

EURADOS Winter School on Foetal Radiation Risk: *Biological and Genetic Effects*



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Disclosures

- No financial disclosures
- I am neither a radiation biologist nor a geneticist
- However, the most common and greatest anxiety of my patients in imaging is: will the radiation effect my fetus/baby?
- And...I do imaging of premature infants that should be foetuses!



Outline:

- ICRP Publications 84 (2000), 90 (2002), 95 (2004): mortality, human teratogenesis, cancer, *later adult diseases*
- NCRP Report 174 (2013)
- Cancer risk: “foetal risk equals early childhood”
 - Richard Wakeford
 - Paediatric cancer (*genetic*) predisposition syndromes
- Frequencies/doses of medical imaging exposures of pregnant women
 - Recent CT publications
- Research gaps and questions

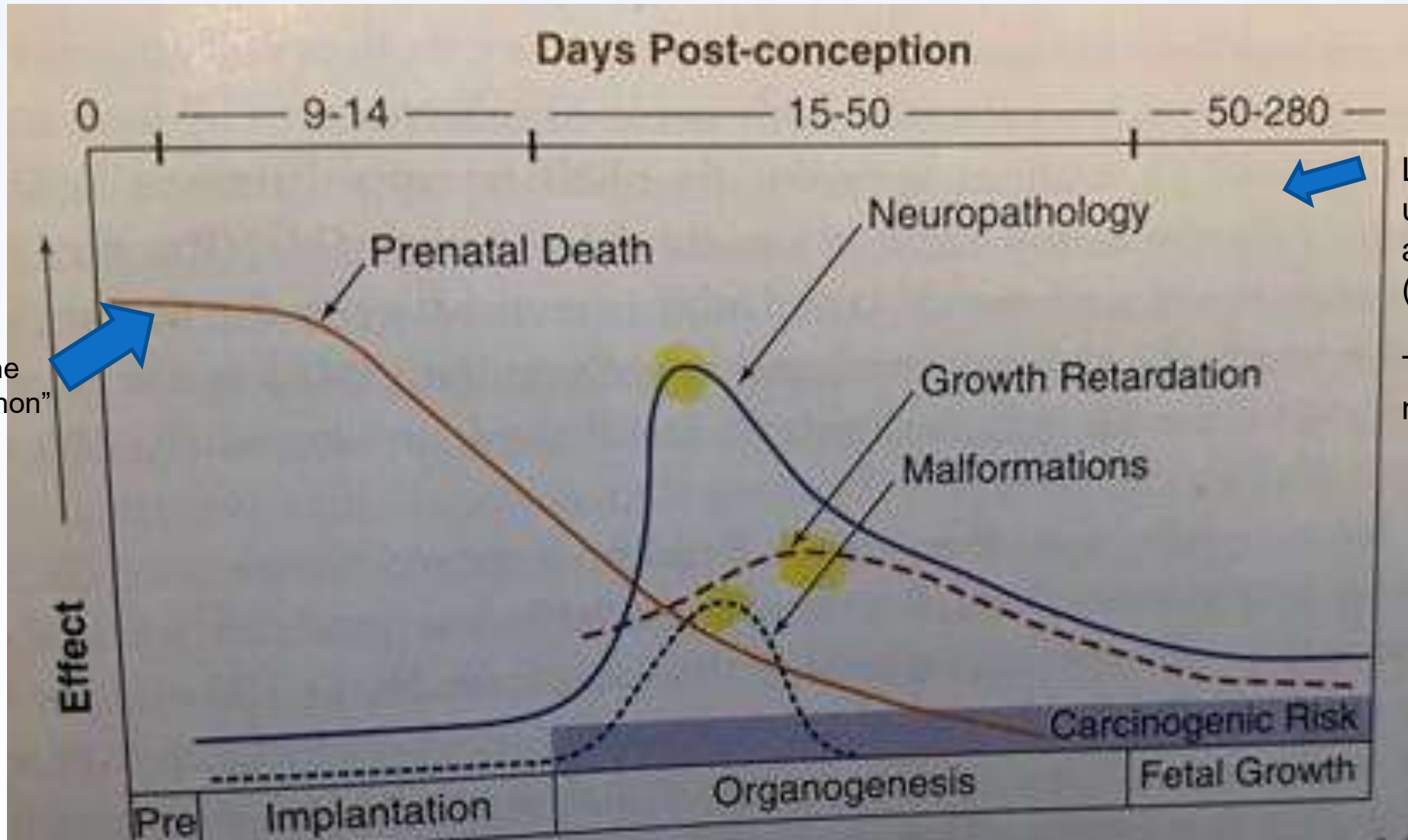
Brief Biological Evidence Review

- Pre-conception IR
 - No known *human* germline mutation from IR--but are we unable to detect it?
 - Somatic cell mutations are known to occur in both humans and animals
 - No increased heritable genetic mutations in several cohorts: offspring of LSS, childhood cancer survivors, radiation workers-- for an excess of cytogenetic syndromes, single-gene disorders, malformations, stillbirths, neonatal deaths, cancer, or cytogenetic markers

Non-cancer embryo/foetal IR effects

- Baseline Reproductive/Congenital Risks
 - 15% spontaneous pregnancy loss
 - 3% major malformations; 4% minor malformations
 - 0.4% mental retardation; 4% microcephaly
- Tissue Effects: (teratogenesis)
Congenital malformations, mental retardation, decreased intelligence quotient (IQ), microcephaly, neurobehavioral effects, seizure disorders, growth retardation (height and weight), and embryonic and fetal death (miscarriage, stillbirth)
- Genetic Risks: not definitive in humans, estimated to be very small and higher in female fetus than male; (first report by Muller in fruit flies, 1927...gonad shields)

IR Health Effects on Embryo/Foetus: Timing



