Stockholms universitet

"Radiosensitivity" of children - health issues after radiation exposure at young age
Article 31 scientific seminar 1 December 2020

Individual Response to Ionising Radiation – Radiosensitivity of Children

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Overview of radiation health effects and their relation to age at exposure

Generally speaking

Radiosensitivity decreases with age

Generally speaking

Radiosensitivity increases with age

Stochastic effects

Cancer
Cardiovascular disease
Hereditary effects

Deterministic (tissue) effects

Early effects

Inflammatory responses
Cell death in early reacting tissues
Death of the organism

Late effects

Tissue necrosis
Loss of organ function

All generalizations are dangerous, even this one (Alexandre Dumas)

Deterministic effects and age at exposure

Generally speaking

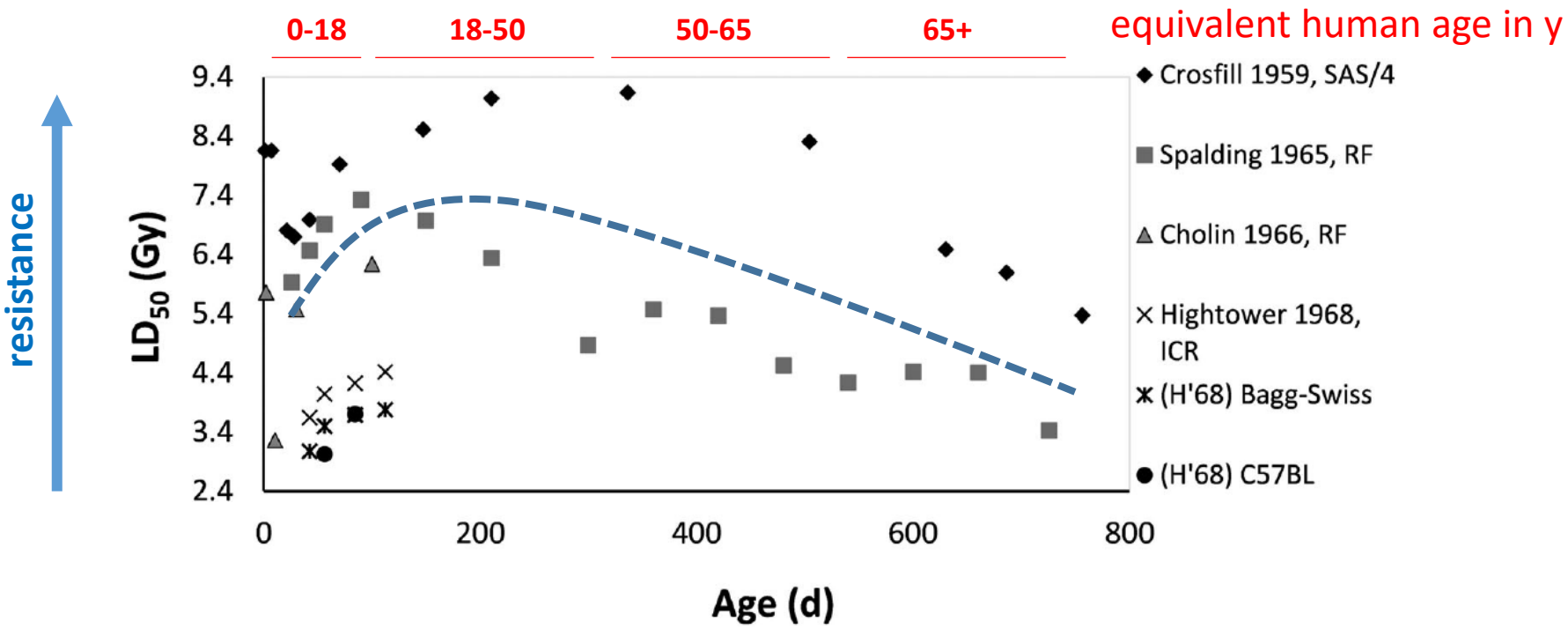
Radiosensitivity increases with age

Deterministic (tissue) effects

Early effects	*Inflammatory responses* *Cell death in early reacting tissues* *Death of the organism*
Late effects	*Tissue necrosis* *Loss of organ function*

