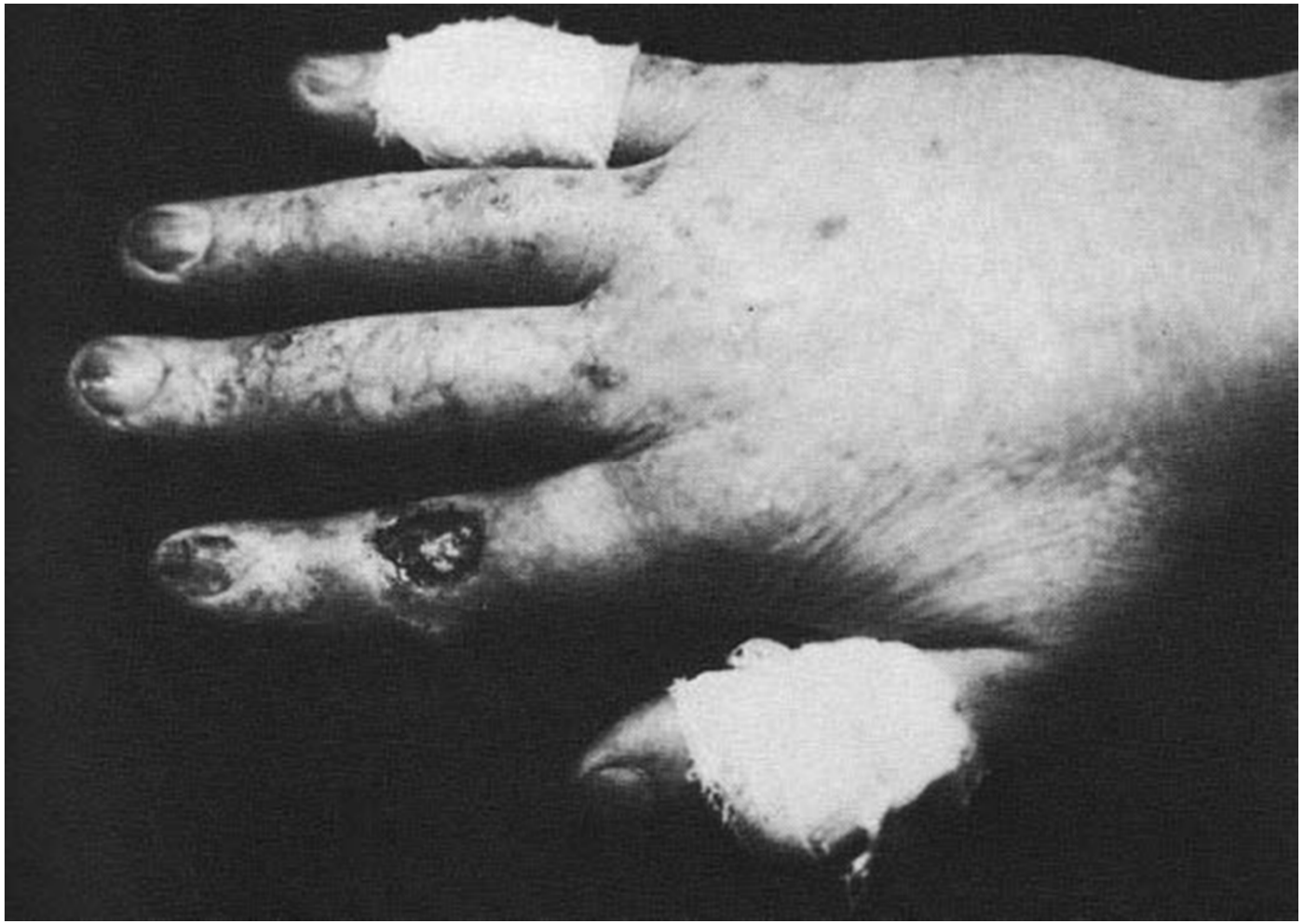
RADIATION CARCINOGENESIS

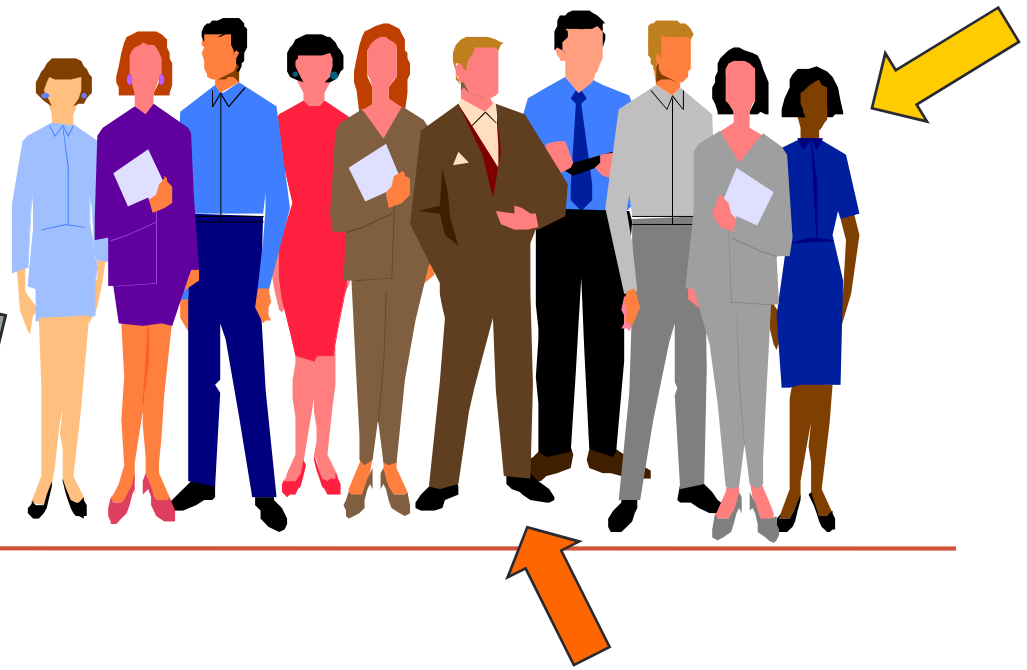
Risks associated with radiotherapy

Radiation induced cancer known since 1902.

Spinocellular carcinoma of a RX operator’s finger



WHAT IS CANCER?

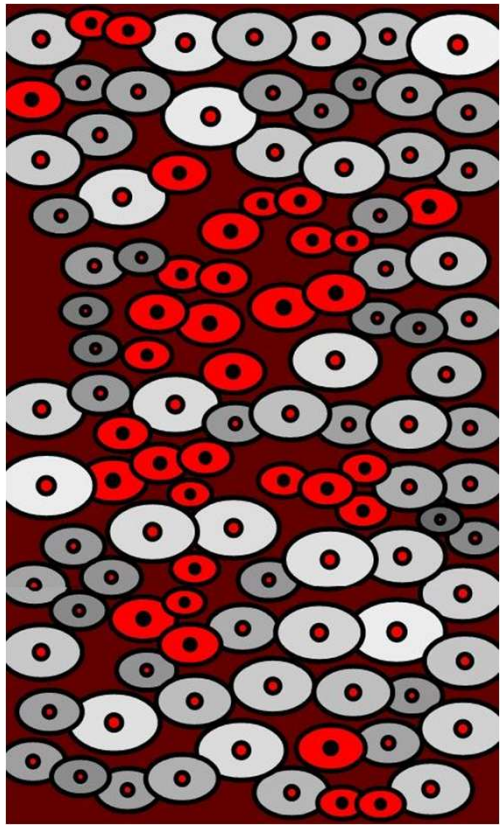


Cancer is a frequent disease.

1 in 4 in Western populations.

1 in 2 children born today…

What is cancer ?
What is life ?

