The Carcinogenic Effects of Radiation: Experience from Recent Epidemiologic Studies

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Columbia University Radiation Course
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Radiation Epidemiology Branch
National Cancer Institute

Epidemiology is the study of the distribution and determinants of disease in human populations

Epidemiologic Studies

- Observational rather than Experimental
- Possibility of confounding or bias
- Uncertainties in dose estimation
- Problem of multiple comparisons
- Low statistical power can limit detection of effects

Types of Epidemiologic Studies

- Clinical Trial
- Cohort
- Case-Control
- Ecologic

Methodological Issues

- Appropriate study population
- Statistical power to detect radiation effects
- Reliable individual dose estimates
- Accuracy and completeness of outcome measure
- Information on potential confounders and risk modifiers
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Radiation Epidemiology
To characterize and quantify the risk of cancer in populations exposed to radiation, alone or in combination with other agents or risk factors

Radiation Epidemiology: Some History
- 1920s: Bone cancer excess among radium dial painters
- 1940s: Leukemia excesses among radiologists
- 1950s: Leukemia in A-bomb survivors
- 1960s: Lung cancer risk from underground mine exposure to radon

Why Study Radiation?
- To recommend or regulate protection standards for workers and the general public
- To modify radiotherapy
- To better understand individual susceptibility
- To learn more about carcinogenesis

Ionizing Radiation: Some History
- X-rays discovered in 1895
- First used medically in 1896
- Identified as a human carcinogen at turn of century
- Since then, extensively studied and quantified carcinogen
- In last few decades, occupational exposure declined, medical exposure increased

Radiation Exposures
- Medical
- Environmental
- Occupation
- Military

Epidemiologic Studies
- Atomic bomb survivors
- Medical exposure
  - Diagnostic
  - Radiotherapy
- Environmental exposure
  - Radon
  - Radiation accidents
  - Fallout from nuclear testing
  - Emissions from nuclear plants
  - High background areas
- Occupational exposure
  - Medical and nuclear workers
  - Miners
Background

- Radiation cancer risks derive mostly from:
  - Acute single-dose A-Bomb survivors’ exposures
  - Fractionated, high-dose radiotherapy exposures
- Protracted low-dose radiation less studied:
  - Ongoing public concern
  - Medical, environmental, occupational, military exposures
  - Most quantitative data from nuclear worker studies and now Techa River

Magnitude of Doses (Sv)

Radiotherapy: up to 80 (tumor)
50% survival probability: 4
A-bomb survivors: mean ~ 0.25
Occupational limit: 0.02 per yr
  - Nuclear worker study: mean ~ 0.004 per yr
Background radiation: 0.003 per yr
Diagnostic medical exams: 0.00001-0.01*
Round-trip flight, NY – London: 0.0001

* Lower doses for screening x-rays higher for CT

Describing Radiation Risks

- Excess Relative Risk (ERR)
  - Percentage change in risk for a unit dose, Gy (Relative change in rate)
- Excess Absolute Rate (EAR)
  - Absolute change in rates for a unit dose, Gy (Rate difference)
- ERR and EAR can vary with age, time and gender; provide complementary information

Objectives of Incidence Report

- Quantify cancer risks attributable to radiation
- Explore the shape of the dose-response
- Assess how the risk is modified by age, time, gender and other factors
- Help clarify site-specific differences in risk patterns
- Highlight issues and cancer sites needing more research
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LSS Cohort

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

TOTAL PEOPLE 120,321

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

Atomic Bomb Survivors: LSS Cancer Incidence

- 105,427 people; 2.8 million PYR
- Follow-up 1958-1998
  - >50 years after bombings
  - 48% alive in 1998
  - 86% alive of those <20 at exposure
- Hiroshima and Nagasaki tumor registries
- 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>

Preston et al, 2007

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

Distribution of Solid Cancers

- TOTAL 17,448
- Digestive system 10,052
- Respiratory system 2,001
- Female genital 1,457
- Breast 1,082
- Urinary system 741
- Thyroid 471
- Skin 347
- Male genital 420
- Nervous system 281
- Oral cavity 277

Preston et al, 2007
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### Solid Cancer Incidence

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Observed</th>
<th>Excess</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.005</td>
<td>9,597</td>
<td>3</td>
<td>0.0</td>
</tr>
<tr>
<td>0.005 - 0.1</td>
<td>4,406</td>
<td>81</td>
<td>1.8</td>
</tr>
<tr>
<td>0.1 - 0.2</td>
<td>968</td>
<td>75</td>
<td>7.6</td>
</tr>
<tr>
<td>0.2 - 0.5</td>
<td>1,144</td>
<td>179</td>
<td>15.7</td>
</tr>
<tr>
<td>0.5 - 1</td>
<td>688</td>
<td>206</td>
<td>29.5</td>
</tr>
<tr>
<td>1 - 2</td>
<td>460</td>
<td>196</td>
<td>44.2</td>
</tr>
<tr>
<td>2+</td>
<td>185</td>
<td>111</td>
<td>61.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17,448</td>
<td>853</td>
<td>10.7*</td>
</tr>
</tbody>
</table>

*Attributable risk % among people with dose >0.005 Gy.