Early determinisitc effects as function of age at exposure

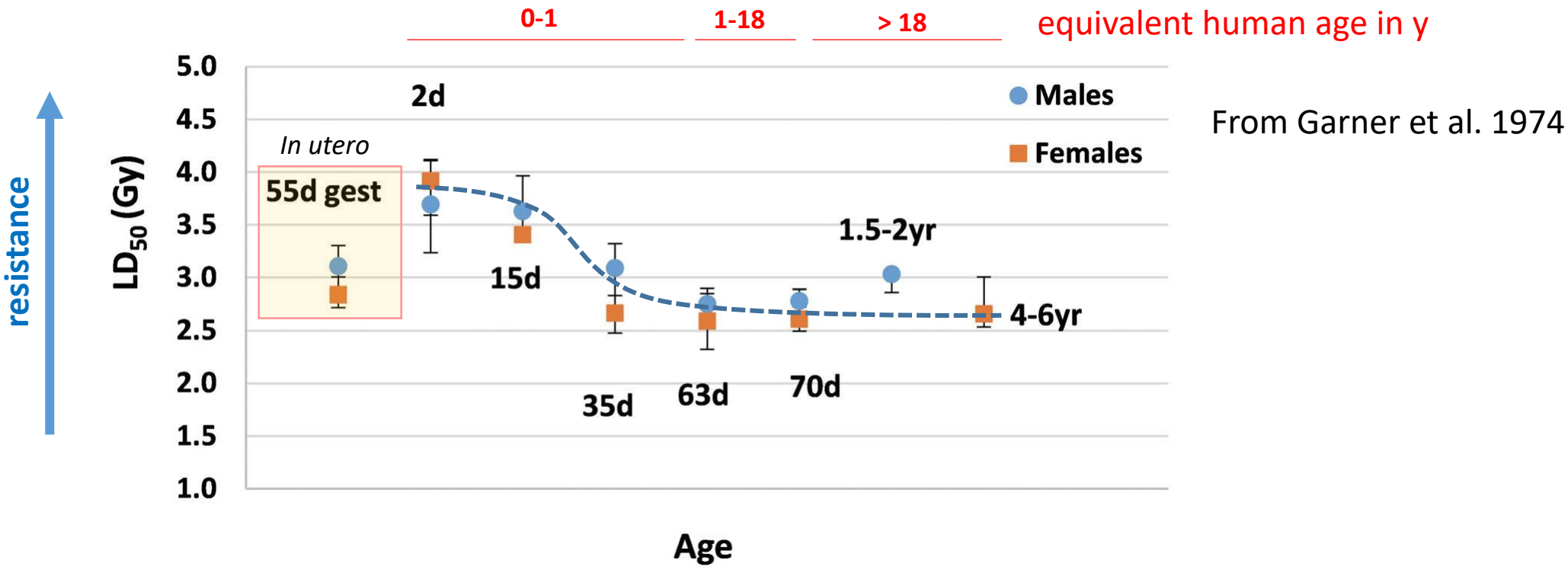
$LD_{50/30}$ in mice of different age at exposure



Source: Daniela Stricklin et al. Development of age-dependent dose modification factors for acute radiation lethality. Int J Radiat Biol 96: 67–80, 2020

Early determinisitc effects as function of age at exposure

$LD_{50/60}$ in beagles of different age at exposure



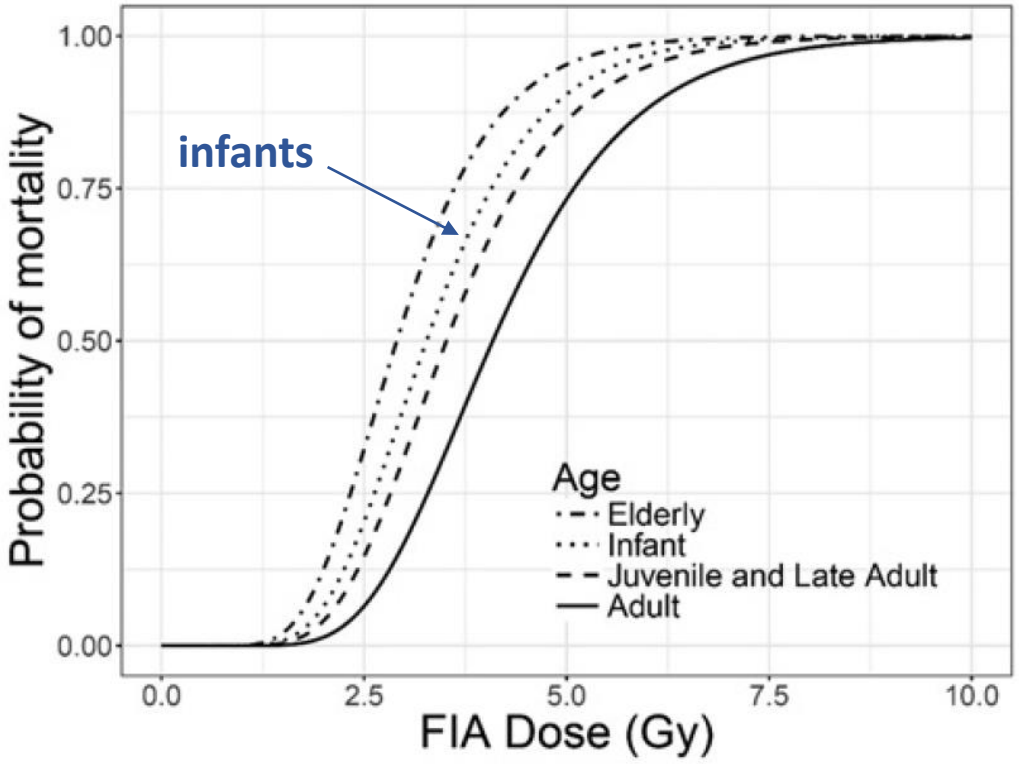
From Garner et al. 1974

Source: Daniela Stricklin et al. Development of age-dependent dose modification factors for acute radiation lethality. Int J Radiat Biol 96: 67–80, 2020

Why is it interesting to study the relationship between LD_{50} and age at exposure?

