Radiation exposure and the risk of breast cancer in BRCA 1/2 mutation carriers

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Radiation exposure and breast cancer risk in BRCA 1/2 carriers

- Background
- Diagnostic radiation in BRCA carriers
- Therapeutic radiation in BRCA carriers
- Radiation in women with a family history of breast cancer
- Conclusions
Ionizing radiation and breast cancer in BRCA1/2 mutation carriers

• **Hypothesis**
  BRCA1/2 carriers have an increased risk of radiation-induced breast cancer

• **Mechanism**
  function BRCA1/2 genes: DNA repair of double strand breaks caused by ionizing radiation

• **Concerns**
  - Low dose: frequent (mammographic) screening of BRCA1/2 carriers, from a relatively young age onwards
  - High dose: radiotherapy treatment for primary breast cancer
Early literature on risk of radiation-induced breast cancer in genetically predisposed women prior to BRCA1/2 test


- Den Otter et al, *Anticancer research*
  - 1993: view-presenting paper: exclusion from mammographic screening of women genetically predisposed to breast cancer will probably eliminate mammographically-induced breast cancer
  - 1996: theoretical/mathematical study: calculations suggest that in women with an inherited gene for breast cancer one excess tumor in one out of 10 women will be induced by 20 mammograms
# Diagnostic radiation and breast cancer risk in BRCA1/2 carriers

<table>
<thead>
<tr>
<th>Study design</th>
<th>N</th>
<th>Exposure</th>
<th>Association BC risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrieu et al, JCO ’06</td>
<td>1601</td>
<td>Chest X-rays before and after age 20</td>
<td>+</td>
</tr>
<tr>
<td>Gronwald et al, BCRT ’08</td>
<td>296</td>
<td>Chest X-rays before age 30</td>
<td>+</td>
</tr>
<tr>
<td>Narod et al, Lancet Onc ’06</td>
<td>3200</td>
<td>Age at 1\textsuperscript{st} screening mammography</td>
<td>−</td>
</tr>
<tr>
<td>Goldfrank et al, CEBP ’06</td>
<td>213</td>
<td>Number of mammograms</td>
<td>−</td>
</tr>
</tbody>
</table>
IBCCS Study of X-ray exposure and breast cancer risk in BRCA carriers, Andrieu et al, JCO 2006

International BRCA1/2 Carrier Cohort Study
Retrospective cohort, N=1,601 carriers (53% affected)

2 Analytic approaches:
• Whole cohort
  Weighted vs. unweighted analysis
  – Necessary since breast cancer dx may have led to genetic testing → oversampling of affected individuals in cohort
• Incident cohort
  – Necessary to reduce survival bias (some women interviewed long after breast cancer dx → bias if exposure related to survival)
  – Restriction to individuals diagnosed/ censored within 5 yrs prior to interview (n=969, 295 affected)
Andrieu et al, JCO 2006

*chest X-rays before and after age 20*

- International BRCA1/2 Carrier Cohort Study
- Retrospective cohort, N=1,601 carriers (53% affected)

<table>
<thead>
<tr>
<th>Chest X-ray exposure</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever/never</td>
<td>1.54 (1.1 - 2.1)</td>
</tr>
<tr>
<td>Ever/never <em>(pseudo-incident cohort)</em></td>
<td>1.75 (1.1 – 2.8)</td>
</tr>
<tr>
<td>Ever/never &lt; age 20</td>
<td>1.76 (0.9 - 3.4)</td>
</tr>
<tr>
<td>Exposed &lt; age 20 only <em>(attained age&lt;41)</em></td>
<td>2.61 (1.3 - 5.4)</td>
</tr>
<tr>
<td>Exposed &lt; age 20 only <em>(born&gt;1949)</em></td>
<td>4.64 (2.2 - 10.9)</td>
</tr>
</tbody>
</table>
Andrieu et al, JCO 2006  
*chest X-rays before and after age 20*

