Assessment and Management of Genetic Predisposition to Breast Cancer

Dr Munaza Ahmed
Consultant Clinical Geneticist
2/7/18
Overview

• The role of the Cancer Genetics team
• NICE guidelines for Familial Breast Cancer
• Genetic predisposition to Breast cancer
  - \textit{BRCA1} & \textit{BRCA2}
  - \textit{PALB2}
• Moderate and low risk breast cancer predisposition genes
All cancer is genetic but not all cancer is hereditary.
Genetic Testing

**Somatic mutations**
- Occur in *nongermline* tissues
- Cannot be inherited

**Germline mutations**
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only (for example, breast)  
**Nonheritable**  
Mutation in egg or sperm  
**Heritable**  
All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Genetic Architecture of Cancer Risk

- Common variants (low penetrance)
- Rare variants (moderate penetrance)
- Rare variants (high penetrance)
Assessment of risk in cancer genetics

- Risk/chance of carrying a disease-causing variant in a cancer susceptibility gene
  - AD inheritance
  - Number of relevant cancers
  - Young ages of cancer diagnoses
  - Type of cancer, histology
- Risk/chance of developing cancer
  - patient’s current age
  - penetrance of the gene

NICE recommend BRCA testing in those with a 10% chance of a mutation
Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer

Chemoprevention for women with no personal history of breast cancer

1.7.20 Healthcare professionals within secondary care or specialist genetic clinics should discuss the absolute benefits and risks of options for chemoprevention with women at high or moderate risk of breast cancer. Discussion, using a decision aid, should include the following to promote shared decision-making and informed preferences:

- the reduced risk of invasive breast cancer
- the lack of effect on mortality
- the side effects of the different options
- alternative approaches, such as surveillance alone and, for women at high risk, risk-reducing surgery.

Women should all be given information in an accessible format. [2013, amended 2017]
Boadicea
Centre for Cancer Genetic Epidemiology

BOADICEA

BOADICEA is a computer program that is used to estimate BRCA1/BRCA2 mutation carrier probabilities and breast/ovarian cancer risks on the basis of family history.

Some key features:

› Unlimited access via the Web
› No specialist knowledge required
› Risk calculations are quicker and easier
› Online pedigree building module
› Pedigree data upload module
› Processes large and complex pedigrees
› Checks input pedigree data for errors
› Online pedigree drawing module
› Automatic processing report generation
› Pedigrees built online can be downloaded

Boadicea

› BOADICEA model
› BOADICEA Web Application
› Apply for a BOADICEA user account
› Run a BOADICEA risk calculation
› Download the BOADICEA user guide

Further information

› Boadicea – FAQs
› Advice for the public
› Publications
2.0 BOADICEA risk calculation results

Index or subject of the BOADICEA calculation

Firstname/identifier of index: Paula
Unique identifier of index: 1

The BOADICEA model predicts the following BRCA1/BRCA2 mutation carrier probabilities and breast/ovarian cancer risks for this individual:

<table>
<thead>
<tr>
<th>Genetic status</th>
<th>Mutation carrier probabilities (Percent)</th>
<th>Age</th>
<th>Breast cancer risks (Percent)</th>
<th>Ovarian cancer risks (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>0.3</td>
<td>46</td>
<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>BRCA2</td>
<td>2.9</td>
<td>47</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>No mutation</td>
<td>96.8</td>
<td>48</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
<td>2.9</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>3.7</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>7.8</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>11.8</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>15.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>19.6</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75</td>
<td>22.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>24.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Model parameters

Family member | Paula (1)

