RC-1b
Gender, Age, and Age-at-Exposure Effects on Radiation Cancer Risks

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Gender, Age, and Age-at-Exposure Effects on Radiation Cancer Risks
Dale L. Preston
Outline

1. Issues
   - Relative versus absolute risks
   - Describing (smoothing) risk patterns
     - ERR or EAR
     - A “simple” descriptive effect modification model

2. Data
   - Atomic bomb survivors
     - Solid cancer incidence 1958-94
     - Leukemia mortality 1950-2000
   - Mayak workers
     - Solid cancer and leukemia mortality 1948-1997
   - Pooled breast cancer cohorts

3. Results
   - All solid cancers
   - Selected cancer types
   - Leukemia

4. Related Issues
   - Time-since-Exposure versus attained age
   - Latent periods
   - Identifying “real” differences
The Old Debate
Relative versus Absolute Risks

• Do excess risks increase or become relatively less important as time goes by?

• By early 1980’s it was agreed that relative risk provided a better description

• Time-constant (excess) relative risk became standard risk summary
Evolving Understandings
Excess Risk is Not a Number

• (Relative) risk depends on gender and age at exposure

![Graph showing LSS Solid Cancer Incidence](chart)

• Are excess relative risks constant in attained age (time) given age at exposure and sex?
• How should we interpret gender differences in the ERR?
Evolving Understandings
Describing Excess Risks

Excess relative risk (ERR) model

\[ \lambda_o(a,s,b)[1 + \rho(d)\varepsilon_R(s,e,a)] \]

Excess absolute rate (EAR) model

\[ \lambda_o(a,s,b) + \rho(d)\varepsilon_A(s,e,a) \]

- \( \lambda_o(a,s,b) \) Baseline (zero dose) risk function; \( a \) age at risk; \( s \) gender; and \( b \) birth cohort
- \( \rho(d) \) Dose-response shape, e.g. linear, linear-quadratic, threshold, …
- \( \varepsilon(s,e,a) \) Effect modification function; \( e \) age at exposure
Evolving Understandings
ERR versus EAR description

- ERR and EAR are (in principle) equivalent descriptions of the excess risk

$$\varepsilon_R(s,e,a) = \frac{\varepsilon_A(s,e,a)}{\lambda_0(a,s,b)}$$

- Both ERR and EAR descriptions are important
- ERR and EAR provide complimentary information
  - Patterns in ERR effect modifiers may reflect factors such as gender and birth cohort effects in baseline rates
- Description may be simpler or more informative on one scale than the other
Describing Gender and Age-Time Effects

- Smoothing the excess is essential to understanding
  - Subset analyses have little power
  - Uncertainty can make it difficult to see patterns
- Requires choice of variables and model form
  - RERF analyses generally based on log-linear descriptions

\[ \varepsilon(s,e,a) = \exp(\beta_s + \theta e + \gamma \log(a)) \]

- \( \exp(\beta_f) / \exp(\beta_m) \) female:male excess (relative) risk ratio
- \( \exp(10 \theta) - 1 \) % change per decade increase in age at exposure
- \( \gamma \) power of age at risk
Describing Gender and Age-Time Effects

• Extensions of basic model possible
  – Sex-dependent age and age at exposure effects
  – More general functions of age and age at exposure

• However, available data usually too limited to support such detailed descriptions
## LSS Solid Cancer Incidence 1958-94

### By age at exposure

<table>
<thead>
<tr>
<th>Age at exposure</th>
<th>People</th>
<th>Person years</th>
<th>Cases</th>
<th>Estimated Excess</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>16,533</td>
<td>435,613</td>
<td>1,220</td>
<td>113</td>
<td>9%</td>
</tr>
<tr>
<td>20-39</td>
<td>6,117</td>
<td>156,586</td>
<td>1,633</td>
<td>76</td>
<td>5%</td>
</tr>
<tr>
<td>40+</td>
<td>9,761</td>
<td>133,347</td>
<td>2,261</td>
<td>60</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>32,411</td>
<td>725,546</td>
<td>5,114</td>
<td>249</td>
<td>5%</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>18,340</td>
<td>511,746</td>
<td>1,234</td>
<td>200</td>
<td>16%</td>
</tr>
<tr>
<td>20-39</td>
<td>16,256</td>
<td>472,019</td>
<td>2,880</td>
<td>208</td>
<td>7%</td>
</tr>
<tr>
<td>40+</td>
<td>13,173</td>
<td>224,856</td>
<td>2,278</td>
<td>81</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>47,769</td>
<td>1,208,621</td>
<td>6,392</td>
<td>489</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>80,180</td>
<td>1,934,167</td>
<td>11,506</td>
<td>738</td>
<td>6%</td>
</tr>
</tbody>
</table>

