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Biological foundation of radiation protection

Summary part 1

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Deterministic vs. Stochastic effects

- Deterministic effects:
  -has a threshold of dose
  -severity of the effect is dose-related
- Stochastic effects:
  -probability of an effect increases with dose
  -no dose threshold
  -severity of the effect is not dose related

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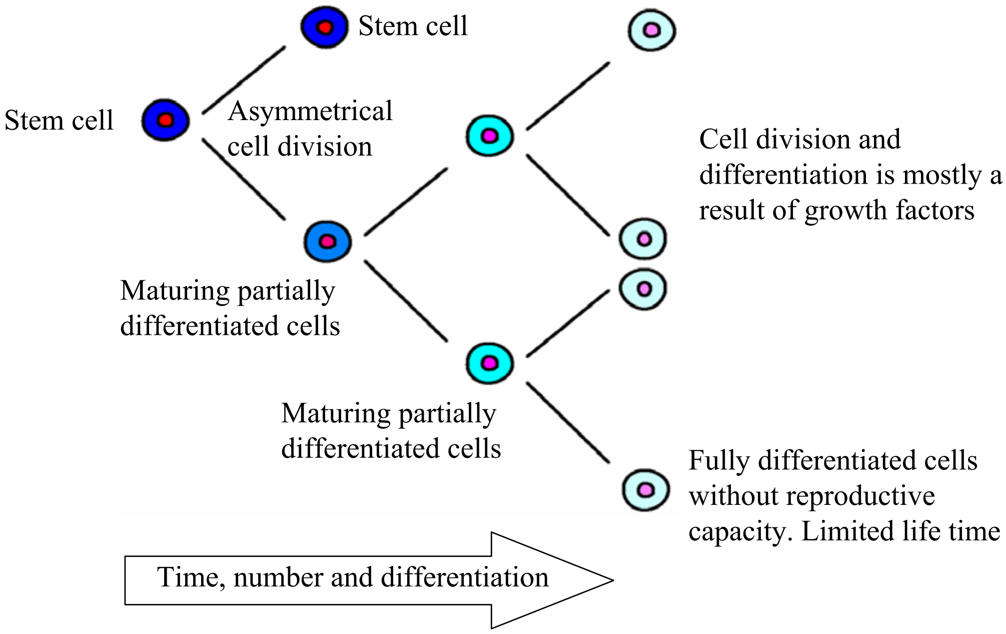
Stem cells

- Hierarchy of stem cells and differentiated cells



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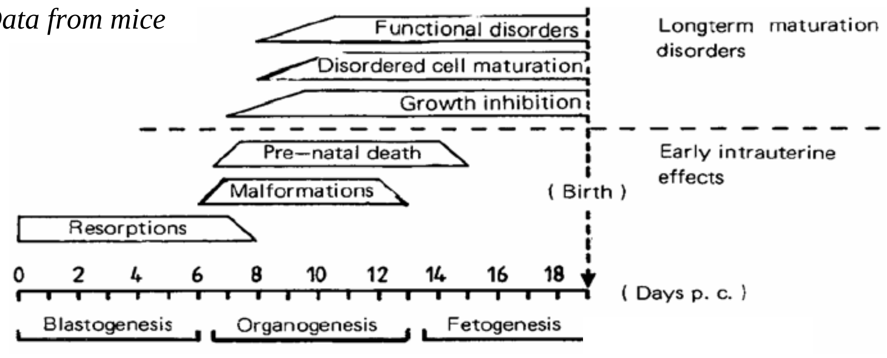
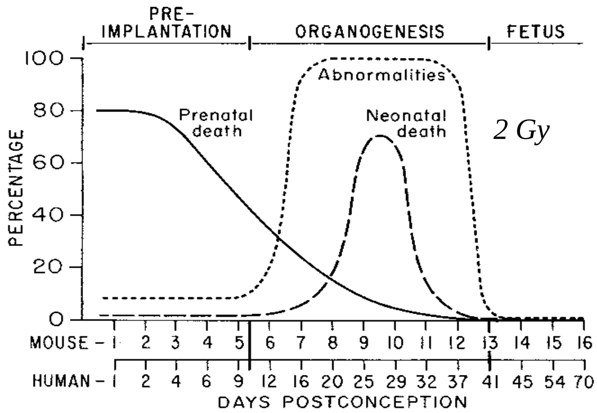
Acute effects