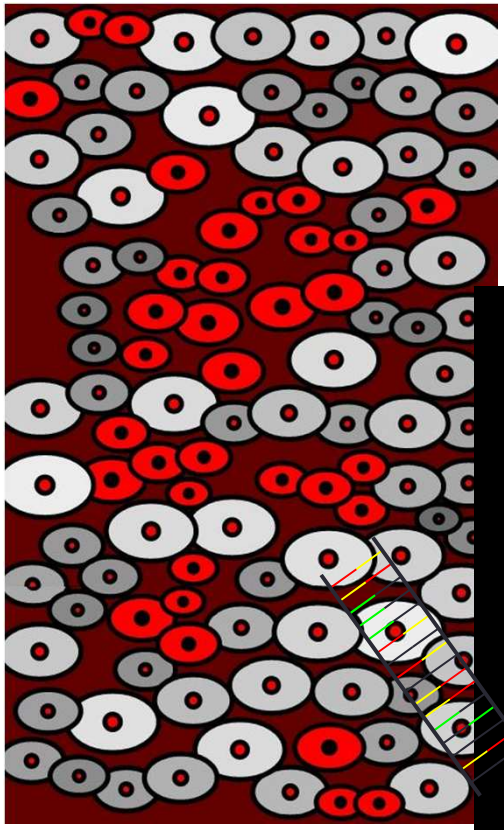


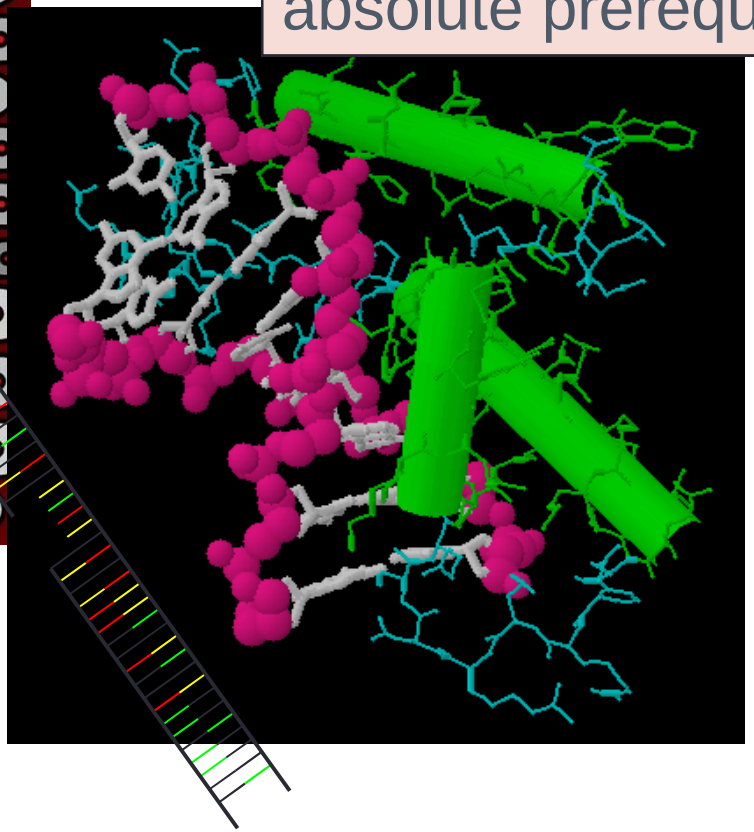
Our body is made of billions of cells, highly specialised.

Each cell follows a program

Each cell has a very precise idea of its function and role; it is permanently aware of what's going on in the neighbourhood as well as elsewhere in the body.

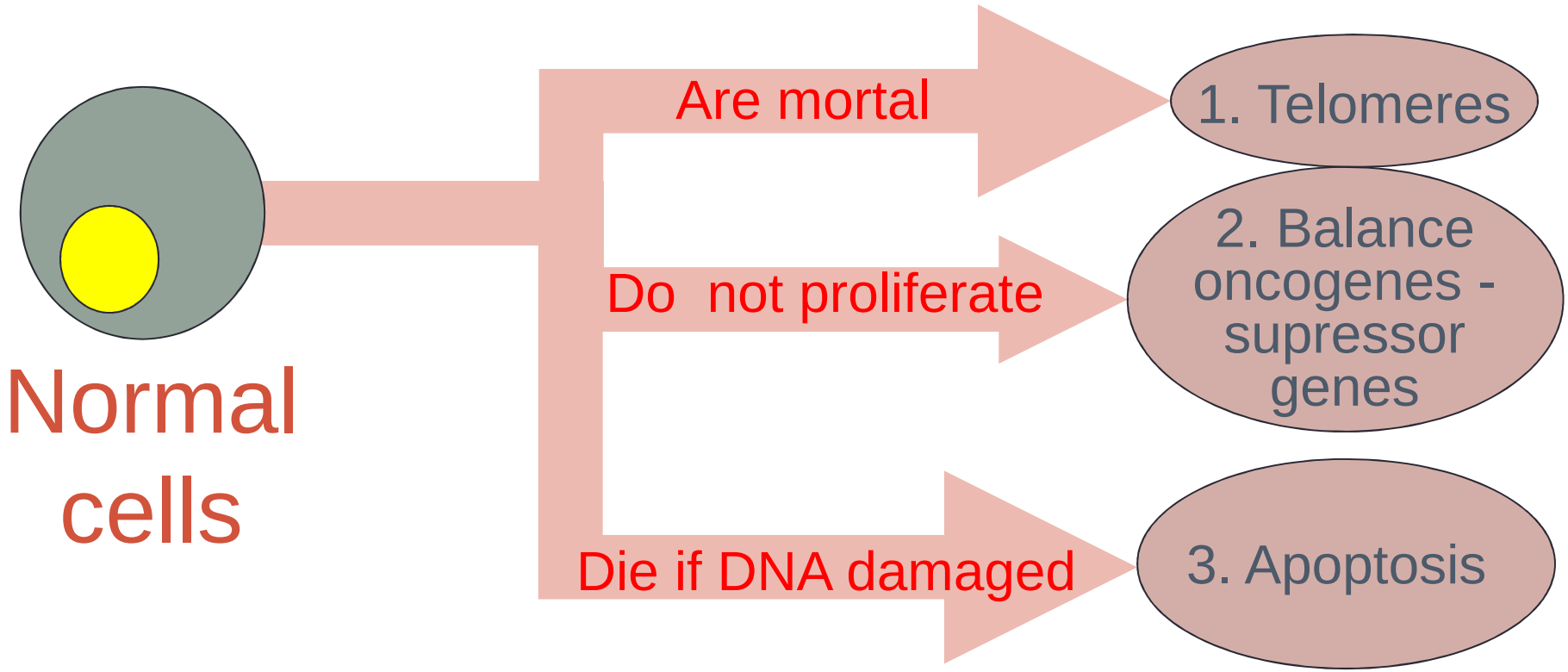
What is life?