Mutation frequencies

UK
BRCA1: 6.394d-4
BRCA2: 0.00102

Mutation search sensitivities

Default
BRCA1: 0.7
BRCA2: 0.8

Cancer incidence rates

UK
Manchester Scoring System

Testing offered if score >15

<table>
<thead>
<tr>
<th>Pathology</th>
<th>BRCA1 adj</th>
<th>BRCA2 adj</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2+</td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td>Lobular</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>DCIS only</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>LCIS only</td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1 IDC</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2 IDC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 IDC</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>ER pos</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>ER neg</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 triple neg</td>
<td>+4</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC&lt;30</td>
<td>6</td>
</tr>
<tr>
<td>FBC 30-39</td>
<td>4</td>
</tr>
<tr>
<td>FBC 40-49</td>
<td>3</td>
</tr>
<tr>
<td>FBC 50-59</td>
<td>2</td>
</tr>
<tr>
<td>FBC&gt;59</td>
<td>1</td>
</tr>
<tr>
<td>MBC &lt;60</td>
<td>5</td>
</tr>
<tr>
<td>MBC&gt;59</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian cancer &lt;60</td>
<td>8</td>
</tr>
<tr>
<td>Ovarian cancer &gt;59</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>0</td>
</tr>
<tr>
<td>Prostate cancer &lt;60</td>
<td>0</td>
</tr>
<tr>
<td>Prostate cancer &gt; 59</td>
<td>0</td>
</tr>
</tbody>
</table>
BRCA testing in those without a family history of breast or ovarian cancer

- Triple negative tumour diagnosed below the age of 60 years
- Bilateral primary breast cancers both diagnosed below 50 years
- Breast and ovarian cancer at any age
- Male breast cancer at any age
- Women with Ashkenazi Jewish or Polish ancestry diagnosed with breast cancer at any age*
Classic BRCA1 Pedigree

- Male with Ovarian cancer, dx 49
- Female with Breast cancer, dx 42
- Female with Breast cancer, dx 38
- Male with Ovarian cancer, dx 53
Classic BRCA2 Pedigree

Prostate, dx 55

Breast, dx 45
Pancreatic, dx 55

Ovarian, dx 58

Breast, dx 52
# Lifetime Cancer Risks conferred by a BRCA mutation

## BRCA1
- **Breast ca**: 60-80% / Population Risk: 12%
- **Ovarian ca**: 40-60% / Population Risk: 2%

## BRCA2
- **Breast ca**: 40-60% / Population Risk: 12%
- **Ovarian ca**: 20-30% / Population Risk: 2%
- **Prostate ca**: 20-25% / Population Risk: 12%
- **Male breast ca**: 5-10% / Population Risk: 0.1%
- **Pancreatic ca**: 5% / Population Risk: 0.5%
Cancer risk management options for BRCA mutation carriers

**Surveillance**
- MRI from 30 years
- mammograms and MRI scans annually from 40 - 50 yrs
- mammograms only from 50 yrs

**Chemoprevention**
- Tamoxifen/Raloxifene/Anastrozole
- Treatment for 5 yrs leads to 40-50% risk reduction

**Risk-reducing bilateral mastectomy**
- Can be done with or without reconstruction
- Reduces breast cancer risk to <5%
Benefits of BRCA testing at breast cancer diagnosis

- Identification of a mutation would support use of platinum-based chemotherapy which may allow a better prognosis for the patient
- May aid in decisions regarding the appropriateness of contralateral mastectomy
- Radiotherapy may be avoided
- Treatment with a PARP inhibitor may become an option
Treatment with PARP inhibitors

Figure 1. Mechanism of Cell Death from Synthetic Lethality, as Induced by Inhibition of Poly(Adenosine Diphosphate [ADP]–Ribose) Polymerase 1 (PARP1).

In normal cells, both base-excision repair and homologous recombination are available for the repair of damaged DNA (Panel A). In cells that have lost either BRCA1 or BRCA2 (e.g., cancer cells in carriers of a BRCA1 or BRCA2 mutation), homologous recombination is non-functional, and base-excision repair and other DNA-repair processes can compensate for the loss of homologous recombination (Panel B). In cells that have lost base-excision repair function because of PARP1 inhibition but retain at least one functioning copy of BRCA1 and BRCA2 (e.g., normal cells in carriers of a BRCA1 or BRCA2 mutation), homologous recombination is intact and can repair DNA damage, including damage left unrepaired because of the loss of base-excision repair (Panel C). In the cancer cells of mutation carriers, all BRCA1 or BRCA2 function is absent, and when PARP1 is inhibited, cancer cells are unable to repair DNA damage by homologous recombination or base-excision repair, and cell death results.
The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer

Lynn C. Hartmann, M.D., and Noralane M. Lindor, M.D.
Most studies show at least a 90% breast cancer risk reduction following bilateral mastectomy.

