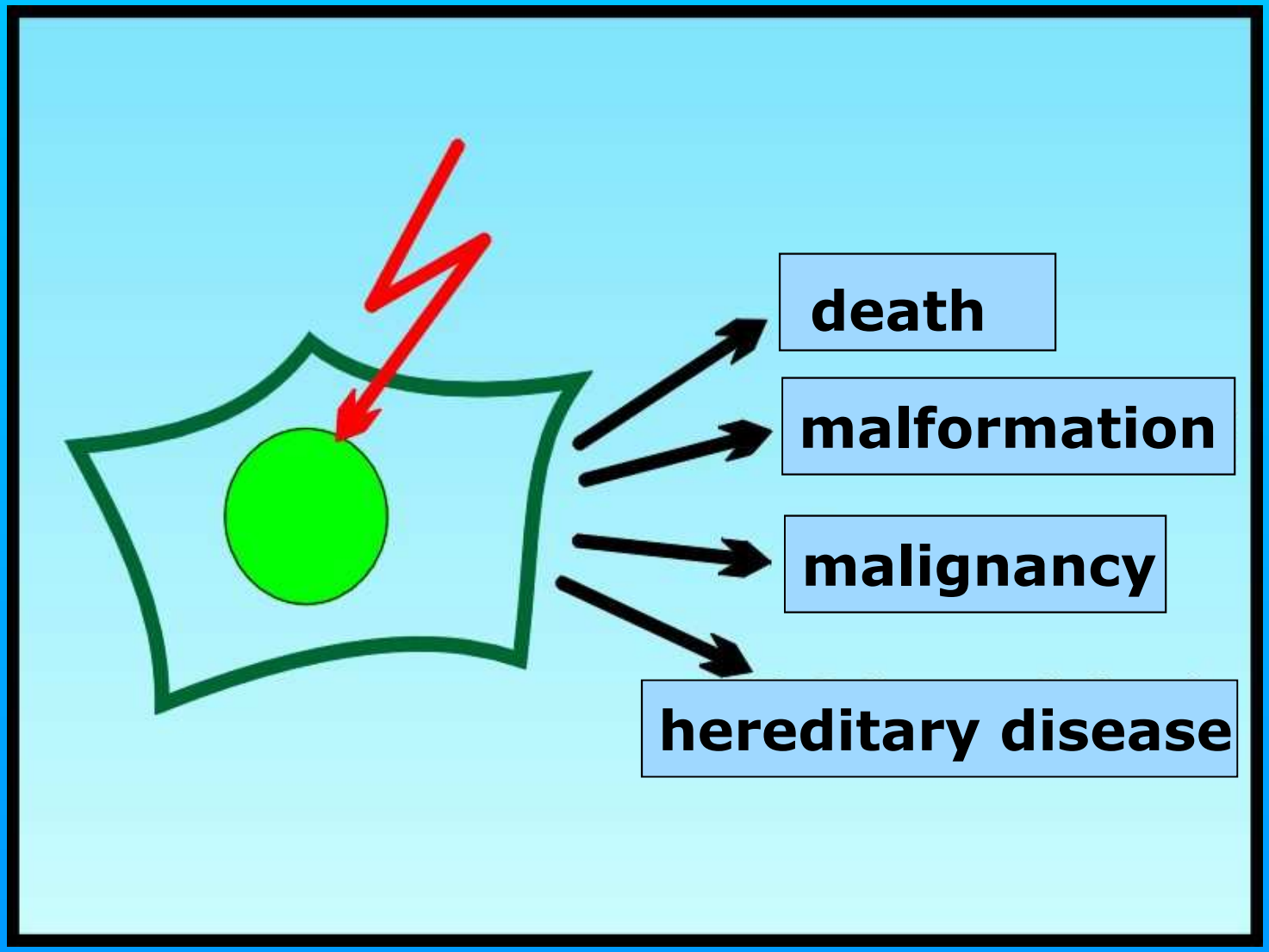
Age and gender relevance for the evaluation of radiation risk