### By colon dose

<table>
<thead>
<tr>
<th>Colon Dose</th>
<th>People</th>
<th>Person years</th>
<th>Cases</th>
<th>Estimated Excess</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.005</td>
<td>35,545</td>
<td>851,102</td>
<td>4,701</td>
<td>3</td>
<td>0%</td>
</tr>
<tr>
<td>- 0.1</td>
<td>27,789</td>
<td>676,209</td>
<td>3,787</td>
<td>69</td>
<td>2%</td>
</tr>
<tr>
<td>- 0.2</td>
<td>5,527</td>
<td>135,764</td>
<td>827</td>
<td>65</td>
<td>8%</td>
</tr>
<tr>
<td>- 0.5</td>
<td>5,935</td>
<td>143,477</td>
<td>1,010</td>
<td>155</td>
<td>15%</td>
</tr>
<tr>
<td>- 1</td>
<td>3,173</td>
<td>75,709</td>
<td>611</td>
<td>178</td>
<td>29%</td>
</tr>
<tr>
<td>- 2</td>
<td>1,647</td>
<td>38,923</td>
<td>411</td>
<td>172</td>
<td>42%</td>
</tr>
<tr>
<td>2+</td>
<td>564</td>
<td>12,982</td>
<td>159</td>
<td>98</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>80,180</td>
<td>1,934,167</td>
<td>11,506</td>
<td>738</td>
<td>6%</td>
</tr>
</tbody>
</table>

- Information on gender and age-time patterns depends (only) on radiation-associated ("excess") cases
- Excess cases not explicitly identified
- Number of relevant cases is relatively small, especially for specific sites

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### LSS Leukemia Mortality
1950-2000

<table>
<thead>
<tr>
<th>Age at exposure</th>
<th>People</th>
<th>Person years</th>
<th>Cases</th>
<th>Estimated Excess</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>16,827</td>
<td>783,098</td>
<td>60</td>
<td>24</td>
<td>41%</td>
</tr>
<tr>
<td>20-39</td>
<td>6,411</td>
<td>229,330</td>
<td>49</td>
<td>14</td>
<td>28%</td>
</tr>
<tr>
<td>40+</td>
<td>12,449</td>
<td>227,441</td>
<td>47</td>
<td>13</td>
<td>28%</td>
</tr>
<tr>
<td>Total</td>
<td>35,687</td>
<td>1,239,869</td>
<td>156</td>
<td>51</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>18,569</td>
<td>891,288</td>
<td>42</td>
<td>17</td>
<td>41%</td>
</tr>
<tr>
<td>20-39</td>
<td>16,750</td>
<td>702,633</td>
<td>57</td>
<td>17</td>
<td>30%</td>
</tr>
<tr>
<td>40+</td>
<td>15,605</td>
<td>350,566</td>
<td>41</td>
<td>9</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>50,924</td>
<td>1,944,487</td>
<td>140</td>
<td>43</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>86,611</td>
<td>3,184,356</td>
<td>296</td>
<td>94</td>
<td>32%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colon Dose</th>
<th>People</th>
<th>Person years</th>
<th>Cases</th>
<th>Estimated Excess</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.005</td>
<td>38,507</td>
<td>1,415,828</td>
<td>95</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>- 0.1</td>
<td>27,995</td>
<td>1,035,428</td>
<td>62</td>
<td>3</td>
<td>5%</td>
</tr>
<tr>
<td>- 0.2</td>
<td>6,907</td>
<td>251,569</td>
<td>17</td>
<td>4</td>
<td>25%</td>
</tr>
<tr>
<td>- 0.5</td>
<td>7,359</td>
<td>267,476</td>
<td>32</td>
<td>13</td>
<td>41%</td>
</tr>
<tr>
<td>- 1</td>
<td>3,005</td>
<td>112,394</td>
<td>25</td>
<td>16</td>
<td>62%</td>
</tr>
<tr>
<td>1+</td>
<td>2,838</td>
<td>101,661</td>
<td>65</td>
<td>57</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>86,611</td>
<td>3,184,356</td>
<td>296</td>
<td>94</td>
<td>32%</td>
</tr>
</tbody>
</table>