Weighted Cox regression Analysis of combined X-ray exposure in the pseudo-incident cohort with follow-up beginning five years prior to interview

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pyrs (BC)</th>
<th>HR(^1)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined X-ray vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>773 (28)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Before age 20 only</td>
<td>137 (12)</td>
<td>5.21</td>
<td>1.6-17.5</td>
</tr>
<tr>
<td>After age 20 only</td>
<td>256 (26)</td>
<td>1.91</td>
<td>0.9-4.1</td>
</tr>
<tr>
<td>Before and after age 20</td>
<td>978 (88)</td>
<td>1.98</td>
<td>1.1-3.7</td>
</tr>
<tr>
<td>1-4 X-rays before and after age 20</td>
<td>705 (50)</td>
<td>1.76</td>
<td>0.9-3.4</td>
</tr>
<tr>
<td>5+ X-rays before or after age 20</td>
<td>666 (76)</td>
<td>2.69</td>
<td>1.4-5.3</td>
</tr>
</tbody>
</table>

\(^1\)Adjusted for parity (ever/never), stratified by country group and birth cohort
Mammograms not included in analysis

Why?

Concern about bias:
Family history of early breast cancer

Early start of mammographic screening

Confounding by indication might explain more mammographies at early ages in carriers with breast cancer at young ages
Narod et al, Lancet Onc 2006
age 1st screening mammography

• Case-control study in 44 centers, six countries: North America, Europe and Israel
  • N=1,600/1,600 matched on BRCA, year of birth, and country
  • Only prediagnostic mammograms included

• 41% cases and 46% controls exposed
• Mean age 1st mammography: 35.3 ±7.8; 14% had 1st mammography < age 30
• No association between earlier start of mammography and breast cancer risk

Narod S et al. Lanc Onc 2006;7(5):402-6
Goldfrank et al, CEBP 2006

**number of mammograms**

- 213 BRCA carriers from New York (US) and Barcelona (Spain); 85 affected
- Information on mammograms before enrollment/diagnosis (retrieved prior to test result)

- 89% exposed
- Median age 1\textsuperscript{st} mammogram 35 years
- No association between prediagnostic mammograms (number and age at 1\textsuperscript{st}) and breast cancer
Gronwald et al, BCRT 2008

*chest X-rays before age 30*

- Case-case study; all drawn from national breast screening registry Poland
- 138 BRCA1+ vs. 158 BRCA1-
- BRCA1+:
  - More frequent chest X-ray < age 20
  - 1.8 chest X-rays < age 30 vs. 1.0 in BRCA1- (p<0.01)
  - Breastca risk associated with ever chest X-ray < age 30 for BRCA1+ vs. BRCA1- carriers: OR =1.8 (1.2 - 2.9)
Limitations of 4 studies on diagnostic radiation in BRCA1/2 carriers

- Small sample size in 2/4 studies
- Incomplete exposure measurement
- Retrospective design
  - Self-reported exposure; no objective verification
  - Differential recall of exposure?
  - Literature: largely non-differential misclassification → attenuated risk estimates
  - Prevalent cases: potential survival bias
- Mammography exposure: self-selection for screening by family history? Would lead to spurious positive association and not to null finding.
Diagnostic radiation and breast cancer risk in BRCA1/2 carriers in the Netherlands

Pijpe et al, in preparation

- Retrospective cohort
- N=1,113 BRCA1/2 carriers
- Chest X-rays and fluoroscopies

*Preliminary results*

- Exposure to fluoroscopy and chest X-rays < age 20: 1.49 (0.98 – 2.25)
- Stronger risk increases in pseudo-incident cohort and subgroups

*Funding: Dutch Cancer Society and EU Gene Rad Risk*
Does benefit from early mammographic screening outweigh the radiation risk?