Wolfgang-U. Müller

Institut für Medizinische Strahlenbiologie

Universitätsklinikum Essen

Radiation risks



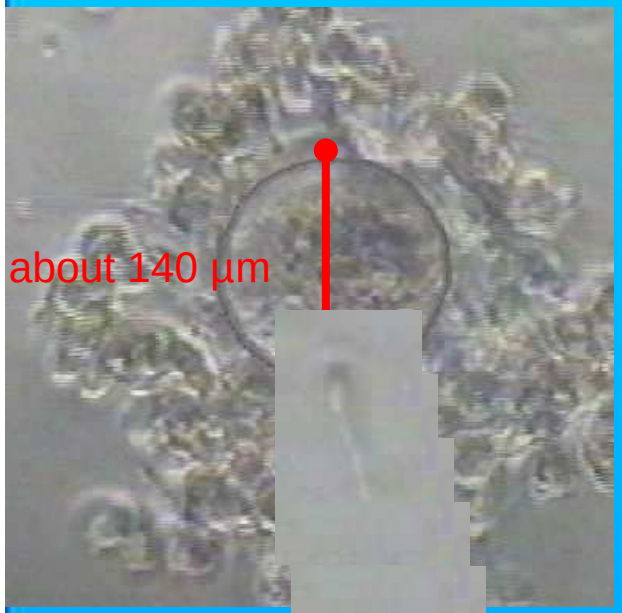
Dependence of radiosensitivity on age

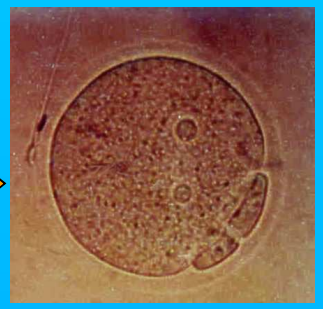
Examples where specific age groups show a higher radiosensitivity compared to middle-aged adults

- Leukaemia (fetus and young children)
- Thyroid carcinoma (young children)
- Basal cell carcinoma (children and teens)
- Breast cancer (girls during puberty)
- Breast cancer (women under 30 years)
- Lung cancer (individuals older than 50)

