Cancer Risks from Low-dose Ionizing Radiation: The JNCI Monograph

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International Multi-disciplinary Study Team

Epidemiologists
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- Dan Stram (USC)
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Dosimetrists
- Harry Cullings (RERF)
- Doug Daniels (NIOSH)
- Gerry Kendall (Oxford)
- Isabelle Thierry-Chef (ISGlobal)
NAS BEIR VII 2006 report on low-dose radiation and cancer……“the available scientific evidence is consistent with a linear dose-response relationship between ionizing radiation and the development of cancer in humans…. the smallest dose has the potential to cause a small increase in risk to humans”.
Pooled Analyses

Highly Susceptible Populations

New Era of Low-Dose Studies

Electronic Record Linkage

New Exposures
Aims of the Review

Aim 1
• Summarize findings of epidemiological studies published since NAS BEIR VII

Aim 2
• Systematically assess impact of potential biases & conduct meta-analysis
Study Eligibility

- Cancer risks in humans published 2006-17
- Mean ionizing radiation dose <100mGy
- Risk estimates for dose-response
Environmental Exposures
• 8 eligible studies
• 4 natural background & 4 accidental

Medical Exposures
• 4 eligible studies
• 3 pediatric imaging/therapy & 1 adult cardiac imaging

Occupational Exposures
• 14 eligible studies
• 11 nuclear workers, 1 medical & 2 clean-up workers
Primary outcomes: 91,000 solid cancers & 13,000 leukemias

Mean dose range: 0.1mSv (Three Mile Island) to 82mSv (Chernobyl liquidators)

Most study participants exposed to <100mSv (21 studies <10% had doses >100mSv)
Cancer Risk Following Low-Dose Exposure in Childhood

**Leukemia**

**Excess Relative Risk at 100mGy**

- Chomobyl residents
- GB Background
- Swiss background
- Finnish background
- French Pediatric CT
- UK Pediatric CT

**Solid Cancers**

**Excess Relative Risk at 100mGy**

- GB Background
- Swiss background
- French pediatric CT (Brain tumors)
- UK Pediatric CT (Brain tumors)
- PIRATES (Thyroid cancer)
### Ineligible Studies: Failed on 1 Criterion (n=14)

<table>
<thead>
<tr>
<th>Population</th>
<th>Author</th>
<th>Year</th>
<th>Reason for exclusion</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>US scoliosis (thyroid)</td>
<td>Ronckers</td>
<td>2008</td>
<td>Mean dose = 120mGy</td>
<td>+ (ns)</td>
</tr>
<tr>
<td>Kerala background</td>
<td>Nair</td>
<td>2009</td>
<td>Mean dose = 161mGy</td>
<td>- (ns)</td>
</tr>
<tr>
<td>Chornobyl clean-up</td>
<td>Kesminiene</td>
<td>2012</td>
<td>Mean dose = 100-200mGy</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Techa river (leukemia)</td>
<td>Krestinina</td>
<td>2013</td>
<td>Mean dose = 410mGy</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Mayak workers</td>
<td>Solkinokov</td>
<td>2015</td>
<td>Mean dose = 354mGy</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Chornobyl clean-up</td>
<td>Kashcheev</td>
<td>2015</td>
<td>Mean dose = 132mGy</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Chinese medical workers</td>
<td>Sun</td>
<td>2016</td>
<td>Mean badge dose = 250mGy</td>
<td>+ (s)</td>
</tr>
<tr>
<td>US Shipyard workers</td>
<td>Matanoski</td>
<td>2008</td>
<td>Categorical risk estimates</td>
<td>+ (ns)</td>
</tr>
<tr>
<td>Australian nuclear test</td>
<td>Gun</td>
<td>2008</td>
<td>Categorical risk estimates</td>
<td>+/- (ns)</td>
</tr>
<tr>
<td>French biology researchers</td>
<td>Guseva</td>
<td>2008</td>
<td>Categorical risk estimates</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Finnish reindeer herders</td>
<td>Kurtttio</td>
<td>2010</td>
<td>Categorical risk estimates</td>
<td>+ (s)</td>
</tr>
<tr>
<td>Childhood X-rays</td>
<td>Hammer</td>
<td>2009</td>
<td>Categorical risk estimates</td>
<td>+/- (ns)</td>
</tr>
<tr>
<td>French background</td>
<td>Demourey</td>
<td>2017</td>
<td>Risk for dose rate not cumulative dose</td>
<td>+/- (ns)</td>
</tr>
<tr>
<td>German background</td>
<td>Spix</td>
<td>2017</td>
<td>Risk for dose rate not cumulative dose</td>
<td>+ (ns)</td>
</tr>
</tbody>
</table>

