Radiation Carcinogenesis

Eric J. Hall, D.Phil., D.Sc., FACR, FRCR
Columbia University Medical Center, N.Y.

Marie Curie and Her Daughter Irene –
Thought to have Died of Leukemia
Knowledge of Radiation-Induced Cancer Comes from:

- A-bomb survivors
- Accidents
- Individuals medically exposed
  - Includes second cancer in RT patients

Radiation Carcinogenesis – The Human Experience

<table>
<thead>
<tr>
<th>Leukemia &amp; Solid Tumors</th>
<th>Japanese survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Patients irradiated for alkyllosing spondylitis</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Children irradiated for enlarged thymus</td>
</tr>
<tr>
<td></td>
<td>Children epilated for tinea capitis</td>
</tr>
<tr>
<td>Breast</td>
<td>Patients treated with x-rays for postpartum mastitis</td>
</tr>
<tr>
<td></td>
<td>Patients fluoroscoped repeatedly during management of tuberculosis</td>
</tr>
<tr>
<td>Lung</td>
<td>Uranium miners</td>
</tr>
<tr>
<td>Bone</td>
<td>Dial painters who ingested radium</td>
</tr>
<tr>
<td></td>
<td>Injections of radium for tuberculosis or ankylosing spondylitis</td>
</tr>
</tbody>
</table>
Leukemia follows an **absolute risk model**, i.e., a discrete dose-related “crop” of radiation-induced cancer over and above the spontaneous level.

Some cancers may follow a **relative risk model**, i.e., the natural incidence increased by a constant factor.

Since natural cancer incidence increases with age, this model would predict a large number of **excess cancers** late in life following irradiation.
### Latency

- **Leukemia** has the shortest latency of about **5 years**
- **Solid tumors** have a latency of **20 or more years**

### Favored Time-Related Relative Risk Model

Factors considered:

- Dose ($Dose^2$)
- Gender
- Age at exposure
- Time since exposure
Radiation Epidemiology

- To characterize and quantify the risk of cancer in populations exposed to radiation, alone or in combination with other agents.

Types of Epidemiologic Studies

- Cohort
- Case-Control
- Ecologic
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Excess Cancer Mortality
Lifetime Risk/100,000/0.1 Sv

<table>
<thead>
<tr>
<th>BEIR V (U.S. Population)</th>
<th>UNSCEAR 88 (Japanese Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Breast</td>
<td>--</td>
</tr>
<tr>
<td>Respiratory</td>
<td>190</td>
</tr>
<tr>
<td>Digestive system</td>
<td>170</td>
</tr>
<tr>
<td>Other solid</td>
<td>300</td>
</tr>
<tr>
<td>Leukemia</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>770</td>
</tr>
<tr>
<td>Total</td>
<td>770</td>
</tr>
</tbody>
</table>

Dose Rate Effectiveness Factor (DREF)

- The factor by which cancer risks should be **reduced** when radiation is delivered at **low doses** and **low dose-rates**, compared with a single high dose rate acute exposure.
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### DREF
- **NCRP** (1978) 2 to 10 (animal studies)
- **BEIR III** (1980) 2.25 ($\alpha/\beta$ ratio)
- **BEIR V** (1990) 2 to 10 (best estimate 4)
- **UNSCEAR** (1977) 2.5 (leukemia at high & low doses)
- **UNSCEAR** (1986) 2 to 10
- **BEIR VII** (2005) 1.5 (Cf Linear/Quadratic)

### Total Excess Fatal Cancer (ICRP) %/Sv

<table>
<thead>
<tr>
<th></th>
<th>High dose</th>
<th>Low dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High d/r</td>
<td>Low d/r</td>
</tr>
<tr>
<td>General population:</td>
<td><strong>10%</strong></td>
<td>5%</td>
</tr>
<tr>
<td>Working population:</td>
<td><strong>8%</strong></td>
<td>4%</td>
</tr>
</tbody>
</table>
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**Solid Cancers – A-Bomb Survivors**