Radiosensitivity of the unborn child

Fertilisation and Preimplantation Period





zygote

2-cell embryo

4-cell embryo

6-cell embryo

8-cell embryo

morula

blastocyst

hatching blastocyst

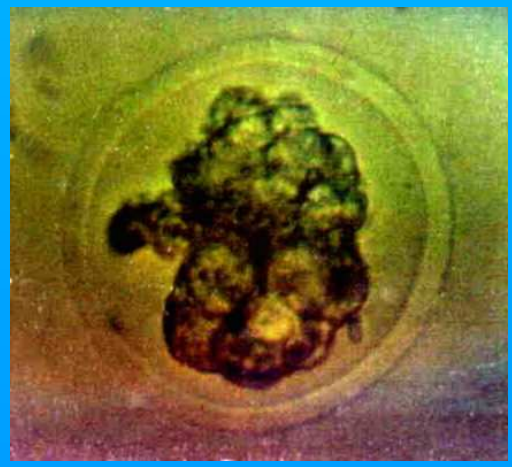
hatched blastocyst

Radiation Effect on Early Embryonic Development

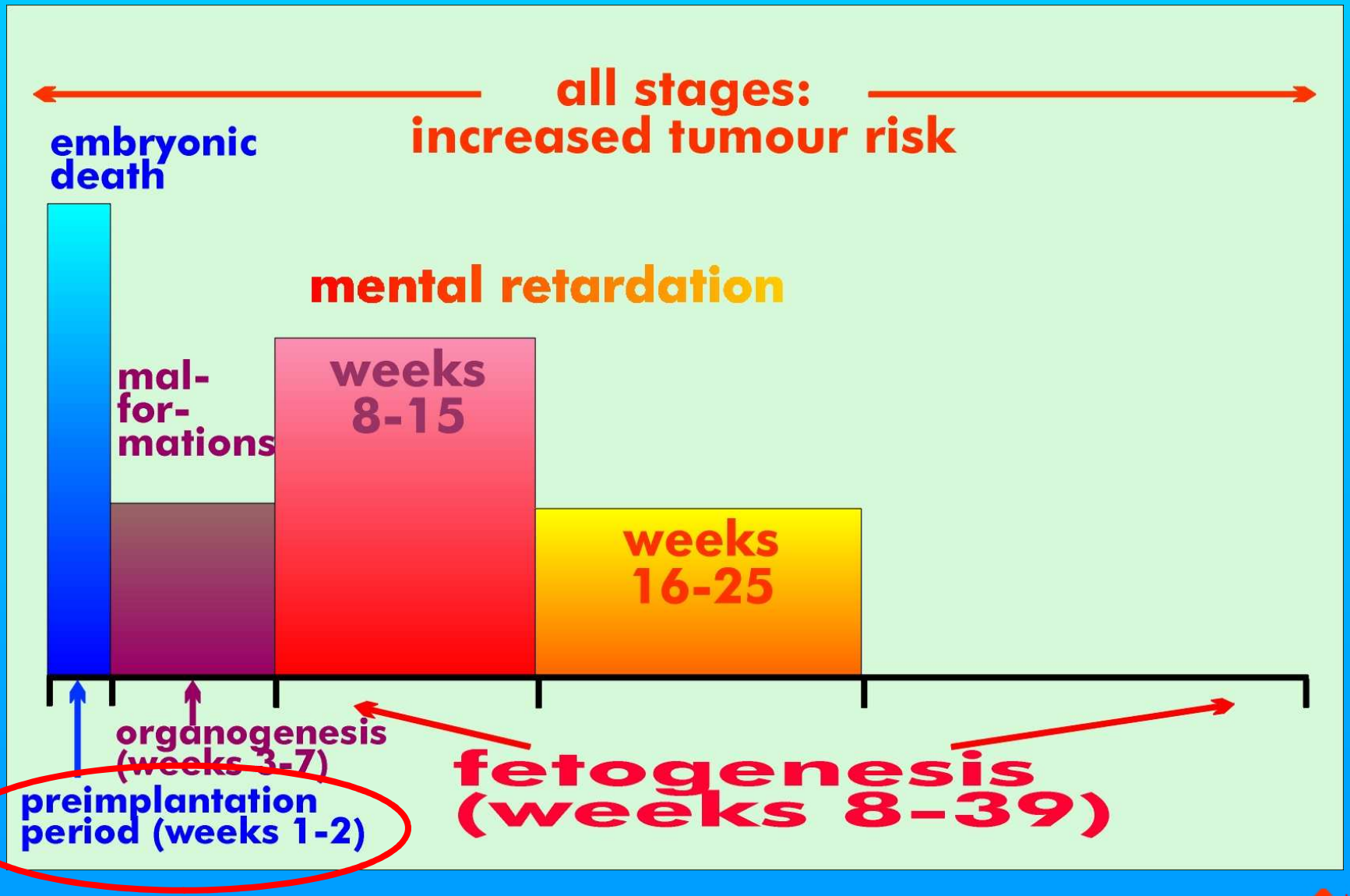
One cell embryo (zygote)