- Skin: ~2Gy, 3w. lost of hair after, but regrowth
  ~5Gy, 1d. red skin, 2w. thin skin, >3 dry "deskvamering"
  >15Gy, >3w. wet "deskvamering
- Bone marrow: ~5 Gy, 50% death after 2-4 week
- Intestinal: >7Gy, epithelium layer disappear, nosiness, diarrhea, bleeding and dehydration
- Brain: ~50Gy, death 1. day
- Lungs: ~10Gy, inflammation after 80-180d.

Effects in fetus period

Data from mice





- Brain most sensitive, as it develop most compare to other organs in this period

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Biological foundation of radiation protection

Part 2: Stochastic effects

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Stochastic effects

- Radiation is proven to have a carcinogen effect, but is less associated to genetic effects
- *Stochastic effects:*
  A change in cells *can* lead to:
  - Cancer
  - Genetic effects

  Can happen independent of dose, but probability increase with dose
- Survivors of Hiroshima and Nagasaki constitute the most important material in the study of this effects

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The bombing of H&N

- Population: 330,000 and 250,000
- >100,000 dead immediately from the shock wave of the bombs
- Gamma and neutrons gave the radiation doses to the survivors
- The survivors have amongst other been check for:
  - Cancer and deadliness
  - Genetic effects expressed in the descendants

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Cancer

- Complicated diseases which depend on among other things:
  - Age
  - Sex
  - Nutrition
  - Genes
  - Intake of cancer developing substances
- Large differences between Europe and Asia
- Cancer develop trough several stages (multi-step process)

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Cancer 2)

- Generation of cancer takes long time – often 20- 30 years from starting point to detection (Latency time)
- Exception: f. ex. Leukemia (cancer in the Hamatopoietic system) and Thyroid cancer
- Studies of the cause of cancer depend of nice historical data
- Generally difficult to separate single factors responsible for the disease

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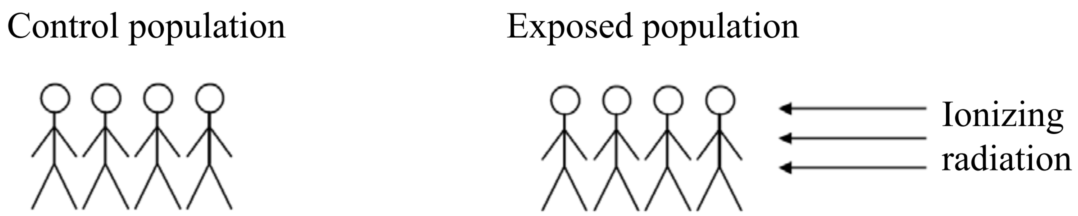
Population studies

- Epidemiology most be used in studies of a population
- H & N: f. ex. *Cohort studies* of cancer frequency



- By comparing the exposed population of the control population risk estimates is composted

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Population studies 2)

- Models of radiation induced cancer (example):

Risk = Back ground risk x (1 + Excess Relative Risk)