Preston et al, 2007

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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

Preston et al, 2007

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### Solid Cancer Risks by Gender

- ERR per Gy = 1.8
- EAR per 10⁴ PYGy = 0.9

Sex ratio: F:M 1.6

For person age 70 exposed at age 30

Preston et al, 2007

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### Interpretation of Site-Specific Risks

- Site-specific differences likely exist
- But much of observed variability is consistent with random variation
- Formal statistical tests generally lack power to detect real differences

Preston et al, 2007

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### Solid Cancer Temporal Patterns

For person age 70 exposed at age 30

Preston et al, 2007

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### Site-Specific Cancer Risk Estimates

ERR at age 70 for exposure at age 30

Preston et al, 2007
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Summary

- Age-time patterns don’t differ substantially for most individual sites
- With more detailed analyses, age at exposure and attained age differences difficult to distinguish
- Overall patterns similar to those seen in previous analyses
- Continue to find new results

Gender Effects

ERR at age 70 for exposure at age 30

Medical Radiation Dilemma

➢ Necessary tool
➢ Potential carcinogen

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

Medical Radiation Studies

- Hundred’s of studies
- Different types of radiation
- Broad range of doses
- Various organs and tissues
- Diverse populations
- Impact on radiotherapy practice
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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

Time Trends for CT Use in US

Brenner & Hall, 2007

Scoliosis and Breast Cancer

- 4,822 exposed
  - 644 unexposed
- Mean breast dose = 0.11 Gy
- 77 deaths 45.6 expected
- ERR_{Gy} = 2.7 (-0.2-9.3)
- Results consistent with A-bomb survivors

Doody et al, Spine 2001

Radiation Treatment for Benign Diseases

- Used frequently from 1930’s to 1960’s for various benign diseases
- Overall use has declined, but now treating some new diseases
- $^{131}$I still treatment of choice for hyperthyroidism

How We Estimate Doses

- Mathematical phantom with measurements in water
- Anthropomorphic phantoms
- Treatment-planning computer systems
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Peptic Ulcer Mortality

- 1859 irradiated and 1860 non-irradiated peptic ulcer patients followed >30 years
- Doses to stomach and pancreas ~15 Gy, but lower to other organs
- Risks significantly elevated for stomach, pancreas and lung cancer deaths

Carr et al, Rad Res 2002

Non-Cancer Mortality After Peptic Ulcer Radiotherapy

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>1.28</td>
<td>1.06-1.54</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.44</td>
<td>1.11-1.86</td>
</tr>
</tbody>
</table>

Coronary heart disease increased with heart dose:

<table>
<thead>
<tr>
<th>Dose, Gy</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1-1.6</td>
<td>1.05</td>
<td>0.78-1.40</td>
</tr>
<tr>
<td>1.7-2.0</td>
<td>1.22</td>
<td>0.93-1.69</td>
</tr>
<tr>
<td>2+</td>
<td>1.52</td>
<td>1.10-2.10</td>
</tr>
</tbody>
</table>

(10 year survivors)

Thyroid Cancer after Radiotherapy for Childhood Cancer

- 69 cases; 265 matched controls
- Identified from 14,054 5-year survivors diagnosed 1970-86
- Thyroid cancer risk increased with dose up to 20-29 Gy (OR=9.8, 3.2,35)
- Risk higher among survivors
  - <10 yr at 1st primary
  - With Hodgkins lymphoma

Sigurdson et al, 2005

Second Cancers Following Radiotherapy

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

Childhood Cancer Survivor Study

- 14,000 five-year U.S. survivors of childhood cancer, diagnosed 1970-86
- Detailed treatment information
- Periodic resurvey to update risk factor and outcome information
- Buccal cell DNA; tumor DNA
- Current mean age, 30 years

Radiotherapy Epidemiology Studies

Occupational Exposures

- Nuclear workers
- Uranium miners
- Radium dial painters
- X-ray technologists
- Radiologists
- Airline crew
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

US Radiologic Technologist Study

- 146,022 technologists certified 1926-82
- Mostly female (73%)
- Age certified = 21, Current age = 53
- Two postal surveys
  - ~70% response rate
- Cancer mortality, cardiovascular & musculoskeletal diseases, early menopause, cataracts, pregnancy outcomes

Doody et al 2002

International Nuclear Worker Study

407,391 workers
5.2 million PYR
Mean cumulative dose 20 mSv

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

*Excluding leukemia
** Excluding CLL

Cardis et al, 2005

Incident Cancer Risk: USRT

<table>
<thead>
<tr>
<th>Year began working</th>
<th>&lt;1940</th>
<th>1940s</th>
<th>1950s</th>
<th>1960s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>2.1*</td>
<td>0.9</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8.4*</td>
<td>1.6</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>1.9</td>
<td>0.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Basal cell skin</td>
<td>2.0*</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05
Referent is 1970’s, adjusted for age, work in other years

Medical Radiation Workers

- Medical radiation workers represent largest exposed occupational group
  - about 2.3 million worldwide
  - half of radiation work force
  - large number are women
- Number of medical workers increasing