- Despite smaller number of excess cases, a considerably larger proportion of the cases are radiation-associated.
LSS Solid Cancer Incidence
Site-Specific Risks

- Interest in gender effects and age-time patterns for specific cancer types – but data are limited
- Real differences may exist, but power to detect them is limited

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
<th>Excess Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Solid</td>
<td>11,506</td>
<td>738</td>
</tr>
<tr>
<td>Stomach</td>
<td>3,229</td>
<td>137</td>
</tr>
<tr>
<td>Colon</td>
<td>831</td>
<td>58</td>
</tr>
<tr>
<td>Liver</td>
<td>926</td>
<td>45</td>
</tr>
<tr>
<td>Lung</td>
<td>1,346</td>
<td>118</td>
</tr>
<tr>
<td>Breast</td>
<td>726</td>
<td>136</td>
</tr>
<tr>
<td>Thyroid</td>
<td>371</td>
<td>70</td>
</tr>
<tr>
<td>Bladder</td>
<td>292</td>
<td>29</td>
</tr>
<tr>
<td>Other Solid</td>
<td>3,968</td>
<td>168</td>
</tr>
<tr>
<td>Leukemia</td>
<td>296</td>
<td>94</td>
</tr>
</tbody>
</table>
## Mayak Worker Mortality
### 1948 - 97

<table>
<thead>
<tr>
<th>Cumulative Dose</th>
<th>Person years</th>
<th>Deaths</th>
<th>Excess Deaths</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>External</td>
<td>Internal</td>
</tr>
<tr>
<td>Zero</td>
<td>236,731</td>
<td>287</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>-0.5</td>
<td>293,390</td>
<td>598</td>
<td>26</td>
<td>62</td>
</tr>
<tr>
<td>-1</td>
<td>68,233</td>
<td>193</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>-3</td>
<td>93,685</td>
<td>472</td>
<td>107</td>
<td>72</td>
</tr>
<tr>
<td>-5</td>
<td>22,678</td>
<td>130</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>5+</td>
<td>6,958</td>
<td>50</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>721,675</strong></td>
<td><strong>1,730</strong></td>
<td><strong>220</strong></td>
<td><strong>221</strong></td>
</tr>
</tbody>
</table>

### Solid Cancer

<table>
<thead>
<tr>
<th>Cumulative Dose</th>
<th>Person years</th>
<th>Deaths</th>
<th>Excess Deaths</th>
<th>AR%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>External</td>
<td>Internal</td>
</tr>
<tr>
<td>Zero</td>
<td>188,178</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-0.5</td>
<td>322,779</td>
<td>23</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>75,025</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>-3</td>
<td>103,073</td>
<td>13</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>-5</td>
<td>24,972</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5+</td>
<td>7,649</td>
<td>7</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>721,676</strong></td>
<td><strong>66</strong></td>
<td><strong>25</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

### Average Doses
- Average external dose: 0.8 Gy, 21,557 workers
- Average internal (lung) dose: 0.2 Gy, No childhood exposure
- 24% female

- Internal exposures affect limited set of tissues and may have different temporal patterns
- Separation of internal and exposure efforts complicates use of solid cancer data, but leukemia excess is essentially all due to external exposure
Pooled Breast Cancer

- Pooled analyses provide more information, but
  - Number of cases still limited
  - One must assume patterns are the same for different types of exposure (perhaps not unreasonable)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cases</th>
<th>Excess Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSS</td>
<td>707</td>
<td>128</td>
</tr>
<tr>
<td>TB</td>
<td>211</td>
<td>38</td>
</tr>
<tr>
<td>Mastitis</td>
<td>114</td>
<td>37</td>
</tr>
<tr>
<td>Thymus</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Benign Breast</td>
<td>210</td>
<td>75</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>176</td>
<td>-20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,452</strong></td>
<td><strong>275</strong></td>
</tr>
</tbody>
</table>
LSS Solid Cancer Excess Relative Risk
Temporal Patterns

