An epidemiologic view of low dose ionizing radiation and cancer: Putting risk into perspective

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“And it was so typically brilliant of you to have invited an epidemiologist.”
Questions

• What do we think we know about radiation-related cancer risk in humans?
• What are some basic principles in studying risk?
  – Relative and absolute risk (in simple terms)
  – Example from medical radiation studies (CT scans)
  – Learn about risk from different sources of exposure
• Why can’t we directly measure cancer (or any) risk in humans at low radiation doses? Say, under 100 mGy?
  – Power (detecting “signal” above the background cancer rates)
  – Confounders (and uncertain measurement of confounders)
  – Uncertain radiation organ absorbed dose estimates
• How else to assess low dose risk?
  – Predictive human models of risk from “higher” to “lower” doses
  – Use intermediate endpoints, such as chromosome aberrations
• What do recent air crew studies show?
• Summary?
What we think we “know”

• Organs and tissues vary in their radiation sensitivity
  – Sensitive: Breast, brain, thyroid, bladder, ovary
  – “Resistant”: Small intestine, prostate

• Radiation-related cancer risks decrease as age at exposures increases
  – Many studies have shown this

• Increased cancer risk persists indefinitely after radiation exposure
  – A-bomb survivors, childhood cancer survivors

• Radiation-related cancer risk is likely linear at low doses
  – Roughly defined as <100 mSv; linearity is highly controversial

• Some factors can markedly change the radiation-related cancer risk
Fitted breast cancer risk by radiation dose to the breast and ovary.
What are some basic principles in studying health risks in humans?
Methods to assess risk

- Case reports or series
  Early etiologic clues

- Analytic studies (cohort or case-control)
  Quantitative estimates of overall risk
  Dose response and excess risks (ERR/Gy)
  Collect information on other factors
    Assess interaction (age at exposure, gender, smoking)
    Control for confounders (age, gender, sun exposure)
Methods to assess risk

- Case reports or series
  Early etiologic clues

- Analytic studies (cohort or case-control)
  Quantitative estimates of overall risk
  Dose response and excess risks (ERR/Gy)
  Collect information on other factors
    Assess interaction (age at exposure, gender, smoking)
    Control for confounders (age, gender, sun exposure)

**A confounding factor must be related to the outcome and the exposure of interest.**
Measures of risk (1)

**Relative Risk (multiplicative)**
- Rates of disease in exposed divided by rates of disease in unexposed (cohort study, Rate Ratio)
- Odds of exposure in cases relative to the odds of exposure in controls (case-control, Odds Ratio)

**Absolute Risk (additive)**
- Number of excess cases of disease expected due to the exposure, expressed per unit of time
- Public health, risk/benefit, policy decisions
Measures of risk (2)

EXAMPLE:
Relative Risk and Absolute Risk

- Radiation exposure from CT scans in childhood and subsequent risk of leukemia and brain tumors: a retrospective cohort study
  - Pearce et al, Lancet 2012
  - ~178,000 under age 22 at time of CT scan
  - Followed over 1985-2008
  - England, Scotland and Wales
    - Nat’l Health Service records and GB cancer registry
# Diagnostic Imaging - Effective & Organ Doses

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X-ray (mSv)</th>
<th>CT scan (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td>Chest</td>
<td>0.1</td>
<td>7</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.7</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT scan</th>
<th>Brain (mGy)</th>
<th>Lung (mGy)</th>
<th>Stomach (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chest</td>
<td>0</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

Mettler F et al (Radiology 2009)  
Slide courtesy of Dr. Amy Berrington de Gonzalez
Comparing effective doses

- **Airline pilots and flight crews**
  - Flying 600-1000 hours per year
  - Annual effective dose 0.2-6 mSv
    » Friedberg and Copeland, 2003
  - Working lifetime cumulative effective dose
    - On average, 10-30 mSv
    - Rarely over 80 mSv
      » Hammer et al, Rad Prot Dosim, 2009

- (All comparison caveats due to assumptions in effective dose, dose rate, radiation quality, etc)
Cancer Risk from CT scans in childhood - 1