Impact analysis of age on radiation casualty estimations for nuclear detonation scenarios

Estimated effect of age on radiation sensitivity: dose-response curves



Source: Jacob Bellman et al. Impact analysis of age on radiation casualty estimations for nuclear detonation scenarios. Int J Radiat Biol 96: 1-12, 2020

Factors influencing sensitivity to deterministic effects

Sensitivity to radiation induced deterministic effects is a function of:

- the developmental dynamics and status of the organ,
- its regenerative potential,
- the extent to which it has begun to senesce.

The expression of deterministic effects results from a complex array of issues related to cellular proliferation, developmental stage of the tissue, regenerative potential and cell attrition.

Factors responsible for differences in radiosensitivity of children vs adults

Protecting

Children

- High regenerative capacity
- High capacity of DNA repair

Adults

- Low organizational and maturational processes
- Short life expectancy

Sensitizing

Children

- Active organizational and maturational processes
- Long life expectancy

Adults

- Low regenerative capacity
- Low capacity of DNA repair
- Cell attrition
- Comorbidities

Not touched here: the problem of doses and dosimetry when comparing effects in children and adults

Long-term survivors of pediatric cancer are more likely to have diminished health status and to die prematurely than are adults who never had childhood cancer

30-year cumulative incidence for severe (grade 3) or disabling/life-threatening (grade 4) conditions or death (grade 5) due to a chronic condition is 42%.

30-year cumulative mortality is 18% among long-term survivors; radiotherapy increases the risk 2.2-fold.

60-90% of childhood cancer survivors will develop one or more chronic health conditions, and 20-80% will experience severe or life-threatening complications.

Cancer survivors are eight times as likely as their siblings to have severe or life-threatening chronic health conditions (e.g., myocardial infarction, congestive heart failure, premature gonadal failure, second cancers, and severe cognitive dysfunction).

Sources:
KC Oeffinger et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355: 1572e1582, 2006.
GT Armstrong GT et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol27:2328e2338, 2009.
MM Geenen et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705e2715, 2007.
MM Hudson et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 309:2371e2381, 2013.
N Bhakta et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet 390:2569e2582, 2017.

PENTEC (Pediatric Normal Tissue Effects in the Clinic) 2019: to explore and define normal tissue tolerance in developing children as a function of radiation dose/volume, type and scheduling of chemotherapy and surgery

The potential to ameliorate or prevent normal tissue damage in paediatric cancer patients requires an **understanding of normal tissue tolerances** to radiation and systemic therapy across the age spectrum. This is affected by the total and fractional dose of radiation, the dose rate, overall treatment time, radiation modality, radiation dose distribution and adjuvant therapies.

Major problems in studying normal tissue tolerances across age

- Late effects are observed in patients treated many years ago with poor records of doses to normal tissues
- Reports of paediatric late effects often have a relatively small sample size
- Non-uniform toxicity evaluation methods and scales

Source: LS Constine et al. Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose Volume Response Relationships for Paediatric Cancer Patients. Clinical Oncology 31: 199e207, 2019

An attempt to define the radiosensitivity for deterministic effects of various organs in children

Organ	Sensitivity vs adult: Less	same	More	Effect
Brain				Neurocognitive reduction
Neuroendocrine				Reduction in hormone secretion
Cataracts				
Cerebrovascular				Stroke
Heart				Growth prevention, valvular abnormalities
Breast hypoplasia				Most severe during puberty
Lung				Capacity decrease if chestwall growth is inhibited
Thyroid hypofunction				
Thyroid nodules				
Thyroid autoimmune			?	
Kidney				
Bladder				Reduction in capacity
Testes				Sperm and hormone reduction
Ovaries				
Uterus				Uterine vasculature impaired
Musculoskeletal				Hypoplasia, deformity, osteochondroma
Immune			?	
Bone marrow				Less available marrow when older

Source: UNSCEAR 2013, Volume II

Stochastic effects and age at exposure

Generally speaking

Radiosensitivity decreases with age

Stochastic effects

Cancer
Cardiovascular disease
Hereditary effects

Three mechanisms generally believed to explain the high sensitivity of children to radiogenic cancers