s – statistically significant (p<0.05)
ns – not statistically significant (p≥0.05)
Summary Study Findings

Solid cancers: 16 of 22 studies positive ERR

Leukemia: 17 of 20 studies positive ERR

Ineligible (1 criterion): 10 of 14 studies positive
Bias Assessment Framework

Assess whether there is potential bias from each of the following sources.
- Dose error?
- Confounding?
- Selection bias?
- Outcome ascertainment?

Assess the likely direction of the bias from each source.
- Towards null?
- Away from null?*
- Uncertain?*

If possible, estimate the magnitude of the bias.
- Is bias large enough to explain the result (i.e., bias correction would move ERR/Gy to 0)?

Berrington et al (JNCI Monograph 2020)
Distinctiveness of Bias Assessment Approach

Study Quality?

- No adjustment for smoking
- Low quality dosimetry

Bias?

- Direction & strength of confounding?
- Impact of dose error on risk coefficient?
Our priority is to identify +ve studies with potential bias away from null.
Potential Biases…Common misconceptions

No unexposed comparison group

- Exposed vs unexposed more likely to be biased (e.g., confounding, selection bias) than a dose-response in exposed subjects

Retrospective cohort study

- Equally valid as a prospective study if using passive data collection (no recall bias)
Bias impact assessment

Assess whether there is potential bias from each of the following sources.

- Dose error?
- Confounding?
- Selection bias?
- Outcome ascertainment?
Bias impact assessment: radiation dose error

Dosimetry quality assessed for each study, emphasizing potential to lead to spurious dose-response findings

18/24 studies had minimal dosimetry error, which would not be expected to cause substantial bias

- Bias toward null association from non-differential dose error likely for most studies
- 3 case-control studies potentially biased away from null

Daniels et al (JNCI Monograph 2020)
Bias impact assessment: confounding & selection bias

For each study, assessed methods used to control for confounding and selection bias in design & analysis

• Identified confounders of concern for environmental, medical, and occupational exposure studies

Evaluated direct and indirect evidence demonstrating likely impact of confounding

Where no data were available, used theoretical worst-case assessment of confounding impact
Confounders of concern by exposure type

Environmental
- Lifestyle-related factors

Medical
- Confounding by indication (children)
- Lifestyle-related factors (adults)

Occupational
- Lifestyle-related factors
- Other occupational carcinogens
- Healthy worker effect & healthy worker survivor bias (HWSB)

Schubauer-Berigan et al (JNCI Monograph 2020)
Direct & indirect evidence of confounding

**Environmental**
- Lifestyle-related factors
  - Most studies controlled for age, sex, birth cohort
  - Most studies controlled for lifestyle correlates [smoking, education, or socioeconomic status (SES)]
  - Some studies adjusted for region of residence and natural background radiation

**Medical**
- Lifestyle-related factors
  - All studies adjusted for age, sex, calendar year
  - Confounding by indication
  - Most studies excluded children with predisposing conditions [e.g., cancer susceptibility syndromes (CSS)]

**Occupational**
- Lifestyle-related factors & other occupational carcinogens
  - Most studies adjusted for age, sex, birth cohort & SES
  - Healthy worker effect & HWSB
  - Most studies adjusted for employment duration
Direct & indirect evidence of confounding