Relative risk of leukemia and brain tumors in relation to estimated radiation doses to the red bone marrow and brain from CT scans

(A) Leukemia ERR/mGy 0.036
   (95% CI 0.005-0.120, p=0.01)

(A) Brain tumors, ERR/mGy 0.023
   (95% CI 0.01-0.049, p < 0.0001)

Dotted line is the fitted linear dose response model (excess relative risk per mGy). Bars show 95% CIs.
Cancer Risk from CT scans in childhood - 2

Relative risk of leukemia and brain tumors in relation to estimated radiation doses to the red bone marrow and brain from CT scans

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Note: Relative risks are about 3-fold higher for doses above 30 and 50 mGy relative to under 5 mGy for leukemia and brain tumors, respectively.
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Note: Relative risks are about 3-fold higher for doses above 30 and 50 mGy relative to under 5 mGy for leukemia and brain tumors, respectively.

The cumulative absolute risks are low: one excess case of leukemia and one of brain cancer expected in the 10 years following 10,000 head CT scans performed before age 20

Pearce et al, Lancet, June 2012
Absolute risks from CT scans are small because these cancers are relatively rare.

Benefits of CT scans can outweigh the small cumulative absolute risks.

Arguably one excess cancer is not zero; CT scan use should be clinically indicated, other tests considered, and doses kept as low as possible.

Policy and societal questions: Is the risk “worth it” for the medical benefit?
Evaluation of radiation-related health risks—is it “real”

- Is the risk in the studied group greater than expected in the general population?
- Does the risk increase with increasing radiation dose?
- Is risk related to a radiation-associated condition (e.g. breast cancer, cataracts)
- Is the increased risk consistent across studies, study designs, and populations?
- Are there biases that could explain the apparent association of health risk with radiation exposure?
Radiation studies in humans

**Military**
- A-bomb
- Nuclear testing
  - Atomic Vets

**Environmental**
- Nuclear discharges & accidents
- Radon
- Cosmic

**Medical**
- Diagnostic
- Therapeutic

**Occupational**
- Radium dial painters
- Radiologists & radiologic tech’s
- Uranium miners
- Nuclear facilities
Dose Range Across Studies

- Low Chronic
- Low Protracted
- Low to Moderate Acute
- Low to High Local Fractionated
- Environmental
- Nuclear Workers
- A-bomb
- Diagnostic
- Therapeutic
RERF Life Span Study (LSS) of Atomic Bomb Survivors

“Gold Standard” of radiation epidemiology

Radiation Effects Research Foundation (RERF)
Hiroshima/Nagasaki, Japan
**Atomic Bomb Survivors**

**Dose distribution, 1950-1997**

<table>
<thead>
<tr>
<th>Dose (Sv)</th>
<th>No. subjects</th>
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<tbody>
<tr>
<td>&lt;0.1</td>
<td>69,108</td>
</tr>
<tr>
<td>0.1-1</td>
<td>15,363</td>
</tr>
<tr>
<td>1-2</td>
<td>1,613</td>
</tr>
<tr>
<td>2+</td>
<td>488</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>86,572</strong></td>
</tr>
</tbody>
</table>

80% under 100 mSv

Many incorrectly believe that the A-bomb study is a “high dose” study but the distribution by dose shows that most people were exposed to low radiation doses.

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### Solid cancer deaths, 1950-1997

<table>
<thead>
<tr>
<th>Dose (Sv)</th>
<th>No. subjects</th>
<th>All Deaths</th>
<th>Expected Background</th>
<th>Fitted Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>69,108</td>
<td>7,110</td>
<td>7,065</td>
<td>44</td>
</tr>
<tr>
<td>0.1-1</td>
<td>15,363</td>
<td>1,869</td>
<td>1,635</td>
<td>245</td>
</tr>
<tr>
<td>1-2</td>
<td>1,613</td>
<td>274</td>
<td>157</td>
<td>103</td>
</tr>
<tr>
<td>2+</td>
<td>488</td>
<td>82</td>
<td>38</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>86,572</td>
<td>9,335</td>
<td>8,895</td>
<td>440</td>
</tr>
</tbody>
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Breast cancer incidence (1059 cases) 1950-1990