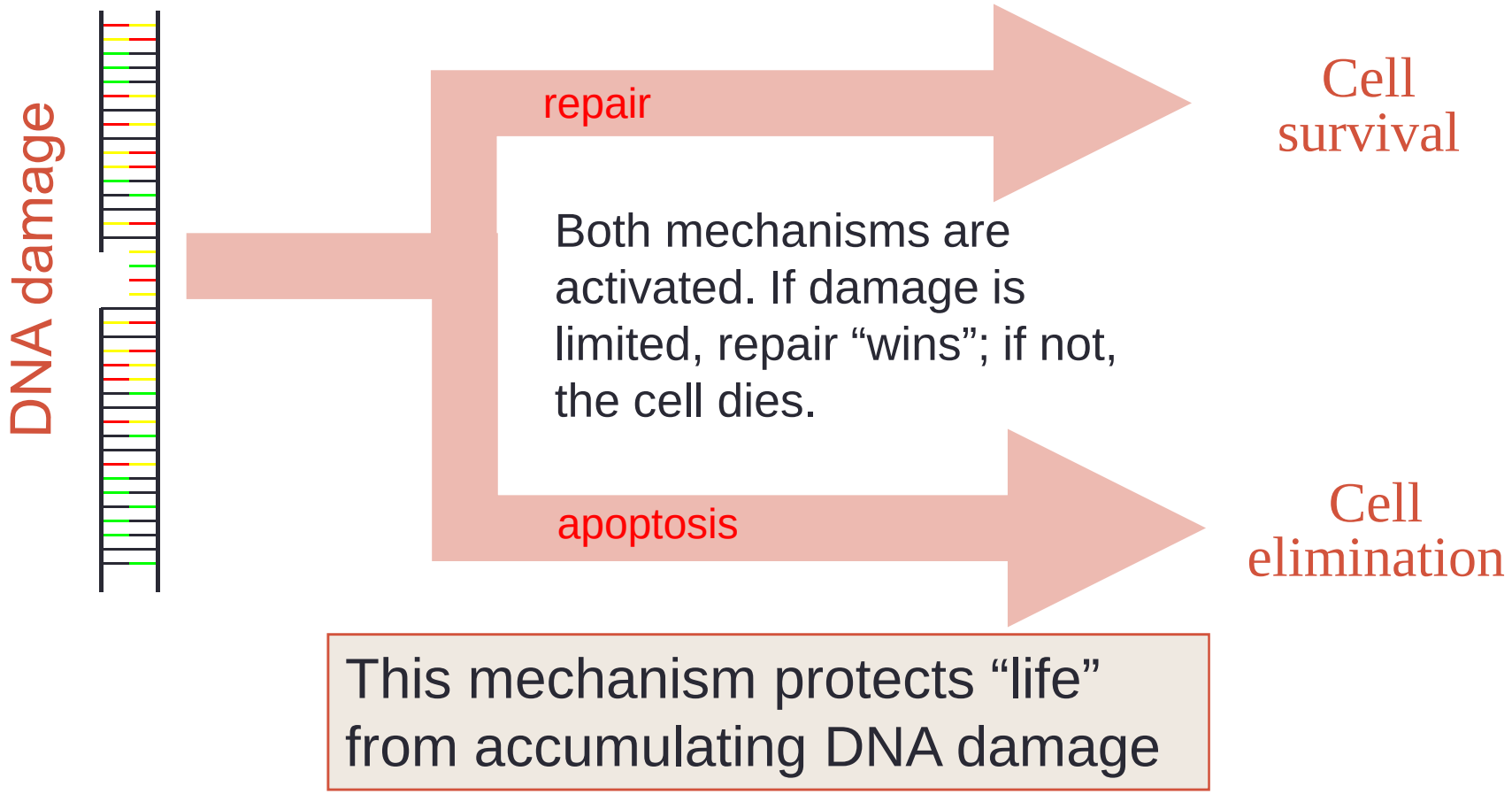


Normal cells follow a program coded in the DNA. This code is under high surveillance and protection since its integrity is an absolute prerequisite for normal life.

What is life?

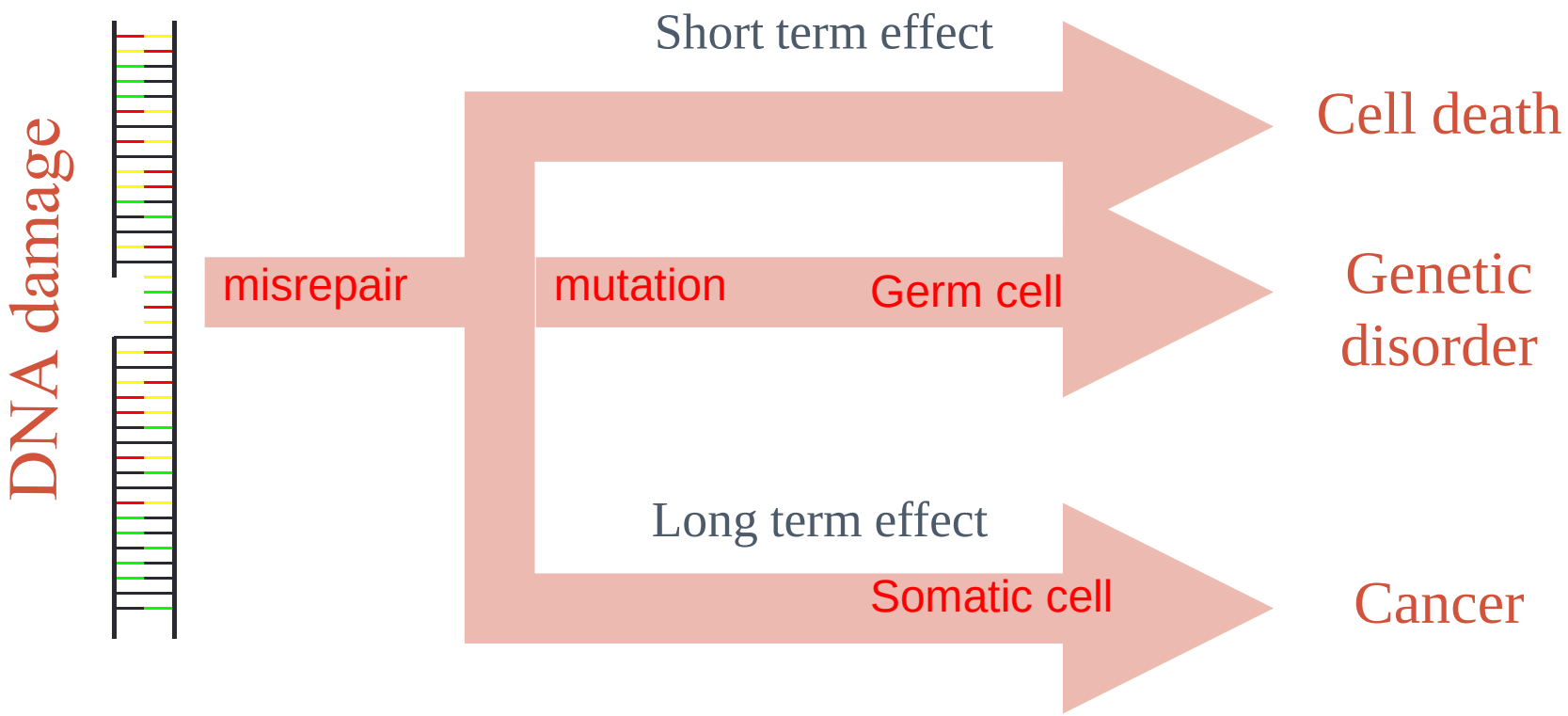

Normal cells
Are mortal
Do not proliferate
Die if DNA damaged
1. Telomeres
2. Balance oncogenes - supressor genes
3. Apoptosis

What is apoptosis?

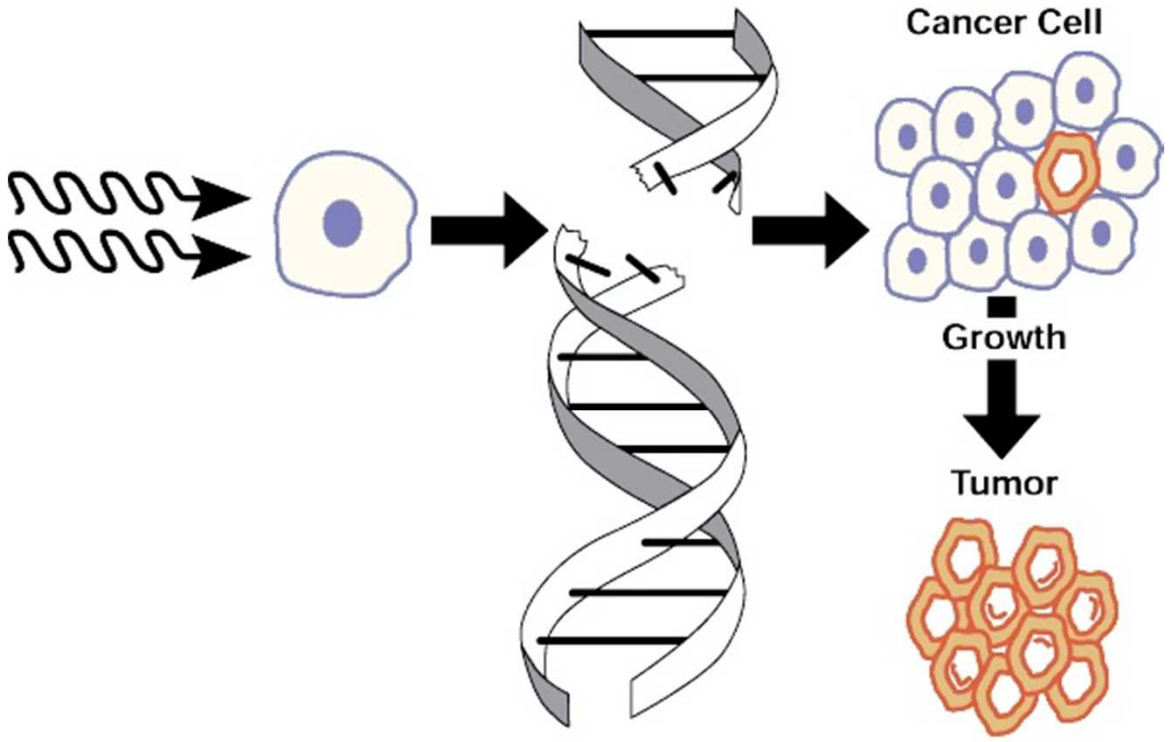


This mechanism protects “life” from accumulating DNA damage

What is cancer ?