“All or none Phenomenon”

Linear increase frequency of mental retardation with dose (40%/Gy) without threshold, whereas a Threshold... later was not excluded...P90

Thresholds for non-cancer IR effects:

- Pre-implantation: “All or none” phenomenon of pregnancy loss if doses ≥ 150 mGy
- 2-8 weeks post-conception (major organogenesis): critical risk malformations but high dose ≥ 250 mGy
- 8-15 weeks post-conception: neuropathy, growth retardation with doses ≥ 100 mGy
- 15-27 weeks post-conception: neuropathy, growth retardation, but at higher doses
- >27 weeks post-conception: from the standpoint of counseling, one of the most important conclusions in Otake and Schull (1998) states: “No evidence of a radiation effect on intelligence was seen among children exposed *prior to week 8 or at 26 or more weeks after ovulation.*” Animal studies support the conclusion that the CNS is less vulnerable to the effects of radiation during early organogenesis, probably because of its resiliency and repairability.’*

Some risk estimates for CNS effects



IR effect

foetal age
(peak risk periods)

post conception

excess occurrence

baseline

for 10 mGy dose

- | | | | |
|----------------------|---------------|------------------|----------|
| • Microcephaly | at 4-7 weeks | 5/1,000 | 40/1,000 |
| • Microcephaly | at 8-11 weeks | 9/1,000 | 40/1,000 |
| • Mental retardation | at 8-15 weeks | below threshold# | 4/1,000 |

*You can have microcephaly with or without MR and vice versa therefore detecting microcephaly does not lead to any counseling decision alone

P90 inconclusive about threshold

CNS Effects



- In utero Japan cohort (2,000 babies):
 - Decreased IQ 25 points per Gy (at 8-15 weeks, most sensitive period)
 - Later school performance reduced: Foetal dose 1 Gy
 - Seizures and behavioral effects
 - Brain heterotopia, neuronal depletion, disorganized synapses (also in animal studies)
- *Animal studies much more extensive, important, and beyond scope of this discussion*