Regular development to blastocyst

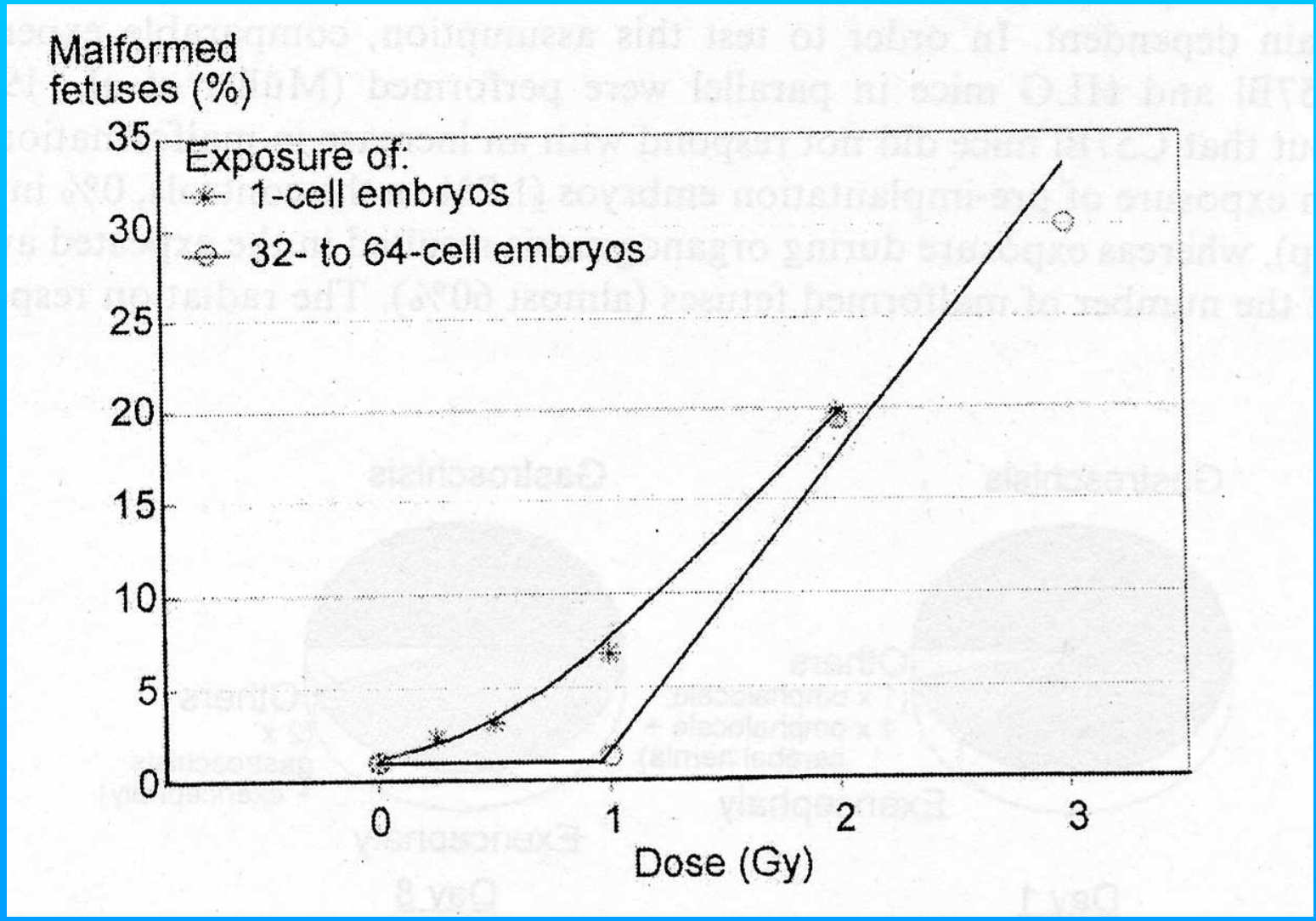
Impaired development after 2 Gy



Pregnancy risks



The threshold question

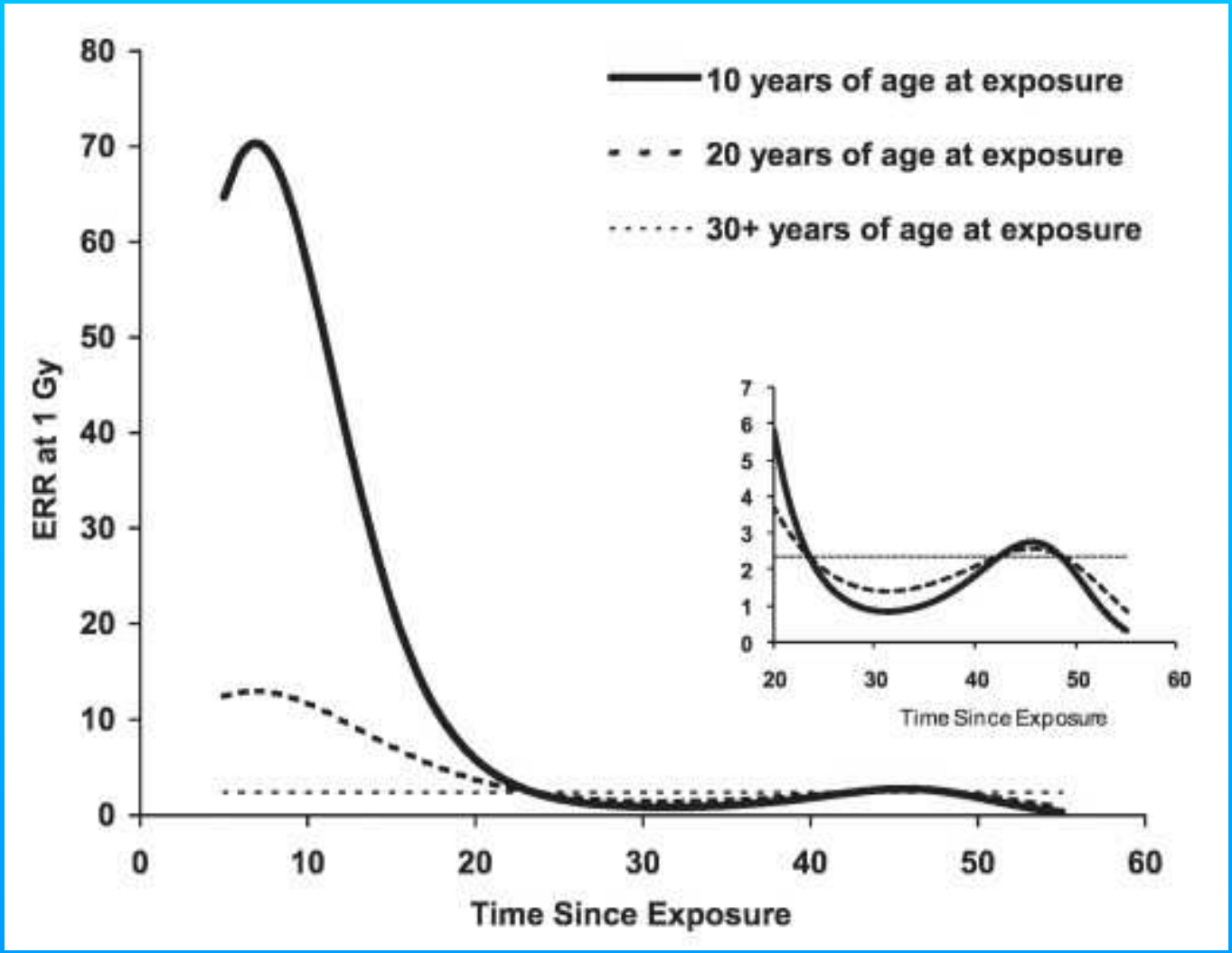


ERR (Excess Relative Risk) and EAR (Excess Absolute Risk)

$$ERR = \frac{\text{probability of disease after radiation exposure}}{\text{probability of disease without radiation exposure}} - 1$$