Estimated risk of radiation-induced breast cancer from mammographic screening in young BRCA mutation carriers (Berrington de Gonzalez et al, JNCI 2009)

• **Annual mammographic screening of carriers at**
  ─ age 25-29: no benefit
  ─ age 30-34: no or small benefit
  ─ Age 35 or older: some net benefit

• **Results dependent on number of assumptions: e.g.**
  ─ Mortality reduction mammography 15-25%
  ─ Lead time for breast cancer of 2 years
  ─ Survival probability carriers same as general population
  ─ Linear no-threshold model
  ─ Additive/(supra)multiplicative interaction BRCA and radiation
Overall contralateral breast cancers in BRCA1/2 mutation carriers and sporadic controls. HR, hazard ratio.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>No. of Events</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>445</td>
<td>12</td>
<td>9.57</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Genetic</td>
<td>160</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pierce et al JCO 2000
Radiotherapy for first breast cancer

- 71 BRCA 1/2 carriers with BC and 213 women with sporadic BC
- Median follow-up 5.3 years
- No increased risk of radiation-associated complications in carriers (skin, subcutaneous tissue, lung)
- No effect on CBC, but power very low (22 cases)
- Pierce 2006 with 160 carriers and 445 controls does not report on RT effect
Metcalfe et al JCO 2004

Radiotherapy for first breast cancer

- 491 BRCA 1/2 carriers with breast cancer
- Mean follow-up 9.2 yrs
- 10-year actuarial risk of CBC: 29.5%
- 46% received RT
- Multivariate HR associated with RT: 0.86 (95%CI 0.56 – 1.34)
- Reduced HRs for oophorectomy and tamoxifen (n.s.)
- Testing and survival bias
Broeks et al BCR 2007
Do DNA-damage repair pathway genes increase the risk of radiation-induced breast cancer?

- Case-only study of contralateral breast cancer (ideal for assessment of gene-environment interactions)
- 247 patients (80% response) with contralateral breast cancer after 1st breast cancer before age 50 (1966-2000)

**Assumption:** independence between genotype and exposure (RT)

Case-only study examining role of DNA damage repair pathway genes in radiation-induced contralateral breast cancer (CBC)

<table>
<thead>
<tr>
<th>Mutations in</th>
<th>CBC after RT (n=169)</th>
<th>CBC after surgery only (n=78)</th>
<th>OR for CBC after RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>14.2%</td>
<td>10.3%</td>
<td>1.5 (0.6-3.4)</td>
</tr>
<tr>
<td>ATM</td>
<td>2.4%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>CHECK2</td>
<td>7.7%</td>
<td>2.6%</td>
<td>3.2 (0.7-14.4)</td>
</tr>
<tr>
<td>Any DDRP mutation</td>
<td>24.3%</td>
<td>12.8%</td>
<td>2.2 (1.1-4.6)</td>
</tr>
</tbody>
</table>

Carriers of germline mutations in DDRP genes have increased risk of RT-induced breast cancer, compared to non-carriers

Radiotherapy and contralateral breast cancer risk in BRCA1/2 carriers

- BRCA carrier studies observed no association (Metcalfe et al, JCO 2004; Pierce et al, JCO 2000/2006), but low power

Recent Dutch Study:

- Among women with breast cancer, the risk of radiation-induced CBC ≥ 5 yrs after RT: OR 2.5 (1.03 – 6.10) for carriers of mutations in DNA damage repair pathway genes* vs. non-carriers (Broeks et al BCR 2007)
  Association due to BRCA 1/2?

* note: mutation in DNA damage repair pathway: BRCA1, BRCA2, CHEK2 and ATM
Radiation exposure and breast cancer in women with positive family history

- Inconsistent findings!

