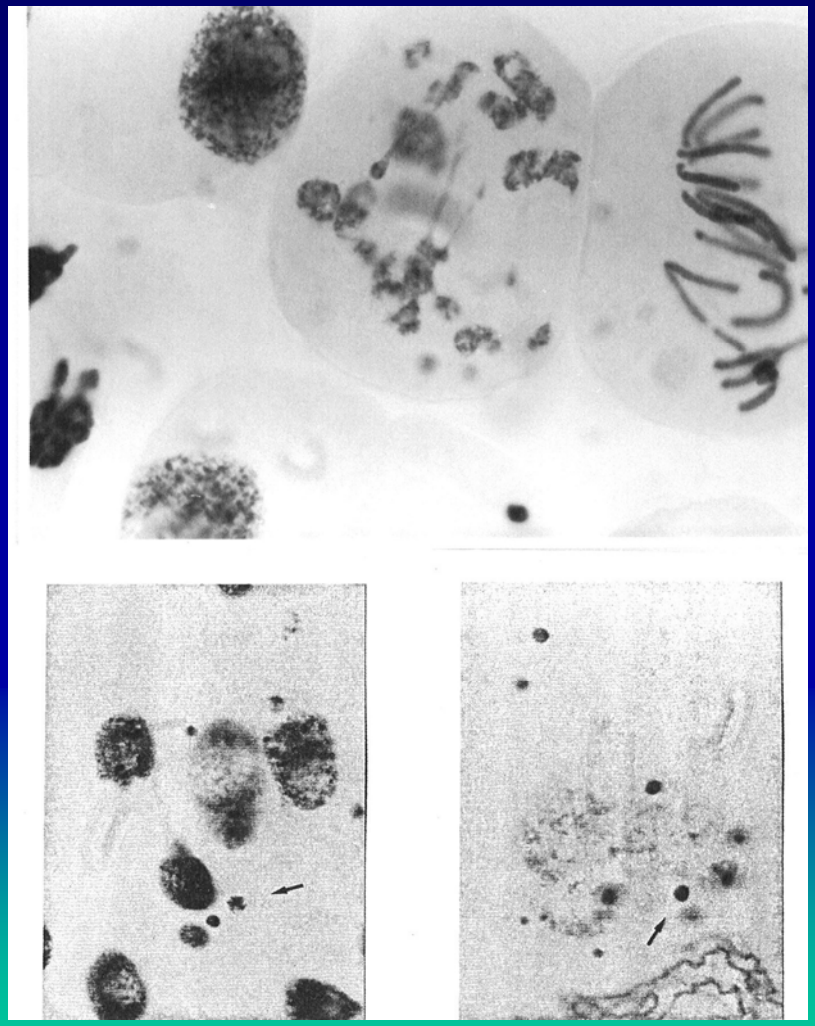
When only 10% of cells have been irradiated or all have been irradiated the same % of oncogenic transformation is observed (Sawant et al. 2001)

Others examples of enhanced effects by fractionation at low doses



Vicia faba beans
irradiated with negative pions
(Diehl-Marshall I. and Bianchi M. 1981)

Particular cellular damage observed from 250 GeV protons



The progression of damage to tissues and organs

The **cell death** in irradiated tissues is due to the reproductive failure

- of regenerative stem cells (apoptosis before or after mitoses)
- of proliferating differentiating cells.

- Stem and progenitor cells in the tissues die as function of dose and this produce a transitory or permanent lack of mature cells in the tissues or organs.
- Restoration of tissues component will depend on their rate of renewal and is dose dependent at low doses.
- The structure of tissues and organs plays an important role on their response.

Late reactions in tissues are due:

- to the slow rate of renewal and death of component cell populations and
- to the dysfunction of inter-cellular signalling pathways

Tissue reactions (Deterministic effects) of radiations

Early tissues and organ reactions

- Early tissues reactions may be modified by cytokines and growth factors whereas late reactions may be delayed using vascular modifying agents
- Early tissue reactions are observed from few hours to few weeks after irradiation
- Responses from tissues depends on the size of the irradiated volume (larger for large size irradiations)
- At large doses a sufficient amount of cell killing occurs causing detectable tissues reactions
- Presence of a threshold dose for the appearance of the injury
- High tolerance to partial-body irradiation

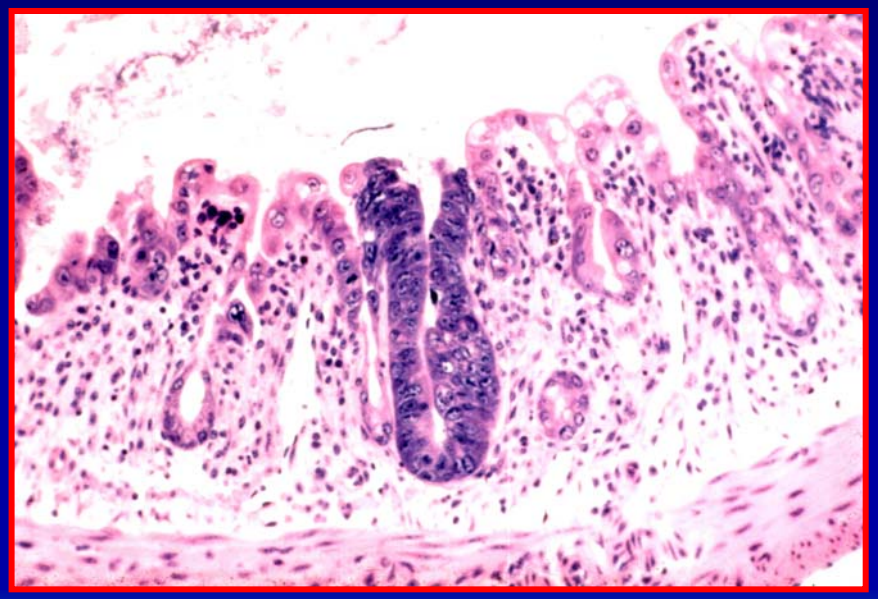
Late tissues and organ reactions

- Late tissue injury is progressive and strongly dose dependent
- Late tissue reactions are observed from months to years after irradiation

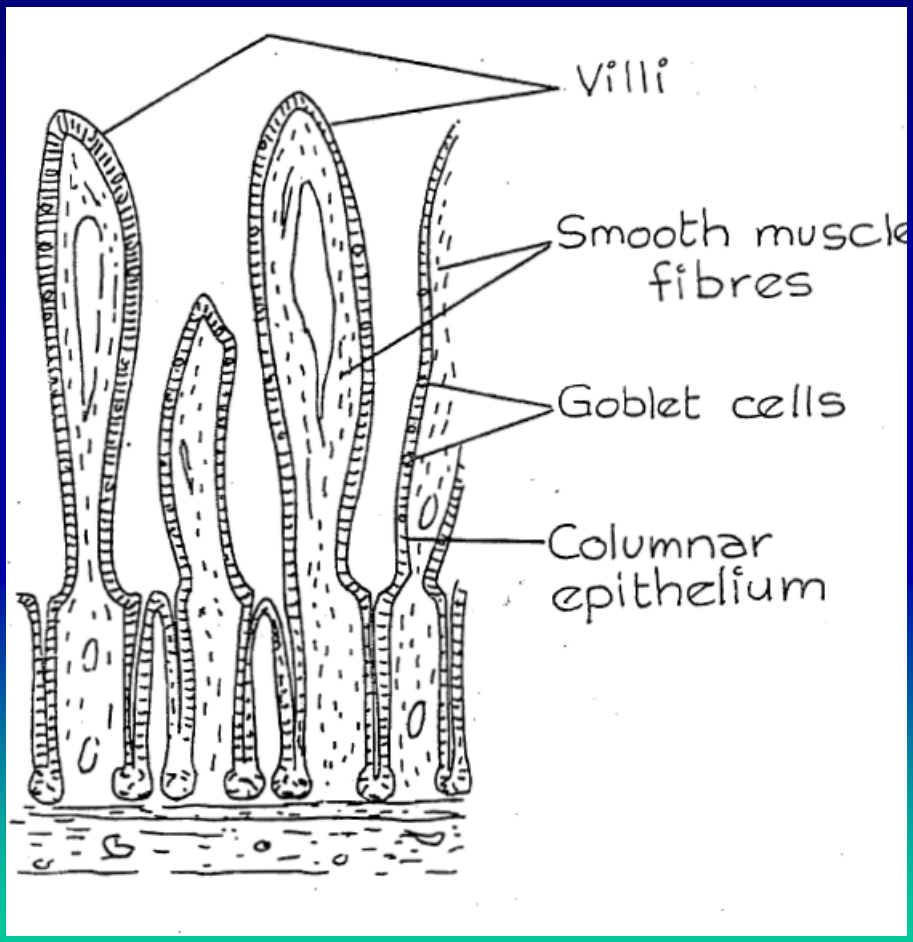
The most radiosensitive tissues

- The testes,
- The ovary
- The bone marrow
- The lens of the eye (visual impairment after several years)

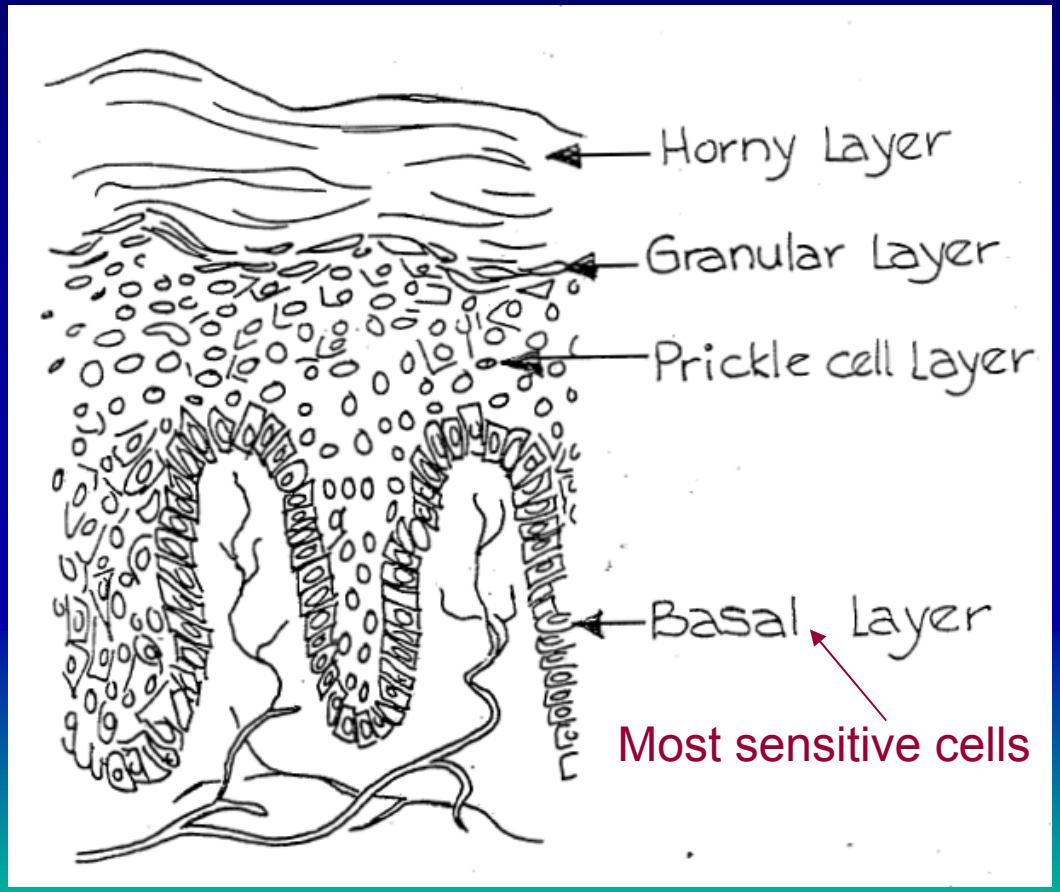
Damage to the intestine



Mouse section



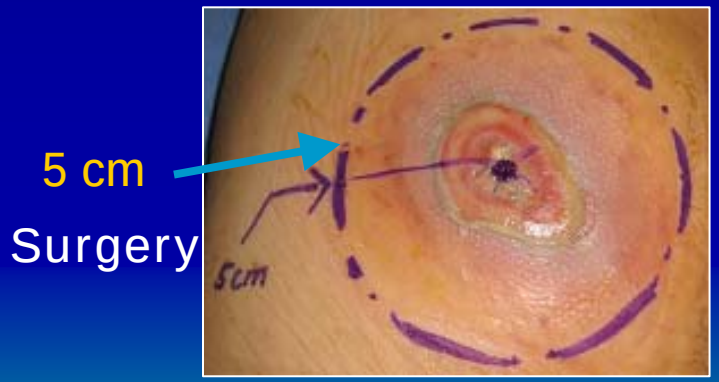
Damage to the skin (erythema, necrosis)