Dose-specific relative risk, with 90% confidence limits
Case-weighted breast tissue dose, in Sv

Radiation-related breast cancer risk by age at exposure

Excess relative risk at 1 Sv (90% confidence limits)

Age at the time of the bombings

Solid Cancer Incidence Dose Response

- No evidence of non-linearity in dose response
- Statistically significant trend in 0–0.15 Gy range
- Low dose range trend consistent with full dose range trend

$ERR/\text{Gy} = 0.46 \ [90\% \text{CI}=0.40-0.54]$  

Sex-averaged at age 70 for exposure at age 30

Why can’t we measure risk directly at really low doses? Say, below 10 mSv?
Lifetime risk for incidence of solid cancer and leukemia in US

If 100 people exposed to 0.1 Gy (100 mGy), expect
- 1 cancer from this exposure
- 42 cancers from other causes
Cancer Risks from Low-dose Radiation Exposures

Difficult to Quantify Risks from Low Doses Directly
• Infeasibly large sample size & lifetime follow-up

Cancer risk from 2 Mammograms at age 35

60 million women & 20 years follow-up 50% power (Land, 1981)
Cancer Risks from Low-dose Radiation Exposures

Difficult to Quantify Risks from Low Doses Directly
• Impractically large sample size & lifetime follow-up

Estimate indirectly using existing data
• Japanese atomic bomb survivors and others
• Provides a more timely assessment of potential risk
• Predictive models contain several assumptions
  – Linear no threshold, risk transfer from one population to another, dose rate, age at exposure, radiation type, etc

2 Mammograms at age 35
60 million women & 20 years follow-up 50% power (Land, 1981)
Other endpoints might be used as a surrogate for risk at low doses, such as chromosome translocations.

Chromosome rearrangements are a hallmark of malignant tumors.
Human cell with an apparently reciprocal chromosome translocation (arrows) detected by fluorescent *in situ* hybridization (FISH) using whole chromosome paints. Chromosome pairs 1, 2, and 4 are painted red, and 3, 5, and 6 are painted green.
Chromosome translocations in airline pilots

- Translocations increased with years of flying
  - 83 pilots (mean age 47)
  - Average flight years was 18 (range 1-37 years)
  - Average 5 years with international flights
  - Adjusted for age, diagnostic medical radiation exposure, and military flying

Yong et al, Occupational Environmental Medicine, 2009
What do some of the recent air crew studies of cancer risk show?
Studies in airline pilots, flight crew, air traffic control officers

– Overwhelming healthy worker effect
  • Reduced risk of all cancers, overall mortality, and markedly lower cardiovascular disease

– Specific cancer sites elevated
  • Brain (pilots), breast (flight attendants), melanoma (all groups)

– Real risk relationships unlikely
  • No dose response for brain tumors
  • Melanoma related to host factors
    – Skin, hair color (dos Santos Silva et al, Int J Cancer, 2013)
  • Reproductive factors explain some breast cancer risk (but not all); risks inconsistent across all studies
Studies in airline pilots, flight crew, air traffic control officers

• Review of all studies since 1990 (n=65)
  – Mortality from cancer and other causes
  – Cancer incidence
    • Hammer et al, Radiat Prot Dosim, 2009

• General summary
  • Zeeb et al, J Radiol Prot, 2012

• Focus on preventable deaths?
  • 3-fold Increased mortality from alcoholism, drowning (alcohol related), intentional self-harm
    ----Pinkerton et al, Pan Am flight attendant cohort, 2012
Summary

• Ionizing radiation is a known carcinogen
• Cancer risk decreases as dose decreases
• Excess absolute risk at low doses is minimal, but it is not zero
  – Exact risk, based on human studies, will never be known
  – Model projections could estimate absolute risk with uncertainties for airline crews, frequent fliers
• Airline pilots and crew unique occupational group
• Risk vs Benefit:
  – Int’l Air Transport Association estimated 1.8 billion passengers flew in 2010; 40% international flights
• High dose space weather events likely call for prudent avoidance to reduce unnecessary exposure
The End

“And it was so typically brilliant of you to have invited an epidemiologist.”