EAR = incidence of diseased individuals after radiation exposure
minus
incidence of diseased individuals without radiation exposure

Age and leukaemia risk



Source: Richardson et al. Rad. Res. 172, 368–382 (2009)

The major radiation problem during pregnancy:

Leukaemia risk!

Statistically significant effect at:

10 mSv

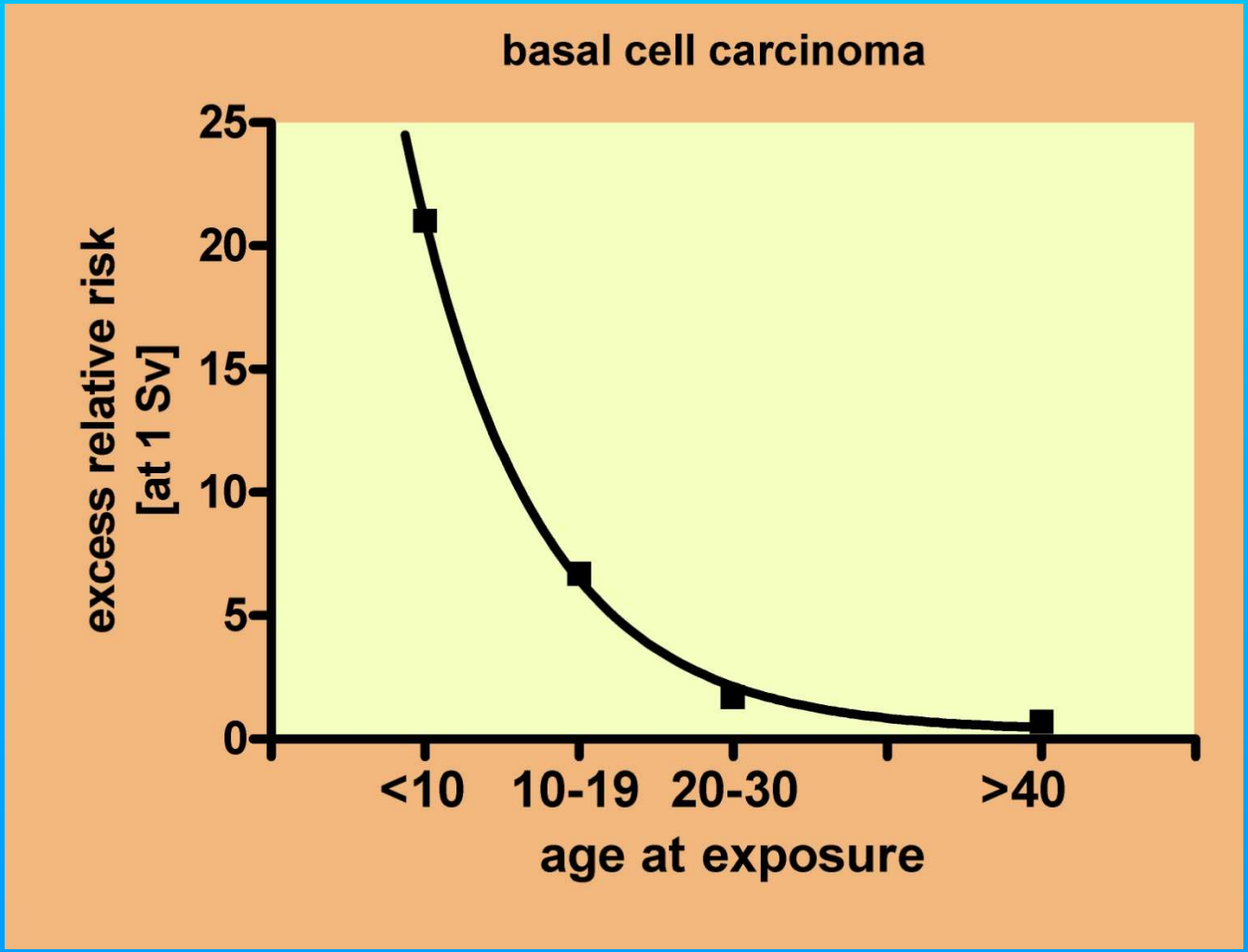
Doubling dose:

about 50 mSv

But, also look at the absolute numbers:

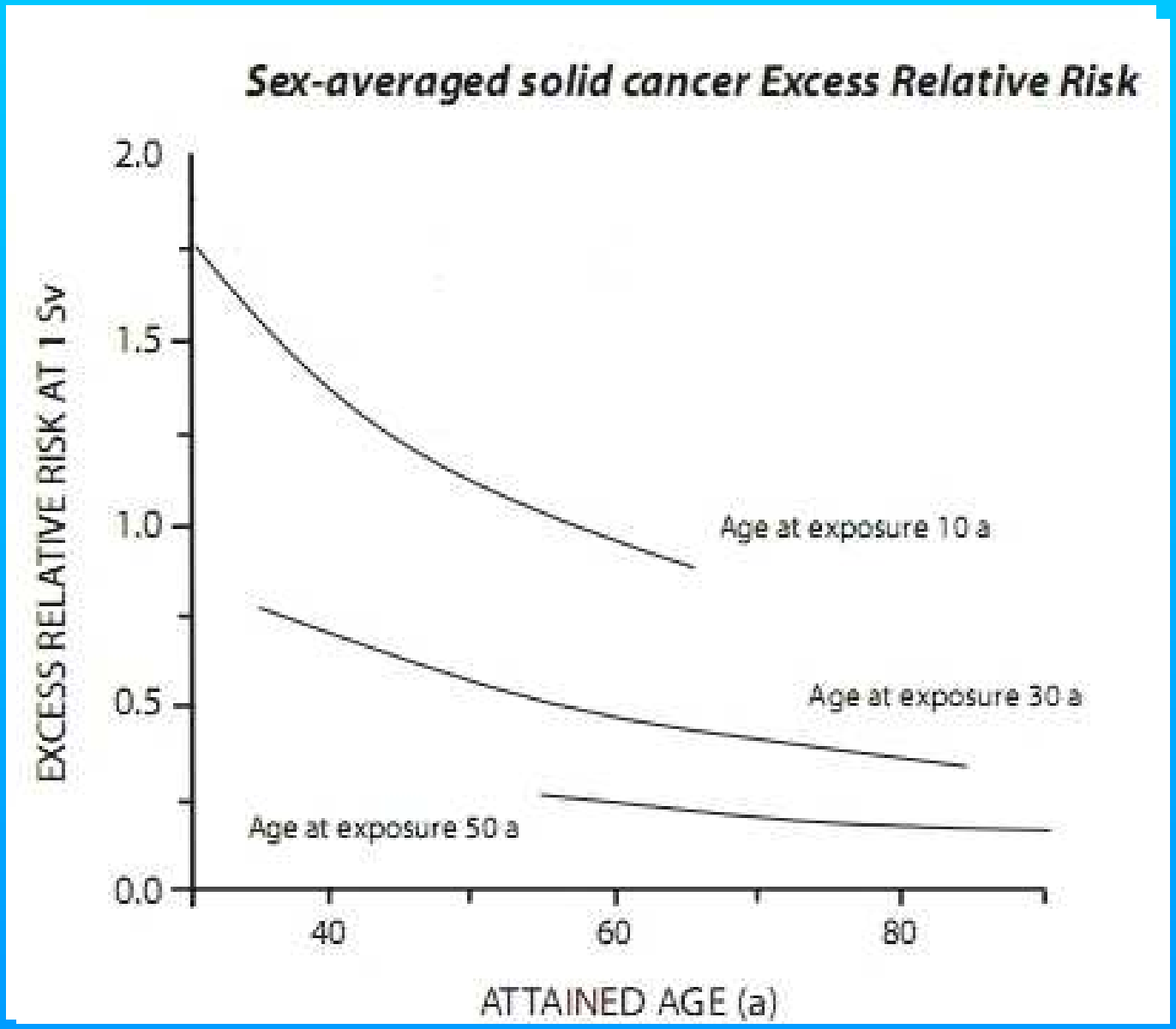
The spontaneous frequency is 5 cases per 100,000 children per year