Skin burns: 2-3 weeks

Industrial radiography accident
Chile, December 2005

Courtesy J-F Bottolier-Depois, IRSN

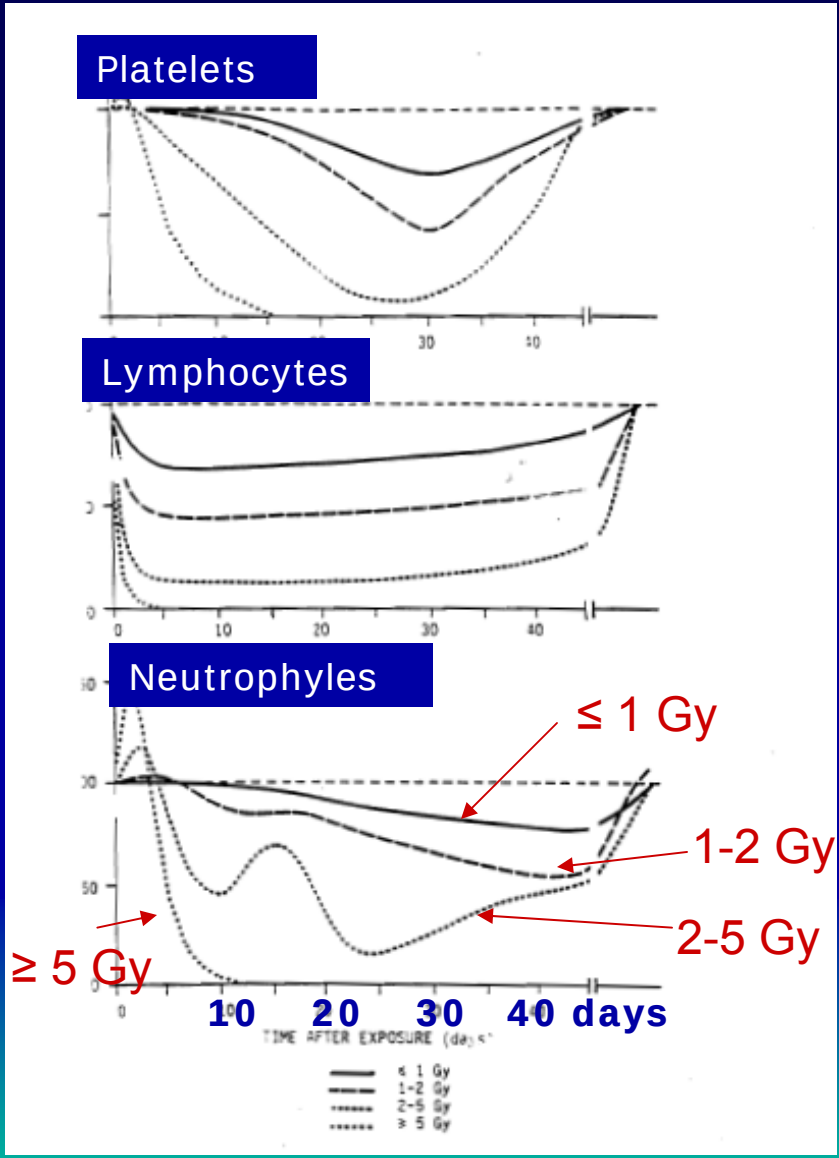


Acute effects

- Circulating Blood cells:

5 to 40 days

after irradiation



From UNSCEAR 1988

Bone marrow

- **Depression of haematopoiesis at 0.5 Gy**

Changes in blood count from Chernobyl

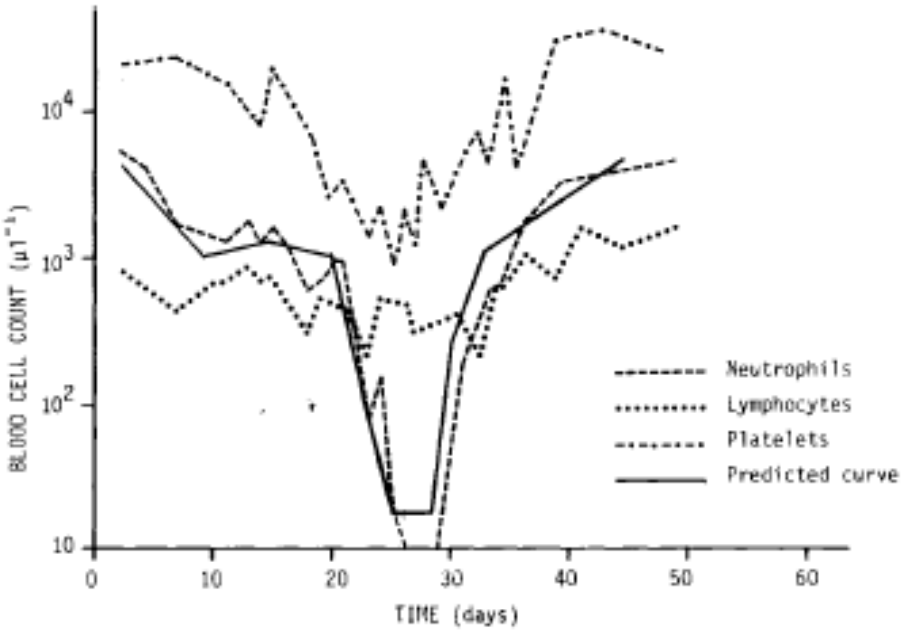


Figure IV. Example of the changes in neutrophils, lymphocytes and platelets observed in a patient (case 39) suffering from acute radiation sickness (estimated dose 2.4–3.3 Gy) and the predicted neutrophil curve for a total gamma dose of 3.0 Gy.

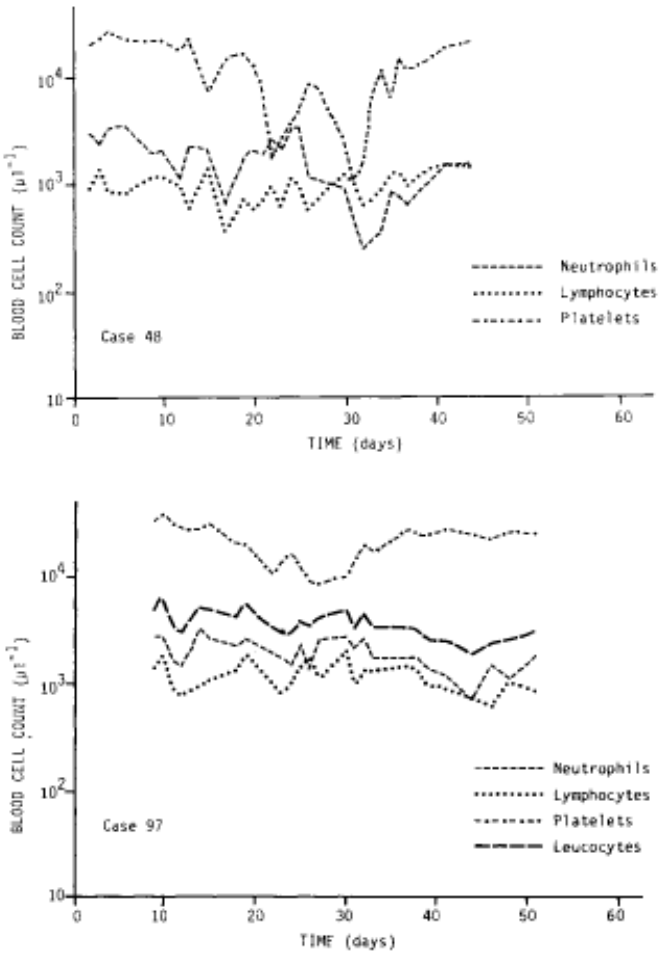


Figure VI. Changes in neutrophil, lymphocyte, platelet and leucocyte counts after whole-body gamma irradiation. Case 48, estimated dose 1.1–1.4 Gy. Case 97, estimated dose 0.3–0.9 Gy.

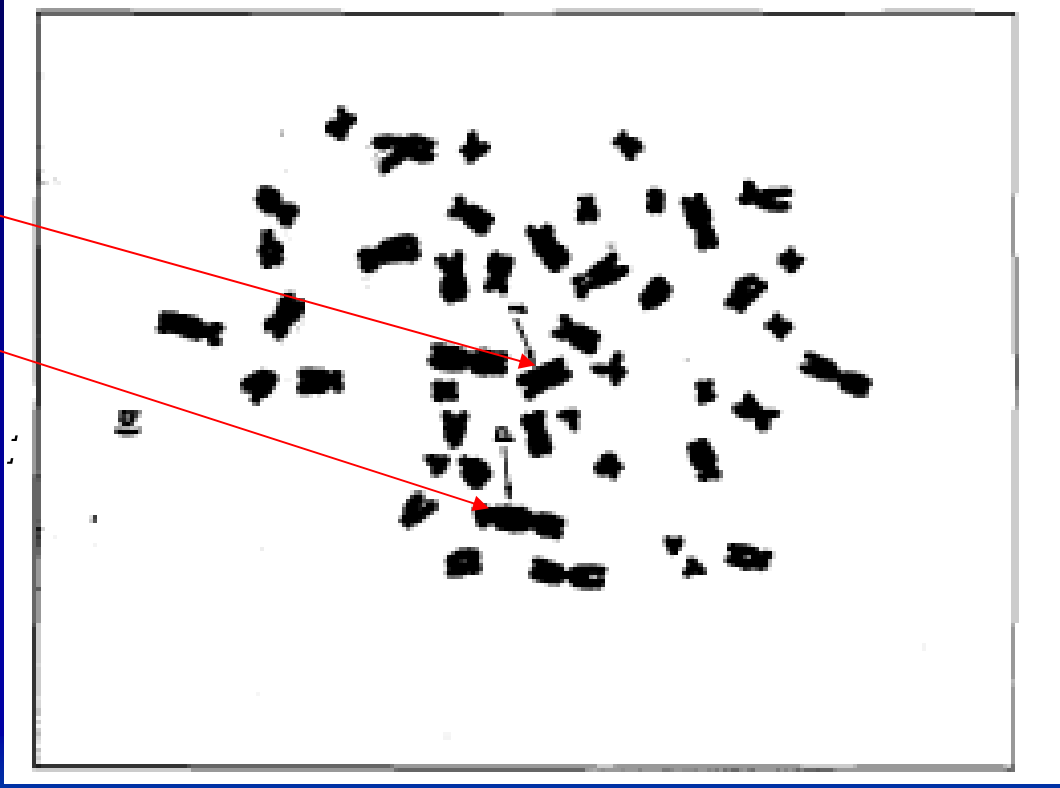
From UNSCEAR 1988

Blood chromosome aberrations

Most easy and common analysed aberrations: dicentrics & rings

FISH staining technique to identify translocation

Others chromosome analysis:
- Immuno-fluorescence techniques
- Premature chromosome condensation