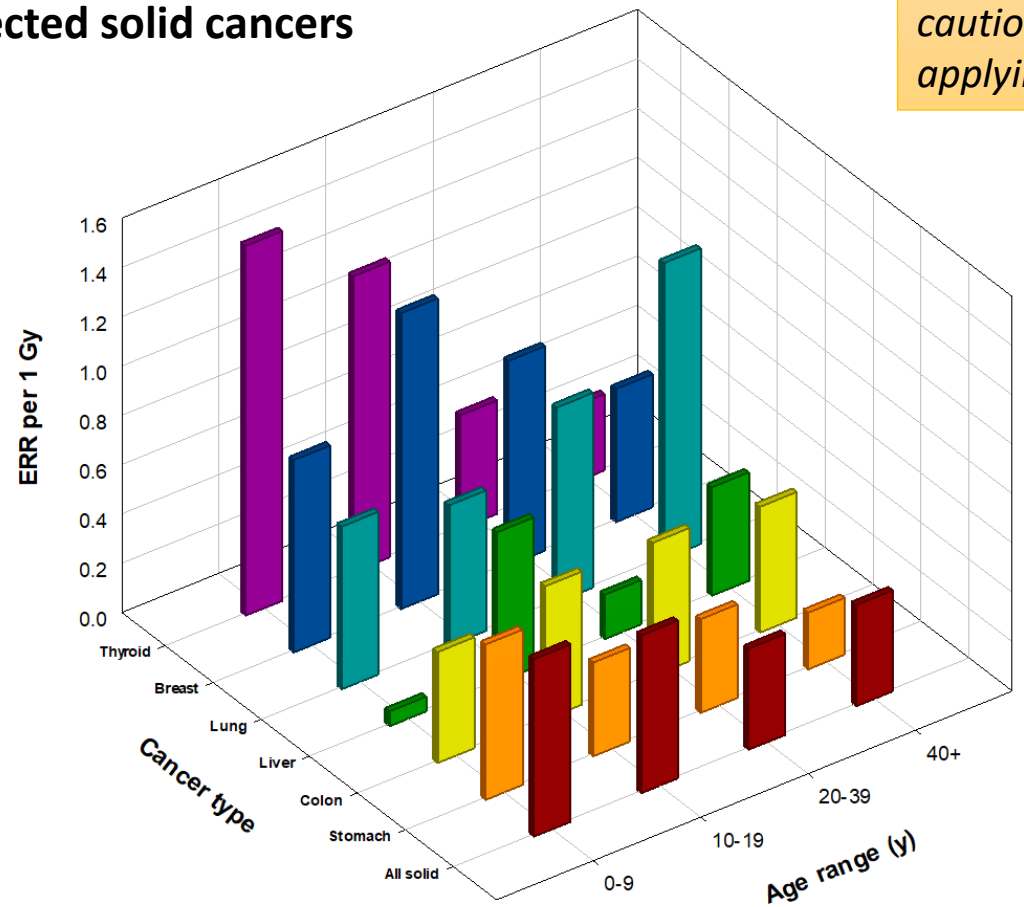
- First, because there generally is a **long latency period** between the primary injury (unrepaired mutations in a cell's DNA) and the outbreak of a cancer, children are more likely than older people to experience the longterm consequences;
- Second, the bone-seeking radionuclides acumulate more rapidly in **growing bones** than in bones of the adult, with the possible consequence of an alteration of the immune system, resulting not only in impaired defense against infection, but also in impaired ability to recognize and kill cancer cells;
- Third, in cells with a **high frequency of division** (such as those in a growing organism), there is a higher probability that mutations of DNA will not be repaired as rapidly or completely as mutations occurring in adults.

Source: R. Scholz. On the Sensitivity of Children to Radiation Medicine & Global Survival 1, 1994

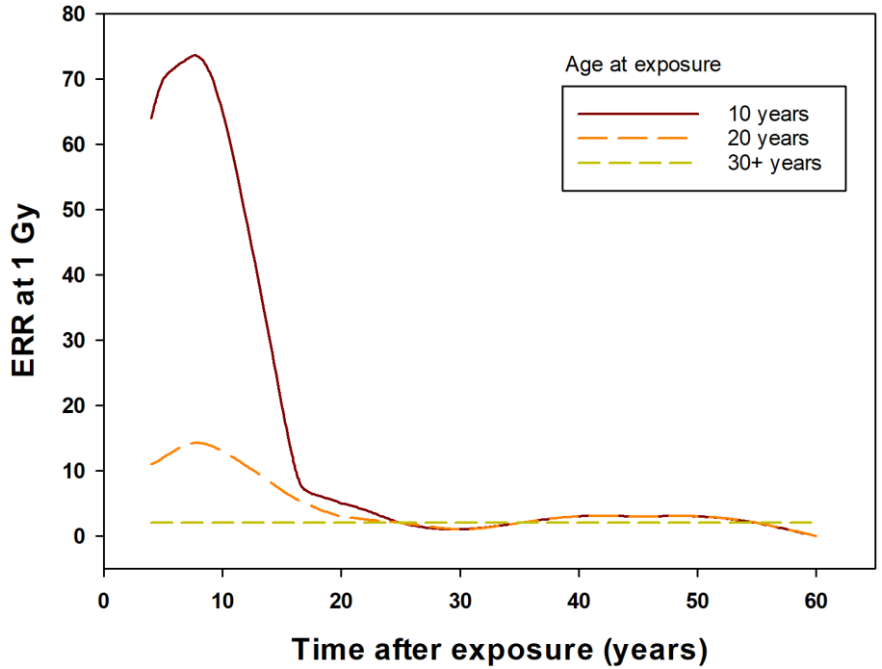
Organ-specific excess relative risk (ERR) for radiation-induced solid cancers and leukaemia as a function of age at exposure in the LSS cohort

