Ionising radiation and childhood cancer – an overview

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Radiation-induced Cancer

• It is established beyond reasonable doubt that exposure to moderate and high doses of ionising radiation can cause most types of cancer in humans, including some forms of cancer that are experienced in childhood.

• Ionising radiation is one of the few established causes of some childhood cancers.

• This presentation will review the evidence for ionising radiation being a cause of cancers in children.
Hiroshima and Nagasaki
6th and 9th August 1945
Leukaemia among Japanese Atomic-bomb Survivors

• In 1948, alert clinicians noted an increase of leukaemia among the A-bomb survivors.

• This observation contributed to the establishment in October 1950 of the Life Span Study (LSS) cohort of ~90 000 Japanese atomic-bomb survivors who were exposed after birth.

• Pronounced and highly significant radiation-related excess of leukaemia in the LSS.
Leukaemia Mortality, 1950-2000

(Richardson et al., Radiat Res 2009; 172: 368-82)
Childhood Leukaemia in the LSS

- After October 1950, 10 cases of leukaemia were incident among Japanese A-bomb survivors under the age of 15 years.
- This compares with ~1.6 cases expected among these children from contemporaneous Japanese national mortality rates.
- A clear excess risk of childhood leukaemia exists as a result of radiation exposure from the Japanese atomic-bombings.
Radiotherapy in Childhood

• The high relative risk of childhood leukaemia following irradiation of infants or young children during the atomic-bombings is largely (but not completely) confirmed by studies of those exposed therapeutically to treat a variety of malignant and benign medical conditions.

• Groups therapeutically exposed include: childhood cancers, enlarged thymus gland, ringworm of the scalp, and skin haemangioma.
Oxford Survey of Childhood Cancers (OSCC) – Diagnostic Exposure

- In the early-1950s a nationwide case-control study of mortality from leukaemia and other cancers among children in Great Britain was initiated by Dr Alice Stewart and her colleagues. This became the Oxford Survey of Childhood Cancers (OSCC).
- First results reported in *The Lancet* in 1956 showed a statistical association between childhood cancer and an abdominal X-ray examination of the pregnant mother.
Antenatal Radiography

(Doll & Wakeford, Br J Radiol 1997; 70: 130-139.
Wakeford, Radiat Prot Dosim 2008; 132: 166-174)

• The initial report of an association between the risk of childhood cancer and antenatal radiography was received with scepticism, but more refined analyses of the OSCC data (including those using records of maternal exposure) have confirmed the findings.

• The OSCC results have now been supported by the collective findings of many independent case-control studies from around the world.
### Relative Risk of Childhood Cancer Associated with Antenatal Diagnostic Exposure to Radiation found by Case-control Studies

<table>
<thead>
<tr>
<th>Case-control Study</th>
<th>Cases (Exposed/Total)</th>
<th>Statistical Information (Precision)</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Childhood Cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSCC (singleton plus twin births)</td>
<td>2392/15437</td>
<td>872</td>
<td>1.40</td>
<td>(1.31, 1.49)</td>
</tr>
<tr>
<td>All Except OSCC (singleton plus twin births)</td>
<td>635/6815</td>
<td>376</td>
<td>1.29</td>
<td>(1.17, 1.43)</td>
</tr>
<tr>
<td><strong>Childhood Leukaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSCC (singleton plus twin births)</td>
<td>620/4122</td>
<td>308</td>
<td>1.51</td>
<td>(1.35, 1.69)</td>
</tr>
<tr>
<td>All Except OSCC (singleton plus twin births)</td>
<td>811/11661</td>
<td>442</td>
<td>1.27</td>
<td>(1.16, 1.40)</td>
</tr>
<tr>
<td><strong>All Childhood Cancers Except Leukaemia</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>OSCC (singleton plus twin births)</td>
<td>672/4552</td>
<td>325</td>
<td>1.46</td>
<td>(1.31, 1.62)</td>
</tr>
<tr>
<td>All Except OSCC (singleton plus twin births)</td>
<td>292/3318</td>
<td>196</td>
<td>1.26</td>
<td>(1.09, 1.45)</td>
</tr>
</tbody>
</table>
Antenatal Radiography
(Boice & Miller, *Teratology* 1999; 59: 227-233)

- A causal interpretation of the statistical association between the risk of childhood cancer and antenatal radiography is not universally accepted.
- One of the main objections is the similarity between the relative risk of leukaemia and that of most of the other typical cancers of childhood.
Types of Childhood Cancer
(Bithell & Stewart, Br J Cancer 1975; 31: 271-287)

Relative Risk of Specific Types of Childhood Cancer Associated with an Antenatal Abdominal X-ray Examination.
Error Bars and Band Show 95% Confidence Intervals.
Risk Coefficients


- A tentative estimate of the ERR/Gy may be obtained from the OSCC data and the assessed average fetal dose in 1958 made by the Adrian Committee (6.1 mGy):
  
  \[51 \text{ Gy}^{-1} \]
  
  (95% CI: 28,76) Gy\(^{-1}\)

  for all childhood cancers (including leukaemia).