Some caveats for what we know about IR risk to foetus/embryo

- NCRP 174 states ‘lifetime risk of oncogenic effects following *in utero* irradiation appears to be lower than that following irradiation during childhood. There [are] not data available that inform on which stages of pregnancy may be the most vulnerable to the oncogenic effects of irradiation”
- Sugiyama (Jan 2021, Eur J Epi): cont’d risk of tumors in females but not males; complex factors interact in non cancer disease mortality (birth weight, small head size, parental loss)



Avoid IR Exposures in Medical Imaging: Shared decision-making, disclose uncertainties (ICRP TG 109)

- Ataxia Telangiectasis (AT) and AT-like disorder
- Bloom syndrome
- Hereditary retinoblastoma
- Fanconi anemia
- Gorlin Syndrome (basal cell nevi s.)
- Nijmegen breakage syndrome
- Rothmund-Thomson syndrome
- Werner syndrome
- X-linked agammaglobulinemia (SCID)
- More syndromes keep being identified, see OMIM registry, RIDDLE syndrome

*Trisomy 21?; BRAC1/BRACA2? (CXR in children ... breast ca. Andreu. JClinOnc 2006)

Population impact of AT: Carriers

- **AT cases – 1 in 40-100,000 live births – *very rare!***
- 40% develop cancer, mainly leukaemia and lymphoma
- **Approx 1% of western populations are heterozygous AT carriers**
- Modestly increased cellular radiosensitivity in some assays
- Increased risk of breast cancer (2.37 relative risk)

Renwick et al (2006) Nature Genet 38:873-875

Paediatric Cancer Predisposition Syndromes (CPS) and IR Exposure



- Pediatric Cancer Working Group of the American Association for Cancer Research (AACR) mtg 2016 guidelines
- Recommendations for surveillance of children with a wide spectrum of cancer predisposition syndromes, outlined in a series of 17 open access articles
- Definition: risk of cancer $\geq 5\%$ by age 20; effective surveillance
- Current estimate of paediatric cancer associated with a germline mutation in a CPS is at least 10%