When examining differentials by age (or other modifying factors) caution needs to be taken not to overgeneralize, as for example in applying overall age-at-exposure effects to individual tumour sites

Selected solid cancers



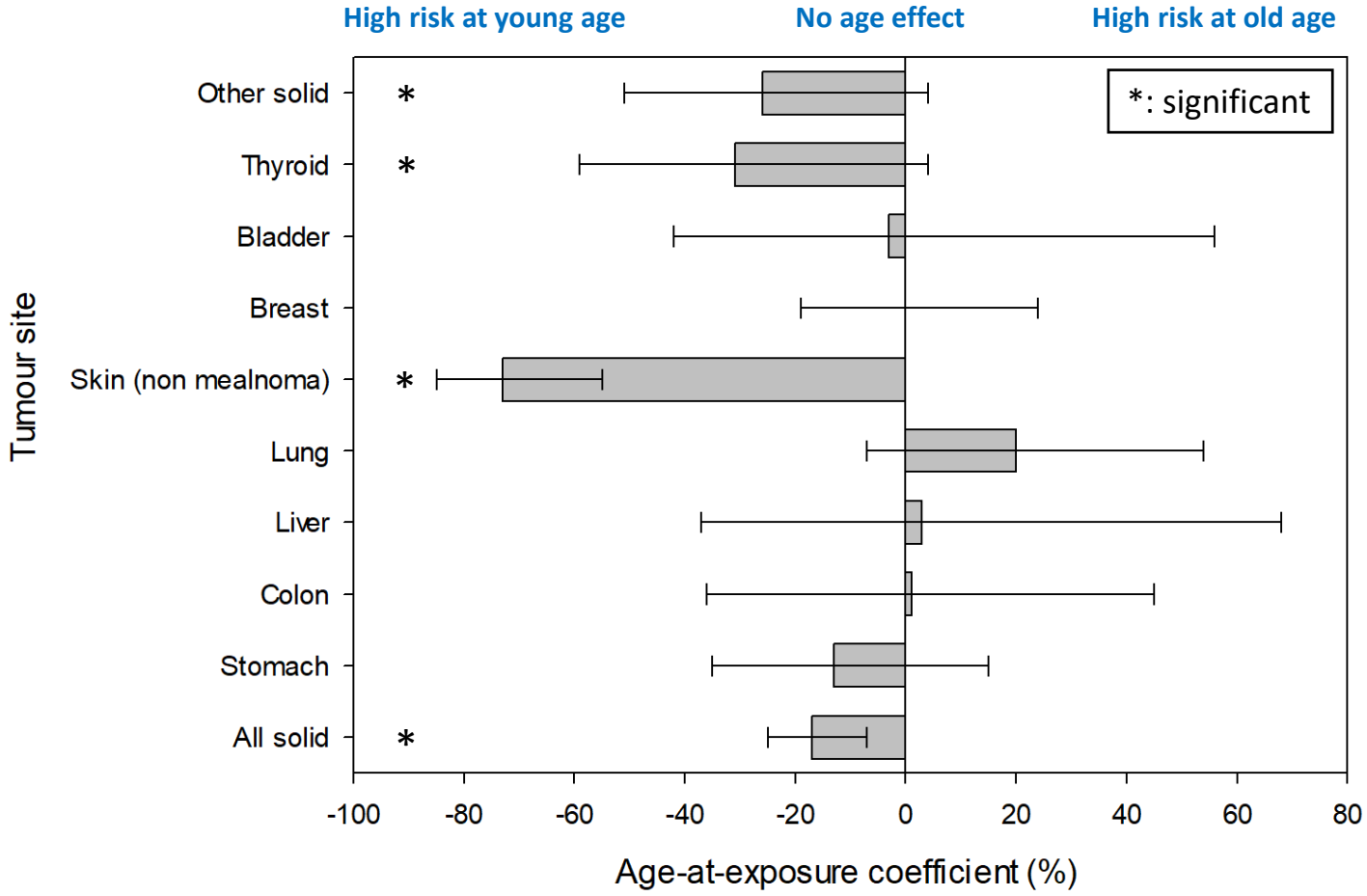
Leukaemia



Source: DL Preston et al. RADIATION RESEARCH 168, 1–64 (2007)
Source: UNSCEAR 2013, Volume II