Specific example of age dependence: basal cell carcinoma



Source: UNSCEAR 2000, Annex I, p. 422

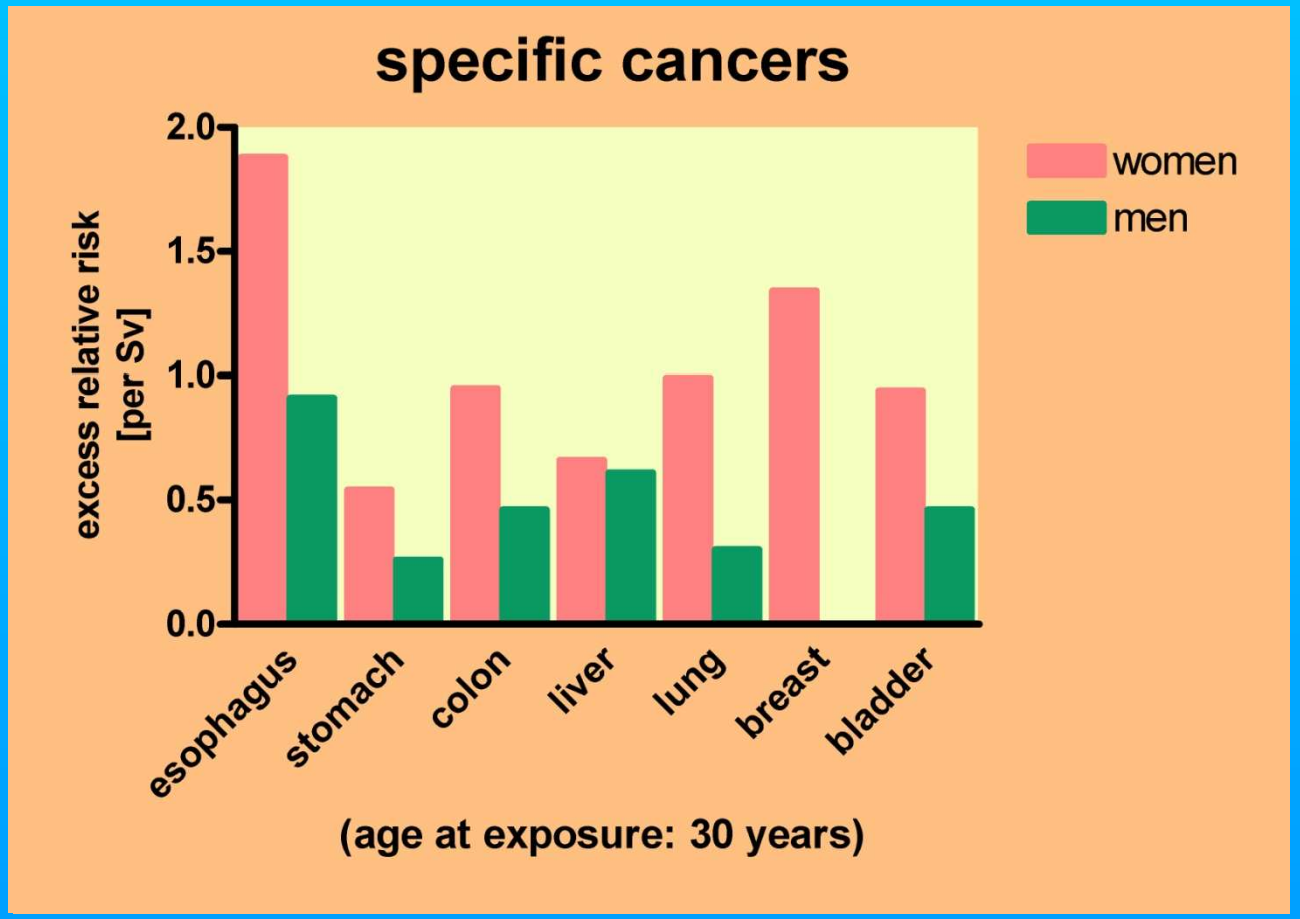
ERR and EAR dependence on age



Source: UNSCEAR 2006, Annex A, p. 46

Dependence of radiosensitivity on gender

Examples where higher radiation risks have been shown for women compared to men



Source: UNSCEAR 2000, Annex I, p. 425

Sources of information

- Epidemiology
- Clinical experience
- Basic research in radiobiology

Serious problem

- Up to now, there are no extensive studies that are looking systematically for gender specific differences.
- All the information that is available was obtained through studies that were not aimed at the detection of gender specific differences.