![Graph showing excess relative risk against weighted dose (Sv).](image)

**Attributable Lifetime Risk**

![Graph showing attributable lifetime risk against age at time of exposure for different genders.](image)
Atomic Bomb Survivors Life Span Study (LSS)


Preston et al. submitted

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 leukemia data from 1945-1950
- Cancer data limited to Hiroshima and Nagasaki area residents
- Limited treatment data

Second Cancer Incidence Report

- 1958-1998
- 105,427 people
- ~50% alive in 1998
  ~85% of those <20 ATB
- First primary tumors
- DS02 organ dose estimates

Preston et al, submitted
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### LSS Incidence Cohort*

<table>
<thead>
<tr>
<th>Dose, Gy</th>
<th>Subjects</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.005</td>
<td>35,545</td>
<td>44.3</td>
</tr>
<tr>
<td>0.005 - 0.1</td>
<td>27,789</td>
<td>34.6</td>
</tr>
<tr>
<td>0.1 - 0.2</td>
<td>5,527</td>
<td>6.9</td>
</tr>
<tr>
<td>0.2 - 0.5</td>
<td>5,935</td>
<td>7.4</td>
</tr>
<tr>
<td>0.5 - 1</td>
<td>3,173</td>
<td>3.9</td>
</tr>
<tr>
<td>1 - 2</td>
<td>1,647</td>
<td>2.1</td>
</tr>
<tr>
<td>2+</td>
<td>564</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Excludes 25,247 NIC

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### Solid Cancer Incidence

**Dose Response**

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

**ERR/Gy = 0.46; 90% CI 0.40; 0.54**

Sex-averaged at age 70 for exposure at age 30
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Distribution of Solid Cancers

<table>
<thead>
<tr>
<th>Site</th>
<th>1958-1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17,448</td>
</tr>
<tr>
<td>Digestive system</td>
<td>10,052</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>2,001</td>
</tr>
<tr>
<td>Female genital</td>
<td>1,457</td>
</tr>
<tr>
<td>Breast</td>
<td>1,082</td>
</tr>
<tr>
<td>Urinary system</td>
<td>741</td>
</tr>
<tr>
<td>Thyroid</td>
<td>471</td>
</tr>
<tr>
<td>Skin</td>
<td>347</td>
</tr>
<tr>
<td>Male genital</td>
<td>420</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>277</td>
</tr>
<tr>
<td>Nervous system</td>
<td>281</td>
</tr>
</tbody>
</table>

Site–Specific Risk Estimates

For person age 70 exposed at age 30
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Mean Dose (rad)

ERR for Cancer Mortality (A-bomb Survivors 1950-97)

- Significant
- Not significant

2.5 5.0 7.5 10.0

0 1 2 3 4 5 6 7 8 9 10

 Lowest dose category in which a significant increase in cancer risk is seen in A-bomb survivors

- Cancer incidence: 5-100 mSv. Mean: 29 mSv
  (Pierce et al 2000)

- Cancer mortality: 5-125 mSv. Mean: 34 mSv
  (Preston et al. 2003)
**Summary**

- Strong evidence for linear dose-response with no threshold
  - Increased risk 0–100 mSv
- Women have significantly higher risk
- Excess risk continues throughout life
- ERR decreases with increasing age at exposure and attained age
- EAR increases with attained age

**Pooled Thyroid Cancer Studies**

**Cohort Studies**
- A-Bomb Survivors
- Thymus, Rochester
- Tinea Capitis, Israel
- Tonsils, Chicago
- Tonsils, Boston

**Case-Control Studies**
- Cervical Cancer, Intl
- Childhood Cancer, Intl

120,000 people
3,000,000 person years
700 thyroid cancers
Exposure age ≤15

*Ron et al, 1995*
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### Pooled Thyroid Cancer