Changes in cancer-incidence risk estimates by age at radiation exposure in LSS of atomic bombing survivors expressed as age-at-exposure coefficient

Age-at-exposure coefficient: per cent change in ERR coefficients by decade of year of age at exposure



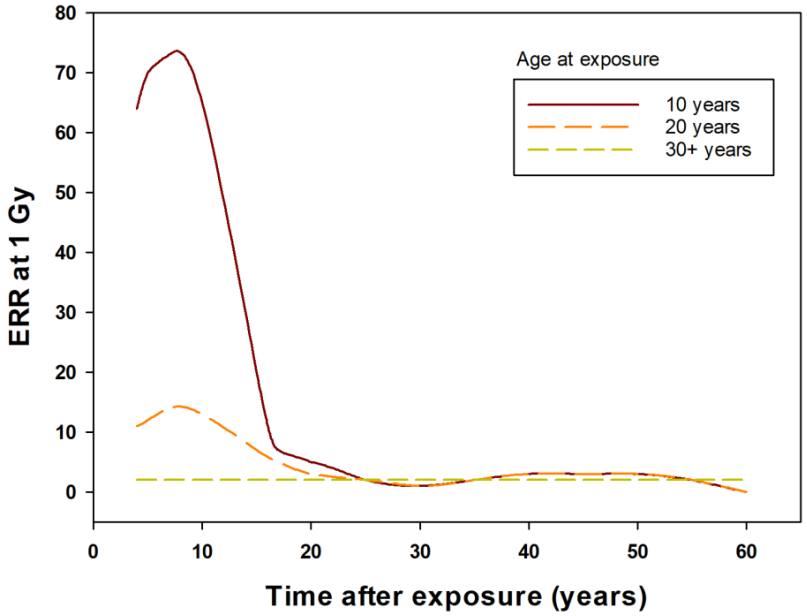
Not show: leukaemia for which the ERR is high at young age but which does not show a continouos increase of risk with attained age

Other solid: includes cancers of small intestine, certain other parts of the digestive and respiratory tracts, nasal cavity, larynx, thymus, bone and connective tissues, melanomas, male breast cancers, female and male genital organs, parts of urothelial and endocrine systems, and ill-defined sites.

Source: UNSCEAR 2013, Volume II

An attempt at mechanistic explanation of differences in age-dependent sensitivity of organs with resect to radiogenic cancer induction