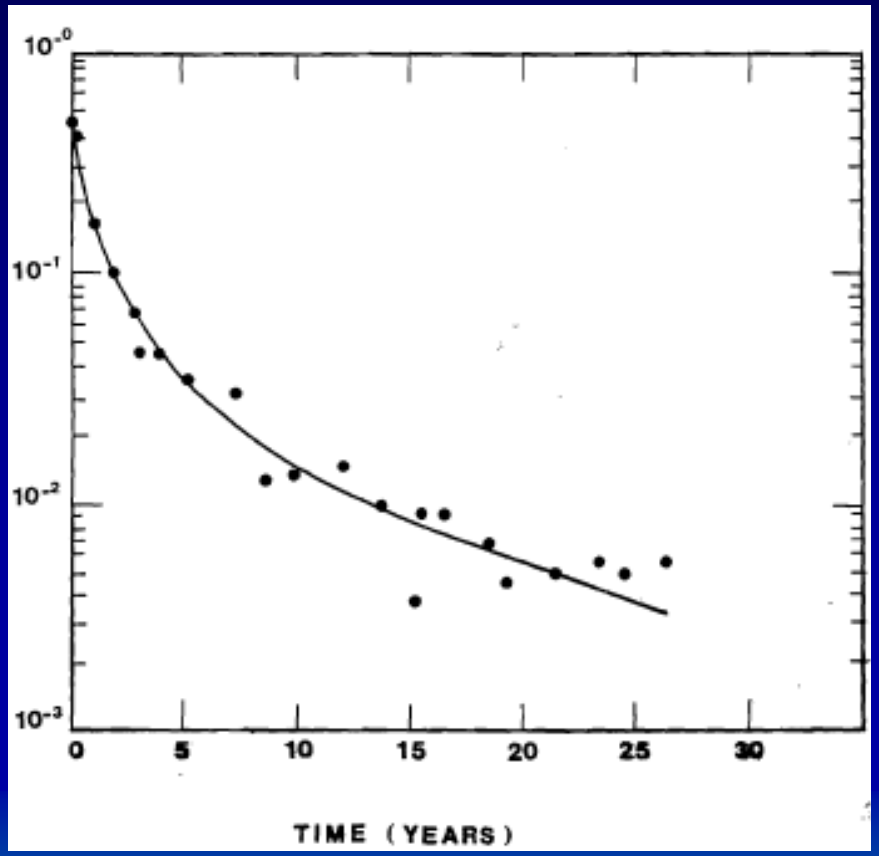
- For X rays linear dose-response at low doses with a limit of resolution ~ 20 mGy

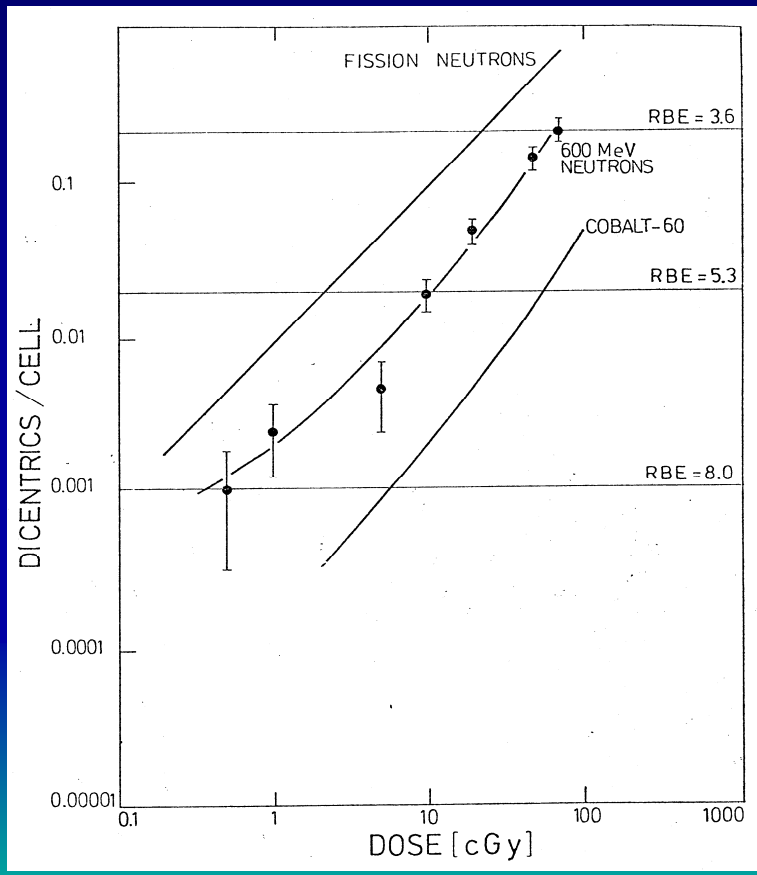
Chromosome aberration in blood in time and for different radiations

From Vulpis N. and Bianchi M. 1982

CERN experiments with blood irradiations

Dicentrics+ rings in human lymphocytes

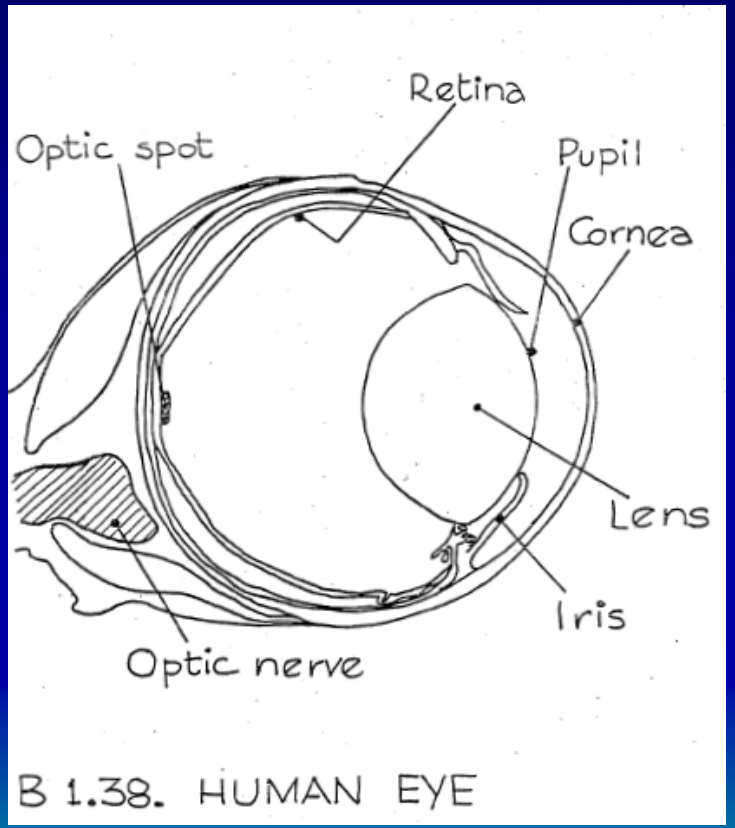




- Half-life 3 years, aberrations still presents many years after irradiation
- Analysis for partial body irradiation possible,
- Calibration curves exist for low doses and dose-rate of many types of radiations

Radiation effects on lens

Lens opacities are formed in the posterior part of the lens and thereafter followed by cataract.
Latency inversely related to dose.
Cataract 2-10 Gy single dose or fractionated doses
Radiation opacities observed at Chernobyl, astronauts, CT scan.
Retinopathy and other ocular damage at doses <5 Sv



