Cancer risk prediction via algorithms: identifying individuals at high-risk of breast and ovarian cancer

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University of Cambridge, U.K.
• No conflicts of interest to declare
Cancer risk prediction in the era of NGS

• Next Generation Sequencing technologies

• Multi-gene and SNP panels

• Clinical utility:
  - Reliable cancer risk estimates
  - Comprehensive cancer risk prediction models
Outline

• Cancer risks for rare genetic variants?
• Joint effects of common genetic variants?
• Joint effects of common and rare genetic variants?
• How do genetic and lifestyle/hormonal factors interact?
• Implications for breast cancer risk stratification?
• Available breast cancer risk prediction tools?
• BOADICEA updates: rare and common variants
Progress through collaboration
Consortia

- Breast Cancer Linkage Consortium (BCLC)
- International BRCA1/2 Carrier Cohort Study (IBCCS)
- Breast Cancer Association Consortium (BCAC)
- Ovarian Cancer Association Consortium (OCAC)
- Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)
- GOCS, OncoArray

Open Access Resources

- Breast Cancer Family Registry
- kConFab
Outline

• Cancer risks for rare genetic variants?
  – BRCA₁, BRCA₂, PALB₂, CHEK₂, other.

• Joint effects of common genetic variants?

• Joint effects of common and rare genetic variants?

• How do genetic and lifestyle/hormonal factors interact?

• Implications for breast cancer risk stratification?

• Available breast cancer risk prediction tools?

• BOADICEA updates: rare and common variants
Genetic Variant Characterisation

Study Designs (1)

Case-Control Studies

- Variant frequency in cases VS frequency in controls
- Very large sample sizes required for rare genetic variants
- Possible in the context of large international consortia
  - Breast Cancer Association Consortium
  - Ovarian Cancer Association Consortium
  - e.g. CHEK2: 1100delC
Retrospective family-based studies

- Mutation screening in cancer patients (with or without selection criteria)
Retrospective family-based studies

- Mutation screening in cancer patients (with or without selection criteria)
- Phenotypes of family members and/or mutation testing in relatives

![Family tree diagram]

- Screened for mutations
- dx 41
- dx 50
- 35
Retrospective family-based studies

- Mutation screening in cancer patients (with or without selection criteria)
- Phenotypes of family members and/or mutation testing in relatives
- Modified segregation analysis
  - e.g. $PALB_2$
- Ascertainment issues, self-reported family histories
Prospective cohort studies

• Cohort of unaffected mutation carriers followed over time
• Estimates “free” of ascertainment/reporting biases
• Large numbers of unaffected mutation carriers required
• Long periods of observation

• Largest study until recently:
  ➢ $BRCA_1$, $BRCA_2$
  ➢ <64breast, 31 ovarian cancers

Mavaddat JNCI 2013; Evans JMG 2104; Senst Clin Gen 2013
Subjects: prospective cohort data

- International $BRCA_1/2$ Carrier Cohort Study: 7,666 (Europe)
- Breast Cancer Family Registry: 1,570 (USA, Canada, Australia)
- KConFab: 620 (Australia)
- Recruitment: clinical genetics centres
- Recruitment: 1997 and 2013, baseline questionnaires
- Follow-up: questionnaires, linkage to cancer registries
- 9,856 ($BRCA_1$: 6,036; $BRCA_2$: 3,820), >1 year follow-up
- Average follow-up: 5 years
BRCA₁, BRCA₂ – Prospective risk estimation

- Largest collaborative prospective cohort study to date
- Estimate age-specific breast, ovarian cancer risks
- Contrast to retrospective risk estimates
- Modification of cancer risks by family history?
- Risks by mutation location/characteristics?
Breast and ovarian cancer risk estimation

<table>
<thead>
<tr>
<th>End Point of Interest</th>
<th>BRCA\textsubscript{1/2}</th>
<th>BRCA\textsubscript{1}</th>
<th>BRCA\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer (BC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC, OC, other Cancer and risk-reducing bil. mastectomy free</td>
<td>3,886</td>
<td>2,276</td>
<td>1,610</td>
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<tr>
<td>N incident Breast cancers</td>
<td>426</td>
<td>269</td>
<td>157</td>
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<tr>
<td>Ovarian Cancer (OC)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>OC, other cancer (other than BC), Risk-reducing salp.-oophorect. free</td>
<td>5,066</td>
<td>2,905</td>
<td>2,161</td>
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<tr>
<td>N incident Ovarian cancers</td>
<td>109</td>
<td>85</td>
<td>24</td>
</tr>
</tbody>
</table>
## Estimated breast cancer incidence