**Dose Response by Age at Exposure**

![Graph showing dose response](image)

**ERR$_{Gy}$ = 7.7; EAR $10^4$ PYG$_{Gy}$ = 4.4**

*Ron et al, 1995*

### Pooled Thyroid Cancer

**Excess Relative Risk**

![Bar chart showing excess relative risk](image)

*Ron et al, 1995*
The Chernobyl Accident
Ukraine, 26 April 1986

- Worst accident in nuclear history
- 10 days of releases into the atmosphere under varying meteorological conditions
- Widespread and spotty fallout due to rain and changing wind directions

Chernobyl-Related Thyroid Cancer

- 40 million Ci of Iodine-131 released
- Worst radiation accident
- Large increases in childhood thyroid cancer in contaminated areas beginning about 4 years after the accident
- Initial reports questioned because of possible bias due to intensive screening
- Evidence of real excess now, but still cannot be quantified precisely
Thyroid Cancer Associated with $^{131}$I Exposure from Chernobyl, Belarus & 4 regions in Russia

- 276 cases, 1300 controls; <15 y at accident
- Majority had thyroid doses of 16-399 mGy
- Doses higher in Belarus than Russia
- At 1 Gy, risk 3-fold higher in iodine deficient area than elsewhere
- KI dietary supplement decreased risk by 1/3

Cardis et al, 2005

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**Thyroid Cancer Associated with $^{131}$I Exposure from Chernobyl, Belarus & 4 Regions in Russia**

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>OR Gy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose</td>
<td>5.5 (2.2-8.8)</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>5.2 (2.2-8.2)</td>
</tr>
<tr>
<td>All iodine isotopes</td>
<td>5.2 (2.2-8.3)</td>
</tr>
<tr>
<td>Adjusted all iodine isotopes*</td>
<td>5.9 (1.6-10.2)</td>
</tr>
</tbody>
</table>

*Adjusted for external and long-lived nuclides
Cardis et al, 2005
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Occupational Exposures

- Radiation workers can provide direct estimates of low-level exposure
- Medical workers are majority of radiation workers
  - Some early workers had substantial doses
- Nuclear workers carefully monitored
  - High exposure in FSU in early years
  - High exposure in special conditions

IARC 15 Country Study (Cardis et al. 2005)

- 600,000 nuclear workers
- Average cumulative dose = 19.4 mSv
- All cancers (except leukemia) ERR
  \[ = 0.97 (0.14 \text{ to } 1.97)/\text{Sv} \]
- Leukemia ERR = 1.93/Sv (NS)
## International Analysis

### 407,391 Nuclear Workers

<table>
<thead>
<tr>
<th>Deaths</th>
<th>ERR/Sv (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>0.97 (0.14, 1.97)</td>
</tr>
<tr>
<td>6,519</td>
<td>0.97 (0.14, 1.97)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.93 (&lt;0, 8.47)</td>
</tr>
<tr>
<td>196</td>
<td>1.93 (&lt;0, 8.47)</td>
</tr>
</tbody>
</table>

*Cardis et al, 2005*

## IARC 15 Country Study

### (Cardis et al. 2005)

- Canada
- Sweden
- UK - all
- USA - Hanford
- USA - NPP
- USA - ORNL
- All combined

*Cardis, E et al. BMJ 2005;331:77*
# Mortality in Radiologists

100 years of Observation on British Radiologists: Mortality from Cancer and Other Causes 1897-1997

A. Berrington, S.C. Darby, H.A. Weiss & R. Doll


## All Cancers British Radiologists

<table>
<thead>
<tr>
<th>Years</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1897-1920</td>
<td>1.75</td>
</tr>
<tr>
<td>1921-1935</td>
<td>1.24</td>
</tr>
<tr>
<td>1936-1954</td>
<td>1.12</td>
</tr>
<tr>
<td>1955-1979</td>
<td>0.71</td>
</tr>
<tr>
<td>all post 1920</td>
<td>1.04</td>
</tr>
</tbody>
</table>

SMR’s compared with other medical professionals.
### British Radiologists

All years post 1920

- SMR for cancer: 1.04 n.s.
- SMR non-cancer: 0.86 s.s.
- SMR all mortality: 0.91 s.s.