Radiation effects on testis

- Temporary sterility (3-9 weeks) 0.15 Gy
- Permanent sterility (3 weeks) >3 Gy

Repopulation of stem germ cells in mice and man

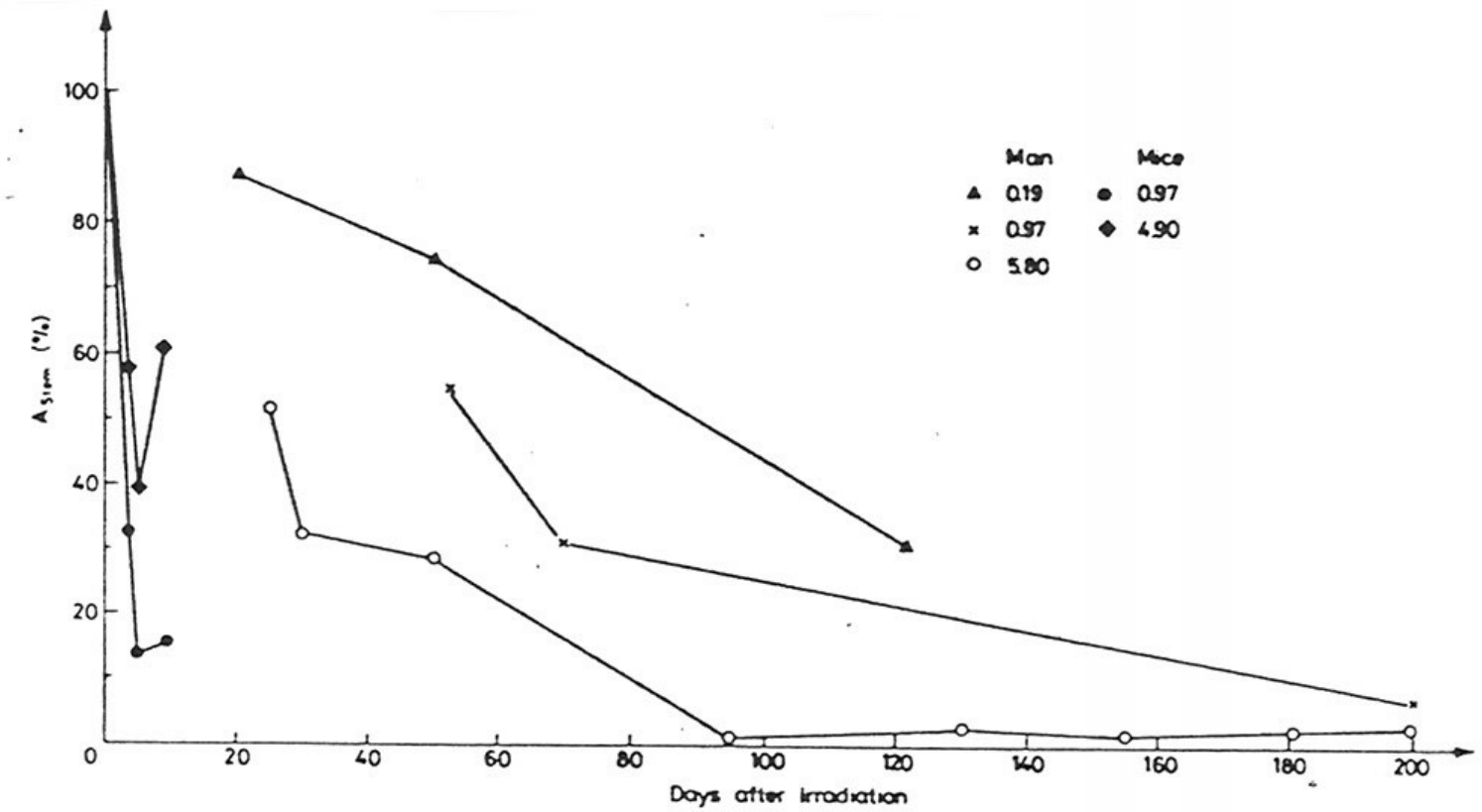


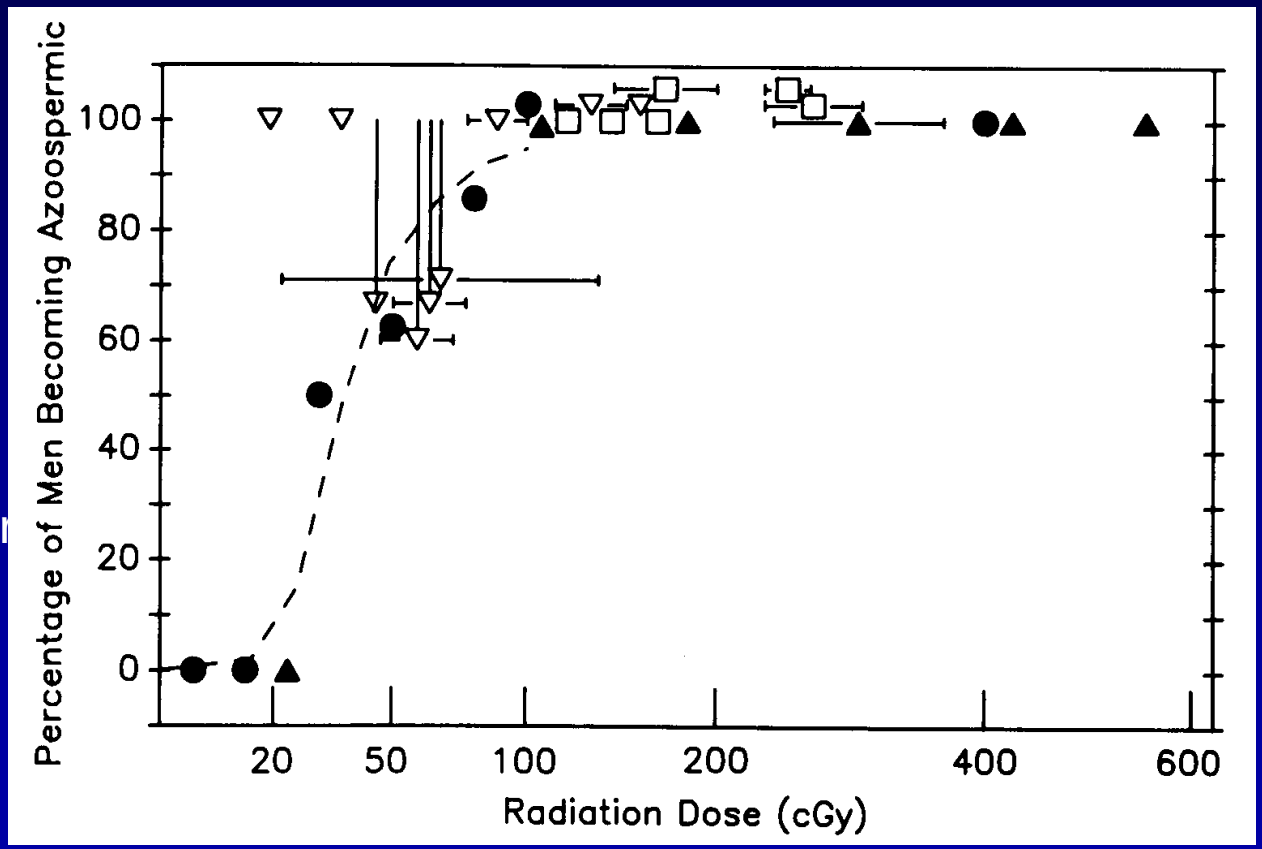
Fig. 7.9 Repopulation of stem cells of mice and men after X–rays as a function of time after various doses (Oakberg 1968, 1971a).

From Bianchi M. 1980

Effects on germ cells (human testis)

Human testis

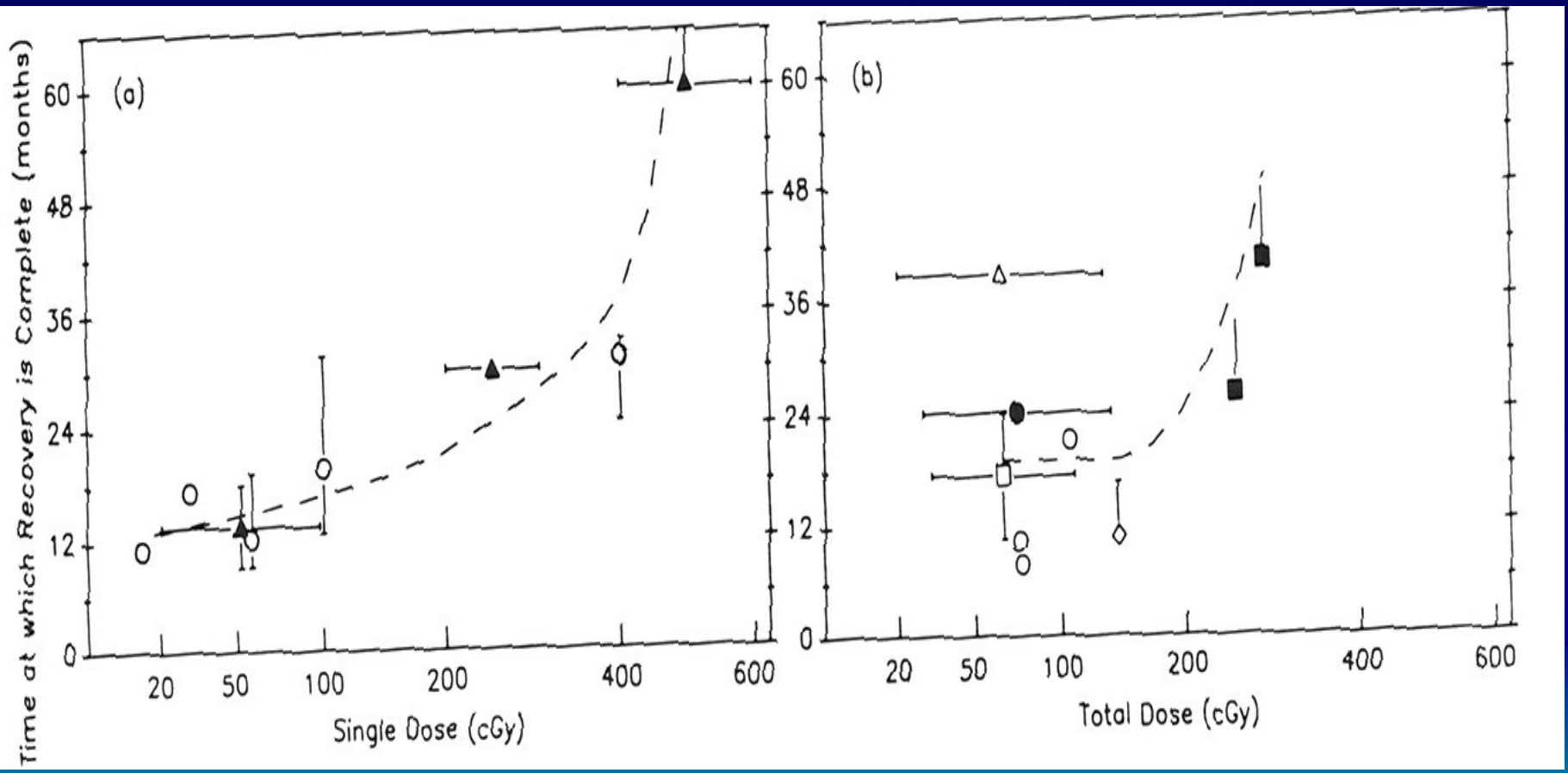
Azospermia as function of dose
●Single dose X-rays
ΔSingle dose n and γ
□Non testicular cancer irradiations



From Meistrich M.L. and Van Beek M.E.A.B. 1990

1.6 fold increase in mutation rate was found in germline of exposed Chernobyl fathers. No effect seen from exposed mothers (From Dubrova Y.E. et al. 2002)

Effects of radiations on human testis



Recovery of sperm production after exposure to 250 cGy completed after 2 years.
No differences between experimental and accidental exposure up to 400 cGy

From Meistrich M.L. and Van Beek M.E.A.B. 1990

Effects on germ cells (human ovary)

Effects in human ovary	Tolerance dose (Gy)
Temporary or reduced sterility	1.5, fractionated 1.7 4 12 fractionated (3 fractions/day) 174 (3 series/2.5 years)
Permanent sterility (<1 week)	3.2 2.5-5, fractionated 4 6.25 8-10 2 (3 series/2years) 6.25-12, fractionated (30 fractions/ 6weeks) 6-20 (30 fractions/ 6weeks) 3.6-7.2 (2-4 fractions)

From UNSCEAR 1988

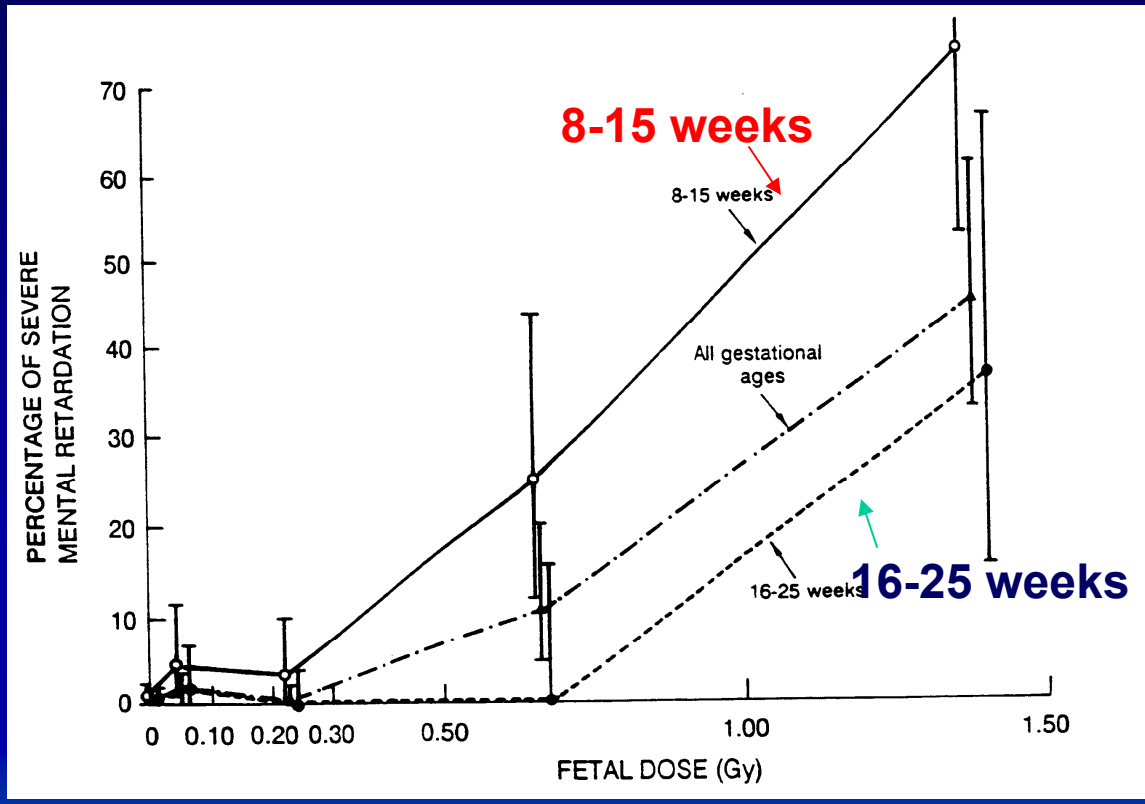
Effects on fetus (Hiroshima & Nagasaki data)

- Increase in abortion rate
- Death in the first months of life
- Risk of malformation (greatest 3-7 weeks after conception)

For mental retardations:
Threshold at 300 mGy of low LET radiations.