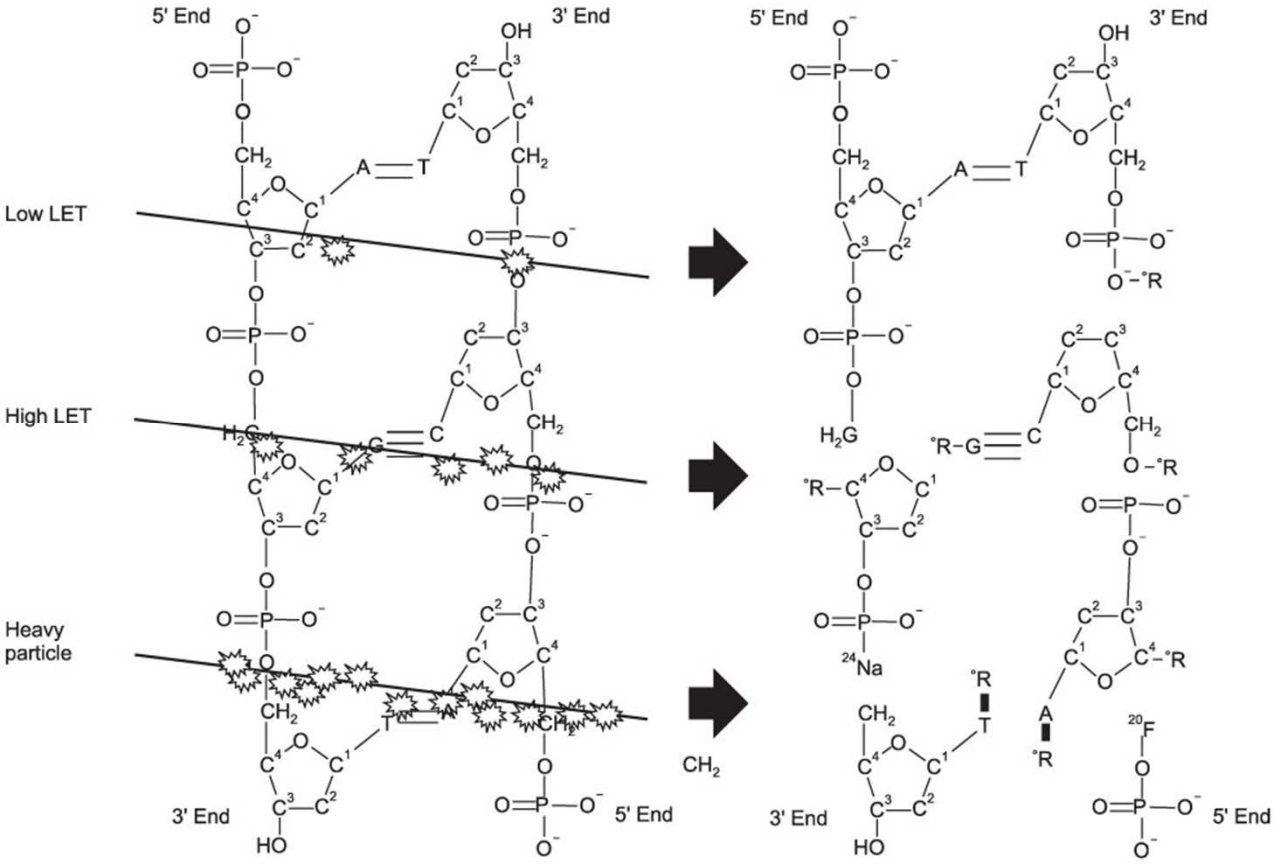
In practice



Mutated surviving cell

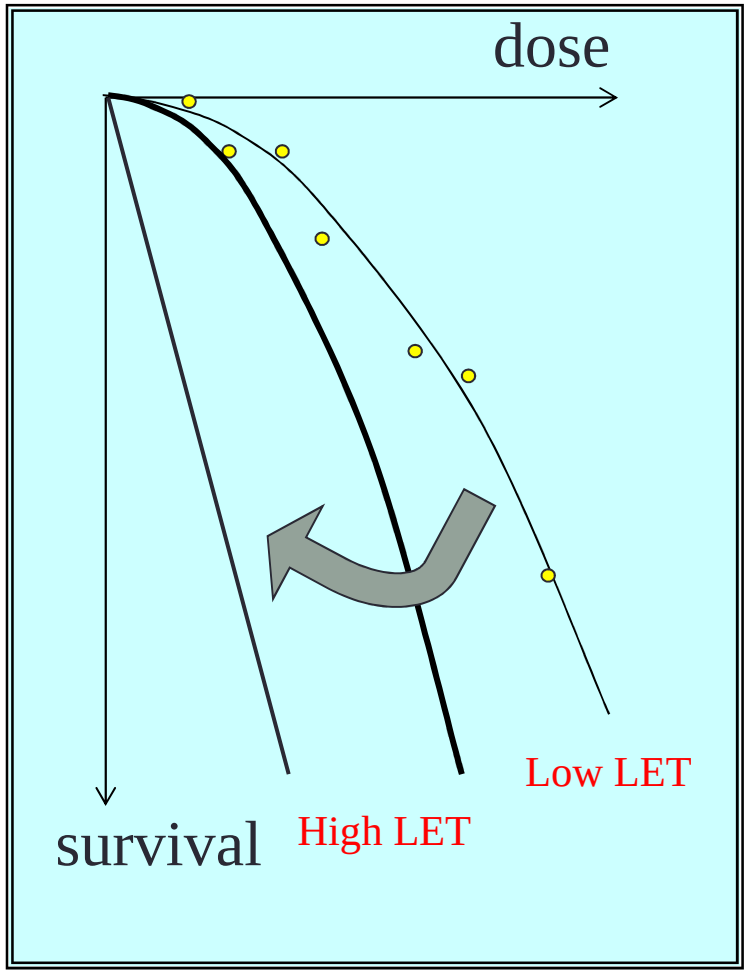
Cancer growth

Ionisations along particle tracks



Linear energy transfer (LET)

- LET is the physical quantity of ionisation density; its unit is the keV/μm.
- The higher the LET, the broader the DNA damage and, hence,the larger the biological effect



Tissue effects

Deterministic

- Cells killed

Most tissues remain unaffected by some degree of cell loss

If the loss exceeds a given threshold, then an effect will be detected

Stochastic

- Cells mutated

Genetic effects of cancer induction:

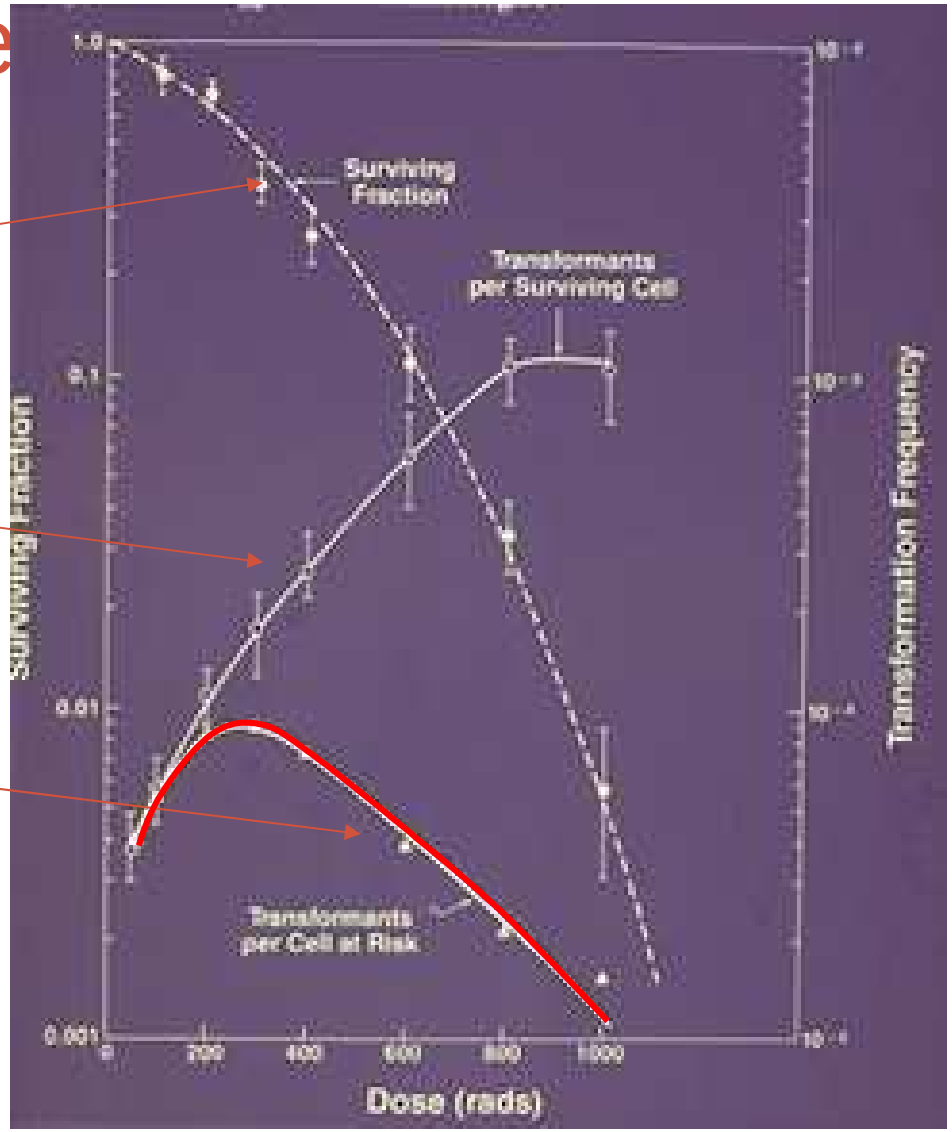
- Frequency increases with dose.
- There is no threshold.
- Severity independent of the dose.

Cancer induction: a bell-shaped curve

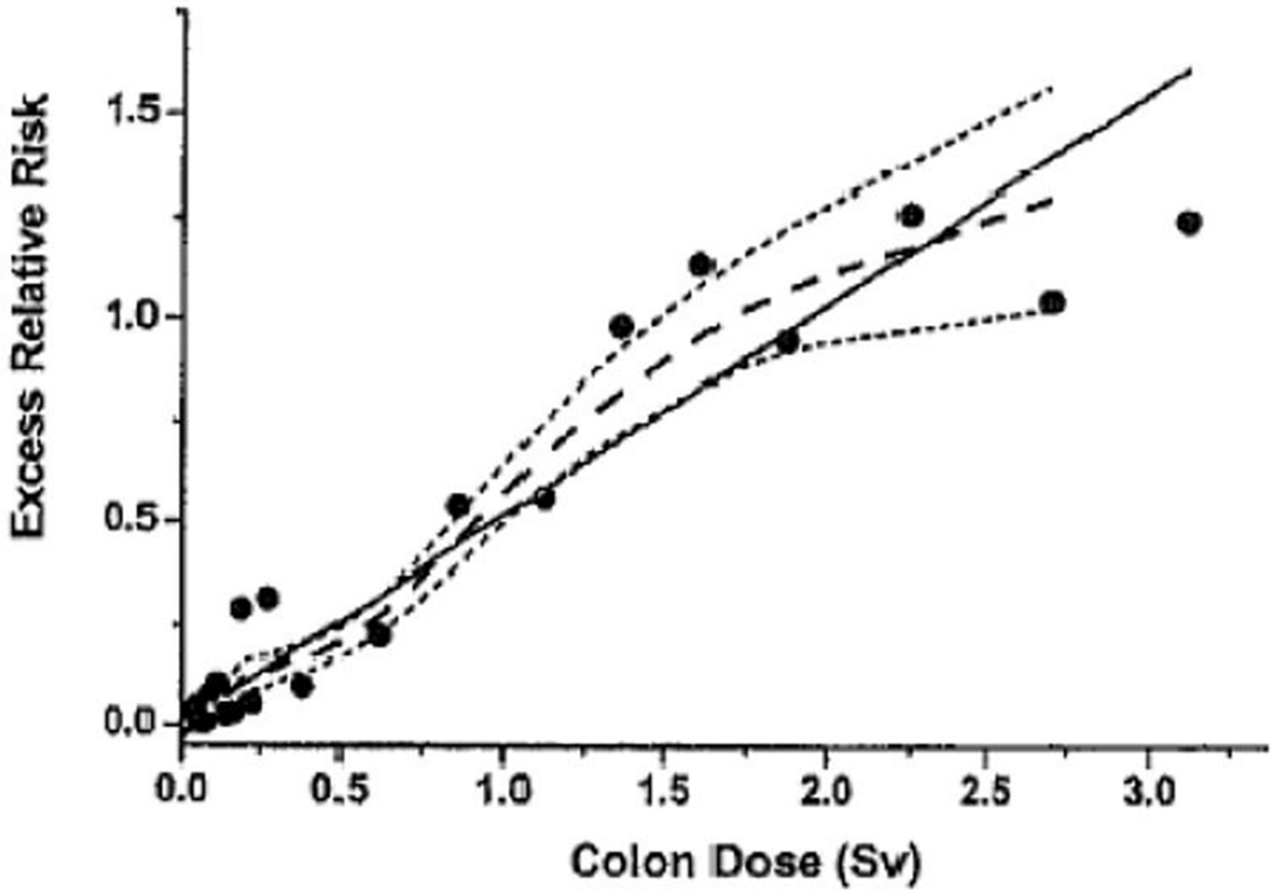
Survival rate

Frequency of transformation

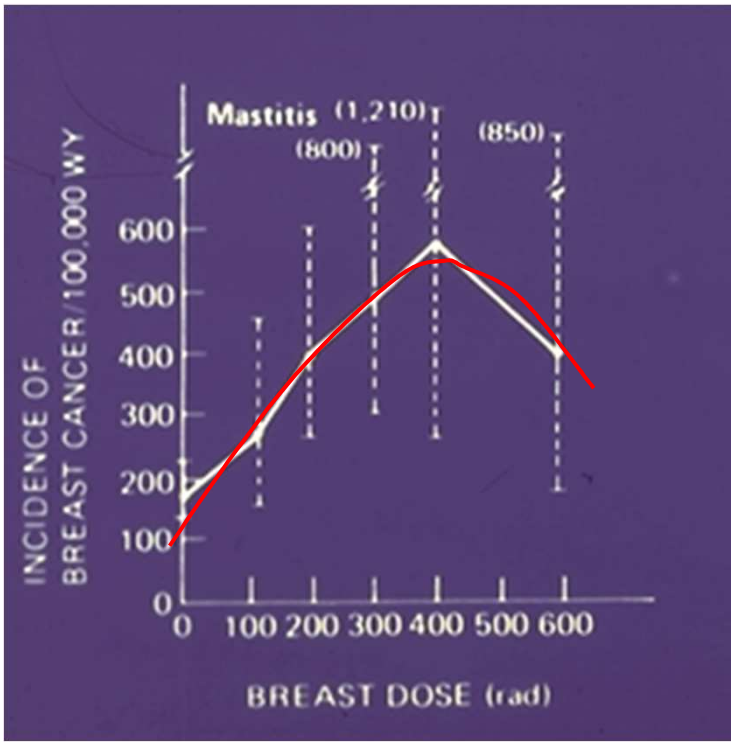
Sum of the 2 curves : cancerogenesis



Solid cancer dose response (A Bomb)