- This is compatible with the ERR/Gy for childhood leukaemia derived from the LSS for exposure after birth.
Bomb Survivors Irradiated *In Utero*


- 807 Japanese A-bomb survivors were irradiated *in utero* and received doses of at least 10 mGy (average dose 0.28 Gy).
- 2 incident cases of childhood (<15 years of age) cancer were observed among these survivors (1 hepatoblastoma and 1 Wilms’ tumour) against, at most, 0.48 case expected from contemporaneous Japanese rates.
Bomb Survivors Irradiated In Utero

- 0 case of childhood leukaemia observed (O), but only 0.2 expected (E)
  - O/E has a 95% CI of (0,15).
- 2 cases of other childhood cancers observed, against 0.28 expected
  - O/E = 7.1 (95% CI: 1.2, 24).
- Possibility that some cases of childhood cancer (particularly childhood leukaemia) occurring among the survivors before October 1950 went unrecorded or undiagnosed.
Chromosome Translocation Frequencies in Peripheral Blood Lymphocytes Sampled from Atomic-bomb Survivors Exposed in utero (●), and from Some of their Mothers (□).
(Ohtaki et al., Radiat Res 2004; 161: 373-9)
Other Childhood Cancers

Childhood Cancers Other Than Leukaemia

• The 2 cases among survivors irradiated *in utero* represent a significant excess
  – ERR/Gy compatible with the OSCC results.
• No case occurred among the Japanese atomic-bomb survivors irradiated *after birth*.
• Little evidence that these childhood cancers are sensitive to induction by radiation exposure *after birth* (with the exception of thyroid cancer, and the possible exception of some brain tumours).
Tentative Overview

Childhood Leukaemia
- Can be caused by exposure *in utero*
- Can be caused by exposure *after birth*

Other Common Cancers of Childhood
- Can be caused by exposure *in utero*
- Cannot, in general, be caused by exposure *after birth*
Antenatal Radiography

- Implication of OSCC findings is that intrauterine doses ~10 mGy of X-rays proportionally increase the risk of childhood cancer (both leukaemia and other cancers) by around 50%.
- A dose of 10 mGy of X-rays produces just a few electron traversals of a cell nucleus.
- Importance of this finding is that it implies that a single electron track can cause cancer, giving support to the linear no-threshold (LNT) dose-response model for radiation-induced cancer.
Paediatric CT Scans

• Estimates of childhood leukaemia risk using current models suggest that the effect of doses of several milligray of X-rays received during paediatric CT scans should be detectable in large case-control studies.

• Statistical power calculations are a prerequisite to ensure such studies are large enough to detect the predicted effect.

• Several large studies of CT scans are underway at the moment.
Sellafield, Cumbria, UK
Leukaemia and Nuclear Sites

(Laurier et al., Radiat Prot Dosim 2008; 132: 182-90)

• Clear evidence of excesses of childhood leukaemia incidence near the Sellafield, Dounreay and Krümmel nuclear facilities.

• Perhaps the risk of childhood leukaemia from the intake of radioactive materials has been *grossly* underestimated?

• Suggestion not supported by the UK Committee Examining Radiation Risks of Internal Emitters (CERRIE).
Cs-137 and Pu in Fallout

(Warneke et al., Earth Planet Sci Lett 2002; 203: 1047-57)
Weapons Testing Fallout

Average Annual Effective Doses in the Northern and Southern Hemispheres from Ingestion and Inhalation of Radionuclides Produced in Atmospheric Nuclear Weapons Testing (UNSCEAR 2000)

- Northern Hemisphere - Ingestion
- Northern Hemisphere - Inhalation
- Southern Hemisphere - Ingestion
- Southern Hemisphere - Inhalation

Calendar Year

Average Individual Effective Dose, µSv
Childhood Leukaemia Incidence

(Wakeford et al., Radiat Environ Biophys 2010; 49: 213-27)

Incidence Rate of All Leukaemias (Except Where Indicated Otherwise) among Children Aged 0-14 Years, 1950-1990. Incidence Data from Eleven Cancer Registries. Error Bars Show 95% Confidence Intervals for Rates.
Childhood Leukaemia Incidence

(Wakeford et al., Radiat Environ Biophys 2010; 49: 213-27)

Incidence Rate of All Leukaemias (Except Where Indicated Otherwise) among Young Children Aged 0-4 Years, 1950-1990. Incidence Data from Ten Cancer Registries. Error Bars Show 95% Confidence Intervals for Rates.