For malformations:
Threshold at 100 mGy of low LET radiations (animal studies)

Mental retardation



From BEIR V 1990
Data from Otake M. et al. 1987

Lethal doses for different species

Animal LD 50 / 30 **in Gy**	
Sheep	1.6-2.1
Swine	2.0-2.5
Goat	2.3-2.4
Dog	2.7-2.5
Man	3.0-5.0
Rabbit	8.4-7.5
Rat	9.0-7.1
Mouse	9.0-6.4
Amoeba	3000

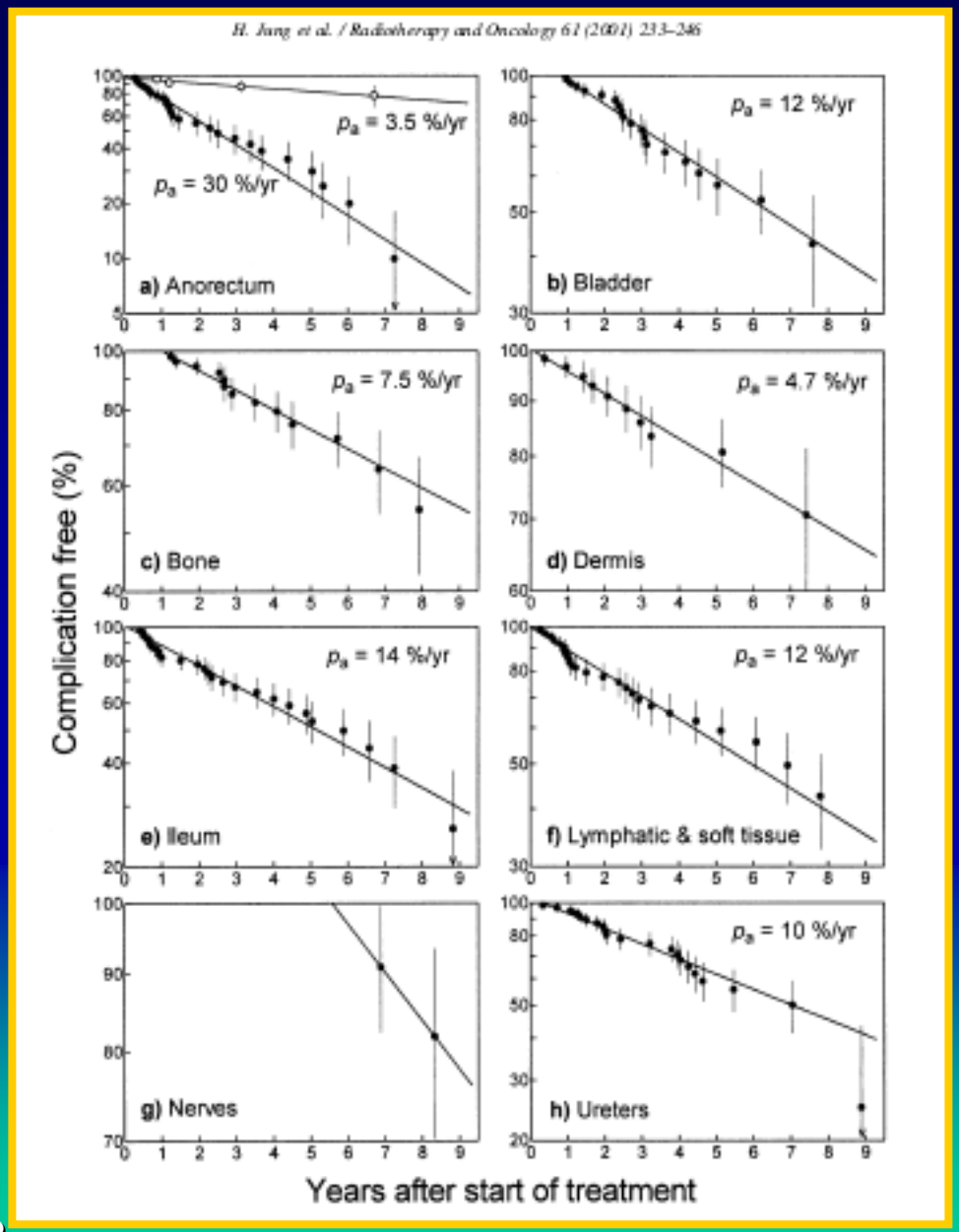
LD10 ~ 1–2 Gy
LD90 ~ 5–7 Gy

Lethal effects in humans from acute low LET irradiation

Whole body dose (Gy)	Effects contributing to death	Time at which death occurs after exposure (days)
3-5 *	Bone marrow	30-60
5-15	Intestine (10 Gy for acute dose) Lungs, kidneys	7-20 60-150
>15	Damage to nervous system (shock)	<5 depend on dose

* medical treatment may increase the LD50/60 to around 5-6 Gy

Late reactions developments



From Jung H.

Stochastics effects of radiations

Late effects of radiations

May occurs few years up (leukaemia) to many years after the radiation exposure (solid tumours) and the probability of increase in appearance last for all life.

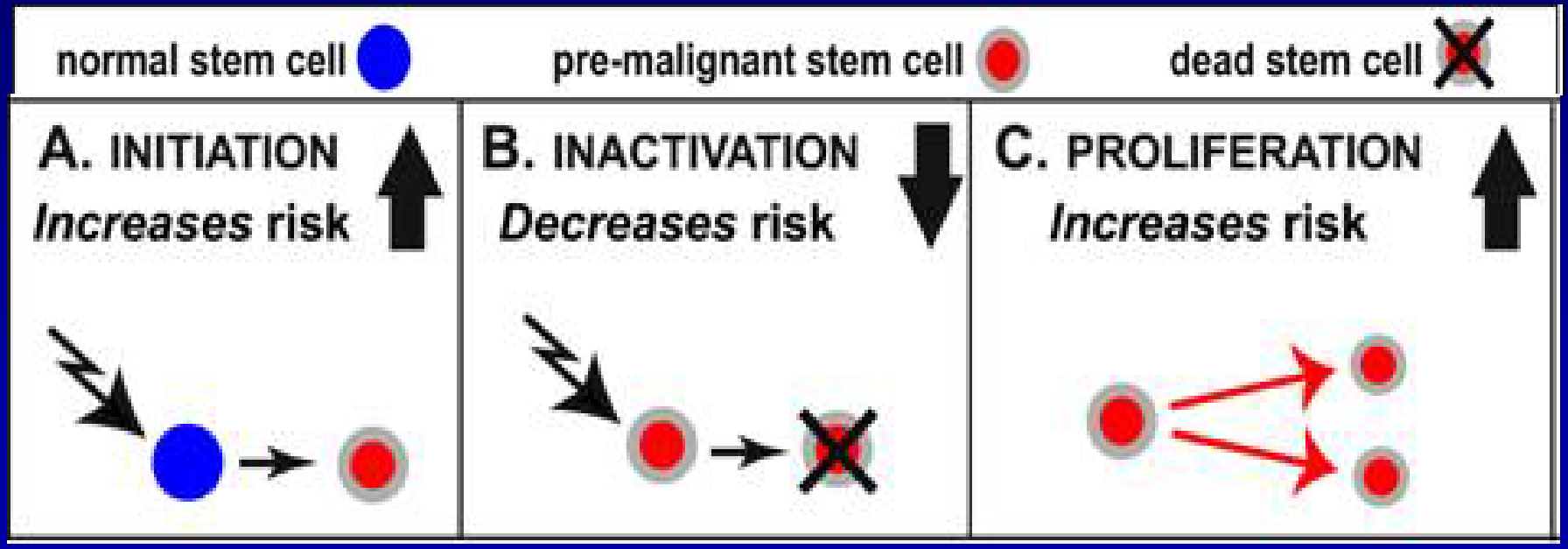
- **No evidence for specific mutational signatures associated with radiation**

Tumour appearance: a multistage process

- Initiation (pre-neoplastic phase)
- Promotion (growth and development of the pre-neoplastic clone)
- Malignant conversion
- Progression (rapid growth with invasive characteristics with accelerated mutation rate independent from radiation)

Cancer risk at high doses

Proliferation of pre-malignant cells during organ repopulation



by courtesy of Hall E.J.

Early initiation process in radiation tumorigenesis

- a linear response in the low-dose region, is to be expected and the process should be independent of dose rate because interactions between different electron tracks are expected to be rare.

Factors influencing the radiation induction of cancer

- **Genetic** (individual susceptibility) (genetic disorders) i.e. individuals carrying single gene cancer prone disorders might be more sensitives.

  Studies are undergoing to determine what facilitate the expression of cancer predisposing genes.
- **Environmental**

Spontaneous and radiation induced mutations

- Humans inherit 3 x 10^9 base pairs of DNA from each parent. Each cell has therefore 6 x 10^9 base pairs of DNA. It has been estimated that in normal conditions each new cell contains some 120 new mutations.

  Ionizing radiations and chemicals have proved mutational capability.

  Molecular and cytogenetic studies using animal models suggest that radiation acts via a gene-loss mechanism.

- Ionizing radiations produce clustered DNA damage which is rarely formed by oxidative processes occurring on cells having spontaneous mutations.

  On average 2 DNA double-strand lesions or 1 complex cluster per cell are produced by 50 mGy of low LET radiations (ICRP 103)

Heritable mutations

- Large multilocus deletions of the genome are most probably the predominant class of radiation-induced mutation which can be compatible with live birth.
- Less than 1% of a general population is **very radiosensitive** because of inherited mutations

Higher incidence of cancers in future generations from irradiated parents?

Table 1. Incidence of leukemia in ICR mice after paternal exposure to X-rays before conception

Stage at exposure	Dose (Gy)	Incidence (%)	
		Acute	Fractionated
Post-gonia	0.36	1/141 (0.71)	–
	2.16	3/356 (0.84)	1/170 (0.59)
	5.04	2/173 (1.16)	0/105 (0.0)
Spermatogonia	0.36	1/132 (0.76)	–
	2.16	1/276 (0.36)	–
	5.04	0/41 (0.0)	0/135 (0.0)
Controls	0	2/548 (0.36)	2/548 (0.36)

Adult ICR males were irradiated 1 to 28 days or more than 64 days before conception for post-gonial or spermatogonial treatment, respectively. For fractionated irradiation, 0.36 Gy of X-rays were given at 2 hr intervals. Details were given in the previous reports[2,3].

From Nomura T. 1978, 1982,1990

Toyoda et al 1990 reported that paternal exposure to ^{252}Cf (65% neutrons) induce in F1 offspring mice 10 times higher incidence of hepatomas

Table 4. Incidence of tumors other than leukemia in ICR mice after maternal exposure to X-rays before conception

Dose (Gy)	Acute		Fractionated	
	Lung tumors	Others	Lung tumors	Others
0.36	6/144 (4.2)	1 OC	–	
1.08	4/73 (5.5)	1 OC	7/100 (7.0)	1 OC
2.16	31/231 (13.4)[a)]	2 OC	8/137 (5.8)	1 OC
3.6	9/66 (13.6)[a)]	–	11/157 (7.0)	–
0	26/548 (4.7)	1 OC	26/548 (4.7)	1 OC

Details are given in the legends to Tables 1 and 3. OC, ovarian tumor.
[a)] $p<0.01$

Further studies on mice offspring

- In utero exposure of mice to X-rays, Co γ-rays, ^{252}Cf neutron, and ^{3}H water resulted in the linear increase of in vivo somatic mutation in PTHTF1 mice, while tumors were induced in the offspring after the postnatal treatment with tumor promoter.
- Significant reduction of leukemia was observed by the low dose rate exposure.
- A significant reduction in the incidences of solid tumors was observed at low dose (0.4 Gy) and low dose rate (0.04 mGy/min) exposure

From Nomura T. 2002

Increase of leukemia skin cancer and lung tumour observed in the offspring of mice exposed to X and γ rays (high dose-rate 189 mGy/min) at spermatogonial stage. No cancer increase at low dose rate (0.04 mGy7min).

Repair deficient (SCID) mice have very high sensitivity to both high and low dose rate for the induction of leukemia, fetal death and malformation

From Nomura T. 2007

Latent periods (Years) for various tumors

Site	Mean	Minimum
Thyroid	20	5
Breast	23	10
Skin	25	10
Bone	20	2-3
Leukemia	7	2

Radiation carcinogenesis evaluation

Cancer: malignant tumour of unlimited potential growth, capable of invading surrounding tissues or spreading in other parts of the body by metastasis.