### Radiation: The Elixir of Life

- Cameron J.R.
  Radiation Increases the Longevity of British Radiologists
  *Br J Radiol* 75:637, 2002

- Cameron J.R.
  Longevity is the Most Appropriate Measure of Health Effects of Radiation
  *Radiology* 229:13, 2003
Mortality of US Radiologists (6,500) Compared with Other Specialists: 1900-69

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>RSNA</th>
<th>RSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td>1.22</td>
<td>1.31</td>
</tr>
<tr>
<td>Cancers</td>
<td>1.34</td>
<td>1.56</td>
</tr>
<tr>
<td>Diseases Nervous System</td>
<td>1.32</td>
<td>1.34</td>
</tr>
<tr>
<td>Diseases Circulatory System</td>
<td>1.20</td>
<td>1.29</td>
</tr>
<tr>
<td>External Causes</td>
<td>1.05</td>
<td>0.96</td>
</tr>
<tr>
<td>All Other</td>
<td>1.22</td>
<td>1.39</td>
</tr>
</tbody>
</table>

* ACP - American College of Physicians
† AAOO - Amer. Acad. Of Ophthalmology & Otolaryngology

The Bottom Line

- There was a clear excess of cancer in the early Radiologists before radiation protection standards were introduced. (1928)
- No excess cancer incidence observed in radiologists now (but the numbers are small).
- On the other hand, there is no evidence that radiologists live longer than other physicians - i.e., radiation is not good for you!
Use of Medical Radiation in the United States

- U.S. has high medical exam rates
- Temporal trends
  - 1980 to 1990
    - Diagnostic exams increased 20-25%
    - Radiation treatments increased 25-30%

UNSCEAR, 2000

Annual Diagnostic Exams in the United States, 1991-96

- 250,000,000 medical x-ray exams
- 8,202,000 nuclear medicine exams

UNSCEAR, 2000
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### Adjusted ORs and CIs for the Association of Child's Postnatal Diagnostic X-rays – and ALL by Gender

<table>
<thead>
<tr>
<th>X-rays (n)</th>
<th>Girls</th>
<th></th>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>275</td>
<td>1.00</td>
<td></td>
<td>295</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73</td>
<td>1.14 (0.66-1.96)</td>
<td></td>
<td>109</td>
<td>0.94 (0.56-1.55)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>68</td>
<td>2.26 (1.20-4.23)</td>
<td></td>
<td>133</td>
<td>1.39 (0.91-2.14)</td>
<td></td>
</tr>
</tbody>
</table>

*Claire Infante-Rivard, Géraldine Mathonnet, and Daniel Sinnett*

*Environmental Health Perspectives – Vol. 108, No. 6, June 2000*

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### Childhood Cancer and Irradiation *in Utero*

- Number of children with Leukemia or cancer before 10 years: 7649
- Number x-rayed in utero: 1141
- Number of matched controls: 7649
- Number of controls irradiated in utero: 774
- Number of films: 1 to 5
- Fetal doses per film: 0.46 to 0.2 rad (4.6 to 2 mGy)
- Relative cancer risk estimate assuming radiation to be the causative agent: 1.52
**Childhood Cancer from Fetal X-Rays**

- Low dose irradiation of the fetus in utero, particularly in last trimester, causes an increased risk of childhood cancer
- 40% increase in risk from an obstetric x-ray examination
- Radiation doses of ~10 mGy (1 rad) increases the risk
- Excess absolute risk is about 6% per Gy

- Doll & Wakeford 1997

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**Irradiation in Utero (Wakeford & Little, 2005)**

