Sources of Data of Stochastic Effects of Radiation

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Biological Effects of Ionizing Radiation (BEIR)

2007

National Academy of Science – National Research Council
Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies
Sources of Data of Stochastic Effects of Radiation

Environmental Radiation Studies

Populations living near nuclear facilities
“..no increased risk...with radiation exposure”

Populations exposed to atomic bomb testing
“..some studies (4 out of 10) show some effect”

Chernobyl
High incidence of thyroid cancer
“..no evidence of an increase in any solid cancer type to date”

Natural background (China / India)
“..did not find higher disease rates in geographical areas with high background levels..”
Cancer Mortality in Moderate/High Background Radiation Area of Yangjiang, China, 1979-1995

- Background radiation
  6.4 mSv / year

- 20-year study in 125,079 subjects

- Risk estimate was negative
  i.e. radioprotective effect

- Conclusion: lower mortality,
  but not statistically significant

(Tao et al, Zhonghua Yi Xue Za Zhi, 1999; 79: 487-492)
Most radioactive place in the world - Ramsar, Iran (due to Radium-226)
Background radiation = 100 – 260 mSv / year

No epidemiological evidence of adverse affects
Lymphocytes from residents demonstrate fewer induced chromosome aberrations
States with significantly higher doses (e.g. Colorado), have lower cancer rates than States with much lower average doses like Georgia, and vice versa. (Frigerio and Stowe, 1976)
Sources of data

• Environmental Radiation Studies
• Occupational Radiation Studies
• Medical Radiation Studies
• Atomic bomb survivor Studies
Occupational Radiation Studies on Workers in the Nuclear Power Industry

U.S. – 9 studies
U.K. – 6 studies
Canada – 1 study
France – 1 study

Six large combined cohort studies
Combined study population > 500,000 subjects
with 30-40 years of follow-up

Cumulative dose levels: 30-60 mSv
Occupational Radiation Studies on Workers in the Nuclear Power Industry

“....in most cases, rates for all causes and all cancer mortality in the workers were substantially lower than the reference populations.”

Findings explained as “healthy worker effect”

(U.S. Academy of Science, BEIR VII, 2007)
Participants 407,391 workers individually monitored for external radiation with a total follow-up of 5.2 million person years.

“risk estimate for Canada is the largest…. Only when we excluded Canada was the excess relative risk no longer significantly different from zero (0.58, −0.22 to 1.55).”

“….our estimate of risk of leukemia is not significantly different from zero…”
Conclusions and Path Forward

- The CNSC’s reanalysis confirms that there is no increased cancer risk among any Canadian nuclear power plant workers for any time period or for AECL NEWs first employed since 1965.
- While the data suggests an increased solid cancer mortality risk for AECL NEWs first employed before 1965 (1956-1964), a comparison using the Canadian Mortality Database shows lower rates of all causes of death and cancer mortality for this group than for the general Canadian population.
Breast Cancer Mortality

Study of 67,979 women who worked with radiation in Nuclear Weapons facilities before 1980 (relative to unmonitored women in same facilities)

Expected mortality = 18,106 deaths / Observed mortality = 13,671 deaths

Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies
Medical Radiation Studies

Focus on therapeutic studies

...most of the information comes from studies of populations with medium to high doses

Lung Cancer – 9 studies, 40,000 subjects

Breast cancer – 11 studies, 20,000 subjects
Breast Cancer Risk after Radiotherapy for skin hemangioma in infancy (<18 months of age)

Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years

Lundell et al, Radiation Research 1999; 151: 626-632
Breast Cancer Risk after Radiotherapy in Infancy

Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years

Lundell et al, Radiation Research 1999; 151: 626-632
Mortality from Breast Cancer after Irradiation during Fluoroscopic Examinations in Patients being treated for Tuberculosis

31,710 women treated between 1930 - 1952
40-year follow-up
Age range 10-40 years

"Risk was statistically significant for all those who received more than 100 mSv of radiation"

Mortality from Breast Cancer after Irradiation during Fluoroscopic Examinations in Patients being treated for Tuberculosis

Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies
Atomic Bomb Survivor Studies