### Table 1. Bilateral Risk-Reducing Mastectomy (BRRM)*

<table>
<thead>
<tr>
<th>Study and Focus</th>
<th>Design</th>
<th>Eligibility</th>
<th>Participants</th>
<th>Follow-up yr</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer risk reduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic; Hartmann et al.*22</td>
<td>Retrospective cohort</td>
<td>Women with high familial risk of breast cancer</td>
<td>214 with BRRM, 403 sisters without BRRM</td>
<td>14</td>
<td>3 breast cancers in BRRM group, 38 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.08 (95% CI, 0.02–0.33)</td>
</tr>
<tr>
<td>Mayo Clinic; Hartmann et al.*23</td>
<td>Subcohort of carriers identified among original 214 women with BRRM</td>
<td>BRCA1 or BRCA2 carriers</td>
<td>18 with BRRM</td>
<td>13.4</td>
<td>0 breast cancers in BRRM group†††</td>
</tr>
<tr>
<td>Rotterdam; Meijers-Heijboer et al.*24</td>
<td>Prospective cohort</td>
<td>BRCA1 or BRCA2 carriers</td>
<td>76 with BRRM, 63 without BRRM</td>
<td>2.9</td>
<td>0 breast cancers in BRRM group†</td>
</tr>
<tr>
<td>Rotterdam; Heemskerk-Gerritsen et al.*25</td>
<td>Prospective cohort</td>
<td>BRCA1 or BRCA2 carriers and noncarriers with hereditary risk of breast cancer</td>
<td>177 with BRRM</td>
<td>4.5</td>
<td>1 breast cancer in BRRM group‡</td>
</tr>
<tr>
<td>PROSE Study Group; Rebbeck et al.*26</td>
<td>Retrospective cohort</td>
<td>BRCA1 or BRCA2 carriers</td>
<td>102 with BRRM, 378 without BRRM</td>
<td>6.4</td>
<td>2 breast cancers in BRRM group, 184 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.05–0.09 (95% CI, 0.01–0.38)</td>
</tr>
<tr>
<td>PROSE; Domchek et al.*27</td>
<td>Prospective cohort</td>
<td>BRCA1 or BRCA2 carriers</td>
<td>247 with BRRM, 1372 without BRRM</td>
<td>3</td>
<td>0 breast cancers in BRRM group, 98 breast cancers in no-BRRM group†</td>
</tr>
<tr>
<td>Multicenter European collaboration; Evans et al.*28</td>
<td>Ascertainment both retrospective and prospective; follow-up prospective</td>
<td>Women with a lifetime risk of breast cancer &gt;25%</td>
<td>314 with BRRM</td>
<td>NR</td>
<td>0 breast cancers in women with BRRM; authors estimated that 21 breast cancers would have occurred in these women from person-years at-risk analysis based on mutation status or family history‡§</td>
</tr>
<tr>
<td>Denmark; Skytte et al.*29</td>
<td>Retrospective national cohort</td>
<td>BRCA1 or BRCA2 carriers</td>
<td>96 with BRRM, 211 without BRRM</td>
<td>NR</td>
<td>3 breast cancers in BRRM group, 16 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.39 (95% CI, 0.12–1.36); P=0.14</td>
</tr>
</tbody>
</table>
Cancer Genetics in the oncology clinic

For breast cancer teams:

1. Please read MCG LRP1 – Breast Unit BRCA testing learning resources pack
2. Please view MCG ELM1, MCG ELM2, MCG ELM3a and MCG ELM4 on the MCG programme YouTube channel: www.youtube.com/MCGprogramme/videos

For gynaec cancer teams:

1. Please read MCG LRP2 – Gynaec Unit BRCA testing learning resources pack
2. Please view MCG ELM1, MCG ELM2, MCG ELM3b and MCG ELM4 on the MCG programme YouTube channel: www.youtube.com/MCGprogramme/videos
Pitfalls of BRCA testing

• Psychosocial issues
• In 5-10% cases tested a variant of unknown significance (VUS) is identified
• This is a genetic alteration which is not a clearly cancer-causing mutation
• The chance of finding a VUS increases when there is no family history and it’s harder to clarify whether it’s a causative mutation because we cannot look for it in other affected family members
Breast-Cancer Risk in Families with Mutations in PALB2


ABSTRACT

BACKGROUND
Germline loss-of-function mutations in PALB2 are known to confer a predisposition to breast cancer. However, the lifetime risk of breast cancer that is conferred by such mutations remains unknown.