Epidemiologic studies

BEIR VII
Excess relative risk (ERR)
(after 1 Gy)

	solid cancers		Higher risk:
	males	females	
ERR cases	0.33	0.57	1.7x
ERR deaths	0.23	0.47	2.0x

BEIR VII
(absolute risk)

	All solid cancers		Leukemia	
	males	females	males	females
excess cases (after 0.1 Gy)	800	1,300	100	70
spontaneous cases	45,500	36,900	830	590

Higher risk: 1.52x

Higher risk: 1.38x

per 100,000 individuals

Based upon the current incidence rates in Hiroshima and Nagasaki

TABLE 10
Solid Cancer Radiation-Risk-Model Parameter Estimates

Model	Risk per Gy[a] Male	Female	Sex-averaged	Sex ratio (F:M)	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
			All solid cancers			
ERR	0.35 (0.28; 0.43)[c]	0.58 (0.43; 0.69)	0.47 (0.40; 0.54)	1.6 (1.31; 2.09)	−17% (−25%; −7%)	−1.65 (−2.1; −1.2)
EAR	43[d] (33; 55)	60 (51; 69)	52 (43; 60)	1.4 (1.10; 1.79)	−24% (−32%; −16%)	2.38 (1.9; 2.8)
			Non-gender specific solid cancers[e]			
ERR	0.34 (0.27; 0.42)[c]	0.61 (0.50; 0.73)	0.48 (0.39; 0.56)	1.8 (1.31; 2.09)	−10% (−20%; −1%)	−2.09 (−2.6; −1.5)
EAR	48[d] (36; 61)	44 (37; 52)	46 (38; 55)	0.9 (0.72; 1.20)	−19% (−29%; −9%)	2.52 (2.0; 3.1)

F:M

All solid cancers

ERR 1.6

EAR 1.4

Non-gender specific solid cancers

ERR 1.8

EAR 0.9

[a] At age 70 after exposure at age 30.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.
[e] Excludes cancers of the breast, prostate and reproductive organs.

Is the situation as clear as it appears to be on the basis of the studies presented up to now?

- Unfortunately: **No!**
- If you look at the details you will find a lot of inconsistencies.
- Many results are not significant.
- For some tumour entities you will even find that men have a higher radiation induced risk.

Incidence Hiroshima/Nagasaki

Preston et al. Rad.Res. 168 (2007) 1-64

Localisation	F/M (ERR)	F/M (EAR)
stomach	2.3	1.0
colon	0.5	0.2
liver	0.9	0.3
lung	4.8	1.5
bladder	3.1	0.7
thyroid	1.3	3.6

Clinical Experience

Clinical aspects

- Unfortunately, clinical data are almost useless, because systematic studies are lacking.
- A crucial problem: the role of chemotherapy.
- Perhaps, there will be some increase in knowledge in the future when the problem of secondary tumours will be analysed systematically.

Radiobiological aspects

Radiobiological informations (1)

- Again, there are no extensive studies that are looking systematically for gender specific differences.
- We urgently need reliable animal models.

Radiobiological informations (2)

- In the few existing studies one finds gender dependent differences with respect to the following endpoints:
  - tumor induction (not always, however, the female animals are more radiosensitive);
  - DNA-damage and –repair;
  - apoptosis;
  - gene expression;
  - epigenetic effects.
- Problem: There are no correlations among the results of the individual studies; this, most probably depends on the very different models.

Biological mechanisms that might be responsible for differences in radiosensitivity of females and males

- Hormones
- Higher cell proliferation in some tissues
- Sex-linked oncogenes and tumorsuppressorgenes
- Epigenetics
- Way of life

Conclusions

Argument of ICRP for a justification of averaging over both genders

- 1.: The uncertainties of the tissue weighting factors, for example, are high.
- 2.: The dose limits are so low that the difference in gender radiosensitivity does not play a significant role.
- 3.: Discriminations must be avoided.
- **But:** In the case of individual retrospective evaluations (e.g. compensation claims) gender-specific differences should be taken into account.

SSK statement (1)

- **Epidemiological, clinical and biological studies have produced indications but no clear evidence of possible sex-specific differences in radiation sensitivity (endpoints: mortality and cancer). There is therefore a need for further research ...**

(SSK = Strahlenschutzkommission = Commission on Radiological Protection)

SSK statement (2)

- **Having analysed the individual studies, the Commission cannot identify any basis for the certainty expressed in some of the statements made by other national and international institutions regarding generally higher radiation sensitivity in females.**

SSK statement (3)

- **After careful analysis, the Commission therefore concludes that it is not necessary, at present, to consider possible sex-specific differences in radiation sensitivity in the context of radiological protection.**