Environmental

- Bias impact evaluation
  - Little evidence that potential confounders were actually related to radiation dose
  - Minimal impact of adjustment on dose-response estimates
- Main concern: potential selection bias in 1 study

Medical

- Bias impact evaluation
  - Most known risk factors for brain cancer & leukemia unlikely related to radiation dose
  - CSS generally very rare and were not strongly related to number of CT scans
  - Positive confounding unlikely by SES in studied countries
- Main concern: residual confounding by indication (lack of adjustment in 1 study; incomplete data for 1 study)

Occupational

- Bias impact evaluation
  - After adjusting for sex, age, birth cohort & SES, little indirect evidence of smoking confounding (e.g. COPD negatively or not associated with dose)
  - Benzene not likely a strong confounder; more potential for asbestos confounding
- Main concern: residual confounding by smoking, asbestos, & HWSB (no adjustment in 3 studies; partial in others)
Bias impact assessment: confounding & selection bias

Worst-case estimation of confounder disparity by dose group that would reduce point estimate to null

This evaluation was done for CSS in CT studies, and for tobacco and asbestos in nuclear worker studies

Example: low-dose radiation in International Nuclear Workers Study (INWORKS)
Bias impact assessment: confounding & selection bias

Assume no radiation-cancer association & calculate distribution of smoking required to explain the dose-response observed for all cancer mortality in INWORKS

- Overall smoking prevalence 50-70%, smoking-related all cancer RR=1.6: **calculated smoking prevalences in highest dose categories exceed 100%**: smoking differences cannot explain observed radiation risks
- Overall smoking prevalence=30%, a 3-fold difference in smoking prevalence across dose categories would be needed to explain observed radiation risks

Similar findings for asbestos exposure in occupational studies and CSS in medically exposed populations
Bias impact assessment: outcome assessment quality

Main concerns for all-cancers & leukemia excluding CLL

• Loss to follow-up (LTFU), over- or under-ascertainment, outcome misclassification, changing classifications over time, combining heterogeneous cancers that may differ in radiogenicity or latency

Most studies had acceptable outcome assessment quality, but with potential for non-differential misclassification

• Low LTFU; 4 studies had differential ascertainment by dose group; few studies had evidence of differential classification by dose group

Linet et al (JNCI Monograph 2020)
**X- and γ-radiation are known human carcinogens**

### Sites with “Sufficient” evidence of human carcinogenicity

- **Oral cavity & digestive**: salivary gland, oesophagus, stomach, colon
- **Respiratory**: lung
- **Urinary tract**: kidney, urinary bladder
- **Other solid cancers**: bone, basal cell of the skin, female breast, brain and CNS, thyroid
- **Lymphatic & hematopoietic**: leukaemia (excluding chronic lymphocytic)
- “In-utero exposure to X-radiation and γ-radiation causes cancer”

### Sites with “Limited” evidence of human carcinogenicity

- **Oral cavity & digestive**: rectum, liver, pancreas
- **Respiratory**: --
- **Urinary tract**: --
- **Other solid cancers**: ovary, prostate
- **Lymphatic & hematopoietic**: non-Hodgkin lymphoma, multiple myeloma

Bias impact assessment: analytical issues

- Adjusting for confounding is important, but over-adjustment should be avoided.
- Pooling of compatible studies can help overcome limited power.
- Estimates derive from Japanese Life Span Study (LSS).

Statistical power is low for most studies, if the ERR/Gy estimates from LSS are generalizable.

Gilbert et al (JNCI Monograph 2020)
Most studies had high-quality dosimetry, although varying levels of individualization.