- Cancer Induction
- Cancer Mortality
- Baseline rate of cancer
- Absolute risk = rate of a disease in a population
- Relative risk = Ratio of the risk among those exposed to that obtained in the absence of exposure
- Life Span Study = Follow-up of survivors during life span collecting all health information to assess risk.
- Excess Relative Risk = Rate of disease in an exposed population / Rate of disease in an unexposed population, minus 1
- Excess Absolute Risk = Rate of disease in an exposed population minus the rate of disease in an unexposed population.
- Risks are additive?

Epidemiology

Rate = Incidence of new cases of a disease related to a population of 100000. It is time dependent and depends also on the starting point and the length of the interval under study.

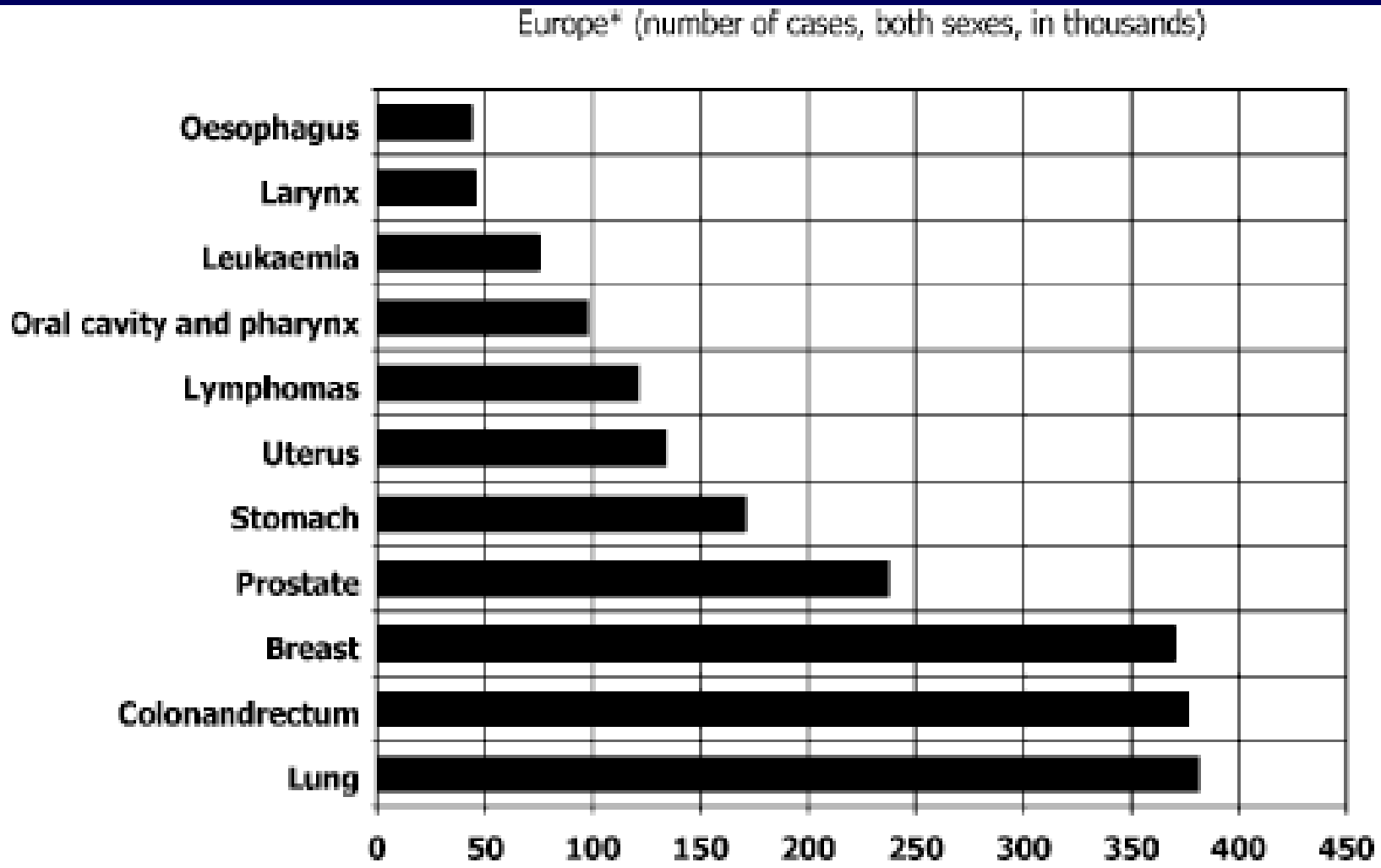
It is function of:

- **age at exposure**
- **sex**
- **type of cancer**

From where the information?

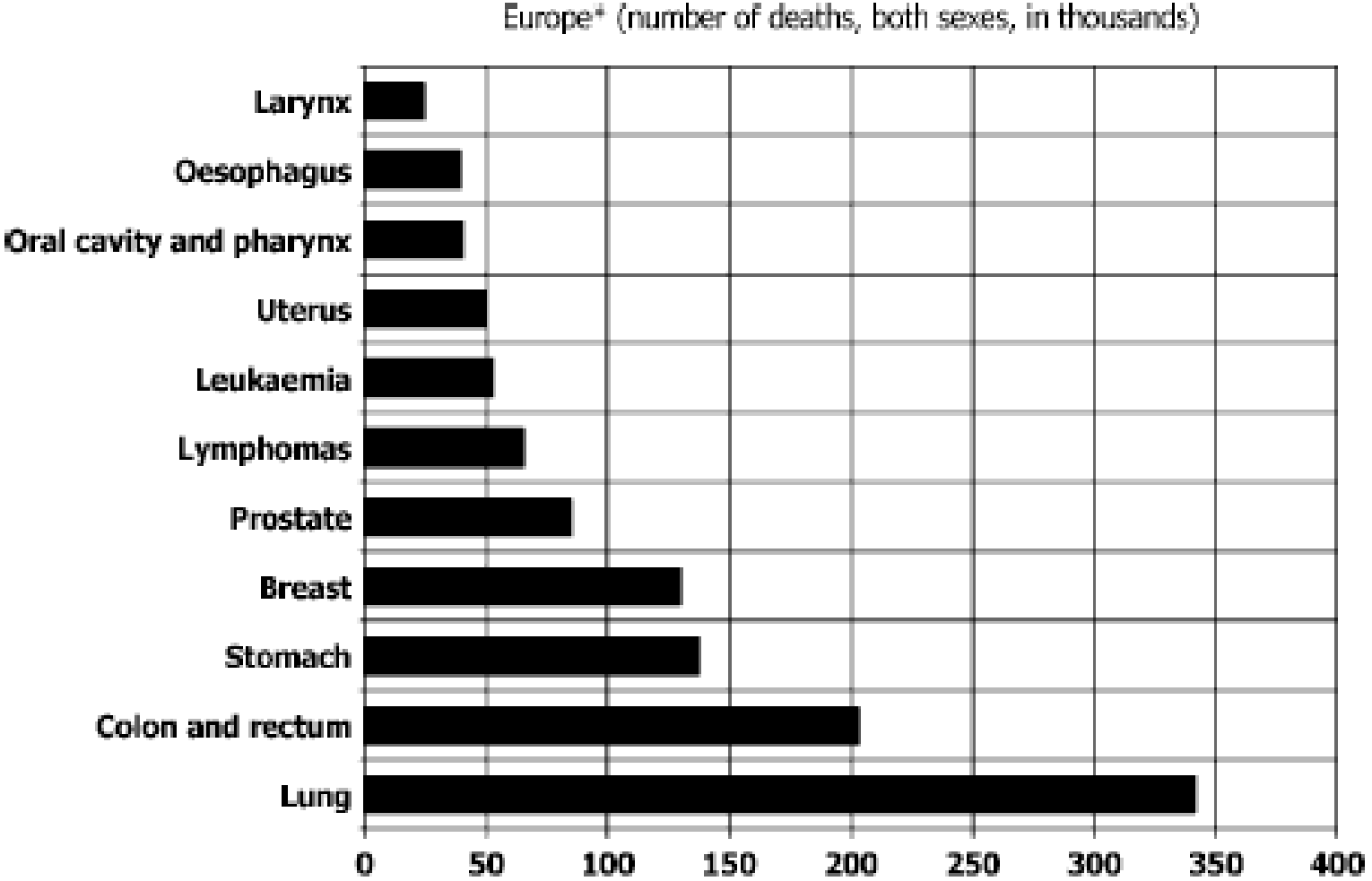
- Hiroshima & Nagasaki
- Chernobyl (2240000 under control in 2005, 94% of liquidators, 89% of evacuees, 85% of residents of radioactively contaminated territory, 79% of children directly or indirectly (643000 children born to the accident liquidators) affected by the accident)
- Accidents
- Occupational exposures
- Radiotherapy patients