METHODS
We analyzed the risk of breast cancer among 362 members of 154 families who had deleterious truncating, splice, or deletion mutations in PALB2. The age-specific breast-cancer risk for mutation carriers was estimated with the use of a modified segregation-analysis approach that allowed for the effects of PALB2 genotype and residual familial aggregation.

RESULTS
The risk of breast cancer for female PALB2 mutation carriers, as compared with the general population, was eight to nine times as high among those younger than 40 years of age, six to eight times as high among those 40 to 60 years of age, and five times as high among those older than 60 years of age. The estimated cumulative risk of breast cancer among female mutation carriers was 14% (95% confidence interval [CI], 9 to 20) by 50 years of age and 35% (95% CI, 26 to 46) by 70 years of age. Breast-cancer risk was also significantly influenced by birth cohort (P < 0.001).
PALB2 Breast Cancer Risks

Breast-Cancer Risk for Female PALB2 Mutation Carriers

- 95% CI
- Mean
- 5% CI

Mean Cumulative Risk of Breast Cancer (%)

Age (yr)
PALB2 cancer risks

- Partner And Localiser of BRCA2
- Mutations confer up to a 40% lifetime risk of breast cancer
- Risk modified according to family history
- Risk reducing mastectomy can be offered
- Likely increased risk of pancreatic cancer but risks not defined
- May confer an increased risk of ovarian and prostate cancer but more data required to confirm this
PALB2 family tree

I

II
d. 83 years
d. 86 years MI

III

IV

50 years

V

3
Genetic predisposition to breast cancer
Classes of breast and ovarian cancer susceptibility genes/loci

Breast cancer susceptibility loci
- High – BRCA1, BRCA2, TP53, PTEN, CDH1, STK11, PALB2
- Moderate – CHEK2, ATM, NF1, NBN
- Low – multiple genes/loci have now been identified

Ovarian cancer susceptibility genes
- High – BRCA1, BRCA2
- Moderate - RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2, EPCAM
- Low – multiple loci
Moderate Risk Breast Cancer Susceptibility Genes

- Confer an approximately 2-fold relative risk of breast cancer in mutation carriers
- Pathogenic mutations in these genes are rare
- Identified through large case-control studies
- Selected for investigation through the candidate gene approach due to the biological function of the protein
- Involved in DNA repair
Low Penetrance Breast Cancer Susceptibility Loci

• Many loci identified (some loci within known genes)
• Account for 28% of familial breast cancer risk
• Common (a single loci can be present in up to 40% population)
• Low risks conferred: relative risk <1.5
• Thought to confer risk in a multiplicative manner
• It is estimated that a person would need to carry 30-40 such alleles for a x3 RR of breast ca
Gene test 'narrows down breast cancer risk'

By Jenny Walrond
Health Correspondent

08 October 2017
Breast cancer risk prediction using a polygenic risk score in the familial setting: a prospective study from the Breast Cancer Family Registry and kConFab.

Li H1, Feng B2, Miron A3,4, Chen X5, Beasley J6, Bimeh E6, Barrowdale D7, John EM8,9, Daly MB10, Andrulis IL11, Buys SS12, Kraft P13, kConFab investigators, Thorne H14, Chenevix-Trench G5, Southey MC15, Antoniou AC7, James PA16,17, Terry MB18,19, Phillips KA16,17,20, Hopper JL20, Mitchell G16,17, Goldgar DE1,2.

Abstract

PURPOSE: This study examined the utility of sets of single-nucleotide polymorphisms (SNPs) in familial but non-BRCA-associated breast cancer (BC).