<table>
<thead>
<tr>
<th>Age group</th>
<th>Events</th>
<th>BRCA1 Incidence /1000 pyrs</th>
</tr>
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<tbody>
<tr>
<td>21-30</td>
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<td>5.9</td>
</tr>
<tr>
<td>31-40</td>
<td>90</td>
<td>23.5</td>
</tr>
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<td>28.3</td>
</tr>
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<tr>
<td>71-80</td>
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<td>16.5</td>
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SIR: Standardised incidence rate, relative to country-, calendar period specific incidences
## Estimated breast cancer incidence

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P-trend=$10^{-27}$

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<td>44</td>
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<td>14</td>
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<td>5</td>
<td>6</td>
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**P-trend** = $10^{-27}$
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P-trend=10^{-27}  P-trend=10^{-6}

SIR: Standardised incidence rate, relative to country- and calendar-period specific incidences
$BRCA_1, BRCA_2$ : Cumulative breast cancer risk

Kuchenbaecker et al, JAMA 2017

![Graph showing cumulative breast cancer risk for BRCA1 and BRCA2 carriers]

- 43% (61-72%)
- 66% (65-79%)
- 72%
BRCA₁, BRCA₂ : Cumulative breast cancer risk

Kuchenbaecker et al., JAMA 2017
### Estimated ovarian cancer incidence

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<thead>
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<th>$BRCA_1$ Incidence /1000 pyrs</th>
<th>SIR</th>
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<tbody>
<tr>
<td>21-30</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>31-40</td>
<td>10</td>
<td>1.8</td>
<td>41</td>
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<td>25</td>
<td>7.0</td>
<td>57</td>
</tr>
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<td>24</td>
<td>13.8</td>
<td>53</td>
</tr>
<tr>
<td>61-70</td>
<td>24</td>
<td>29.4</td>
<td>69</td>
</tr>
<tr>
<td>71-80</td>
<td>2</td>
<td>5.7</td>
<td>12</td>
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## Estimated ovarian cancer incidence

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<th>BRCA₂ Incidence /1000 pyrs</th>
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*BRCA₁ VS BRCA₂ p=10⁻⁷*

SIR: Standardised incidence rate, relative to country-, calendar period specific incidences
BRCA1, BRCA2: Cumulative ovarian cancer risk

Kuchenbaecker et al, JAMA 2017
Retrospective VS Prospective estimates

**BRCA1 – Breast Cancer**

![Graph showing cumulative breast cancer risk by age for Retrospective and Prospective estimates.](image)

- **Retrospective Average**
- **Prospective**

Cumulative breast cancer risk

Age

20, 30, 40, 50, 60, 70, 80

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## Breast cancer risks by family history

Analyses stratified by birth cohort and study group

<table>
<thead>
<tr>
<th>Family History Category (1\textsuperscript{st} or 2\textsuperscript{nd} degree relatives)</th>
<th>BRCA1</th>
<th>95%CI</th>
<th>BRCA2</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Breast cancer</td>
<td>1.0</td>
<td>1.0</td>
<td>1.53</td>
<td>0.86-2.7</td>
</tr>
<tr>
<td>1 Breast cancer</td>
<td>1.51</td>
<td>1.10-2.11</td>
<td>1.53</td>
<td>0.86-2.7</td>
</tr>
<tr>
<td>\geq2 Breast cancers</td>
<td>2.00</td>
<td>1.40-2.82</td>
<td>1.91</td>
<td>1.08-3.4</td>
</tr>
</tbody>
</table>

P-trend=0.0001 \hspace{1cm} P-trend=0.02

Kuchenbaecker et al, JAMA 2017
BCLC: **BRCA2** genotype-phenotype correlations
Retrospective – family based