USRT Summary

- Early workers often had high exposures
- Suggestive evidence of an increased risk of leukemia (non-CLL), cancers of the skin (melanoma, BCC), and breast among early workers
  - Risk elevated decades after initial exposures
- No excess cancer risk among recent workers
  - Marked improvements in radiation protection standards led to reduction in exposure
- Continued follow-up necessary because recent workers exposed to new procedures
Environmental Exposures

- Excluding radon, is very small component of population exposure
- Exposures typically low
- Dosimetry extremely uncertain
- Causes great deal of public concern
- Try to study populations with unique exposures

Annual U.S. Lung Cancer Deaths for Smokers and Non-smokers:

*Contribution from indoor radon in white circles*

- Estimated deaths from indoor radon
  - Smokers (146,400)
  - Non-smokers (11,000)
  - Lubin, 1999

Lung Cancer And Residential Radon

- Large lung cancer case-control study in China
- Low mobility and high radon levels
- Lung cancer risks equal or exceed extrapolations from miner data

China Cave Dwellings

Wang et al AJE, 2002

The Chernobyl Accident

Ukraine, 26 April 1986

- Worst accident in nuclear history
- 10 days of releases into the atmosphere under varying meteorological conditions
- $^{131}I$ principal radionuclide
  - About 90% of dose
  - Inhaled and ingested

Pathway of Radioiodine Exposure from the Chernobyl Accident

- Concentrates in the thyroid; thyroid dose 15-20-fold higher than overall body dose
- Dose inversely proportional to thyroid mass, so higher dose to children
- Dose larger in iodine deficient areas
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Thyroid Cancer Incidence

Belarus Ukraine

Years

Incidence Rate


Chernobyl Forum, 2005

Thyroid Cancer Prevalence Ukraine-NCI Study; 1998-2000

<table>
<thead>
<tr>
<th>ERR/Gy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>2.21</td>
</tr>
<tr>
<td>female</td>
<td>16.6</td>
</tr>
<tr>
<td>Age at exposure</td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>9.1</td>
</tr>
<tr>
<td>5-9</td>
<td>7.0</td>
</tr>
<tr>
<td>10-18</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Tronko et al, JNCI 2006

Belarus-Ukraine-NCI Collaborative Thyroid Cancer Screening Study

• Cohort study of 25,161 persons exposed <18 yr
• 2 arms:
  • Ukraine (n=13,243) Belarus (n=11,918)
• Direct thyroid activity measurements
• Wide range of thyroid doses
  • 44% <0.3 Gy; 28% >1 Gy
• >100 histologically verified thyroid cancers from first screening

Stezhko et al. Radiat Res 2004

Thyroid Cancer Risk Estimates from External Radiation and 131I

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>EAR/10^6PYGy</th>
<th>ERR/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>External</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int'l pooled analysis (Ron et al. 1995)</td>
<td>4.4 (1.9-10)</td>
<td>7.7 (2.1-29)</td>
</tr>
<tr>
<td>Case-control study in Belarus &amp; Russia (Cardis et al. 2005)</td>
<td>N.A.</td>
<td>4.5 (1.2-7.8)</td>
</tr>
<tr>
<td>Cohort study in Ukraine (Tronko et al. 2006)</td>
<td>N.A.</td>
<td>5.2 (1.7-27)</td>
</tr>
<tr>
<td>Chernobyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecological study in Ukraine (Likhtarov et al. 2006)</td>
<td>1.5 (1.2-1.9)</td>
<td>8.0 (4.6-15)</td>
</tr>
<tr>
<td>Ecological study in Belarus &amp; Ukraine (Jacob et al. 2006)</td>
<td>2.7 (2.2-3.1)</td>
<td>19 (11-27)</td>
</tr>
</tbody>
</table>

Ron E. Health Phys In press

Thyroid Cancer Prevalence Ukraine-NCI Study; 1998-2000

Dose Response

Relative Risk (RR)

RR estimates; 95% confidence interval
Fitted dose-response
Thyroid cancers = 45

Dose, Gy

Tronko et al, JNCI 2006

Chernobyl Summary

• Excess thyroid cancers still occurring
• Risk appears to decrease with increasing age at exposure, little effect for adult exposure
• The number of excess cancers larger among women, but role of gender not clear in terms of relative risk
• Iodine deficiency may enhance the risk
• Deaths have been relatively low (<1%)
• Risks are compatible with estimates from external irradiation
Conclusions (1)

- Most cancers can be induced by radiation
  - Clear evidence for leukemia, breast, thyroid, salivary glands, stomach, colon, lung, liver, non-melanoma skin, ovary, bladder, brain, bone
- Young age at exposure appears to increase risk
- Risk persists throughout life

Conclusions (2)

- Little evidence to suggest a threshold
- For solid cancer, data suggest a linear dose response
- At extremely high doses the dose-response appears to flatten out, probably due to cell-killing

Questions Needing More Research

- How much cancer is caused by radiation?
- How long does risk last after exposure?
- How does radiation cause cancer?
- Why do organs & tissues vary in sensitivity?
- Is there individual susceptibility to radiation?
- How does radiation interact with other exposures?