Errors most likely to be non-differential:
- Can further reduce power
- Can lead to underestimation of risk per unit dose
- Unlikely to cause spurious dose-response association
Summary: Systematic Bias Assessment for Leukemia

Leukemia: 17 of 20 studies reported + ERRs

Sign test median ERR=0 rejected (p=0.001)

After exclusion of 5 + studies with potential for bias away from null (p=0.02)

<table>
<thead>
<tr>
<th>Study</th>
<th>ERR at 100 mGv</th>
<th>(95% CI)</th>
<th>Dose error</th>
<th>Confounding</th>
<th>Outcome misclassification</th>
<th>Could bias adjustment move ERR towards null?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chernobyl residents</td>
<td>3.2</td>
<td>(0.9 to 8.4)</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>Yes, Exclusion of subgroup with potential recall bias reduced risk to null.</td>
</tr>
<tr>
<td>Three Mile Island</td>
<td>19</td>
<td>(-3 to 45)</td>
<td>↓</td>
<td></td>
<td></td>
<td>No, Adjustment would move ERR away from null.</td>
</tr>
<tr>
<td>Chinese background</td>
<td>1.07</td>
<td>(&lt;0 to inf)</td>
<td></td>
<td>↑</td>
<td></td>
<td>Uncertain, Adjustment could move ERR towards or away from null.</td>
</tr>
<tr>
<td>GB background</td>
<td>12</td>
<td>(3.0 to 22.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swiss background</td>
<td>3.6</td>
<td>(-0.3 to 7.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finnish background</td>
<td>-3</td>
<td>(-11 to 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwanese residents</td>
<td>0.15</td>
<td>(0.03 to 0.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Pediatric CT</td>
<td>1.6</td>
<td>(-2.3 to 2.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Pediatric CT</td>
<td>3</td>
<td>(0.3 to 10.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korean workers</td>
<td>1.68</td>
<td>(-3.4 to 14.9)</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td>Uncertain, Adjustment could move ERR towards or away from null.</td>
</tr>
<tr>
<td>Chernobyl liquidators 1</td>
<td>0.5</td>
<td>(-0.38 to 5.70)</td>
<td>↑</td>
<td></td>
<td></td>
<td>Yes, Adjustment possibly moves ERR to null.</td>
</tr>
<tr>
<td>UKNRRW</td>
<td>0.18</td>
<td>(0.02 to 0.44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocketdyne workers</td>
<td>0.06</td>
<td>(-0.50 to 1.23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese workers</td>
<td>-0.19</td>
<td>(-0.61 to 0.86)</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Yes, Adjustment possibly moves ERR towards null.</td>
</tr>
<tr>
<td>Chernobyl liquidators 2</td>
<td>0.22</td>
<td>(0.005 to 0.76)</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>Yes, Adjustment possibly moves ERR towards null.</td>
</tr>
<tr>
<td>Canadian workers</td>
<td>1.44</td>
<td>(-0.15 to 14.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>German workers</td>
<td>0.4</td>
<td>(-0.3 to 1.1)</td>
<td></td>
<td></td>
<td></td>
<td>No, Adjustment would move ERR away from null.</td>
</tr>
<tr>
<td>US nuclear workers</td>
<td>0.17</td>
<td>(-0.02 to 0.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INWORKS</td>
<td>0.3</td>
<td>(0.12 to 0.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US atomic veterans</td>
<td>-0.5</td>
<td>(-14 to 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French workers</td>
<td>0.35</td>
<td>(&lt;0 to 1.6)</td>
<td></td>
<td></td>
<td></td>
<td>No, Adjustment would move ERR away from null.</td>
</tr>
</tbody>
</table>
Summary: Leukemia after adulthood exposure (ERR at 100mGy)