**Slide courtesy:** Deborah Thompson

164 Families
92 mutations

**Thompson et al, AJHG 2001**
Consortium of Investigators of Modifiers of BRCA1/2

- Initiated: 2005
- >70 groups from Europe, North America, Australia, Asia, Africa and South America
- >55,000 BRCA1, BRCA2 mutation carriers
CIMBA: $BRCA_2$ genotype-phenotype correlations
Retrospective studies

~1800 $BRCA_2$ mutations
Prospective studies: IBCCS, BCFR, kConFab

**BRCA1**: Genotype – Phenotype correlations

**BRCA1**: Cumulative breast cancer risk by mutation location

- 5′ to c.2281
- c.2282 to c.4071
- 3′ to c.4072

Breast cancer risk (%)

Age (years)

- 70% (64-76%)
- 55% (46-67%)

HR = 1.5
P-diff = 0.007

Daniel Barnes; Kuchenbaecker et al JAMA 2017
Prospective studies: IBCCS, BCFR, kConFab

**BRCA2**: Genotype – Phenotype correlations

**BRCA2**: Cumulative breast cancer risk by mutation location (wide)

- **5’ to c.2830**
- **c.2831 to c.6401**
- **3’ to c.6402**

HR = 1.9
P-diff < 0.001

Daniel Barnes; *Kuchenbaecker et al JAMA 2017*
PALB2 mutations and breast cancer risk

- Breast Cancer RR estimates: 2.3 – 30.1
- Absolute Breast Cancer Risk estimates: 20% - 91%
- Largest study: 33 PALB2 mutation carriers
- Considerable uncertainty in breast cancer risks
- Counselling of PALB2 mutation carriers unclear

**PALB2**: Penetrance combined families analysis

*PALB2* Interest Group, http://www.palb2.org

- 17 participating studies

- 154 families with ≥ 1 *PALB2* mutation carrier

**Study designs/ascertainment:**

- Population based BC cases screened for *PALB2* mutations
- Families with multiple affected family members

**Statistical methods:**

- Retrospective kin-cohort studies
- Modified segregation analysis
PALB2 Interest Group (http://www.palb2.org)

Family-based studies

**PALB2**: breast cancer risk by family history

**PALB2: Kin-cohort VS Case-Control estimates**

- Cybulski et al (Lancet Oncol, 2015)

  12529 cases/4702 controls

  RR = 4.5 (95% CI: 2.3–8.4)

  ➡ Absolute risk (age 75)\(^1\) ~ 33-37%

- **PALB2 Interest group**

  Absolute risk (age 75) ~ 39%

\(^1\) based on UK incidences (Antoniou et al Lancet Oncol 2015)
CHEK2 – 1100delC
Breast Cancer Association Consortium: 44,777 cases / 42,997 controls

Schmidt et al, JCO 2016
The Collaborative Oncological Gene-environment Study (COGS)

- Breast Cancer Association Consortium (BCAC)
  - 100k cases/100k controls

- Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)
  - 30,000 BRCA1/2 carriers

- Ovarian Cancer Association Consortium (OCAC)
  - 26k cases/18k controls

- Prostate Cancer Association Group (PRACTICAL)
  - 25k Cases/25kControls

- International BRCA1/2 Carrier Cohort Study (IBCCS)
  - 8,000 BRCA1/2 carriers

Co-ordinators: Per Hall, Doug Easton

http://www.cogseu.org/
The OncoArray Consortium: A Network for Understanding the Genetic Architecture of Common Cancers

- >450,000 samples
- Breast Cancer (BCAC)
- Ovarian Cancer (OCAC)
- Prostate Cancer (PRACTICAL)
- CIMBA (BRCA1/2 mutation carriers)
- TRICL (Lung Cancer)
- CORECT (Colorectal cancer)

Amos et al, CEBP (2017)
• Identify and characterise cancer susceptibility variants

• Interactions: Genetic Variants × Lifestyle/Environmental Factors

• Associations with certain tumour subtypes and outcome

• Develop comprehensive risk models
Individual SNP associations

• Each SNP: 0, 1, 2 risk alleles
• Odds Ratio estimates per risk allele: 1.02-1.30
• Minor allele frequencies: >0.01