$R = R_0 \times (1 + ERR)$

↑ Dependent of sex and age

↑ Dependent on sex, age and **radiation dose**

ERR = a x dose, a = constant

↑ Additional risk is *assumed* to increase linearly with the radiation dose

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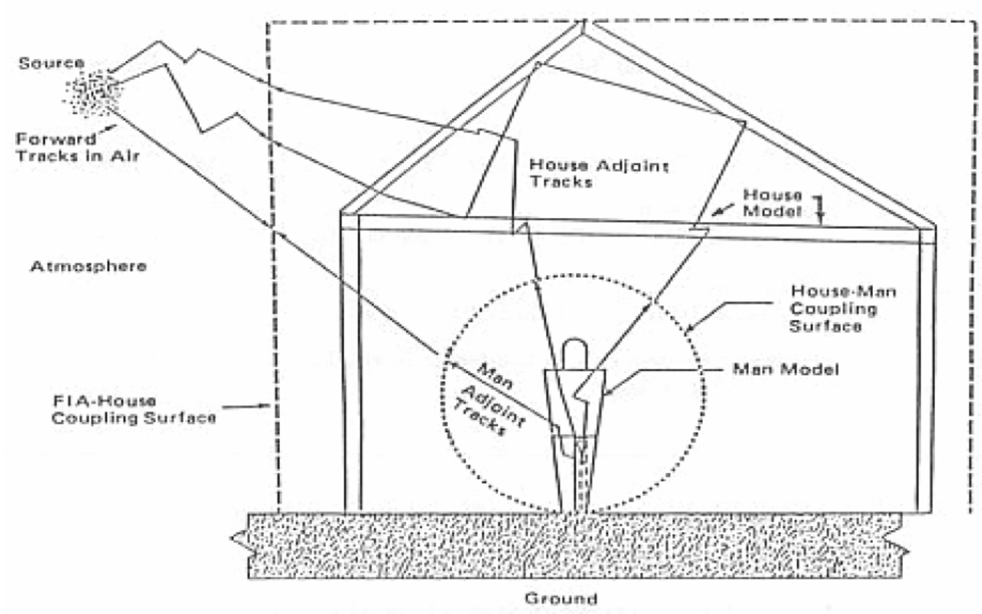
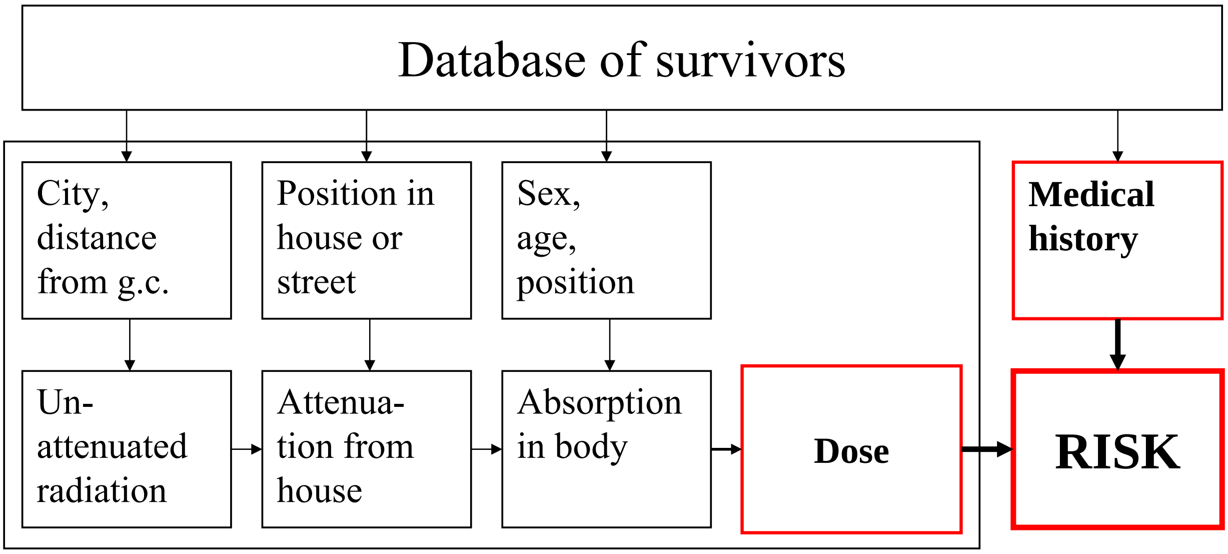
Calculations of radiation dose