- 120,000 survivors
- Monitored over 60 years
- Dose range
  - 37,000 0-5 mSv
  - 32,000 5-100 mSv
  - 17,000 100 mSv – 2000 mSv
Sources of data used in BEIR VII
Atomic bomb survivor Studies

Data from Table 4, Preston et al, 2007

# solid cancers adjusted to per 100,000 people

(Radiation Effects Research Foundation)
Sources of data used in BEIR VII
Atomic bomb survivor Studies

Data from Table 4, Preston et al, 2007

# solid cancers adjusted to per 100,000 people

(Radiation Effects Research Foundation)
Sources of data used in BEIR VII
Atomic bomb survivor Studies

Data from Table 4, Preston et al, 2007

# solid cancers
adjusted to per 100,000 people

“Based on fitting with lower threshold, best estimate of threshold was 40 mGy with upper bound of 85 mGy (90% CI). However model not significantly better than LNT”

Preston et al, Rad Res 2007;168: 1-64. (Radiation Effects Research Foundation)
BRCA1/2 Gene Mutation and Radiation
Are Mammograms safe for these patients?

~50% of studies indicate Yes

MSK Cancer Center – 162 patients
Goldfrank D et al. CEBP

Canadian Study – 1600 patients

~50% of studies indicate No

Combined U.K., France & Netherlands Study – 1993 patients

Polish National Breast Cancer registry – 138 patients
Sample size required to detect a significant change in cancer mortality, assuming lifetime follow-up

Dose range of relevance for most medical imaging procedures

National Research Council (1995)
*Radiation Dose Reconstruction for Epidemiologic Uses*
Thank You
Risk Data and Estimates of Cancer Incidence

Michael K O’Connor, Ph.D.
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Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007

Amy Berrington de González, DPhil; Mahadevappa Mahesh, MS, PhD; Kwang-Pyo Kim, PhD; Mythreyi Bhargavan, PhD; Rebecca Lewis, MPH; Fred Mettler, MD; Charles Land, PhD

Estimated that 29,000 future cancers could be related to CT scans performed in the U.S. in 2007 and would translate into about 14,500 cancer deaths.

Arch Intern Med. 2009;169(22):2078-2086
Biological Effects of Ionizing Radiation (BEIR)

Health Risks from Exposure to Low Levels of Ionizing Radiation
BEIR VII Phase 2

National Academy of Science – National Research Council
TABLE 12D-1 Lifetime Attributable Risk of Cancer Incidence$^a$

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Age at Exposure (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>76</td>
</tr>
<tr>
<td>Colon</td>
<td>336</td>
</tr>
<tr>
<td>Liver</td>
<td>61</td>
</tr>
<tr>
<td>Lung</td>
<td>314</td>
</tr>
<tr>
<td>Prostate</td>
<td>93</td>
</tr>
<tr>
<td>Bladder</td>
<td>209</td>
</tr>
<tr>
<td>Other</td>
<td>1123</td>
</tr>
<tr>
<td>Thyroid</td>
<td>115</td>
</tr>
<tr>
<td>All solid</td>
<td>2326</td>
</tr>
<tr>
<td>Leukemia</td>
<td>237</td>
</tr>
<tr>
<td>All cancers</td>
<td>2563</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>101</td>
</tr>
<tr>
<td>Colon</td>
<td>220</td>
</tr>
<tr>
<td>Liver</td>
<td>28</td>
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<tr>
<td>Lung</td>
<td>733</td>
</tr>
<tr>
<td>Breast</td>
<td>1171</td>
</tr>
<tr>
<td>Uterus</td>
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<tr>
<td>Ovary</td>
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<td>Bladder</td>
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<tr>
<td>Other</td>
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<tr>
<td>Thyroid</td>
<td>634</td>
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<tr>
<td>All solid</td>
<td>4592</td>
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<tr>
<td>Leukemia</td>
<td>185</td>
</tr>
<tr>
<td>All cancers</td>
<td>4777</td>
</tr>
</tbody>
</table>

NOTE: Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy.
Sources of data

• Environmental Radiation Studies
• Occupational Radiation Studies
  • Medical Radiation Studies
• Atomic bomb survivor Studies
Estimate of Cancer Incidence based on

Theory:
Linear No Threshold (LNT) Hypothesis

Source of Data:
Based almost exclusively on Atomic Bomb Survivors Study

Risk models:
Excess Relative Risk (ERR)
Excess Absolute Risk (EAR)
Lifetime Attributable Risk (LAR)

Parameters:
Dose & Dose Rate Effectiveness Factor (DDREF)
Relative Biological Effectiveness (RBE)
Latency period
Risk Models used in LNT

Excess Relative Risk (ERR) model

The ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0.