METHODS: We derived a polygenic risk score (PRS) based on 24 known BC risk SNPs for 4,365 women from the Breast Cancer Family Registry and Kathleen Cuningham Consortium Foundation for Research into Familial Breast Cancer familial BC cohorts. We compared scores for women based on cancer status at baseline; 2,599 women unaffected at enrollment were followed-up for an average of 7.4 years. Cox proportional hazards regression was used to analyze the association of PRS with BC risk. The BOADICEA risk prediction algorithm was used to measure risk based on family history alone.

RESULTS: The mean PRS at baseline was 2.25 (SD, 0.35) for affected women and was 2.17 (SD, 0.35) for unaffected women from combined cohorts (P < 10⁻⁶). During follow-up, 205 BC cases occurred. The hazard ratios for continuous PRS (per SD) and upper versus lower quintiles were 1.38 (95% confidence interval: 1.22-1.56) and 3.18 (95% confidence interval: 1.84-5.23) respectively. Based on their PRS-based predicted risk, management for up to 23% of women could be altered.

CONCLUSION: Including BC-associated SNPs in risk assessment can provide more accurate risk prediction than family history alone and can influence recommendations for cancer screening and prevention modalities for high-risk women. Genet Med 19 1, 30-35.

PMID: 27171545  PMCID: PMC5107177  DOI: 10.1038/gim.2016.43
Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers.

Kuchenbaecker KB¹,², McGuffog L², Barrowdale D², Lee A², Soucy P³, Dennis J², Domchek SM⁴, Robson M⁵, Spurdle AB⁵, Ramus SJ⁷, Mavaddat N², Terry MB², Neuhausen SL⁸, Schmutzler RK⁹, Simard J³, Pharoah PDP¹¹, Offit K¹², Couch FJ¹³, Chenevix-Trench G⁶, Easton DF², Antoniou AC².

Abstract

BACKGROUND: Genome-wide association studies (GWAS) have identified 94 common single-nucleotide polymorphisms (SNPs) associated with breast cancer (BC) risk and 18 associated with ovarian cancer (OC) risk. Several of these are also associated with risk of BC or OC for women who carry a pathogenic mutation in the high-risk BC and OC genes BRCA1 or BRCA2. The combined effects of these variants on BC or OC risk for BRCA1 and BRCA2 mutation carriers have not yet been assessed while their clinical management could benefit from improved personalized risk estimates.

METHODS: We constructed polygenic risk scores (PRS) using BC and OC susceptibility SNPs identified through population-based GWAS: for BC (overall, estrogen receptor [ER]-positive, and ER-negative) and for OC. Using data from 15,252 female BRCA1 and 8,211 BRCA2 carriers, the association of each PRS with BC or OC risk was evaluated using a weighted cohort approach, with time to diagnosis as the outcome and estimation of the hazard ratios (HRs) per standard deviation increase in the PRS.

RESULTS: The PRS for ER-negative BC displayed the strongest association with BC risk in BRCA1 carriers (HR = 1.27, 95% confidence interval [CI] = 1.23 to 1.31, P = 8.2×10⁻53). In BRCA2 carriers, the strongest association with BC risk was seen for the overall BC PRS (HR = 1.22, 95% CI = 1.17 to 1.28, P = 7.2×10⁻20). The OC PRS was strongly associated with OC risk for both BRCA1 and BRCA2 carriers. These translate to differences in absolute risks (more than 10% in each case) between the top and bottom deciles of the PRS distribution; for example, the OC risk was 6% by age 80 years for BRCA2 carriers at the 10th percentile of the OC PRS compared with 19% risk for those at the 90th percentile of PRS.

CONCLUSIONS: BC and OC PRS are predictive of cancer risk in BRCA1 and BRCA2 carriers. Incorporation of the PRS into risk prediction models has promise to better inform decisions on cancer risk management.

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Summary

• BRCA1/2 and PALB2 testing offered to all breast cancer patients with a 10% chance of carrying a mutation
• This can impact treatment options
  - platinum-based chemotherapy
  - avoidance of radiotherapy
  - risk-reducing surgery
• Testing for multiple low risk hereditary factors will allow more personalised medicine for patients with/at risk of breast cancer
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