- Radiation spectra and strength of the bombs
- Radiation transport in air and attenuation in buildings
- Absorption in organs



Dose and risk



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Cancer in H & N

	H&N (1950-1987)	Japan (comparable population)
Population	80114	80114
Cancer as cause of dead	**5859**	**6343**

- The survivors of H&N most be evaluated as a statistical isolated population
- Control is survivors whom was > 2500m from hypocenter during the bomb detonation

→ Excess cancer deaths due to radiation(1950-1990) among the survivors of H&N : 420

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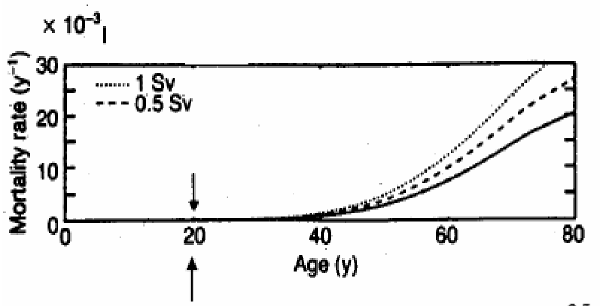
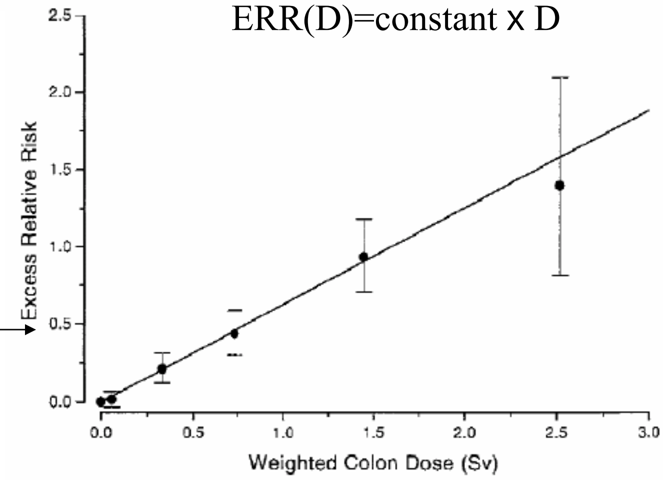
Risk of cancer – solid tumours



Exposition

Risk=Back ground risk x (1+ERR(D))
ERR(D)=constant x D

If the x-axis is cigarettes smoked per day, can the y-axis be divided by 1-2



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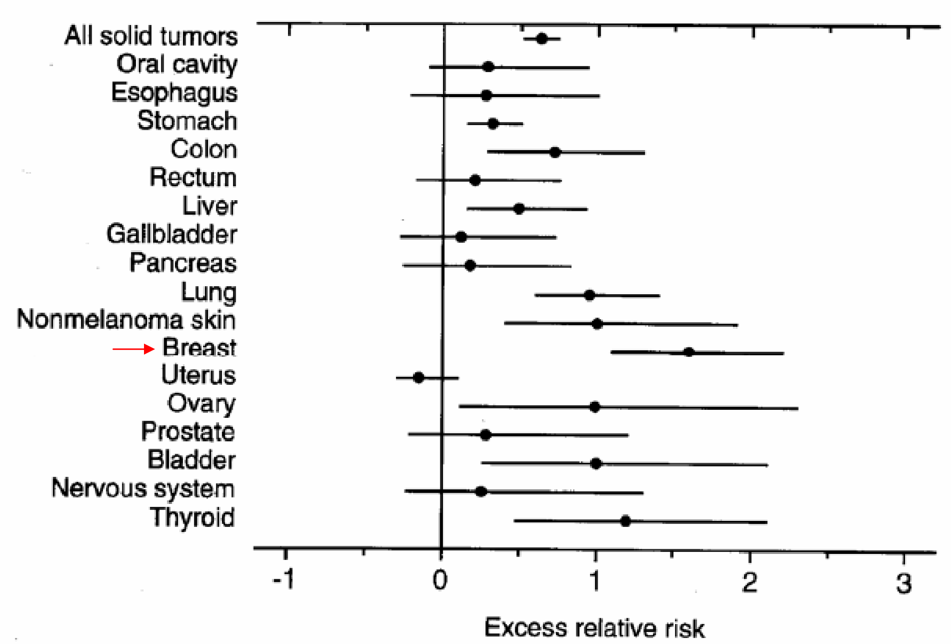
Cancer risk 2)