- Risk of childhood cancer from
  - ~10mSv is not zero – exact risk uncertain.
Second Cancers Following Radiotherapy

- New advances in cancer therapy have increased patient survival
- Growing concern about radiation-induced second cancers
- Accurate dosimetry

Radiotherapy Patients

- In most cases, difficult to assess risk of second cancers because no good control available.
- Exceptions:
  - Ca Prostate & Cervix where surgery is an option.
  - Hodgkin's disease where risk of breast cancer in young women is obvious.
### Radiotherapy Patients

- **Carcinomas**: Site adjacent to and remote from treated area. Large number, small RR.
- **Sarcomas**: In heavily irradiated tissues. Small number, large RR.
- More important as younger patients are treated and/or better cure rates.

### Prostate Cancer, Treated with Radiotherapy or Surgery (SEER Program) 1973-93

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at risk</td>
<td>51,584</td>
<td>70,539</td>
</tr>
<tr>
<td>Person-years at risk</td>
<td>218,341</td>
<td>312,499</td>
</tr>
<tr>
<td>Ave. follow-up after diagnosis (y)</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Ave age at diagnosis (y)</td>
<td>70.3</td>
<td>71.4</td>
</tr>
<tr>
<td>Ave. age at second CA diagnosis (y)</td>
<td>75.3</td>
<td>77.0</td>
</tr>
<tr>
<td>% of person-years at risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 years after primary diagnosis</td>
<td>18.2</td>
<td>17.4</td>
</tr>
<tr>
<td>1-5 years after primary diagnosis</td>
<td>52.1</td>
<td>51.5</td>
</tr>
<tr>
<td>5-10 years after primary diagnosis</td>
<td>22.7</td>
<td>23.4</td>
</tr>
<tr>
<td>10+ years after primary diagnosis</td>
<td>6.9</td>
<td>7.7</td>
</tr>
</tbody>
</table>
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**Second Cancers After Prostate RT**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>37%</td>
</tr>
<tr>
<td>Colon</td>
<td>9%</td>
</tr>
<tr>
<td>Lung</td>
<td>34%</td>
</tr>
<tr>
<td>Sarcoma (in field)</td>
<td>6%</td>
</tr>
<tr>
<td>Sarcoma (out of field)</td>
<td>2%</td>
</tr>
<tr>
<td>Rectum</td>
<td>12%</td>
</tr>
<tr>
<td>Colon</td>
<td>9%</td>
</tr>
</tbody>
</table>

% contribution to total number of radiation-induced second cancers (5+ yrs)

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**Risk of Radiation-Associated Second Malignancy After Prostate-Cancer Radiotherapy**

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk (1 in X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All survivors</td>
<td>290</td>
</tr>
<tr>
<td>5+ yrs survivors</td>
<td>125</td>
</tr>
<tr>
<td>10+ yrs survivors</td>
<td>70</td>
</tr>
</tbody>
</table>

*Brenner et al 1999*
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**Lung Cancer after Hodgkin’s Disease by Type of Treatment**

- **Alkylating agents only**: RR=4.2 (73 Ca 135 Co)
- **Radiotherapy (RT) only**: RR=5.9 (21 Ca 98 Co)
- **RT and alkylating agents**: RR=8.0 (52 Ca 70 Co)

P trend <0.001

*Travis LB, et al. JNCI, 2002*  
*Adjusted for tobacco use*

**Second Cancers After Hodgkin’s Lymphoma**

- 55 cases of Breast CA in 3869 patients treated (obs/exp 2.24)
- Risk of 60% in women treated before 16 years old
- Risk decreases with age at therapy
- Risk only slightly elevated at age >30 years
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**Brain Tumors Following Cranial Irradiation of Children with Leukemia**

![Graph showing relative risk of brain tumors following cranial irradiation at different radiation doses.](image)

Neglia and Inskip, in press
End