- Diagnostic radiation:

- Radiotherapy:
Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer

Maartje Hooning, Berthe Aleman, Michael Hauptmann, Margreet Baaijens, Jan Klijn, Ruth Noyon, Marilyn Stovall, Flora van Leeuwen


Funded by the Dutch Cancer Society
Dutch Late Effects of Breast Cancer Study

- Retrospective cohort study (n=7425)
- Patients with breast cancer stage I-III
- Admitted to NKI (Amsterdam) or DDHK (Rotterdam)
- Primary treatment between 1970-1986
- Age at diagnosis: up to 70 years
- 94% complete follow-up
- Median follow-up 14 years

Risk of CBC by treatment modality, in patients <45 yrs at BC diagnosis

cumulative risk (%)

0 10 20

time (years)

Postlumpectomy RT tangential fields
Postmastectomy RT

HR vs postmast RT: 1.53 (1.11 – 2.09)

1044 patients at NKI, treated before age 45

Detailed data collection:

- Quadrant of CBC
- Details on RT (field configuration, RT technique [rad energy], total dose, fractionation)
- Dose to CBC was estimated by M. Stovall for 31 different RT regimens: various RT regimens for tangential breast field, IMC field, chest wall fields etc., and brachy-therapy
### Effect of radiation dose on risk of medially located CBC; Cox analysis in patients < 45 yrs (n=1044)

<table>
<thead>
<tr>
<th>Radiation dose on medial part of CB</th>
<th>Risk of medially located CBC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gy</strong></td>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td>0</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>0-3.6</td>
<td>1.23 (0.34-4.48)</td>
</tr>
<tr>
<td>3.6-6.6</td>
<td>2.72 (0.75-9.79)</td>
</tr>
<tr>
<td>≥ 6.6</td>
<td>5.26 (1.44-19.3)</td>
</tr>
</tbody>
</table>

### Linear ERR per Gy**

0.37 (0.04-1.78), p=0.013 (trend)

* Adjusted for age (continuous), adjuvant CT
** Based on model RR=1+beta*dose where beta=ERR

Independent and joint effect of radiotherapy (RT) regimen and family history of BV on CBC risk (Cox model) in patients <45 yrs at BC diagnosis, CT, chemotherapy, HR, Hazard ratio.
Distribution of localization of CBC by family history of BC, in patients irradiated < age 45 yrs (n=943)

Overall

- Inner + Central: 46%
- Outer: 54%

≥ 1 Relatives with BC

- Inner + Central: 55%
- Outer: 45%

≥ 3 Relatives with BC

- Inner + Central: 82%
- Outer: 18%

No relatives with BC

- Inner + Central: 42%
- Outer: 58%
Preliminary conclusions

*Increased risk of radiation-induced breast cancer in BRCA carriers?*

- Inconsistent results
- Radiation sensitive subgroup of BRCA 1/2 carriers?
- Or radiation-sensitive subgroup of women with mutations in other BC genes/gene variants?
- Need for large and well-designed studies!
Gene-Rad-Risk
Radiation exposures at an early age: impact of genotype on breast cancer risk

- Coordination: IARC
- Aims:
  - To test whether mutations or polymorphisms in specific DNA repair genes increase the risk of radiation induced cancer, with specific focus on breast cancer.
  - To study the possible modifying effects of reproductive factors and cancer therapies other than radiation on the risk of radiation-induced breast cancer.
- 2 study arms:
  - Cancer survivor cohorts: childhood cancer survivors and Hodgkin’s Disease (HD) patients,
  - BRCA1/2 mutation carrier cohorts
GENE-RAD-RISK
BRCA1/2 mutation carrier cohort

• 3 nationwide cohort studies:
  • UK (EMBRACE), France (GENEPSO), the Netherlands (GEO-HEBON)

• Estimated sample size: N=2000 (43% affected)

• Information on:
  • Fluoroscopies, chest X-rays, mammograms, CT-scans, high dose
    radiotherapy, and other sources of ionizing radiation (incl. occupational)
  • Measures: ever/never, age 1st, number <20 / 20-29 / 30-39 (/ 40-49)

• Analysis
  • Single and combined measures, and cumulative breast dose score based
    on exposure- and calendar-specific dose estimates