Leukaemia



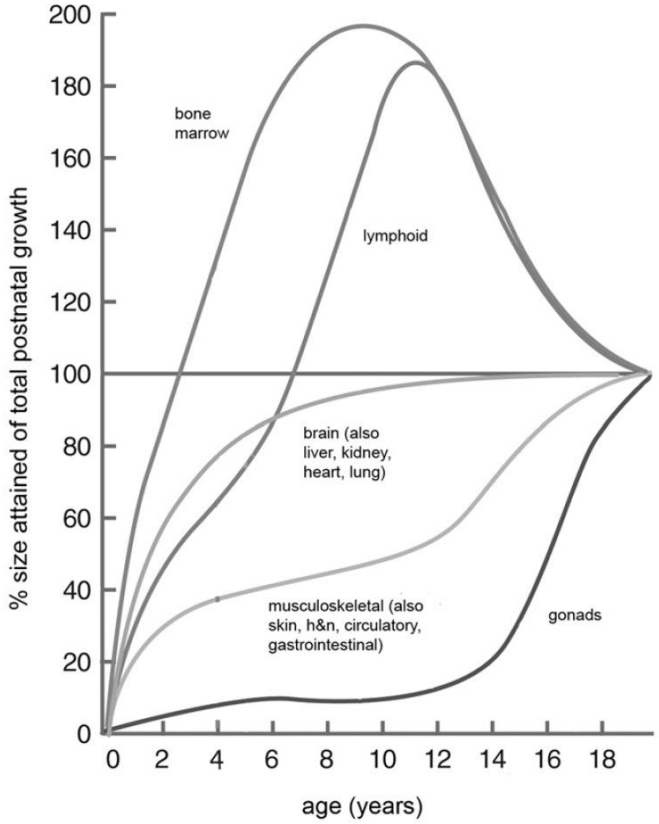
Why high risk at young age

- Two hit initiation model
- High rate of cell growth
- Poor immunosurveillance

Why temporary increase of risk

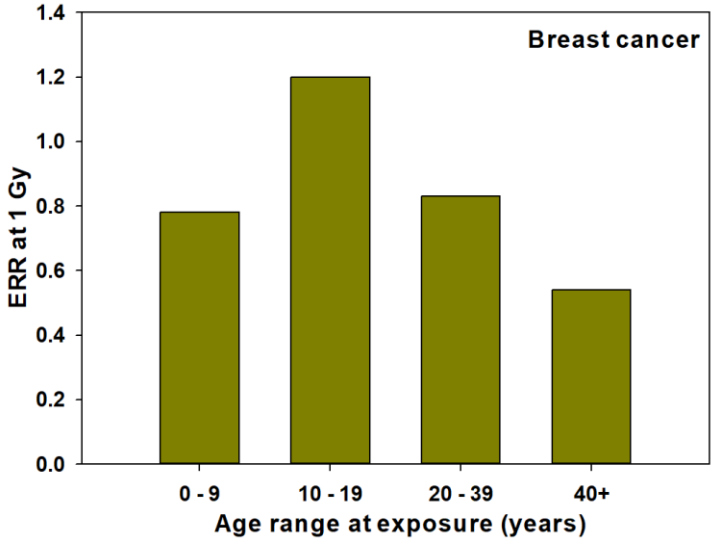
- High tissue turnover

Growth curves of different tissues



Source: Rubin et al. Semin Radiat Oncol 20:3-11, 2010

Possible explanation of differences in age-dependent sensitivity of organs with respect to radiogenic cancer induction



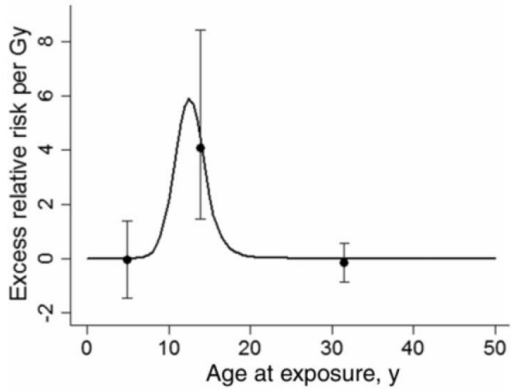
"During puberty, under rising levels of estrogen, the mammary gland undergoes dramatic changes and develops into a highly branched epithelial network mediated by rapid stem cell proliferation."
"Age at menarche (not BMI) is a strong modifier of the radiation effect: for a given dose, both the ERR and EAR decreased with increasing age at menarche."

The size of the effect is surprising.

Brenner et al. Radiation Research 190: 433–444, 2018.

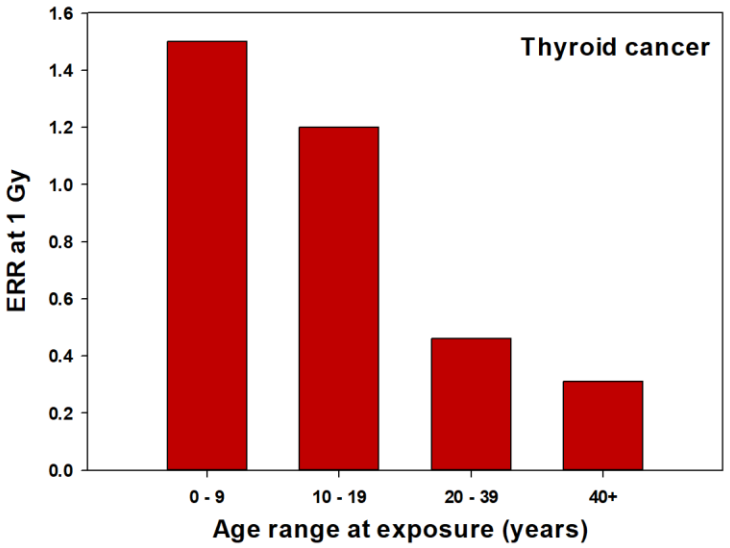
Uterine Corpus Cancer Incidence, LSS, 1958-2009

Adjusted for body mass index, parity, number of pregnancies, time to/from menopause, and probability of hysterectomy



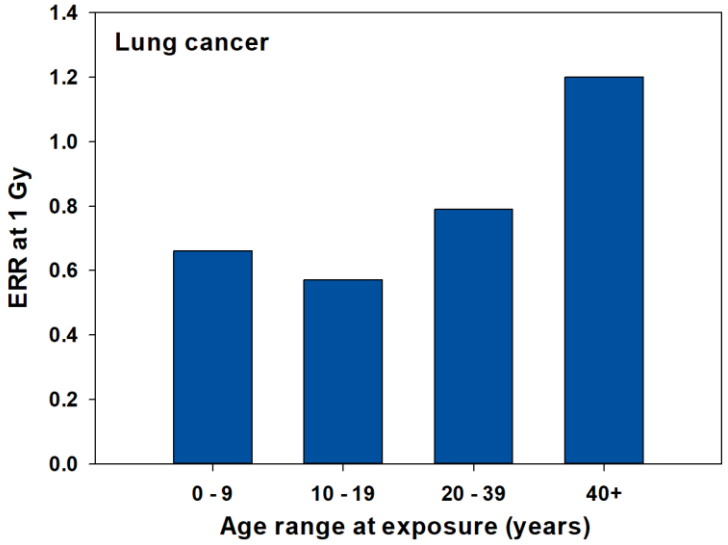
Utada M, et al. *JNCI Cancer Spectrum*, 2019

Possible explanation of differences in age-dependent sensitivity of organs with respect to radiogenic cancer induction



"Children develop radiation-related cancer more often than adults for a number of reasons. Their tissues are growing and cells are dividing more rapidly, making them more prone to the mutagenic effects of ionizing radiation". **High BMI is a risk modifier**.