Age at exposure
-16% per decade
(90% CI -25%; -6%)

Attained age
Age -1.8
(90% CI -2.3; -1.3)

Gender *
M: 0.35 (90% CI 0.27; 0.43)
F: 0.57 (90% CI 0.47; 0.67)
F:M: 1.6 (90% CI 1.3; 2.1)

* ERR per Sv at age 70 following exposure at age 30
LSS Solid Cancer Excess Rate
Temporal Patterns

- Age at exposure
  +24% per decade
  (90% CI 16%; 32%)

- Attained age
  Age 2.3
  (90% CI 1.9; 2.8)

- Gender *
  M: 43 (90% CI 32; 54)
  F: 59 (90% CI 50; 68)
  F:M: 1.4 (90% CI 1.1; 1.8)

* Excess cases per 10000 PY at age 70 following exposure at age 30
Solid Cancer Incidence
Gender Effects

Excess Relative Risk

Excess Rate

Risks at age 70 following exposure at age 30
Solid Cancer Incidence
Sex Ratio

• All solid cancers
  – ERR F:M sex ratio 1.6
  – EAR F:M sex ratio 1.4
  – Baseline M:F sex ratio 2

• Non-sex specific solid cancers
  – ERR F:M Sex ratio 1.8
  – EAR F:M Sex ratio 1.0
  – Baseline M:F sex ratio 2.2

• Suggests that ERR sex ratio largely serves to offset baseline rate ratio
Solid Cancer Incidence
Age-at-exposure and Birth Cohort Effects

Excess risk age at exposure effects relative to age at exposure 30
- Solid cancer excess thick blue line
- Solid cancer excess reference yellow dashed line

Baseline birth cohort effect relative to 1915 births dashed blue line

N.B. Birth cohort and age at exposure are equivalent in the LSS
LSS Solid Cancer Risks

- ERR exhibits significant dependence on age at risk (attained age) even after allowance for age at exposure effects.
- Despite decreasing ERR, EAR increases rapidly with attained age.
- After allowing for attained age effects both ERR and EAR depend on age at exposure and suggest that younger people have higher risks.
- ERR gender difference for non-sex specific solid cancers reflects baseline gender differences.
Age at Exposure Effects

- Age at Exposure
  - Age 10
  - Age 50

ERR at age 70

- Uterus
- Thyroid
- Bladder
- Breast
- All Solid
- Lung
- Stomach
- Colon
- Liver

ERR per Sv
Solid Cancer ERR
Gender Effects

ERR per Sv

Male
Female
ERR at age 70 for exposure at age 30

Bladder, Lung, Breast, All Solid, Thyroid, Stomach, Liver, Colon, Uterus
Stomach Cancer Incidence
Excess Relative Risk

 ERR per Sv

Age ATB
-100%
-50%
0%
50%
100%
150%

ERR Agex effect

1885 1905 1925 1945
-100% -50% 0% 50% 100% 150%

IRPA 11 Refresher Course 1b
Stomach Cancer Incidence
Excess Rate (EAR)
Lung Cancer Incidence
Excess Relative Risk

- Age at exposure effect opposite that seen for other solid cancers
- Large gender difference and age at exposure pattern reflect smoking effects on baseline rates
Lung Cancer Incidence Excess Rate

- Lack of age at exposure effect and reduced gender ratio suggest additive joint effect of radiation and smoking (see Pierce et al 2003)
Breast Cancer Incidence
What is “Known”

- Large relative risk
- Large age-at-exposure effect on ERR
- Indications of very high risk (ERR) of early-onset (under attained-age 35) cancer among exposed
- Pooled breast cancer excess risk (EAR) model developed using LSS and 7 other cohorts
• ERR pattern consistent with large relative risk for early-onset cases
• Large age at exposure effect on EAR
• Is simple EAR pattern adequate
Breast Cancer
Age at Exposure and Birth Cohort Effects