Hopefully it was true!!!! Thanks for the invitation!
Translocation rate by occupational radiation absorbed dose to RBM among US Radiologic Technologists

Excess chromosome aberrations with respect to the background rate, with 95% CI (adjusted for overdispersion), in the combined biodosimetry effort data for quintiles of occupational dose, here shown for under 50 mGy. Background rate is adjusted for age, sex, and study group.

Slope for occupational red bone marrow dose (continuous): $p = 0.02$

Slope for personal diagnostic medical exposures (continuous, $P < 0.0001$) was the same as for occupational dose

Little et al, in press, Radiation Research
Chromosome translocations associated with diagnostic medical radiation in radiologic technologists, airline pilots, and faculty

Translocation frequency as a function of the cumulative diagnostic red bone marrow radiation dose score (n = 362). The trend line with 95% upper and lower confidence bounds is from multivariable Poisson regression analysis [0.04 excess translocations/100 CE/10 bone marrow dose score units (95% CI: 0.02, 0.06; P < 0.001); R^2 = 0.7]. Dose score approximates mGy.

Diagnostic X-ray examinations and increased chromosome translocations: evidence from three studies
Bhatti et al, Radiat Environ Biophysics 2010
Solid Cancer Risks by Gender

For person age 70 exposed at age 30

ERR Sex ratio
F:M 1.6

EAR Sex ratio
F:M 1.4

Sources of Ionizing Radiation

Radon 55%

Internal 11%
Cosmic 8%
Terrestrial 8%
Consumer Products 3%
Nuclear Medicine 4%
Medical X-rays 11%

Source: US Nuclear Regulatory Commission
http://www.nrc.gov/reading-rm/basic-ref/glossary/exposure.html
Increase in Medical Sources of Radiation Exposure in the U.S.

1980

- CT scans: 3 million
- Nuclear medicine: 6 million

Other

Natural background

- 3 mSv
- <0.1 mSv
- 0.5 mSv

NCRP report 160 (2009)

Slide courtesy of Dr. Amy Berrington de Gonzalez
Increase in Medical Sources of Radiation Exposure in the U.S.

1980
- CT scans: 3 million
- Nuclear medicine: 6 million
- Natural: 3 mSv
- Medical: 0.5 mSv
- Other: <0.1 mSv

2006
- CT scans: 70 million
- Nuclear medicine: 18 million
- Natural: 3.2 mSv
- Medical: <0.1 mSv

NCRP report 160 (2009)

Slide courtesy of Dr. Amy Berrington de Gonzalez
Population exposure to medical radiation sources has increased *six-fold* in the last two decades!

NCRP report 160 (2009)
## Comparing Radiation Doses

<table>
<thead>
<tr>
<th>Activity</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Average, all sources</td>
<td>3-6 mSv per year</td>
</tr>
<tr>
<td>Fallout</td>
<td>0.005 mSv per year</td>
</tr>
<tr>
<td>Cosmic rays on earth</td>
<td>0.26 mSv per year</td>
</tr>
<tr>
<td>Cosmic radiation to flight crew</td>
<td>0.2-5.0 mSv per yr</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>~0.1 mSv</td>
</tr>
<tr>
<td>Mammogram (breast)</td>
<td>~3 mSv [ \text{RBE?} ]</td>
</tr>
<tr>
<td>A-bomb (median whole body)</td>
<td>&lt;100 mSv</td>
</tr>
<tr>
<td>Cancer treatment (tumor)</td>
<td>10,000–70,000 mSv</td>
</tr>
</tbody>
</table>
Key analytic aspects

- Quantitative estimation of radiation exposure
  - Dosimetry
  - Formal understanding of uncertainty in dose
- Linear dose-response (few exceptions—leukemia)
  - $RR = 1 + \beta \times \text{dose}$
- $\beta =$ Excess Relative Risk (ERR) per unit dose
  - $\frac{\text{ERR}}{\text{Gy}} = RR - 1$
  - Usually per one Gy but depends
  - ERR significant if the 95% CI excludes zero
Life Span Study (LSS) Cohort