$\leq 1\%$ of global population has known family cancer sensitivity

Background/Justification CPS guidance: G Brodeur

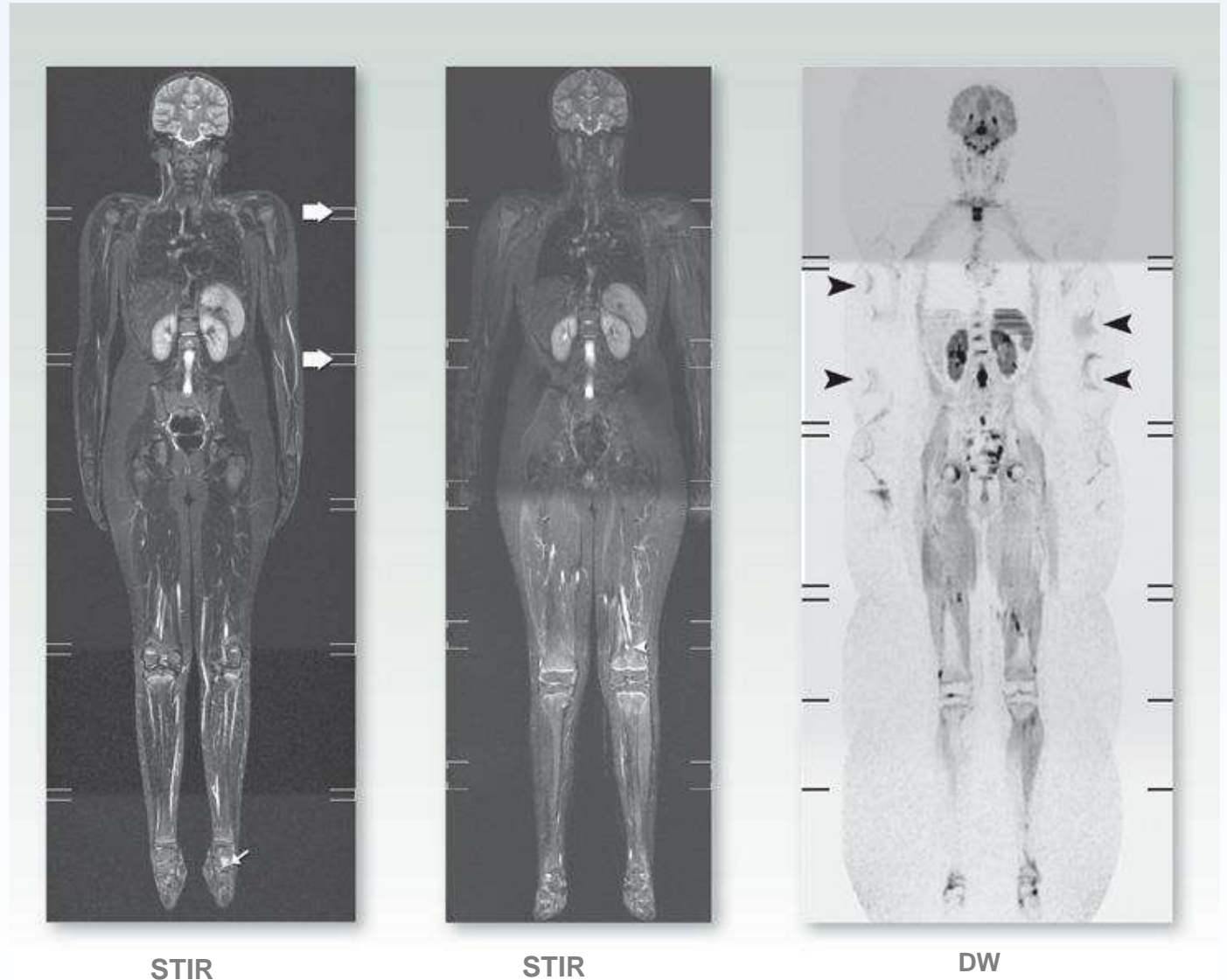
- Tribute to Dr. Alfred G Knudson, described modern cancer genetics and hereditary predisposition
- ‘2-hit theory’ of Retinoblastoma (1971): the dominant inheritance form (1 mutational event via germ cell+1 via somatic cell) or the nonhereditary form (2 mutational events in somatic cells)
- Extended to Neuroblastoma and Wilm Tumor [nephroblastoma] (1972) and to adult tumors
 - *ICRP P79 Genetic Susceptibility to Cancer: “Consider not just the radiation sensitivity due to tumour-suppressor gene deficiency but also reduction in tumour latency”*

Paediatric Cancer Predisposition Syndromes (CPS) and IR Exposure

- *These guidelines recommend avoidance of imaging with ionizing radiation in favor of nonionizing radiation use*
- CPS such as Li Fraumeni syndrome (variable expression associated with a germline mutation in the TP53 tumor suppressor gene) require whole-body screening with MRI (WBMRI) from cranial vertex to toes
- Liver lesions detected at screening can be further characterized with contrast enhanced ultrasound (CEUS), and if needed, MRI

Li Fraumeni and Cancers in Childhood vs Adulthood

- Tumors manifesting in childhood include soft tissue sarcoma, adrenal cortical carcinoma, choroid plexus papilloma, and medulloblastoma
- The early adulthood phase is dominated by breast cancer (median age, 33 years) as well as osteosarcoma, leukemia, astrocytoma, glioblastoma, and colorectal cancer (median age, 38 years)



CPS and Whole Body MRI Surveillance, sometimes with added focused MRI

- NF1, NF2 (NF2 for schw add brain/spine MR)
- CMMRD (w/ Lynch syndrome)
- Hereditary pheochromocytoma/paraganglioma
- Rothmund-Thomson syndrome
- DICER1 (add brain MR Q6 mo from dx)
- Hereditary retinoblastoma

Syndromes needing imaging surveillance but NOT WBMRI:

- Beckwith-Wiedemann syndrome (BWS)/ hemihypertrophy
- PTEN/hamartoma tumor syndrome
- Von Hippel Lindau syndrome (VHL)

Trends in Imaging and Radiation Protection:

- Decreasing dose per exam
 - Improved technology
 - Optimised protocols
- Increasing exam applications
 - e.g., CT pulmonary arteriography
 - E.g., Trauma imaging & interventions
- Lag in justification



How much DOSE do *diagnostic* imaging procedures expose the embryo/foetus?