Breast cancer induction in women irradiated for acute mastitis



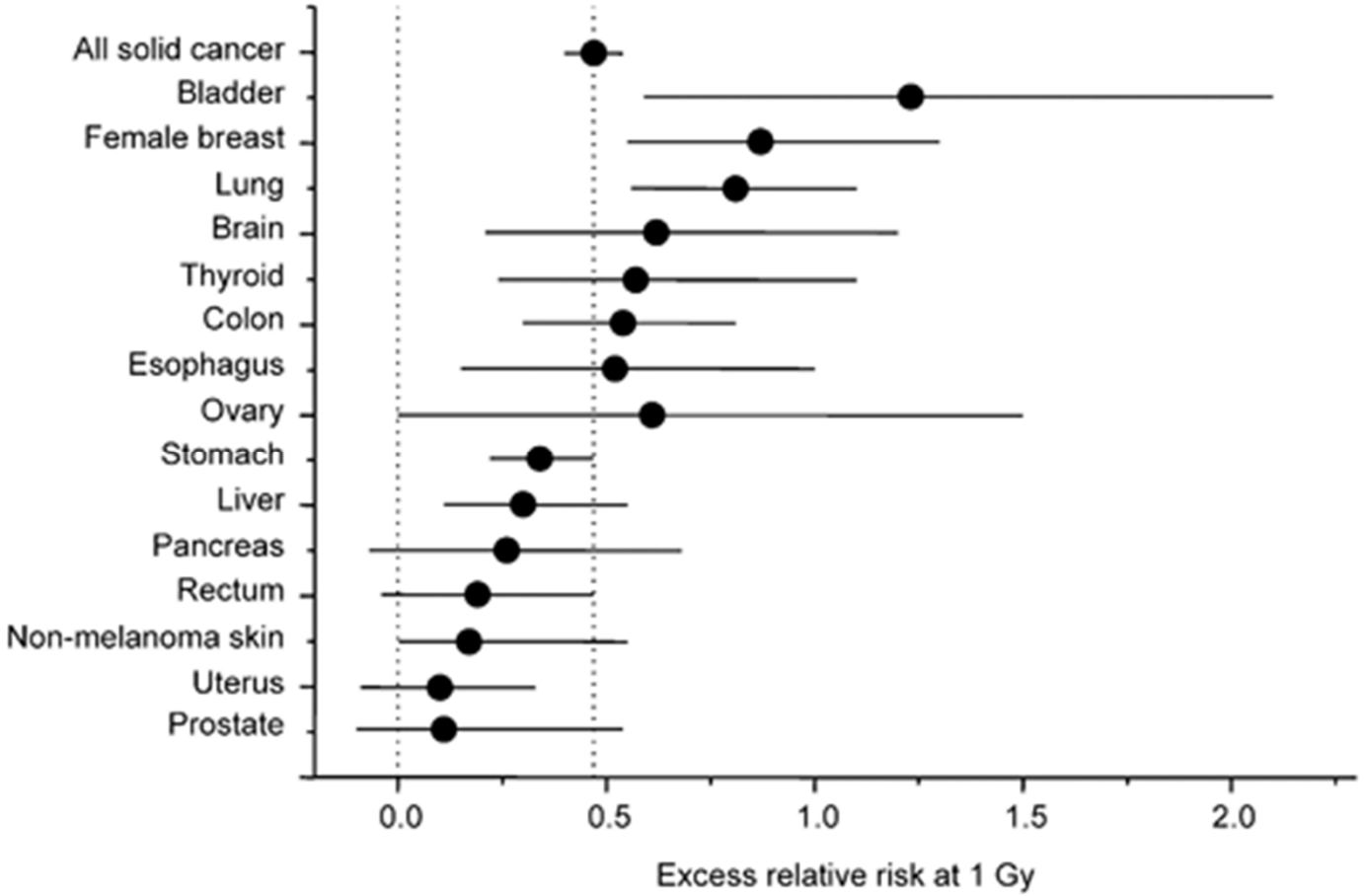
Not all data show a clear bell-shaped curve. There is considerable uncertainty in human data.

Cancer as a result of radiation exposure: Hiroshima-Nagasaki

Table. Excess risk of developing solid cancers in LSS, 1958-1998

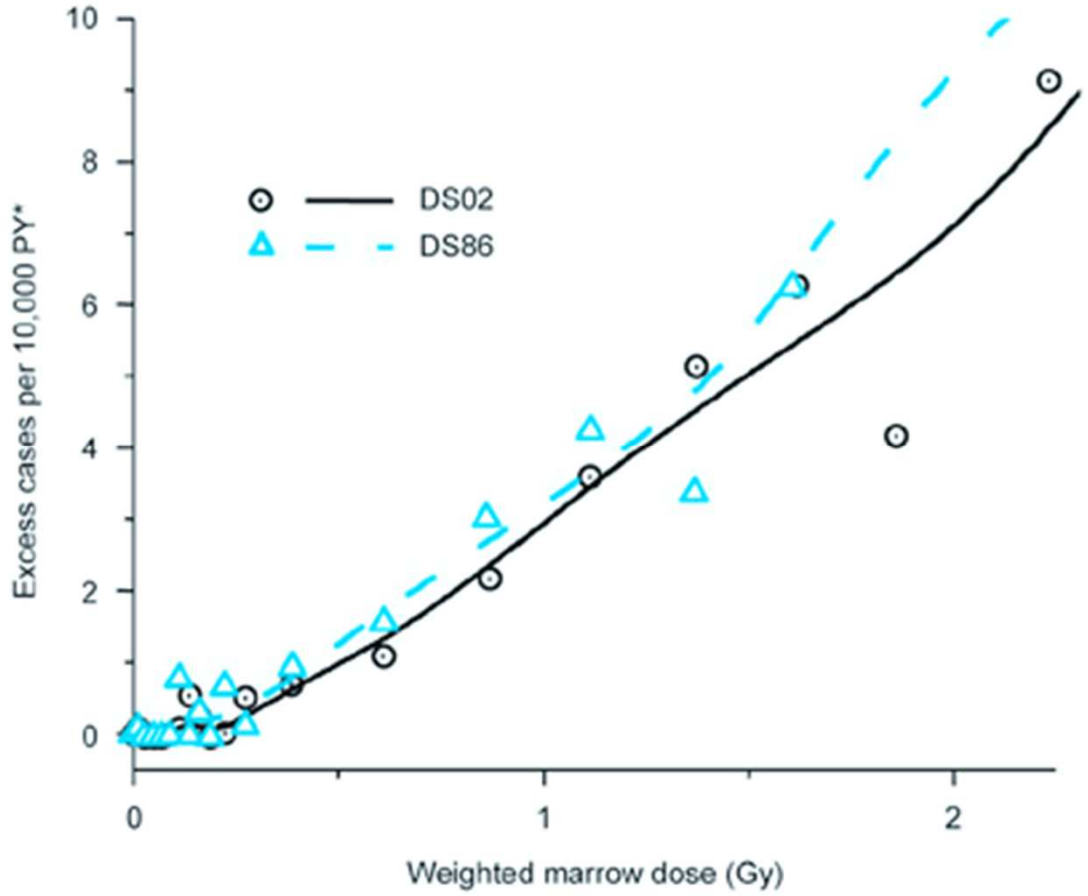
Weighted colon dose (Gy)	LSS subjects	Cancers		Attributable risk
		Observed	Estimated excess	
0.005 - 0.1	27,789	4,406	81	1.8%
0.1 - 0.2	5,527	968	75	7.6%
0.2 - 0.5	5,935	1,144	179	15.7%
0.5 - 1.0	3,173	688	206	29.5%
1.0 - 2.0	1,647	460	196	44.2%
>2.0	564	185	111	61.0%
Total	44,635	7,851	848	10.7%

Cancer as a result of radiation exposure: Hiroshima-Nagasaki



Detected from 10 year after on.

Cancer as a result of radiation exposure: Hiroshima-Nagasaki



Excess of leukemia as a function of dose: a threshold?