Cancer incidence in Europe



By courtesy of CERN Medical Service

Cancer mortality in Europe

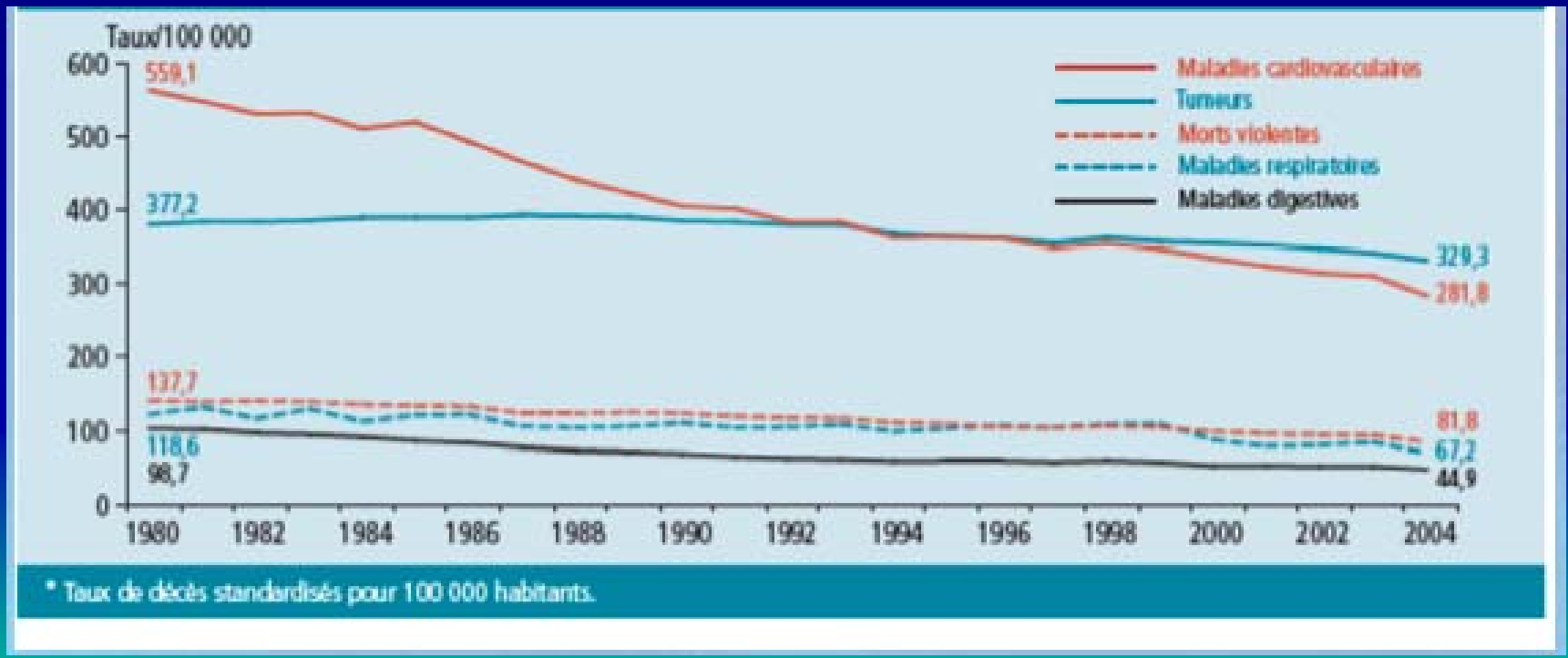


By courtesy of CERN Medical Service

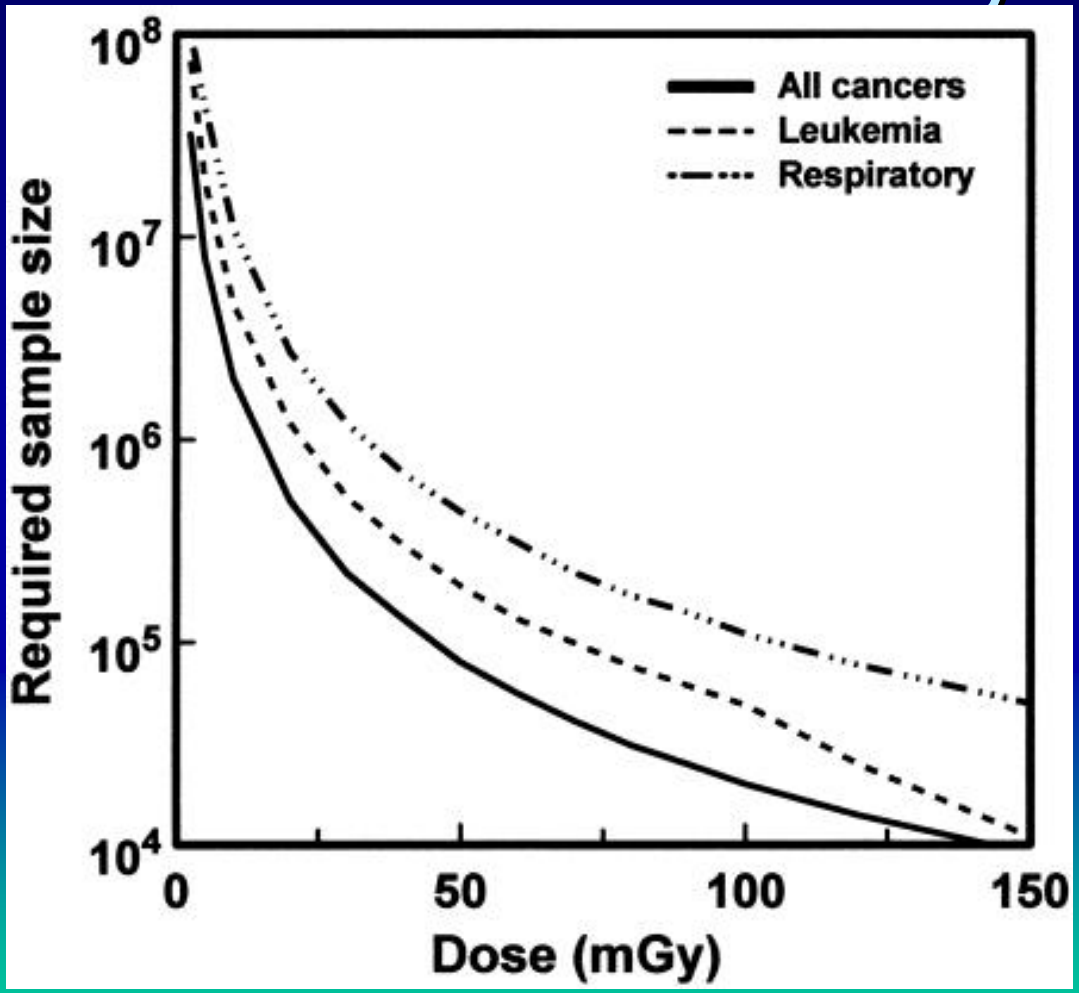
Causes of mortality in France (1980-2004)

from BEH Bulletin épidémiologique hebdomadaire 2007

Figure 3 **Evolution des taux* de décès par grande catégorie de causes de décès, 1980-2004, France métropolitaine, hommes** / *Figure 3 Trends in death rates by main category of causes of death, 1980-2004, Metropolitan France, males*



Sample size to detect statistically significant increase in cancer mortality



From Brenner D. J. et al. 2003

General findings from Hiroshima & Nagasaki

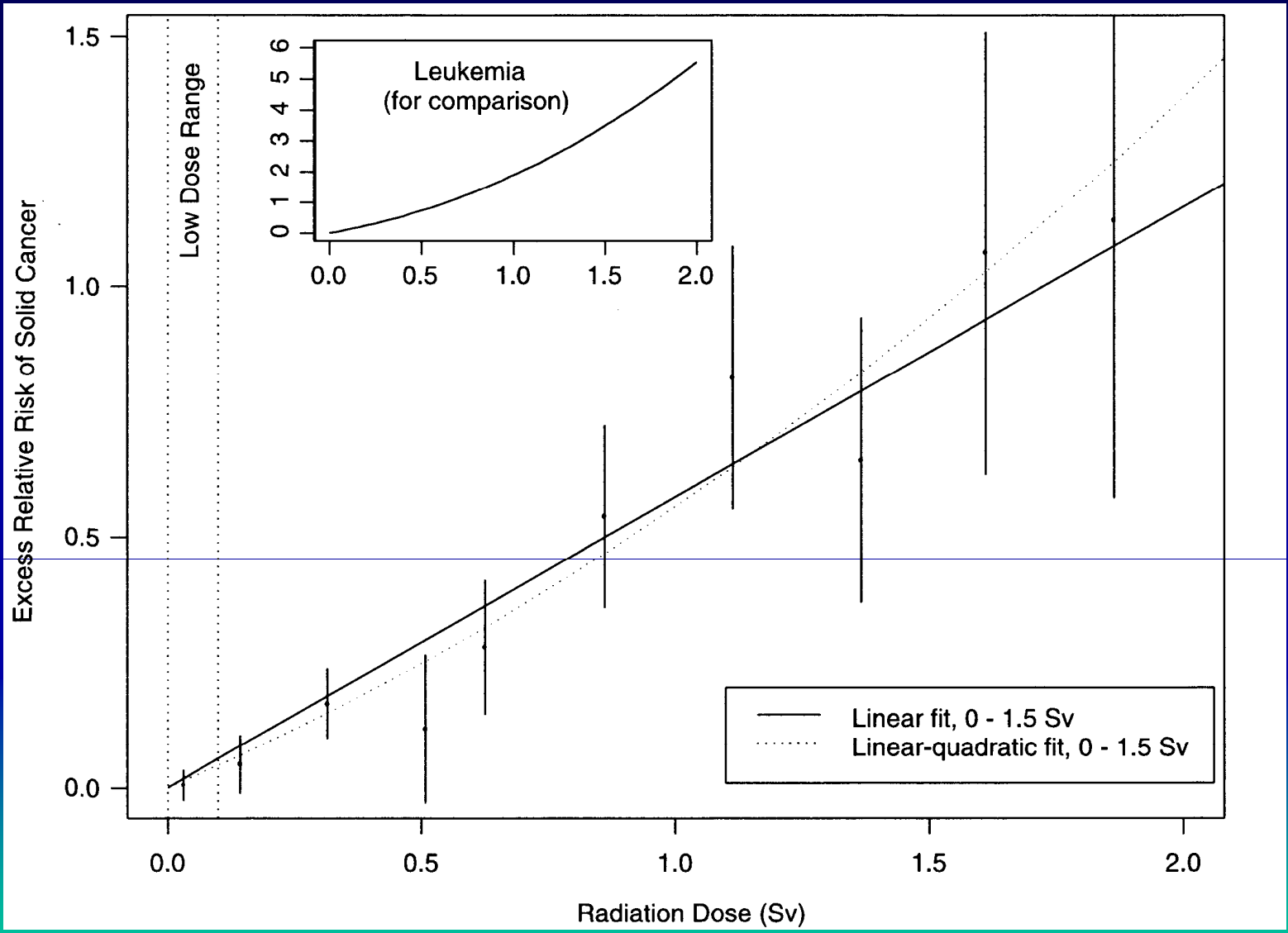
- Young have higher cancer relative and absolute risks than older people
- Women have higher cancer risk for most solid cancers than men
- Radiation-associated increases in cancer rates for solid tumours persist throughout life regardless of age at exposure

45% still alive by end 2000

Life span follow-up

Excess relative risk for solid cancers

in Japanese survivors



From BEIR VII 2006

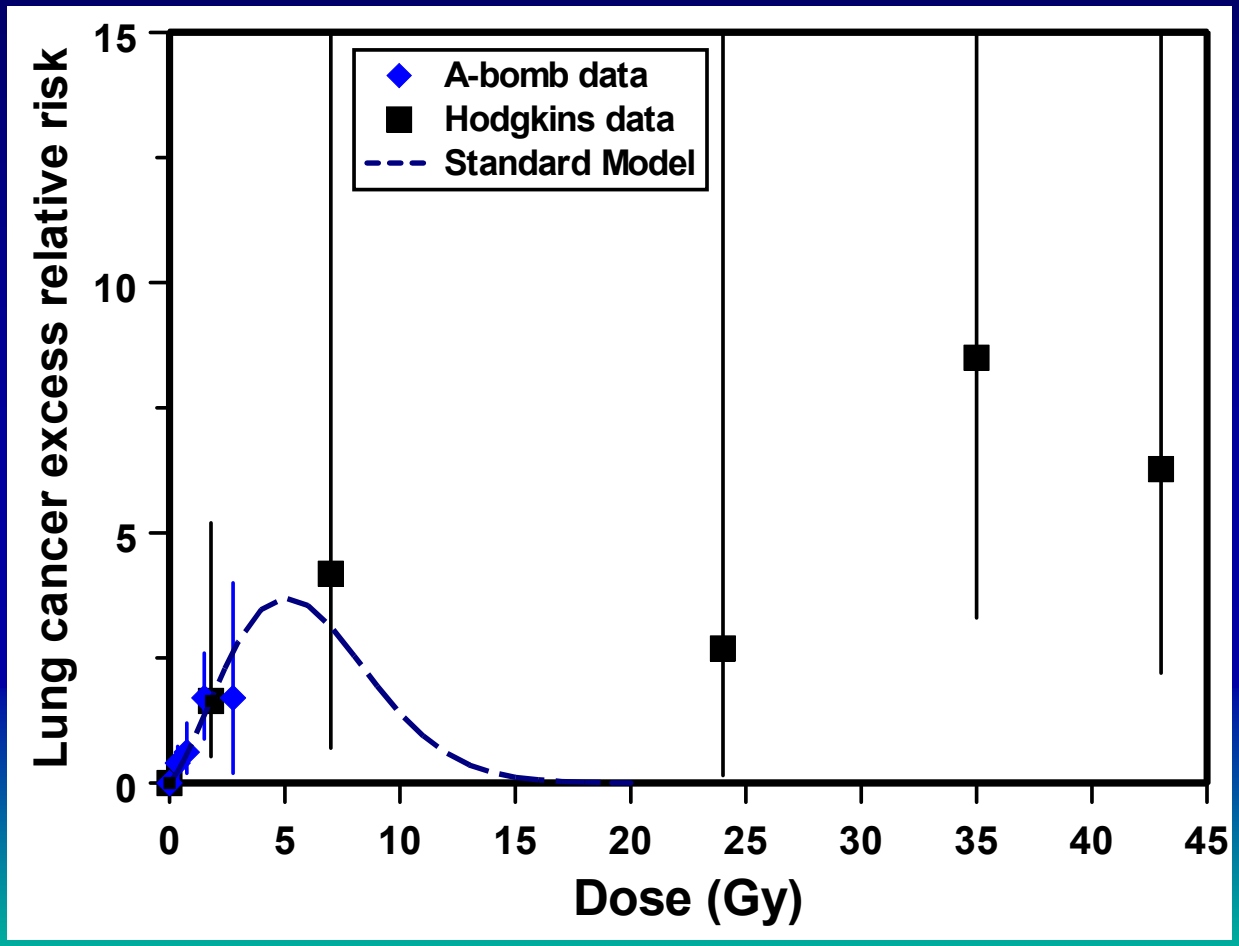
Solid cancer tumours in Hiroshima and Nagasaki

- 17,448 first primary cancers (including non-melanoma skin cancer) diagnosed from 1958 through 1998 among 105,427 cohort members with individual dose estimates who were alive and not known to have had cancer prior to 1958.