- Different types of cancer has different radiation risk factors – ERR



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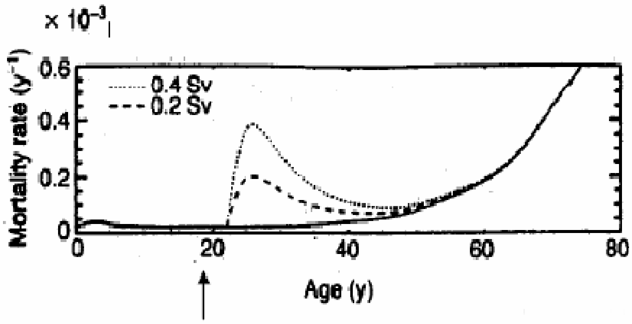
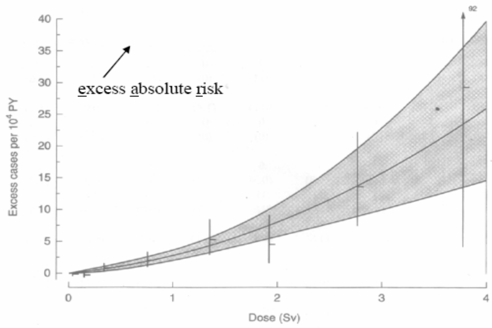
Cancer risk – leukaemia 3)



Exposition



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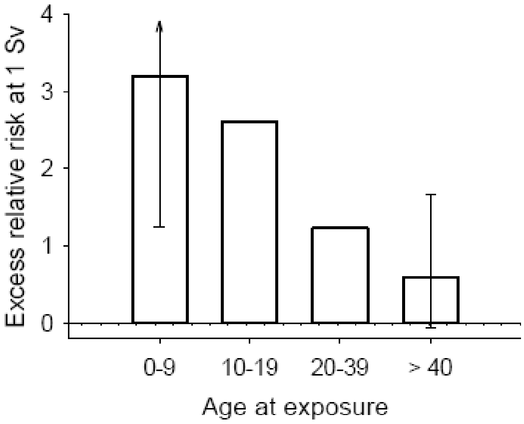
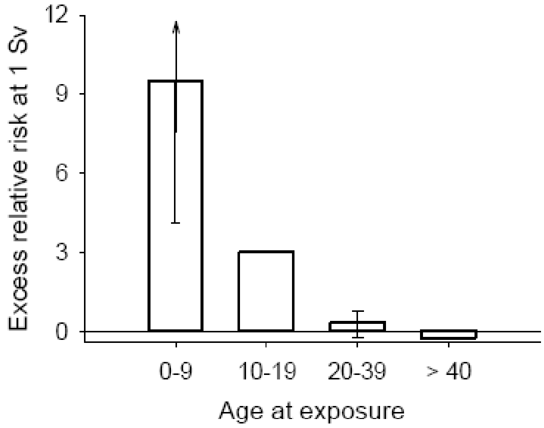
Cancer risk 4)

- The influence of age at exposition:

Breast



Thyroid



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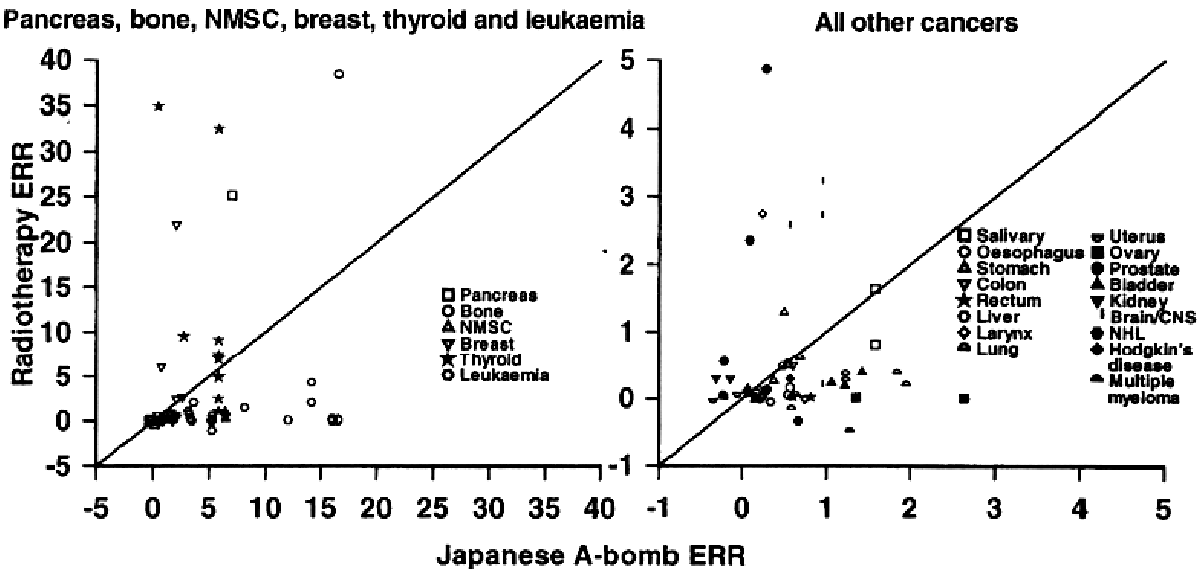
Cancer risk 5)

- Other studies (from therapy and similar) show that the data from H&N are possible overestimating the risk:



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Cancer risk – error estimates

- The errors in the risk factors can origin from amongst other things:
  - Errors: in the radiation estimates, cancer frequency and the models from H&N
  - Small verses large doses
  - Dose distributed over a period verses acute radiation
  - Age and sex
  - Joint effects of other factors with radiation

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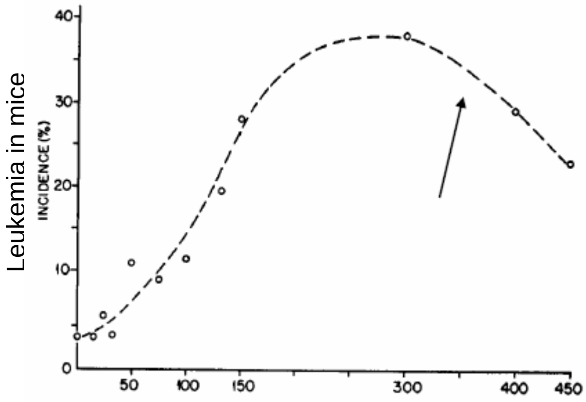
Other studies

- Animal experiments have shown that the cancer risk decreases if the dose gets high enough:



- Radiation induced cancer are therefore seldom seen after cancer therapy

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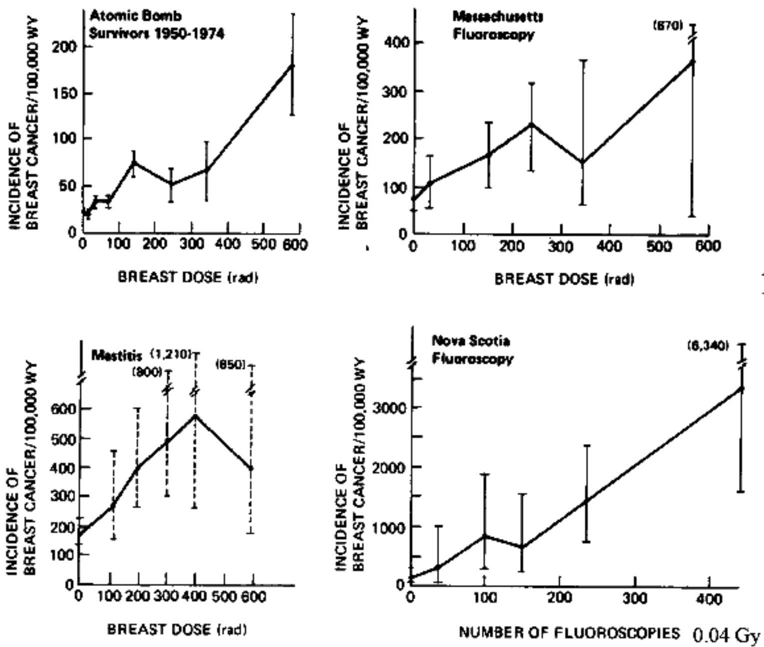
Other studies 2)

- Breast cancer studies:



100 rad = 1 Gy

0.04 Gy < Dose per fluoroskopi < 0.2 Gy

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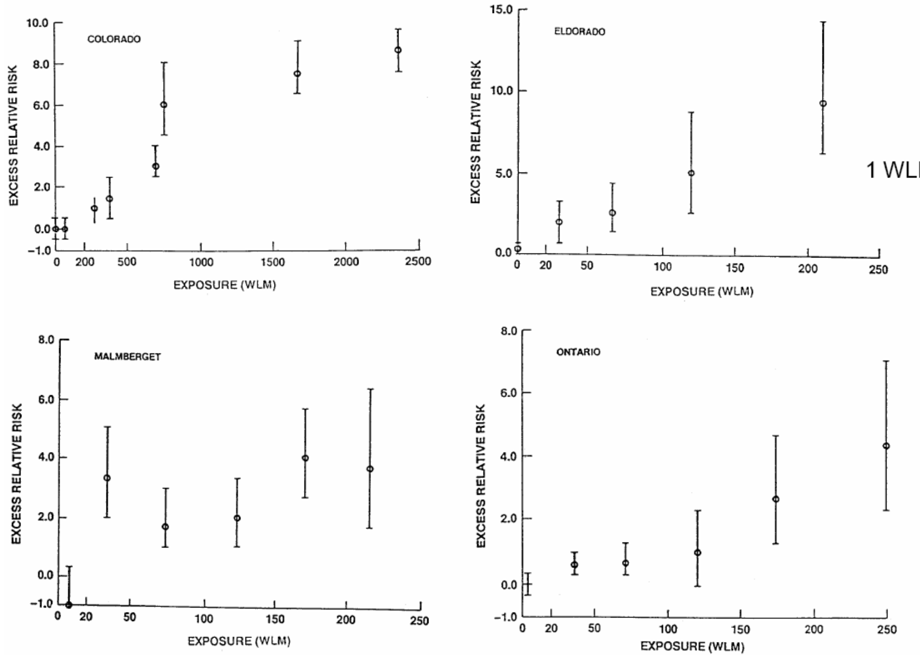
Other studies 3)

- Lung cancer among miners – radon levels:



1 WLM (working level month)
~ 0.05 Sv lungedose

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Genetic effects in offspring

- Search genetic independent distinctions in offspring which origin from (radiation induced) mutations in egg cells and sperm cells
- Mutations are changes in DNA
- Radiation is assumed to increase the frequency of natural mutations (which is low?) – expect also a low frequency of radiation induced mutations

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Mendelian genetic on one page

- Humans have about 50 000 pairs of genes and each of these are located in a defined positions (locus) in a defined chromosome
- Different versions of a gene (at the same locus) is called alleles (f. ex. alleles of blue and brown eyes)
- Dominative alleles: just one is needed to make a distinct feature to occur in the offspring
- Recessive alleles: need two
- Sex related recessive: if the X-chrom. mutated, males gets the feature (f. ex. red-green color blindness), while female only if both X mutated