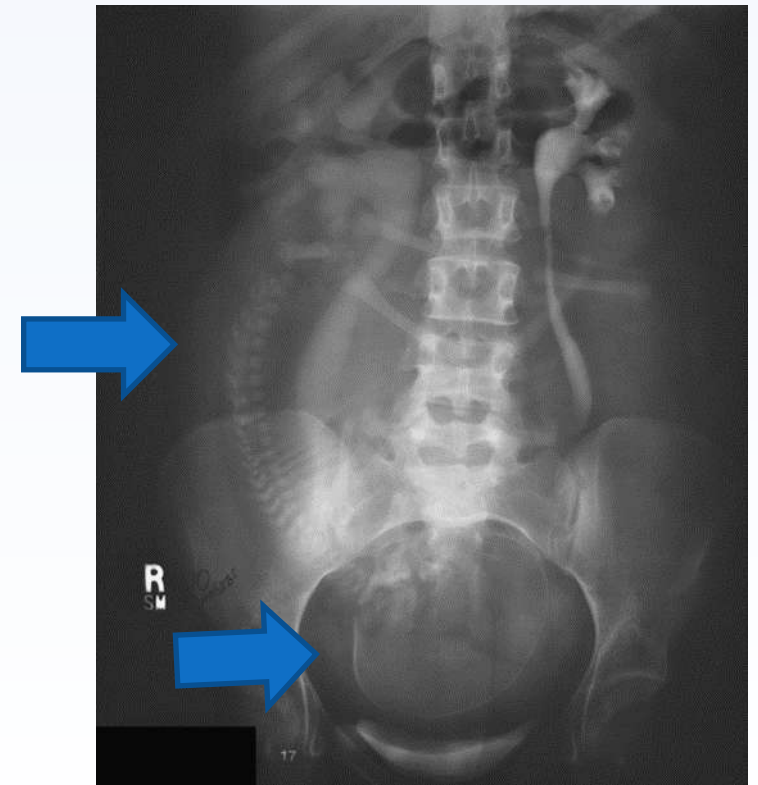
- Today: ≤ 10 mGy with interventional procedures typically < 50 mGy
- But consider cumulative CTs (M Rehani et al 2019):
- “CT in 344 hospitals in 20 countries [showed] 0.64% to 3.4% of the patients undergoing CT examinations reach cumulative effective doses (CED) of ≥ 100 mSv in a 1- to 5-year period.”
- The papers estimated that about 0.9 million patients probably reach a CED ≥ 100 mSv every year globally through recurrent CTs alone. And nearly 20% were aged < 50 years (fertile women).



Our Catscan 4

How frequently do pregnant women get imaged (abdomen/pelvis)?

- Most often first trimester before aware of pregnancy
- Up to 1% of all pregnant women (Mossman 1982)
- 11% of trauma pts unaware of pregnancy (W Mayo-Smith, 2009)



CT Upward Trend (and ionizing imaging) in Pregnant Women

- ABD-Pel CT use: increased (doubled) between 1996 and 2006 at one academic system (W Mayo-Smith, Radiology 2009)
 - Most common dx appendicitis, ureteral stone
 - CTDIvol average 4.3 mGy (range up to 44 mGy)
- USA and Canada large cohort: CT rates increased 3.7 fold in USA, 2.0 fold in Canada, 1996-2016
 - 0.8% of women at US sites and 0.4% in Canada underwent CT
 - 5.3% of pregnant women in US sites and 3.6% in Canada underwent imaging with ionizing radiation
 - (M Kwan, JAMA Network Open, 2019)
- *NCRP Report 184 (2019): CT volume plateau at 2008-9 recession, then increased to 91 million in 2019; optimization resulted in total population doses slightly decreased 2.9mSv 2006 to 2.3mSv in 2016*



Thank you for your attention

Questions are guaranteed in
life.
Answers are not.