  "It was estimated that, at age 70 after exposure at age 30, solid cancer rates increase by about 35% per Gy (90% CI 28%; 43%) for men and 58% per Gy (43%; 69%) for women. For all solid cancers as a group, the excess relative risk (ERR per Gy) decreases by about 17% per decade increase in age at exposure (90% CI 7%; 25%) after allowing for attained-age effects, while the ERR decreased in proportion to attained age to the power 1.65 (90% CI 2.1; 1.2) after allowing for age at exposure."

From Preston D.L. et al. 2007

Lung cancer excess relative risk

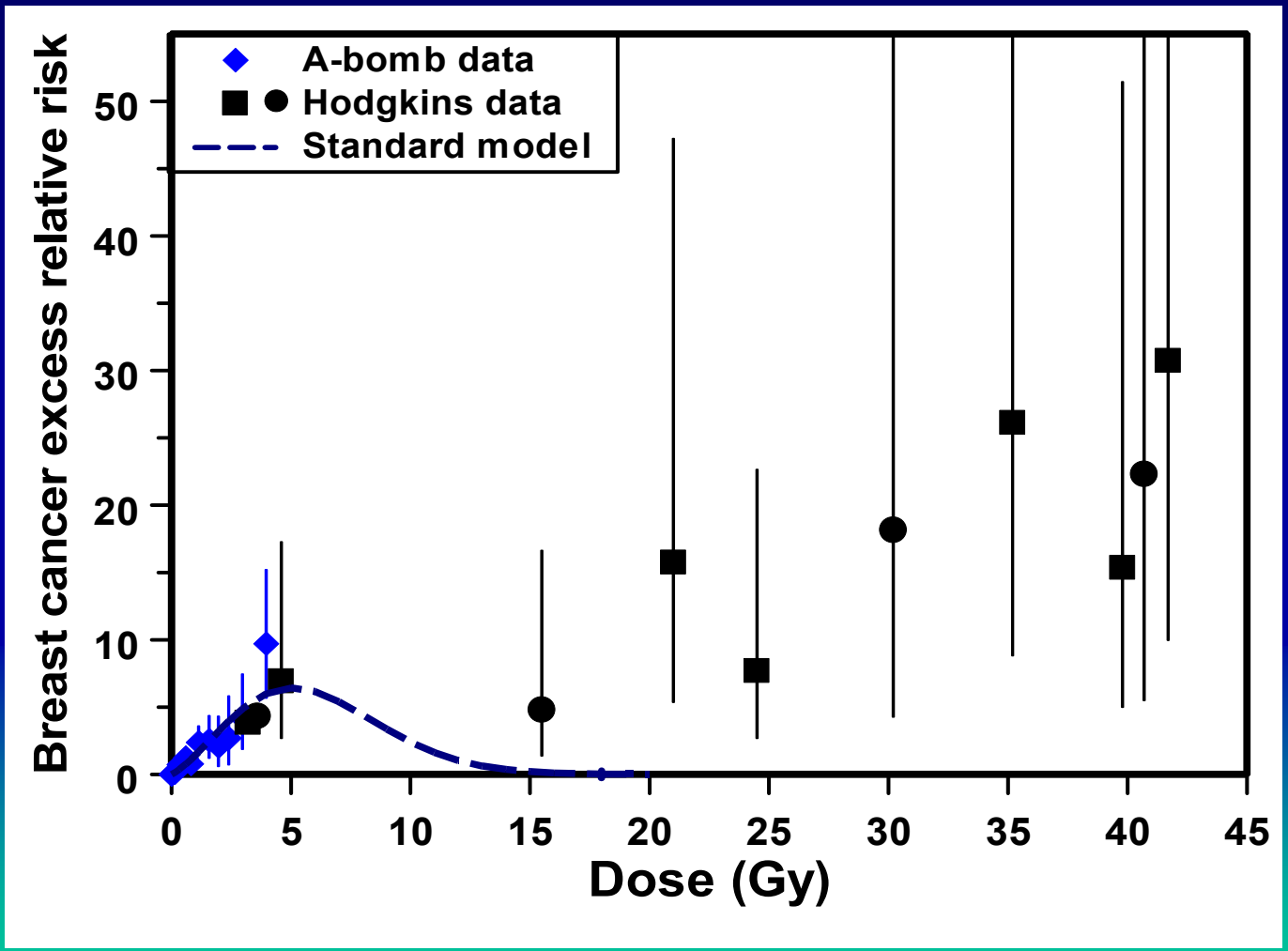


from: Sachs R.K. & Brenner D. J. 2005

Radiations and smoking in lung cancer

- Additive rather than multiplicative risk (however patients treated in The Netherland for Hodgkin's disease show sopramultiplicative effects)
- Discrepancy between results from A bomb survivors and patient that underwent fluoroscopy, Canada and Massachusset study (in the latter no evidence was found of positive association between dose and risk)

Breast cancer excess relative risk



From: Sachs R.K. & Brenner D.J. 2005

A bomb survivors all solid cancer Excess Relative Risk

Variation of ERR/Sv/ per cancer site is not statistically significant

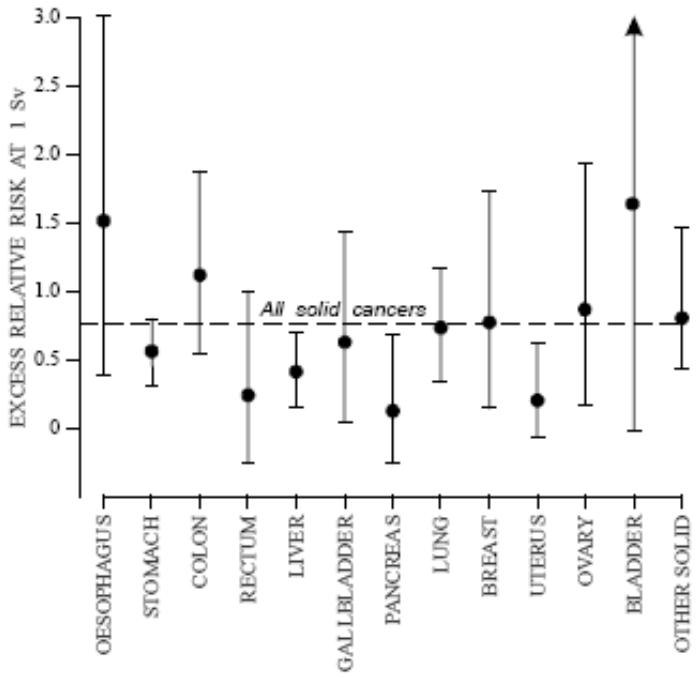
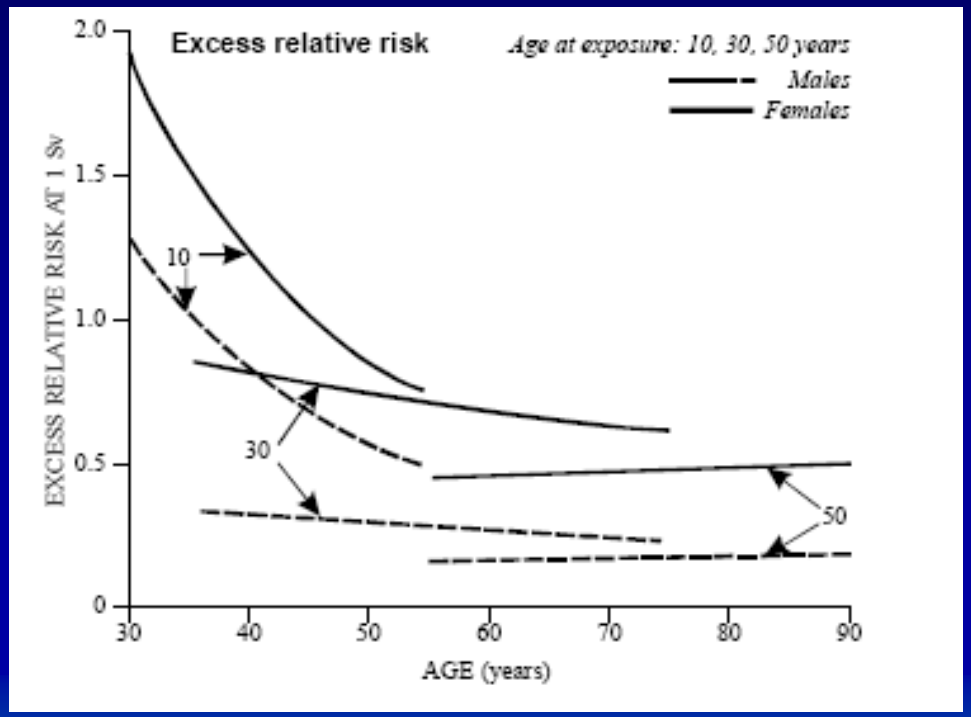


Figure IV. Excess relative risk (and 90% CI) for mortality from specific solid cancers and all solid cancers together (horizontal line) in survivors of the atomic bombings, standardized for females exposed at age 30 years [P9].

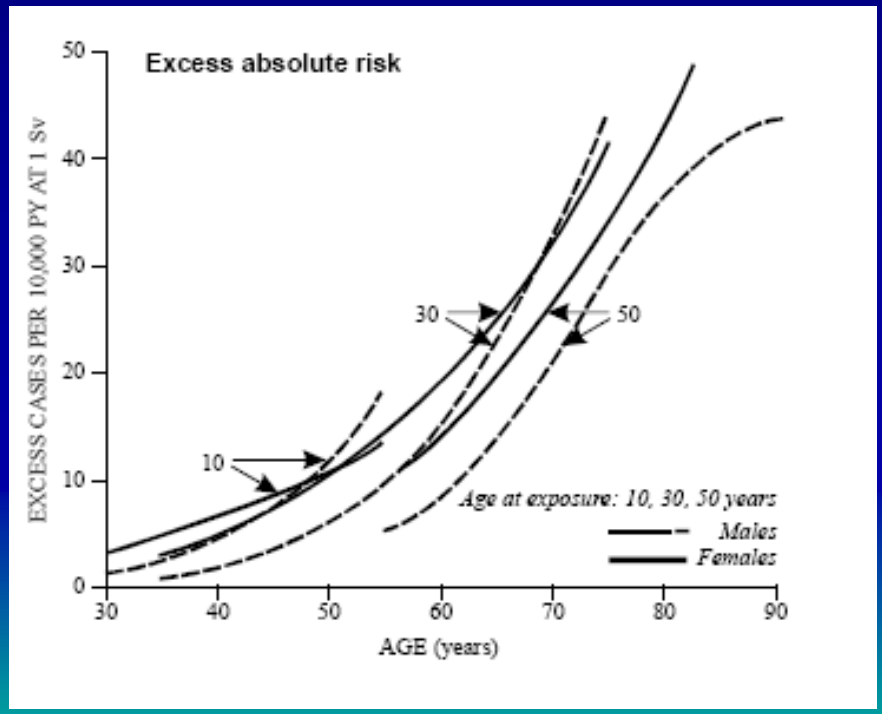
From UNSCEAR 2000

ERR and EAR for solid cancers in A bomb survivors



From UNSCEAR 2000

Pierce D.A. et al. 1996



Loss of life expectancy in Atomic Bomb Survivors

- Median life expectancy decreased with increasing radiation dose at a rate of about 1.3 years per Gy, but declined more rapidly at high doses. Median loss of life among cohort members with estimated doses below 1 Gy was about 2 months, but among the small number of cohort members with estimated doses of 1 Gy or more it was 2.6 years. Median loss of life among all individuals with greater-than-zero dose estimates was about 4 months.

From Cologne J.B. and Preston D. L. 2000