Potential radiation-induced genomic instability in the Swedish hemangioma cohort and consequences for breast cancer risk

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M. Eidemüller, E. Holmberg, P. Jacob, M. Lundell, P. Karlsson,
Breast cancer risk and possible mechanisms of radiation-induced genomic instability in the Swedish hemangioma cohort, in preparation
Outline

1. Swedish Hemangioma Cohort
2. Results from ERR model
3. Mechanistic models with Genomic Instability
4. Risk comparison
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Swedish Hemangioma Cohort

- Between 1920-65 hemangiomas were treated by ionizing radiation in Stockholm and Gothenburg
- Hemangiomas: abnormal collection of blood vessels
  - Usually hemangiomas are situated on the skin
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  - Appear in the first weeks of life, usually disappear by age of 10
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- 17700 female and 8600 male children were treated.
- 226 received Ra or X-rays (10%).

Very early treatment.
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- $^{226}\text{Ra}$ or X-rays (10%)
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Swedish Hemangioma Cohort

Swedish Hemangioma Cohort: Breast cancer incidence

- 17200 females
- First treatment at very young ages (< 18 months)
- 877 breast cancer cases
- Follow-up: From 1/1958 to 12/2009
- January 2010: 13952 women alive, mean (median) age is 61.1 (60.7) years
Update of dosimetry system (2013)

Changes in dosimetry system

- For Stockholm cohort, previous dose planning system did not correctly calculate doses for applicators close to breast
- Re-evaluation for these women by Candela-Juan et al, Lundell et al
- Significant reduction of breast dose (factor 2-4) of highly exposed women in the Stockholm cohort
- Breast dose range (whole cohort): 0-33 Gy, Mean dose: 0.18 Gy (previously: 0.29 Gy)

Candela-Juan et al, Dosimetric characterization of two radium sources for retrospective dosimetry studies, submitted.
M. Lundell et al, New dosimetry for hemangioma treatments with Ra-226 needles or tubes, in preparation.
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Results from ERR model

Results

- No. of children significant baseline confounder
- Highly significant dose response
- Linear dose dependence
- About 72 of 877 breast cancer cases are radiation-induced (previous DS: 55)
- No dependence of ERR on attained age (practically flat)
Results from ERR model

Results

- Risk at central ages:

  $$\text{ERR}_{pd} = 0.48 \ \text{Gy}^{-1} (95\% \text{CI} : 0.28; 0.69)$$

  $$\text{EAR}_{pd}(50) = 10.4 \ \left(10^4 \ \text{PYRs Gy}^{-1}\right) (95\% \text{CI} : 6.1; 14.4)$$

- Previous DS: $$\text{ERR}_{pd}(50) = 0.22 \ \text{Gy}^{-1} (95\% \text{CI} : 0.13; 0.31)$$ and $$\text{EAR}_{pd}(50) = 4.8 \ \left(10^4 \ \text{PYRs Gy}^{-1}\right) (95\% \text{CI} : 2.9; 6.8)$$

- With new DS, central value of excess relative risk per dose increases substantially (about a factor of 2)

- Mean age of cases around 50 years (53 years)
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Mechanistic models of carcinogenesis

- Initiation
  - Rate $v$
- Clonal Expansion
  - Division
  - Apoptosis/Differentiation
  - $\alpha$, $\beta$
- Malignant Transformation
  - Rate $\mu$
  - Cancer cell $t_{lag}$
- Cancer
Two-stage clonal expansion (TSCE) model

Results

- TSCE model with standard dose response gives no good fit results
- Implementing ideas from genomic instability (GI): TSCE model with lifelong effects (Eidemüller et al, Mutat Res 2009)
- TSCE model with GI significantly better than standard TSCE model (p=0.003)
- Results for radiation risk very similar to results from ERR model: similar $ERR_{pd}$ and $EAR_{pd}$, no dependence of risk on attained age
Models of carcinogenesis with separate path of GI

- Healthy stem cells → initiated cells
- Initiated cells with GI → malignant cells
- GI stem cells → initiated cells with GI

Symbols:
- $\alpha_{0,Gi}$, $\alpha_{1,Gi}$, $\beta_{0,Gi}$, $\beta_{1,Gi}$
- $\nu_0$, $\nu_1$, $\nu_{0,GI}$, $\nu_{1,GI}$

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Models of carcinogenesis with separate path of GI

Nowak et al. PNAS 2002 (APC loss, colon cancer)
Genes in breast cancer

- TCGA: 3 genes (TP53, PIK3CA and GATA3) mutated in >10% of all breast cancers
- Basal-like and HER2-enriched breast cancer: dominantly TP53
- Luminal A subtype: dominantly PIK3CA (equally TP53 and PIK3CA for luminal B subtype)
- TP53 mutations associated with adverse prognosis
- Germline variants: mainly BRCA1, BRCA2, ATM
- Substantial genetic diversity of breast cancer

Stephens et al, Nature 2012
Vogelstein et al, Science 2013
Models with separate path of genomic instability

Free parameters:

- $\nu_0, \nu_1, \beta_1$
- $\nu_0, GI; \nu_1, GI, \beta_1, GI$
- $\sigma_0$

Background parametrisation:

- In principle, background risk can originate from upper path ($\nu_0, \nu_1$), or from one of lower paths ($\sigma_0, \nu_0, GI; \nu_1, GI$ or $\nu_0, \sigma_1, \nu_1, GI$)
- Best support for baseline on upper path ($\nu_0, \nu_1$) (fit quality, number of parameters, biological plausibility of parameter values)
- Baseline path via $\sigma_0$ or $\sigma_1$ not supported
Models with separate path of genomic instability

Free parameters:
- $\nu_0, \nu_1, \beta_1$
- $\nu_0, GI, \nu_1, GI, \beta_1, GI$
- $\sigma_0$

Radiation risk:
- Here only spontaneous radiation effects, no life-long effects!
- Early exposure: only radiation on $\nu_0$ or $\sigma_0$ is relevant
- Reference: Radiation on upper path: $\nu_0 = \nu_{0,\text{base}} + r \cdot d$
  $\rightarrow$ TSCE model, $\Delta \text{Dev}=0$, $d$ is dose rate (not accumulated dose)
Models with separate path of genomic instability

Free parameters:
- $\nu_0, \nu_1, \beta_1$
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Test radiation-induced Genomic Instability:
- $\sigma_0 = \sigma_{0,\text{base}} + r \cdot d = r \cdot d$
Models with separate path of genomic instability

Radiation:

\[ \sigma_0 = r \cdot d \]

Radiation-induced Genomic Instability:

Best Model:

\[ \nu_{0,GI}/\nu_0 = \lambda, \quad \nu_{1,GI}/\nu_1 = 1, \quad (\beta_{1,GI} = \beta_1) \]

Result:

<table>
<thead>
<tr>
<th>( \lambda )</th>
<th>10</th>
<th>100</th>
<th>1000</th>
<th>10000</th>
<th>100000</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) Dev</td>
<td>-9.6</td>
<td>-9.4</td>
<td>-9.9</td>
<td>-9.9</td>
<td>-9.9</td>
</tr>
<tr>
<td>( r )</td>
<td>0.049</td>
<td>( 4.9 \cdot 10^{-3} )</td>
<td>( 4.9 \cdot 10^{-4} )</td>
<td>( 4.9 \cdot 10^{-5} )</td>
<td>( 4.9 \cdot 10^{-6} )</td>
</tr>
</tbody>
</table>

- Strongly significant model of GI at biologically plausible values!
- AIC weight compared with TSCE model without GI: > 99%
- \( \lambda \) difficult to estimate on statistical grounds alone
Models with separate path of genomic instability

Best Model:

\[ \sigma_0 = r \cdot d \]

\[ \nu_{0,GI} \gg \nu_0 \]

\[ \nu_{1,GI} = \nu_1 \]

\[ \beta_{1,GI} = \beta_1, (\alpha_{1,GI} = \alpha_1) \]

- Enhancement of \( \nu_{GI} \)
- Analogy to colon cancer: GI increases loss of heterozygosity (Nowak et al. PNAS 2002)
  for \( \nu_{0,GI}/\nu_0 \approx 10^4, r = 3.6 \cdot 10^{-5} \text{ Gy}^{-1} \)
- After exposure of 1 Gy, about 3.6 of 10^5 cells would be genomically unstable. Of 10^9 stem cells, about 3.6 \cdot 10^4 genomically unstable cells would be present.
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Risk comparison

1σ errors

Age

ERR, TSCE-lifelong, GI, TSCE-direct

ERR_

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Risk comparison

![Graph showing risk comparison between different models: ERR, TSCE-lifelong, GI, and TSCE-direct. The graph plots EAR (10^4 PYR Gy)^{-1} against age. 1σ errors are indicated by error bars.](image URL)
Comparison of breast cancer risk to LSS

Radiation-induced cases

- SHC: All breast cancer cases with age at exposure between 0-5 years (71 radiation-induced cases)
- LSS: 15 radiation-induced cases with age at exposure between 0-5 years (from best mechanistic M4 model) (Kaiser et al, Radiat Environ Biophys 2012)

<table>
<thead>
<tr>
<th></th>
<th>SHC</th>
<th>LSS (e=0-5 y)</th>
<th>LSS (e=5-10 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERR(70) [Gy(^{-1})]</td>
<td>0.48</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>EAR(70) [(10(^4) PYR Gy(^{-1}))]</td>
<td>19.5</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

Risk transfer of breast cancer risk

- Results for breast cancer support preference for transfer of absolute risk between different populations
Summary mechanistic GI model

Summary

• Models with built-in radiation-induced GI strongly significant cf. standard mechanistic models
• In SHC, GI is an early event in radiation carcinogenesis
• Preferred model indicates that main effect of GI is to enhance transitions of cells with GI towards initiated cells
• Difference in time evolution of spontaneous and radiation-induced cancer (different molecular pathways?)
• Necessary to test such hypotheses with molecular biological measurements from samples of radioepidemiological cohorts
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