(This is a useful model if the population under investigation is similar to the population on which the model was based.)

Excess Absolute Risk (EAR) model

The EAR is the rate of disease in an exposed population minus the rate of disease in an unexposed population.

(This model is more suited if there are significant differences (ethnicity, diet, etc) between the population under investigation and that on which the model was based.)
Risk Models used in LNT

**Lifetime Attributable Risk (LAR)**

*Attributable risk* is the difference in rate of a condition between the exposed population and an unexposed population.

The LAR is an estimate of the probability of a premature cancer from radiation over the life of the subject.
Risk Models used in LNT

Mrs Smith receives 1 Sv radiation to the breast at age 40

Risk of breast cancer calculated using ERR

At age 45 \[ \text{Risk (age 45)} = \beta \ast (45/60)^{-2} \]
At age 46 \[ \text{Risk (age 46)} = \beta \ast (46/60)^{-2} \]

Lifetime risk \[ \text{LAR}_{\text{ERR}} = \sum_{45}^{80} \text{Yearly risk estimates} \]
Modifying Parameters

• Dose & Dose Rate Effectiveness Factor (DDREF)
  • Range of values 1.1 – 2.5 (possible range 1-40)

• Relative Biological Effectiveness (RBE)
  • Range of values 1 - 4

• Latency period
  • Range 2 – 10 years

• Ethnicity, Environment (diet, lifestyle)
  • Convert cancer risk in Japanese subject in 1940’s to American subject in 2011!
Calculation of ERR - Medical Radiation Studies
Cancer Incidence from radiation exposure to the lungs
9 studies, >40,000 subjects

ERR
Excess risk relative to background risk
Calculation of ERR - Medical Radiation Studies
Cancer Incidence from radiation exposure to the lungs
9 studies, >40,000 subjects

ERR
Excess risk relative to background risk
Same Data – 2 different Risk Models

Comparison of LAR using ERR and EAR

- Breast
- Stomach
- Prostate
Same Data – 2 different Risk Models

Comparison of LAR using ERR and EAR

$R^2 = 0.43$
Risk Models used in LNT

Excess Relative Risk (ERR) vs. Excess Absolute Risk (EAR)

Which model is correct?

Final Risk model = $x \cdot \text{ERR} + (1-x) \cdot \text{EAR}$

where $x$ is determined by committee!
Risk Models

Lifetime Attributable Risk (LAR)

- Uses a combination of ERR and EAR
- Uses different combinations for different organs
- Includes additional assumptions about “modifying factors”
- Risk models then applied to cancer rates for U.S. population

- Cancer incidence from ionizing radiation is based on this parameter LAR!
...range of plausible values for LAR is labeled a “subjective confidence interval” to emphasize its dependence on opinions in addition to direct numerical observation (BEIR VII, page 278)
Lifetime Attributable Risk (LAR) based on LNT Hypothesis

- “Because of the various sources of uncertainty it is important to regard specific estimates of LAR with a healthy skepticism, placing more faith in a range of possible values” (BEIR VII Report, p278)
BEIR VII:

What it does say:

• All estimates are based on multiple models and assumptions

• Regard specific estimates with a healthy skepticism

• Confidence intervals are “subjective” and partly based on opinion

Unfortunately many studies quote cancer estimates from BEIR VII as if they were a proven scientific fact !!!
Future Estimates of Radiation Risk

• LNT based on “single-cell biophysical hit” model and only considers half of the problem!

• Radiation damage appears to increase linearly with dose
• Radiation repair is non-linear and is not considered in the LNT model

• Future models of risk are likely to be based on radiobiology in areas such as DNA repair, bystander effects, adaptive response mechanisms, epigenetics, systems biology, etc.