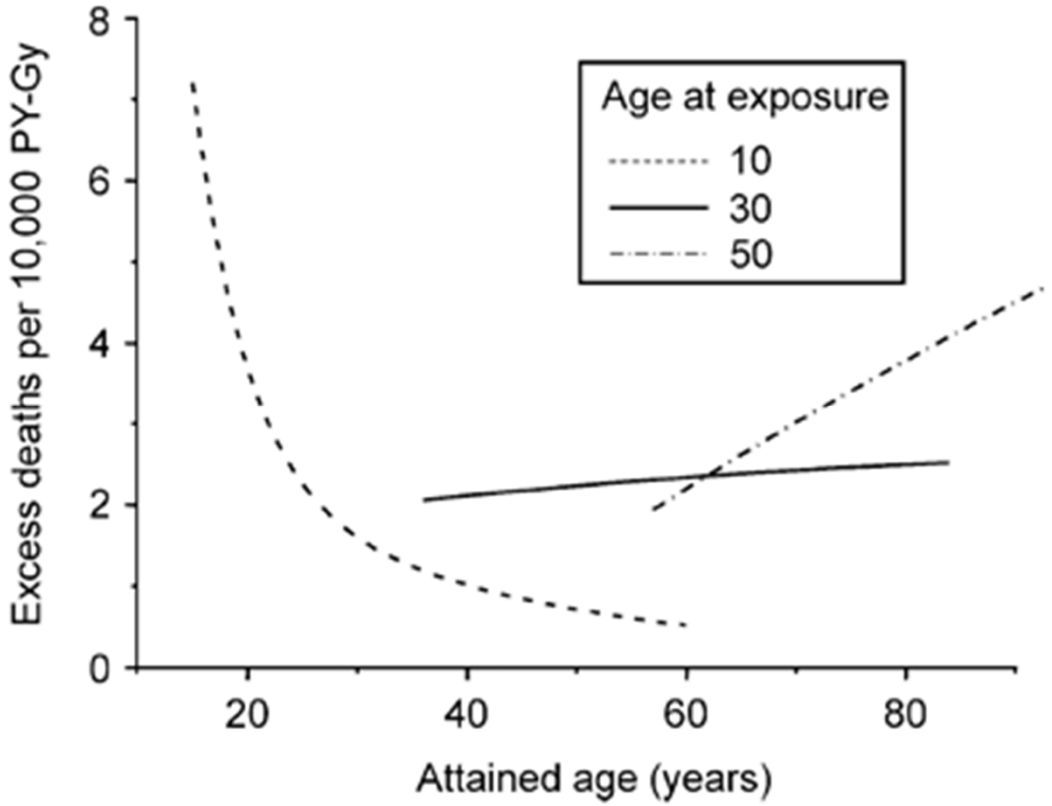
Cancer as a result of radiation exposure: Hiroshima-Nagasaki

Table. Observed and estimated excess number of leukemia deaths in LSS population, 1950-2000

Weighted marrow dose (Gy)	Subjects	Deaths		Attributable risk
		Observed	Estimated excess	
0.005 - 0.1	30,387	69	4	6%
0.1 - 0.2	5,841	14	5	36%
0.2 - 0.5	6,304	27	10	37%
0.5 - 1.0	3,963	30	19	63%
1.0 - 2.0	1,972	39	28	72%
>2.0	737	25	28	100%
Total	49,204	204	94	46%

Leukemias registered from 1950 on

Cancer as a result of radiation exposure: Hiroshima-Nagasaki



Different types of leukemia with age
Different time-span with age
Risk increase from 7/1000 to 10/1000 inhabitant

Cancer as a result of radiation exposure

- Several epidemiological series
- Some examples
  - Male cockpit crew members with >5000h flight have an excess risk of leukaemia of 5.1 (1.03-14.091) .

  - No excess fetal death and congenital malformation in babies born to nuclear industry employees.
  - Decrease in overall cancer incidence and mortality in people treated for hyperthyroidism with radioiodine (RR 0.83, range 0.77-0.90).

Radiation induced cancer

(BMJ 284: 449, 1982)

- 14.111 patients irradiated for ankylosing spondylitis in UK.
- Fivefold excess of death from leukaemia (O/E : 31 vs. 6.5).
- Risk greater 3-5 y after treatment and disappeared after 18 years.
- All neoplasm : O/E = 397/256
- Risk increased 10y after irradiation.
- Dose range 1-7 Gy in field

Second malignant tumours after Hodgkin's disease (AML)

- 1 % after radiotherapy alone.
- 9 % after chemotherapy alone (leukemogenic drugs).
- 7.7 % after RT and CT

NEJM 322: 7-13, 1990

Normal latency for radiation induced large bowel carcinoma after a first treatment for pelvic malignancy

Latency (yr)	*Patient n°*	*Cumulative %*
≤ 10	16	30
11-20	22	73
21-30	12	94
31-40	2	98
≥ 40	1	100

Cancer 57: 728, 1986

Breast cancer in women with scoliosis exposed to multiple diagnostic X rays

- 1.030 women seen between 1935 and 1965.
- Mean age 12.3 year.
- Individual X-rays between 0 and 618 films (0-1.59 Gy)
- Average period of observation was 26 years.
- O/E = 11/6
- RR 1.82 (1.0-3.0)
- RR increased with time and with n° of films

JNCI 81: 1307, 1989

Mortality from breast cancer after irradiation during fluoroscopic examination for tuberculosis treatment

Relative risk at 1 Gy

Age at first exposure	*Relative risk*
10 – 14	4.46
15 – 24	1.77
25 – 34	1.25
≥ 35	1.10

- 31.710 women admitted between 1930 and 1952.

NEJM 321:1285, 1989

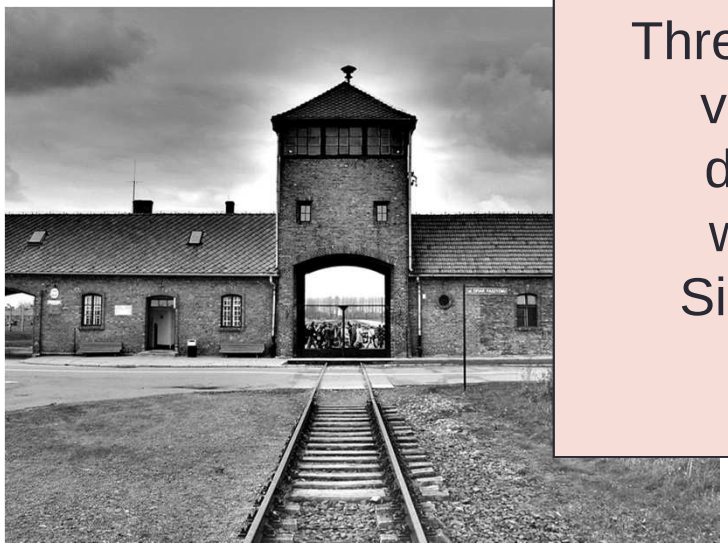
Mortality from breast cancer after irradiation during fluoroscopic examination for tuberculosis treatment

Time since first exposure	*Relative risk*
5 – 14	1.47
15 – 24	1.40
25 – 34	1.48
≥ 35	1.24

Effect of time since first exposure to 1 Gy of radiation as predicted by relative-risk model