Registration Rate of Leukaemia in the 0-4 Year Age Group cases per million person-years

- Connecticut, 1950-1989
- Saskatchewan, 1952-1986
- New Zealand, 1953-1990
- Great Britain, 1953-1990
- Denmark, 1950-1984
- Sweden, 1961-1987
- Norway, 1958-1987
- Finland, 1958-1987
- Baltimore (AL), 1960-1974
- Western Australia (ALL), 1960-1990

Calendar Year of Diagnosis

Radon and Childhood Leukaemia

• Several studies have examined the potential link between exposure to naturally-occurring inhaled radon and childhood leukaemia.

• The most persuasive of these studies is the nationwide Danish case-control study of Raaschou-Nielsen et al. (2008) (Epidemiology 2008; 19: 536-543)

• This study used model-predicted radon concentrations, which avoids participation bias but introduces exposure uncertainty.
Danish Radon Study
(Raaschou-Nielsen et al., Epidemiology 2008; 19: 536-543)

- Found a statistically significant association between radon exposure and childhood ALL, and inferred that 9% of cases in Denmark could be attributable to radon.
- However, statistical power is low (860 ALL cases), and the lower 95% CL for the attributable proportion is 1%, which is compatible with conventional models.
- Accuracy of model-predictions of radon concentrations needs further investigation.
Natural Background Radiation

(Wakeford et al., Leukemia 2009; 23: 770-6.
Kendall et al., Leuk Res 2011; 35: 1039-43.)

• Recent risk models for radiation-induced leukaemia suggest that ~15% of cases of childhood (<15 years of age) leukaemia in Great Britain may be caused by natural background radiation.
  – red bone marrow dose ~1.3 mSv per annum

• Epidemiological studies have been unable to reliably demonstrate this source of risk
  – probably have insufficient statistical power
Natural Background Radiation

(Little et al. Radiat Res 2010; 174: 387-402)

• Power calculations show that large studies are required to detect the predicted excess risk
  – to achieve 80% power, >8000 cases are needed in a case-control or geographical correlation study covering the whole of Great Britain.

• Greatest effect is from γ-rays, not radon.

• The extensive data from the National Registry of Childhood Tumours (Childhood Cancer Research Group) make such a study feasible.
Natural Background Radiation
(Kendall et al., submitted)

• First results from a large nationwide record-based case-control study of childhood cancer in Great Britain will be published soon.

• What would be expected from prior evidence?
  – Childhood leukaemia
    • A detectable positive effect of γ-radiation
    • No detectable effect of radon
  – Childhood cancers other than leukaemia
    • No detectable effect of either γ-radiation or radon
Chernobyl – 26 April 1986
Chernobyl Contamination

Figure VI. Surface ground deposition of caesium-137 released in the Chernobyl accident [11, 13].
Chernobyl – Thyroid Cancer

(Demidchik et al., Arq Bras Endocrinol Metab 2007; 51: 748-62)
# Thyroid Cancer
(<15 years of age at exposure)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Study</th>
<th>ERR/Gy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>External</td>
<td>Pooled Analysis</td>
<td>7.7 (2.1, 29)</td>
</tr>
<tr>
<td>Chernobyl</td>
<td>Case-control (Belarus &amp; Russia)</td>
<td>4.5 (1.2, 7.8)</td>
</tr>
<tr>
<td>Chernobyl</td>
<td>Cohort* (Ukraine)</td>
<td>5.2 (1.7, 27)</td>
</tr>
<tr>
<td></td>
<td>Tronko <em>et al.</em>, <em>J Natl Cancer Inst</em> 2006; 98: 897-903</td>
<td>*&lt;18 years of age at exposure</td>
</tr>
<tr>
<td>Chernobyl</td>
<td>Cohort* (Belarus)</td>
<td>2.2 (0.8, 5.5)</td>
</tr>
<tr>
<td></td>
<td>Zablotska <em>et al.</em>, <em>Br J Cancer</em> 2011; 104: 181-187</td>
<td>*&lt;18 years of age at exposure</td>
</tr>
<tr>
<td>Chernobyl</td>
<td>Cohort* (Ukraine)</td>
<td>1.9 (0.4, 6.3)</td>
</tr>
<tr>
<td></td>
<td>Brenner <em>et al.</em>, <em>Environ Health Perspect</em> 2011; 119: 933-939</td>
<td>*&lt;18 years of age at exposure</td>
</tr>
</tbody>
</table>
Comparison of $^{137}$Cs Contamination around Chernobyl with that around Fukushima (inset)

The two areas shown are approximately to the same scale.

The orange/red areas around Chernobyl correspond approximately to the green/yellow/red areas around Fukushima in level of contamination.
Conclusions

• There is a broad consistency of results from the epidemiological study of childhood leukaemia and exposure to ionising radiation after birth.