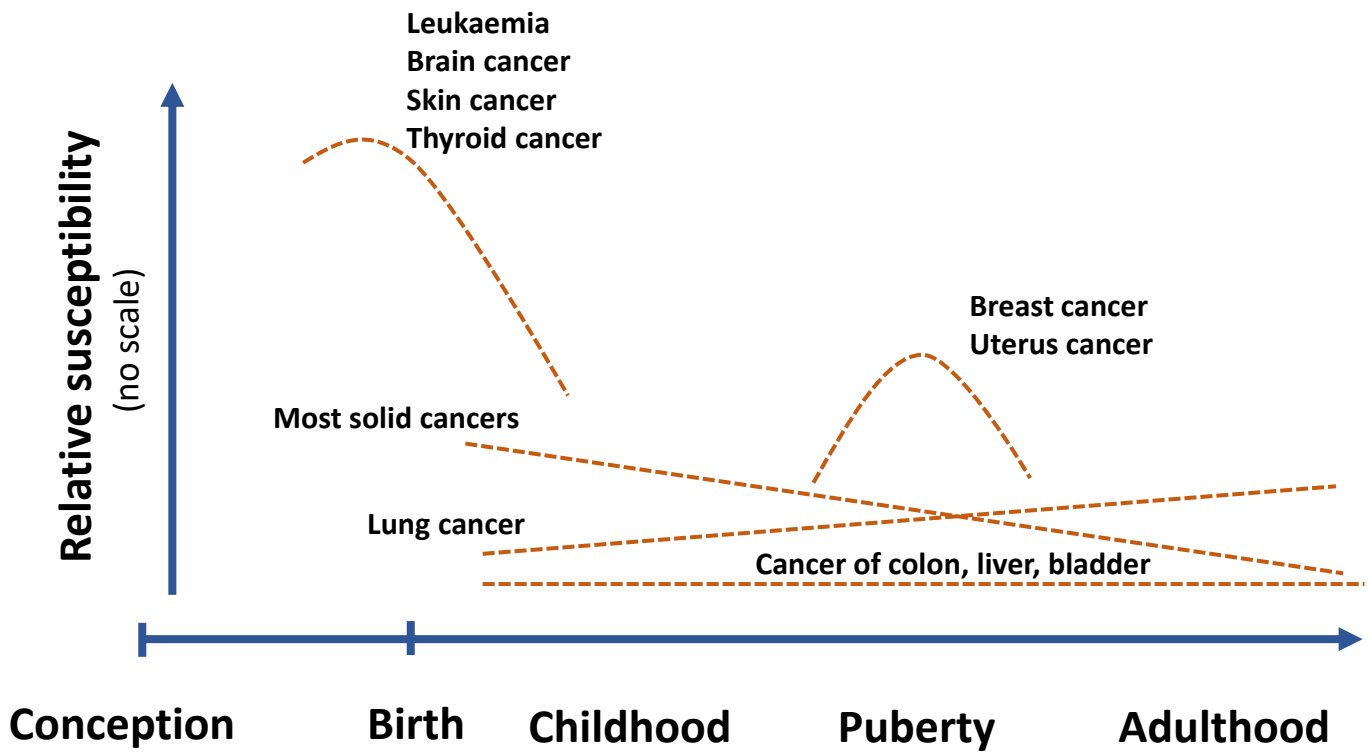
Source: De Vathaire et al. J Clin Endocrinol Metab 100:4282–4290, 2015



Relevant observation: risk of smoking-induced lung cancer decreases after cessation of smoking. Explanation: "tobacco smoking increases mutational burden, cell-to-cell heterogeneity and driver mutations, but quitting promotes replenishment of the bronchial epithelium from mitotically quiescent cells that have avoided tobacco mutagenesis". Source: Yoshida et al. Nature 578: 266–272, 2020.

Perhaps this protective system is active during young age but is lost in advanced age due to accumulation of mutations or cell attrition??? Stem cells damage by gamma radiation cannot be avoided but perhaps damaged cells are preferentially eliminated at young age ???

An attempted summary of organ sensitivities to stochastic effects as a function of age at exposure



Based on K. Ozasa, ICRP 2019, Adelaide