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An advertisement for medical imaging safety. It features a large image of a football player in a white jersey with the number 55, holding a football and a helmet. Next to him is a small baby. Below the images is the text "One size fits all?". At the bottom, there is a small text block: "We understand that every patient is different. We know that medical imaging helps your doctor with your care. So we perform only necessary medical imaging exams, and make sure it's the right test and the right radiation dose for each patient — large or small. Radiation protection is important for children and adults. If you have questions, ask your radiology professional before the test, and you can learn more at the websites imagewisely.org and imagegently.org." Below this are logos for "IMAGE WISELY® Radiation Safety in Adult Medical Imaging" and "image gently" with their respective websites and social media icons.

The Obvious First

- Known radiosensitivities but
- We are all different! (ICRP TG 111)
- Gender specific differences in risk, especially in breast (ERR incidence per Gy, 0.58 in females vs 0.35 in males)
 - Thyroid cancer risk higher in both female children and female adults
 - What about other health effects like CVD and CNS?



Thing 1 and Thing 2

...Perhaps More Research?

- What about (more subtle) fetal IQ deficits at low dose/dose rate exposures?
 - From ICRP P90 (463): “While the existence of a threshold dose for mental retardation is supported by both human and experimental data, the situation is not so clear for the reduction of intelligence quotient (IQ) scores after prenatal irradiation.
 - They also speculate about low dose exposures and potential brain effects at older age (dementia, etc)
- From ICRP P79 genetic susceptibility to cancer: Consider not just the radiation sensitivity due to tumour-suppressor gene deficiency but also reduction in tumour latency
 - Opportunity to encourage dose registries in radiation oncology, esp children

Question: Why is the heart muscle mass smaller on average, in adults that were born premature?

*SOURCE: bit.ly/1QY3kYT Pediatrics, online December 29, 2015

“Previous research has also found that the tiniest and most immature preemies may have poor muscular fitness...current study is important because it suggests this problem may extend to all pre-term babies, even those only slightly early or a little bit under-weight, said lead author Dr. Marjaana Tikanmaki of the National Institute for Health and Welfare and University of Oulu in Finland.”

- Answer: we do not know...but note that ‘fetogenesis period’ of a premie outside of the uterus may be from age 23 weeks gestation.
- Yet there is no specific radiation protection guidance for the premature infant. Many IR exposures occur. hematopoiesis occurs in liver.
- Opportunity to study large premature cohort with imaging linked medical data NICHD?



Question : Do we really know if IR to the foetus is the same as IR to the young child?

- Wakeford: 6%/Gy is the estimated excess cancer risk to AGE 15, not the lifetime cancer risk so what should we then advise about further excess lifetime attributable risk?
 - Can we use childhood CT cohorts cancer risk meta-analyses
- There are many **dietary/chemical** in utero exposures that lead to adult disease that include obesity, heart disease, diabetes, behavior patterns, food preferences (from what mother eats), etc.
- Related to this, there are many studies of how the growth and development and health risks are different in premature infants into adulthood.

CPS Consortium future goals

- Pooling data in registries (e.g., NCI paediatric proton therapy pts)
- Outcomes and further genetic research
- “Notwithstanding advances in cancer surveillance, future research endeavors should also focus on tumor prevention in genetically at-risk patients. The use of animal models to perform large-scale chemical/drug screens to identify agents that might mitigate or eliminate cancer risk”^{area}
- *“Although stopping this sword of cancer from falling may be years away, we may be able to help our patients today by improving our ability to predict when it will fall, where it will land, and how to slow its descent, thus minimizing its damage through the safety net of advances in early tumor detection and treatment.”^{area}*