• Childhood leukaemia risk from OSCC appears compatible with the predictions of leukaemia risk models based upon the experience of the Japanese atomic-bomb survivors in the LSS.

• The fetal haematopoietic system may be hypersensitive to cell-killing by radiation.

• Important additional evidence (e.g. from studies of CT scans and natural background radiation) should be available soon.
Conclusions

• The common cancers of childhood other than leukaemia appear to be capable of induction by irradiation \textit{in utero}, but not (or only rarely) \textit{after birth}.

• The typical cancers of childhood (both leukaemia and other cancers) seem to be capable of induction by low doses (~10 mGy of X-rays) received \textit{in utero}.

• Thyroid cancer (rare in childhood) is particularly susceptible to induction by radiation at a young age.
Fin
The relative risk (RR), and 95% confidence interval (CI), of leukaemia and non-Hodgkin's lymphoma combined (LNHL) at 100 mSv cumulative recorded paternal preconceptional dose from external sources of radiation received while working at the Sellafield nuclear complex, as reported by Dickinson and Parker (2002) from their cohort study of live births in Cumbria during 1950-1991. Results for the offspring of Sellafield workers are given for births in the village of Seascale and in Cumbria outside Sealscale. The Sellafield findings are compared with the results of five studies that have used independent data. (Table after Wakeford (2002).)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose-response model</th>
<th>RR (95% CI) at 100 mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Sellafield radiation workers</strong>&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Exponential&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.6 (1.0, 2.2)</td>
</tr>
<tr>
<td>Seascale subgroup</td>
<td></td>
<td>2.0 (1.0, 3.1)</td>
</tr>
<tr>
<td>Outside Seascale subgroup</td>
<td></td>
<td>1.5 (0.7, 2.3)</td>
</tr>
<tr>
<td><strong>Japanese atomic bomb survivors</strong>&lt;sup&gt;e,g,h&lt;/sup&gt;</td>
<td>Linear</td>
<td>&lt;0.98 (&lt;0.98, 1.10)</td>
</tr>
<tr>
<td>(paternal dose only used in analysis)&lt;sup&gt;e,g,h&lt;/sup&gt;</td>
<td>Exponential</td>
<td>0.76 (&lt;0.31, 1.03)</td>
</tr>
<tr>
<td><strong>Ontario radiation workers</strong>&lt;sup&gt;f,g,h&lt;/sup&gt;</td>
<td>Linear</td>
<td>0.63 (&lt;0.27, 3.40)</td>
</tr>
<tr>
<td></td>
<td>Exponential</td>
<td>0.75 (0.07, 3.31)</td>
</tr>
<tr>
<td><strong>Danish Thorotrast patients</strong>&lt;sup&gt;b,g&lt;/sup&gt;</td>
<td>Linear</td>
<td>&lt;0.97 (&lt;0.97, 1.56)</td>
</tr>
<tr>
<td></td>
<td>Exponential</td>
<td>&lt;0.11 (&lt;0.11, 1.11)</td>
</tr>
<tr>
<td><strong>British radiation workers (RLS)</strong>&lt;sup&gt;[i,j]&lt;/sup&gt;</td>
<td>Exponential&lt;sup&gt;k&lt;/sup&gt;</td>
<td>0.92 (0.28, 2.98)</td>
</tr>
<tr>
<td><strong>US ‘Three Site’ radiation workers</strong>&lt;sup&gt;f,i&lt;/sup&gt;</td>
<td>Linear</td>
<td>0.75 (&lt;0.75, 3.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Linear or exponential dose-response model fitted to the data.
<sup>b</sup> Age at diagnosis: *0–24, *0–19, *0–14 years.
<sup>c</sup> The original study of Gardner et al. (1990) reported a RR of 8.30 (95% CI: 1.36, 50.56) for the cumulative paternal preconceptional dose category ≥100 mSv and using 'local controls', based on 4 cases and 3 controls; 3 of the cases were born to mothers resident in Seascale. The reasons for the difference in RR from the case-control study of Gardner et al. (1990) and that from the cohort study of Dickinson and Parker (2002) are set out by Dickinson et al. (2003).
<sup>d</sup> Exponential dose-response model assumed to have been used by the authors.
<sup>e</sup> Based on the results of Little et al. (1996).
<sup>f</sup> Leukaemia only.
<sup>g</sup> RLS: Record Linkage Study (Draper et al., 1997).
<sup>h</sup> Overlap with Dickinson and Parker (2002) of one case (born in Cumbria outside Seascale and diagnosed after the end of the period studied by Gardner et al. (1990); paternal preconceptional dose <50 mSv).
<sup>i</sup> Adjusted by the authors for radiation worker status.
<sup>j</sup> Hanford, Idaho Falls, Oak Ridge workers; Sever et al. (1997) (see Wakeford, 2000).