<table>
<thead>
<tr>
<th>Study</th>
<th>ERR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three Mile Island</td>
<td>19.000 (-3.000, 45.000)</td>
</tr>
<tr>
<td>Chinese background</td>
<td>1.068 (&lt;-0.000, Inf)</td>
</tr>
<tr>
<td>Taiwanese residents *</td>
<td>0.150 (0.030, 0.240)</td>
</tr>
<tr>
<td>Korean workers *</td>
<td>1.680 (-3.400, 14.900)</td>
</tr>
<tr>
<td>Chornobyl liquidators</td>
<td>0.500 (-0.380, 5.700)</td>
</tr>
<tr>
<td>UK NRRW</td>
<td>0.180 (-0.006, 0.500)</td>
</tr>
<tr>
<td>Rocketdyne workers</td>
<td>0.060 (-0.500, 1.230)</td>
</tr>
<tr>
<td>Japanese workers</td>
<td>-0.190 (-0.610, 0.860)</td>
</tr>
<tr>
<td>Ukrainian Chornobyl liquidators</td>
<td>0.221 (0.005, 0.761)</td>
</tr>
<tr>
<td>Canadian nuclear workers</td>
<td>1.440 (&lt;-0.150, 14.600)</td>
</tr>
<tr>
<td>German nuclear workers</td>
<td>0.400 (-0.300, 1.100)</td>
</tr>
<tr>
<td>US nuclear workers</td>
<td>0.170 (&lt;-0.020, 0.470)</td>
</tr>
<tr>
<td>US atomic veterans</td>
<td>-0.500 (-14.000, 4.000)</td>
</tr>
<tr>
<td>French nuclear workers*</td>
<td>0.350 (&lt;-0.000, 1.600)</td>
</tr>
</tbody>
</table>

**SUMMARY**

0.160 (0.070, 0.250) 

* 90% confidence interval

Consistent with LSS ERR/100mGy 0.08 (0.003-0.19)
Summary: Solid cancers after adulthood exposure

Solid cancers: 16 of 22 studies reported + ERRs

Sign test median ERR=0 rejected (p=0.03)

After exclusion of 4 + studies with potential for bias away from null (p=0.12)

Consistent with LSS ERR/100mGy 0.027 (males)
### Table 3. Meta-analysis of excess relative risks (ERR) at 100 mGy for all solid cancers and leukemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>ERR at 100 mGy (95% CI)</th>
<th>P</th>
<th>Cochran Q (P)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult solid cancer</td>
<td>14*</td>
<td>0.055 (−0.0027, 0.112)</td>
<td>.03</td>
<td>37.25 (&lt;.001)</td>
<td>0.65</td>
</tr>
<tr>
<td>Adult solid cancer excluding the Canadian</td>
<td>13*</td>
<td>0.029 (0.011, 0.047)</td>
<td>&lt;.001</td>
<td>9.89 (.63)</td>
<td>NA</td>
</tr>
<tr>
<td>cardiovascular imaging study due to heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult leukemia</td>
<td>14†</td>
<td>0.160 (0.070 to 0.250)</td>
<td>&lt;.001</td>
<td>4.12 (.99)</td>
<td>NA</td>
</tr>
<tr>
<td>Childhood leukemia</td>
<td>6</td>
<td>2.840 (0.370 to 5.320)</td>
<td>.01</td>
<td>6.40 (.27)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Excluding INWORKS and site-specific results from US Radiologic Technologists.
†Excluding INWORKS.
### Bradford Hill Criteria for Causality

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Has it been repeatedly observed by different persons, in different places &amp; time?</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Is there a dose-response?</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Is there a biological mechanism?</td>
</tr>
<tr>
<td>Strength</td>
<td>Strength of the association – although we must not be too ready to dismiss small risks.</td>
</tr>
</tbody>
</table>
Conclusions: systematic review of low-dose radiation epidemiology studies since BEIR VII

Most studies had low potential for bias that would cause spurious positive dose-response

- Non-differential dose error of relatively low magnitude
- Healthy worker survivor bias in occupational studies
- Non-differential outcome misclassification

Results of meta-analyses indicate risk per unit dose that is generally consistent with BEIR VII models

- Leukemia model results suggest that LSS models may underestimate low-dose effects in non-Japanese populations
Implications for dose and dose-rate assumptions

BEIR VII Bayesian analysis of DDREF, 2006

FIGURE 10-3 Results of a Bayesian statistical analysis of dose-response curvature and associated LSS DDREF values. The
Recommendations for Future Work

Quantification of Risk at Low-Doses
- Pooling projects to improve risk estimates
- Eg EPICT, INWORKs

Routine Bias Assessments
- In the original study manuscripts (preferably)
- As part of systematic reviews
Questions?