What’s new for young women with BRCA mutations?

Mark Robson, MD
Memorial Sloan-Kettering Cancer Center
Weill Medical College of Cornell University
What’s “Young”?  

- Chronological age  
- Life stage
Young adults before full force of predisposition
• Risks and screening recommendations
• Risk reduction
• Reproductive considerations
Oscar Wilde

The truth is rarely pure, and never simple

Oscar Wilde
risk¹ /risk/ n 1 [C]  a thing harmful that wouldn’t allow was a risk/s
1.0-1.8% by age 30

Chen and Parmigiani
J Clin Oncol 2007;25:1329
1 in 5000/year from 20-24

1 in 1000/year from 25-29

Antoniou et al
Am J Hum Genet 2003;72:1117
- Mammogram yearly (start at 25)
- MRI yearly (start at 25)
Is a mammogram necessary?

- ~1/10 cancers are not seen on MRI
Estimated Risk of Radiation-Induced Breast Cancer From Mammographic Screening for Young BRCA Mutation Carriers

Amy Berrington de Gonzalez, Christine D. Berg, Kala Visvanathan, Mark Robson

BRCA mutation carriers are recommended to start mammographic screening for breast cancer as early as age 25–30 years. We used an excess relative risk model (based on a pooled analysis of three cohorts with 7600 subjects who received radiation exposure) to estimate the lifetime risk of radiation-induced breast cancer from five annual mammographic screenings in young (<40 years) BRCA mutation carriers. We then estimated the reduction in breast cancer mortality required to outweigh the radiation risk. Breast cancer rates for mutation carriers were based on a pooled analysis of 22 pedigree studies with 8139 subjects. For BRCA1 mutation carriers, the estimated lifetime risk of radiation-induced breast cancer mortality per 10000 women resulting from annual mammography was 26 (95% confidence interval [CI] = 14 to 49) for screening at age 25–29 years, 20 (95% CI = 11 to 39) for screening at age 30–34 years, and 13 (95% CI = 7 to 23) for screening at age 35–39 years. To outweigh these risks, screening would have to reduce breast cancer mortality by 51% (95% CI = 27% to 96%) at age 25–29 years, by 12% (95% CI = 6% to 23%) at age 30–34 years, and by 4% (95% CI = 2% to 7%) at age 35–39 years; estimates were similar for BRCA2 mutation carriers. If we assume that the mortality reduction from mammography is 15%–25% or less for young women, these results suggest that there would be no net benefit from annual mammographic screening of BRCA mutation carriers at age 25–29 years; the net benefit would be zero or small at age 30–34 years, but there should be some net benefit at age 35 or older. These results

In this analysis, we used this indirect approach to estimate the risk of radiation-induced breast cancer mortality from five annual mammographic screenings in BRCA mutation carriers before age 40 years and calculated the mortality reduction from screening that would be required to outweigh the radiation risk.

An outline of the methods is presented here, and additional details are available in a previous publication (7). To estimate the risk of radiation-induced breast cancer, we used an excess relative risk model (per gray) that was based on a pooled analysis of two cohorts of women who were exposed to multiple fluoroscopies and a cohort of children who received thymic irradiation (n = 7600) (5). The radiation exposures in those studies were from high-dose-rate X-rays similar to those that are used for mammography screening. The assumption underlying the excess relative risk model is that the magnitude of the radiation-induced cancer risk is proportional to the baseline cancer rate in the exposed population. Estimates of the baseline breast cancer incidence rates for BRCA1 and BRCA2 mutation carriers were taken from a pooled analysis of 22 studies of pedigree data (n = 8139) (9). The mean radiation dose to the glandular breast
<table>
<thead>
<tr>
<th>Mutation carrier status and screening period</th>
<th>Original assumptions, (^*) % mortality reduction needed to outweigh radiation risk</th>
<th>Alternative assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radiation risk model, %</td>
<td>Lead time for breast cancer &lt; age 40 y, %</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>Supramultiplicative(^\d)</td>
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<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age 25–29 y</td>
<td>&gt;51</td>
<td>&gt;8</td>
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<tr>
<td>Age 30–34 y</td>
<td>&gt;12</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Age 35–39 y</td>
<td>&gt;4</td>
<td>&gt;1</td>
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<tr>
<td><strong>BRCA2</strong></td>
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<td></td>
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<tr>
<td>Age 25–29 y</td>
<td>&gt;45</td>
<td>&gt;15</td>
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<tr>
<td>Age 30–34 y</td>
<td>&gt;14</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Age 35–39 y</td>
<td>&gt;7</td>
<td>&gt;2</td>
</tr>
</tbody>
</table>

\(^*\) The original assumptions included a multiplicative risk model and a lead time of 2 years.
• “Stacked” or “Split”

• Specificity (false positives) an issue
Other screening modalities

- PET
- Sestamibi
- Ultrasound
- Ductal lavage
- Tomosynthesis
- Contrast-enhanced mammography
PREVENTION
Preventive mastectomy
Supplements
New avenues

Vaccines
PARP inhibitors
Bisphosphonates
Reproductive issues
Oral contraceptives

• Reduce ovarian cancer risk
• Impact on breast cancer risk?
<table>
<thead>
<tr>
<th>Study</th>
<th>OCP ever</th>
<th>OCP &lt; 20</th>
<th>Total Duration</th>
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<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td>BRCA2</td>
<td>BRCA1</td>
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<tr>
<td>Brohet 2007</td>
<td>1.47</td>
<td>1.49</td>
<td>1.41</td>
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<td>Haile 2007</td>
<td>0.64</td>
<td>1.29</td>
<td>0.84</td>
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<td>Milne 2005</td>
<td>0.22</td>
<td>1.02</td>
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<td>Narod 2002</td>
<td>1.38</td>
<td>0.94</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Table courtesy of Ilana Cass, MD
• Decreases risk (most studies)
• Early age not clearly more protective
• Breast-feeding not clearly protective
Pregnancy: Issues

• Screening before and during pregnancy
• Reduced fertility in mutation carriers
• Risks associated with ART not clear
Pre-implantation diagnosis (PGD)
Questions?