- No apparent age at exposure effect on ERR after allowing for age despite large birth cohort effect
- Large age at exposure effect on EAR parallels the birth cohort effect
Breast Cancer Incidence
Early Onset Effect

- Early onset age confounded with early age at exposure
- Significant ERR early-onset effect only if baseline adjusted for under-35 effect
- Adjustment increases under-35 estimated excess cases by 4 (40%)
- Attained-age remains dominant effect on ERR
Breast Cancer Incidence
EAR Models

• EAR pattern is complex
  – Simple trend improved by addition of EAR change points (ages 35 and 50)
• 8-cohort pooled model predicts higher risks at older ages
• Additional follow-up of youngest birth cohorts essential to understanding post-menopausal excess risks
Breast Cancer Incidence

- ERR decreases with increasing attained age
  - Large ERR’s may exist for early-onset cases
  - No significant age at exposure effect on ERR
- EAR has complex pattern
  - Strong age at exposure effect
  - Clear change in pattern near age of menopause
  - Basic pattern seen as in other cohorts but LSS changes may be more pronounced
Leukemia

- LSS data usually described in terms of
  - EAR models
  - Time since exposure (TSE) as primary time scale for excess
  - Include age at exposure by TSE interaction
- Descriptive models used here have same form as solid cancer
  - Attained age as primary time scale for excess
  - No need for attained age by age at exposure interaction
- These models describe data as well as TSE models
Leukemia Mortality
ERR

- Age at exposure effect opposite that seen for most solid cancers
- Little gender effect on ERR
- Attained age trend only slightly more marked than that for solid cancers
Leukemia Mortality

EAR

- Declining EAR is in marked contrast to solid cancers
Comparison of LSS and Mayak Leukemia Risks

- Large risk for “recent” exposures in Mayak cohort and smaller risks for earlier exposures seems consistent with LSS decline with time
- Mayak 1 Sv risks may be less than LSS risks, but there are large uncertainties in estimates from both cohorts
- LSS clearly has non-linear dose response, but Mayak appears linear
Related Issues
Time-Since-Exposure

• Solid cancer
  – LSS data suggest that largest risks occur late in life regardless of age at exposure
  – EAR TSE model fits worse than attained-age model without an agex-by-TSE interaction

• Leukemia
  – TSE models motivated by EAR decrease and the belief that the excess disappeared after 15 to 20 years
  – TSE models involve significant agex-by-TSE interaction
  – Attained age models provide comparable fit without need for interaction
Comparison of Time-Since-Exposure and Attained-Age Fits
Related Issues

Time-Constant ERR models

- LSS data clearly suggest that the ERR varies with attained age (time since exposure)
- It is difficult to conceive of a radiation carcinogenesis mechanism that would lead to time-constant increases in the ERR
Related Issues
Latency

• Concept of limited usefulness
  – Definition is vague
  – Dose response implies reductions in the expected time from exposure to tumor
  – Minimum latency period is at least time from the final conversion into a malignant cell until diagnosis or death but could be longer
    • Mayak and early a-bomb survivor data indicate that radiation-associated leukemia deaths can occur within two to three years of exposure
    • LSS solid mortality data provide some suggestion of elevated risk 5 to 10 years after exposure for older cohort members

• Better to simply describe age-time patterns
Related Issues
Interpreting Site-Specific Risks

• Difficult to interpret and generalize effect modification
  – ERR gender effects mirror baseline gender effects, but baseline
effects may be similar across populations
  – Age at exposure effects in the ERR may depend on birth cohort
    or period effects on baseline rates
  – Can also be problems in generalizing EAR patterns

• Site-specific differences in patterns are likely to exist
  – However much of observed variability is consistent with random
    variation
  – Formal statistical tests generally lack power to detect real
differences
  – Statistical methods for shrinking estimates toward a central value
    are likely to lead to improved estimators of risk levels, gender
    effects and age-time patterns
Summary and Conclusions

• Accumulating data and modern analytical methods make it possible to investigate radiation effect modification in some detail

• Data are limited even in the largest cohort

• Both ERR and EAR descriptions provide equally important and complementary information
  – Attained age is an important factor in both
  – Generalization of age at exposure and gender effects can be difficult

• Pooled analyses may be useful in looking at effect modification