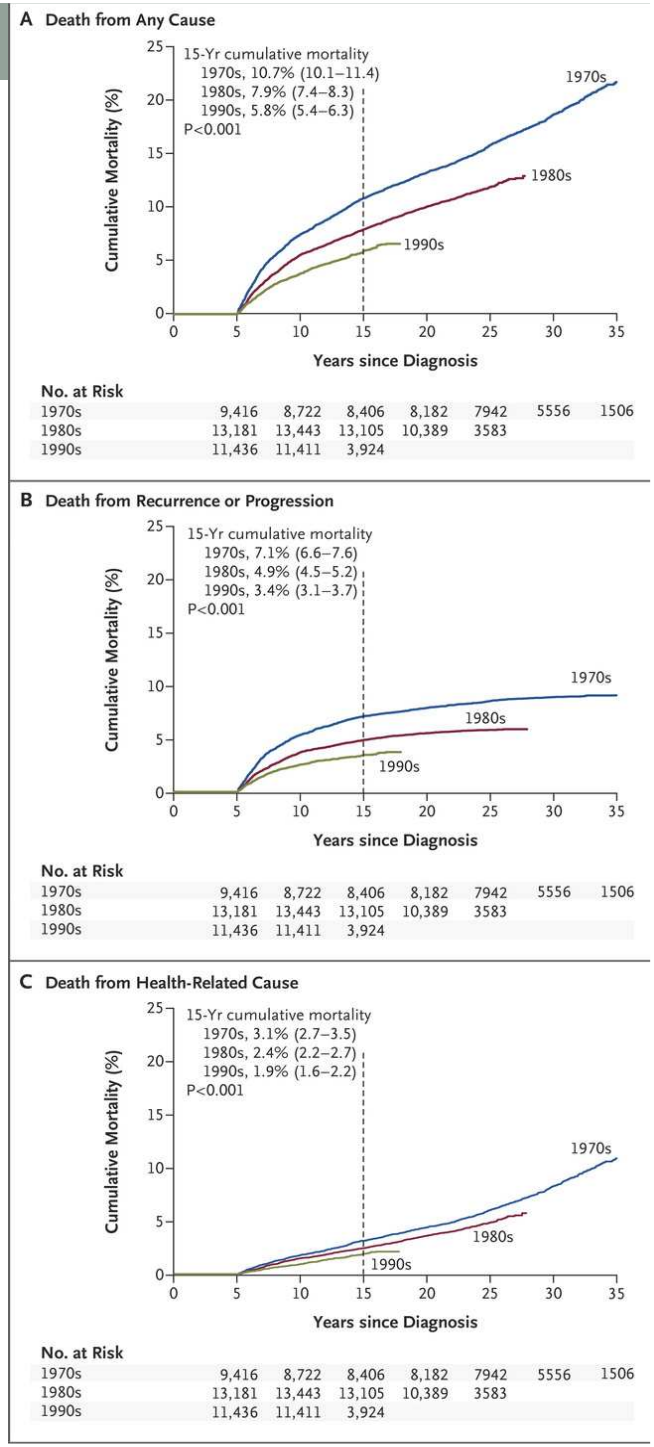
Latency longer in children

- Bowel cancer induced by high single dose delivered in the frame of sterilisation experiments by nazis in Auschwitz (1943)



Three young women, aged 17 and 19, were victims of a war crime in 1943; all three developed colon cancer 40 years later, whereas the usual latency is 20 years. Similar observation made in Hiroshima & Nagasaki survivors.

All-Cause and Cause-Specific Cumulative Mortality among 5-Year Survivors of Childhood Cancer, According to Decade.



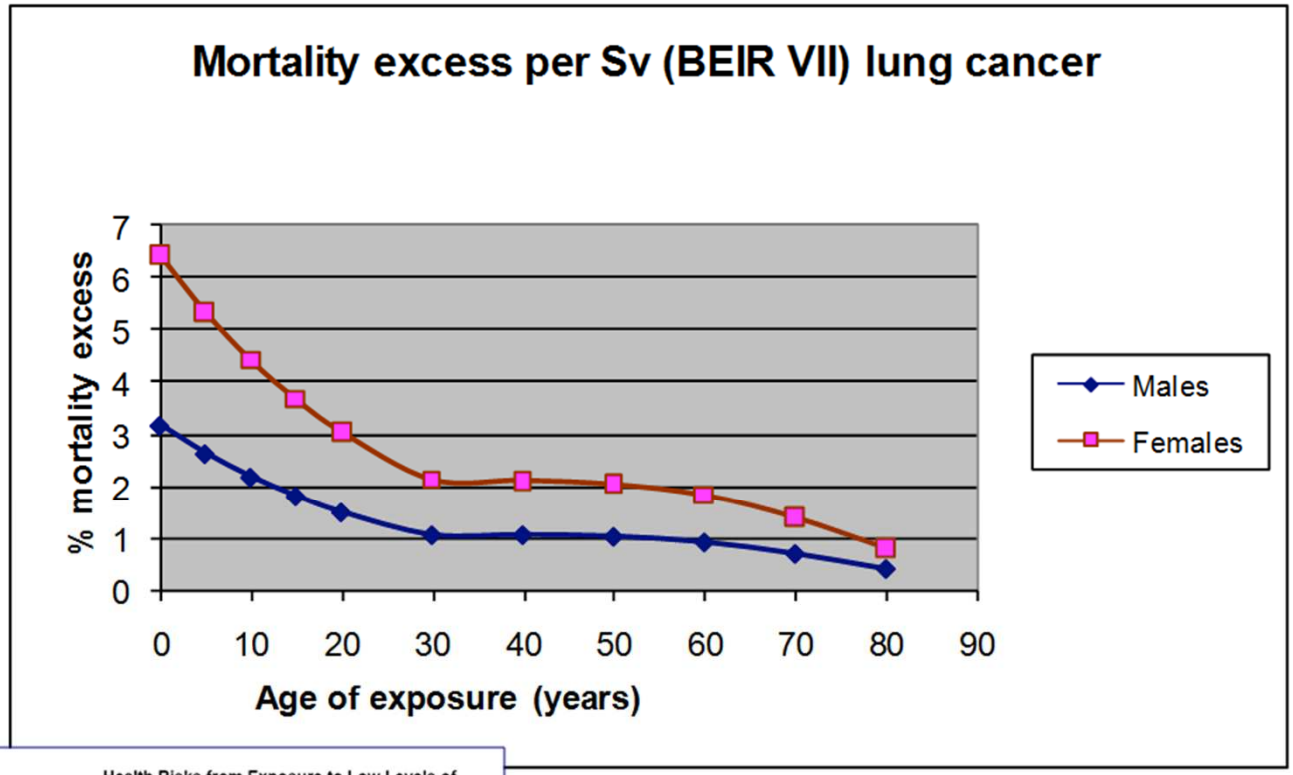
Armstrong GT et al. N Engl J Med 2016;374:833-842.

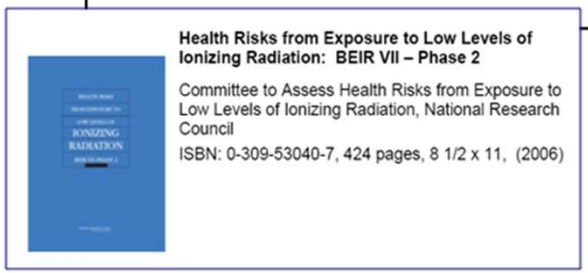
Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood

factors	*Odds ratio (95 % CI)*	*p*
FI 0-2 vs. 0	1.7 (0.1-21)	0.01
FI ≥ 2 vs. 0	6.6 (1.5-29)	
FI 0 & <0.5 Gy	1	Ns
FI 0 & ≥0.5 Gy	4.1 (0.8-21.3)	Ns
FI>0 & <0.5 Gy	8.3 (0.7-10.4)	Ns
FI>0 & ≥0.5 Gy	15.5 (2.1-114)	0.01

FI = family index.
A coefficient including n° of relatives with cancer, at a given age, with a given level of kinship

Lung cancer and age





Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, National Research Council

ISBN: 0-309-53040-7, 424 pages, 8 1/2 x 11, (2006)

Fukushima

Test frequency ?
Basal frequency of abnormalities ?
Latency 4-5 ans minimum

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journal homepage: www.clinicaloncologyonline.net

Overview

Childhood and Adolescent Thyroid Cancer in Fukushima after the Fukushima Daiichi Nuclear Power Plant Accident: 5 Years On

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Received 29 December 2015; accepted 29 December 2015

Sweden : why I-131 exposure? And at what age?

IJC International Journal of Cancer

Epidemiology

Thyroid cancer risk after thyroid examination with ^{131}I: A population-based cohort study in Sweden

FREE

Paul W. Dickman[1,†,*], Lars-Erik Holm[2], Göran Lundell[3], John D. Boice Jr.[4,5] and Per Hall[1]

Article first published online: 30 MAY 2003

DOI: 10.1002/ijc.11258

Issue

International Journal of Cancer

Volume 106, Issue 4, pages 580–587, 10 September 2003

Overall risk?

- Cumberlin et al. Published estimates of the expected number of SMN induced in selected sensitive sites by scattered radiation during radiation therapy for cancer, based on 192.761 new patients with cancer treated in 1987.
- The model projected a 0.7 % incidence for leukaemia and 0.3 % for solid tumours.

IJROBP 17: 623, 1989

Risk of cancer after low doses (industrial) in 15 countries

- 407 391 workers individually monitored for 5.2 million person/year.
- Excess risk solid cancer 0.97 (0.14 - 1.97)
- Excess risk leukemia 1.93 (<0 - 8.47)
- Overall 1-2% death from cancer attributable to radiation

BMJ 2005

Take home message

- The younger the patient the higher the risk.
- The younger the patient the longer the latency.
- Beware genetic factors.
- Some tissues are more vulnerable.
- Leukaemia up to 10y after.
- Solid tumours from 10y on.
- Screening necessary