- Survivors within 2.5 km of the bombings (0.005-4Gy)
- Survivors within 2.5-10 km
- Not-in-city (NIC)

TOTAL PEOPLE 120,321

- Hiroshima and Nagasaki tumor registries (1958-98)
- 17,448 first primary tumors
- DS02 organ dose estimates

# LSS Cancer Incidence Cohort

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Person Years</th>
<th>Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in city</td>
<td>680,744</td>
<td>25,247</td>
<td>23.9</td>
</tr>
<tr>
<td>&lt; 0.005 in city</td>
<td>918,200</td>
<td>35,545</td>
<td>33.7</td>
</tr>
<tr>
<td>0.005 - 0.1</td>
<td>729,603</td>
<td>27,789</td>
<td>26.4</td>
</tr>
<tr>
<td>0.1 - 0.2</td>
<td>145,925</td>
<td>5,527</td>
<td>5.2</td>
</tr>
<tr>
<td>0.2 - 0.5</td>
<td>153,886</td>
<td>5,935</td>
<td>5.6</td>
</tr>
<tr>
<td>0.5 - 1</td>
<td>81,251</td>
<td>3,173</td>
<td>3.0</td>
</tr>
<tr>
<td>1-2</td>
<td>41,412</td>
<td>1,647</td>
<td>1.6</td>
</tr>
<tr>
<td>2+</td>
<td>13,711</td>
<td>564</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Solid Cancer Temporal Patterns

[Graph showing age at exposure (yr) vs. attained age with data points and lines for different age groups (0-9, 10-19, 20-39, 40+, 40+). The x-axis represents attained age ranging from 30 to 80 years, and the y-axis represents ERR per Gy and EAR per 10^4 PYGy.]

Site–Specific Cancer Risk Estimates

ERR at age 70 for exposure at age 30

Summary LSS

• Solid cancer incidence data
  – Linear dose-response with no threshold
  – Excess risk continues throughout life
  – Risks vary with age
  – Some variation by cancer site

• Leukemia
  – Linear quadratic dose-response
Strengths of LSS Cohort

• Large, healthy non-selected population
• All ages and both sexes
• Wide range of well characterized dose estimates
• Mortality follow-up virtually complete
• Complete cancer ascertainment in tumor registry catchment areas
• More than 50 years of follow-up
Limitations of LSS Cancer Incidence Data

• Inadequate solid cancer data from 1945-1958 and no leukemia data from 1945-1950
• Cancer patterns different in Japanese
  – Eg stomach and liver cancer common
  – Breast and prostate cancer less common
• Single acute exposure
CT Scans
70 Million CT scans U.S. 2007

- Abd/pelvis (24 million)
- Head (22 million)
- Chest (11 million)
- Spine (4 m)
- CTA chest (2.5 m)
- Other (6.5 m)

Slide courtesy of Dr. Amy Berrington de Gonzalez

Mettler F et al (Radiology 2008); IMV 2008
International Trends in Diagnostic Imaging

Per 1000 popn/yr

<table>
<thead>
<tr>
<th>Year</th>
<th>CT scans</th>
<th>Nuclear medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997-2007</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>1991-96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997-2007</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

United States
Well developed countries

Mettler F et al (Radiology 2009)
Cancer Risk from CT scans in childhood - 3

Study has been criticized because:

- Reason for scan not collected
  - Could be reverse causation
  - Indolent brain tumor causes an accident for which a CT scan is ordered
  - Risk for brain tumor appears spuriously elevated

- Underlying conditions such as Downs Syndrome are associated with more scans
  - Downs Syndrome children at higher risk for myelodysplasias
  - Risk for leukemia appears spuriously elevated when myelodysplasias included

- Brain tumor risk increased with age at exposure rather than decreased

Dr. Mark Pearce et al, Lancet, June 2012
Summary

• Ionizing radiation is a weak carcinogen

• Carcinogenicity shown beyond doubt

• Good exposure assessment required

• Shape of dose response well established for many different cancer sites

• Promising to study gene-environment interactions (e.g., DNA repair, apoptosis genes) and interaction with polygenes (multiple genes/variants combined)

• Late effects of low-dose radiation remain controversial --- statistical power