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The mega mouse project

- Millions of mice used to examine genetic effects of radiation
- Example: Mice with 7 pairs of recessive alleles; give 7 different features (6 give special colors, 1 short ears)
- Normal mice is radiated and matted with mice's with such recessive alleles:

Normal mouse with two normal alleles · Recessive mouse

If no mutations: $\frac{N}{N} \times \frac{R}{R} = \frac{N}{R}\;\frac{R}{N}$

Offspring always normal

Radiation induced mutation in radiated normal mouse · Some of the offspring gets radiation f. ex. short ears

If mutations: $\frac{R}{N} \times \frac{R}{R} = \frac{R}{R}\;\frac{R}{N}$

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The mega mouse project 2)

- Important: *at which period in the generation of sperm or egg cells the exposition occur*.
- Male: continues spermatogenesis; 40/70 days (mice and men) to generate sperm cells
- Female: egg cells ready before birth; only matures
- If mice is radiated and mutations in sperm cells (spermatogenesis) is to be examined, most at leased wait for 40 days

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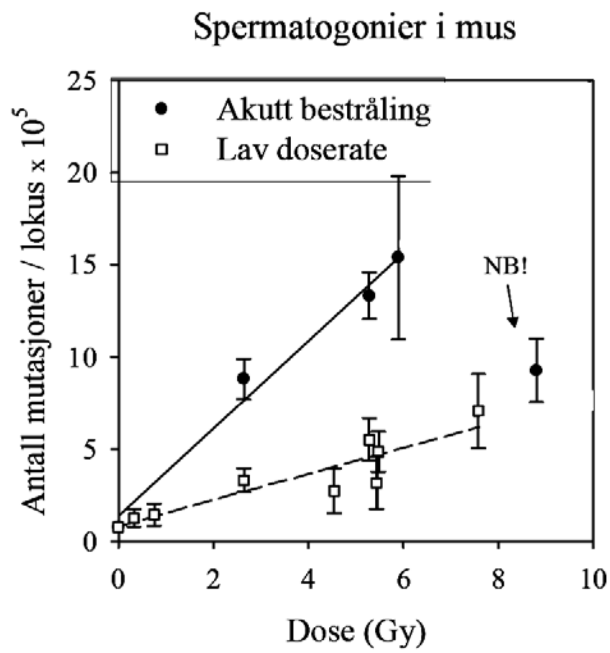
The mega mouse project 3)

- The number of mutations observed in offspring increase almost linearly with dose, but at high doses the mutation rate decrease
- Reduction of the effect at low dose rate – indicate repair
- Dose Rate Effectiveness Factor - DREF



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The mega mouse project 4)

- Matured sperm cells are more radiation sensitive (concerning mutations) than in spermatogenesis
- Egg cells not ass sensitive to mutations
- Dominant mutations have also been examined:
  - Abnormities in skeleton
  - Cataract (unclear eyes)
- Problem: the number of genes contributing to these effects are not known

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Offspring off H & N

- Offspring (over 30 000) have been examined among other things for:
  - Natal mortality (< 2 weeks) and abnormalities (Untoward Pregnancy Outcome, UPO)
  - Mortality (from 2 weeks and 26 years of age)
  - Protein mutations
  - Cancer
  - XY-aneuploidi (f. ex. XXY)
- Problem: effect depend probably not of mutations in only one gene, but are multifactor effects

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Offspring off H & N 2)

- The studies show a doubling dose about 2 Gy:

Feature	Frequency/dose(%/Sv)	Natural frequency
UPO	0.264 (±0.277)	
Mortality	0.076 (±0.154)	0.330-0.530
Protein mutations	0.001 (±0.001)	
Cancer	(-0.008) (±0.028)	0.002-0.005
XY aneuploidi	0.044 (±0.069)	0.030
Total	0.375	0.632-0.835

- Radiation is a weak mutagen