• Individual SNP predictive ability poor
• SNPs combine multiplicatively on risk scale
Combined SNP associations

• Polygenic Risk Scores (PRS)

\[ \text{PRS} = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n \]

- Log(Odds Ratio) estimate
- Number of risk alleles at each SNP
SNP Polygenic Risk Score

- Breast Cancer Association Consortium (BCAC)
- 33,673 breast cancer cases and 33,381 control women
- PRS normally distributed in both cases and controls
- Mean PRS (cases) = 0.69
  Mean PRS (controls) = 0.49

Mavaddat et al JNCI 2015
Empirical PRS Odds Ratios VS predicted under multiplicative model
77-SNP PRS and risk stratification

Mavaddat et al JNCI 2015
77-SNP PRS and risk stratification

Mavaddat et al JNCI 2015
77-SNP PRS and risk stratification

Mavaddat et al JNCI 2015
PRS and lifetime breast cancer risk

Mavaddat et al. JNCI 2015
PRS and lifetime breast cancer risk

Mavaddat et al. JNCI 2015

29%

3.5%
PRS and lifetime breast cancer risk

- 8% of all UK women
- 17% of all breast cancer cases
Outline

• Cancer risks for rare genetic variants?
• Joint effects of common genetic variants?
• **Joint effects of common and rare genetic variants?**
• How do genetic and lifestyle/hormonal factors interact?
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• Available breast cancer risk prediction tools?
• BOADICEA updates: rare and common variants
Consortium of Investigators of Modifiers of $BRCA_{1/2}$

- >70 groups from Europe, North America, Australia, Africa and South America
- >55,000 $BRCA_{1}$, $BRCA_{2}$ mutation carriers
Approaches in identifying genetic modifiers of risk

- GWAS specifically in \( BRCA_1 \) and \( BRCA_2 \) mutation carriers

- Common breast or ovarian cancer susceptibility alleles identified in the general population

- Meta-analyses:
  - \( BRCA_1 \) breast cancer and ER-negative breast cancer
  - \( BRCA_1/2 \) ovarian cancer and serous ovarian cancer

- Fine mapping of known loci

iCOGS, OncoArray high-density custom arrays

Characterising cancer loci

>35,000 BRCA1 and BRCA2 samples genotyped
CIMBA: OncoArray results

   - 39 modifiers of BC risk for BRCA1 carriers
   - 37 modifiers of BC risk for BRCA2 carriers

2. Meta-analysis with OCAC: 3 new ovarian cancer susceptibility loci
   - 19 modifiers of OC risk for BRCA1/2 carriers (Phelan et al, Nat Genet, 2017)
Risk modifying loci – patterns of association

• Most SNPs associated with risk in the unselected population also modify risk for carriers

• \textit{BRCA}_1 \textit{BC} modifiers: Primarily associated with ER-negative breast cancer in population
  ➢ Partitioned heritability analysis: Correlation (ER-, \textit{BRCA}_1)=0.72

• \textit{BRCA}_2 \textit{BC} modifiers: Associated with overall breast cancer in the population

• Some loci are specific to mutation carriers
  ➢ 6p24.3 for risk of \textit{BRCA}_2 breast cancer
  ➢ 4q32.3 for risk of \textit{BRCA}_1 ovarian cancer

Polygenic Risk Scores (PRS)

**BRCA1 – Breast Cancer**

BRCA1 iCOGS sample: 7,797 affected vs 7,455 unaffected

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<tr>
<th>PRS type (from BCAC)</th>
<th>HR</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Overall breast cancer (88 SNPs)</td>
<td>1.14</td>
<td>2x10^{-18}</td>
</tr>
<tr>
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<td>1.11</td>
<td>3x10^{-13}</td>
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Kuchenbaecker et al, JNCI (2017)
## Polygenic Risk Scores (PRS)

### BRCA1 – Breast Cancer

**BRCA1 iCOGS sample:** 7,797 affected vs 7,455 unaffected

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Kuchenbaecker et al, JNCI (2017)
BRCA1 mutation carriers: Breast cancer risk by PRS

Kuchenbaecker et al, JNCI 2017
## PRS and breast cancer risk associations in CHEK2*1100delC carriers

**BCAC**

<table>
<thead>
<tr>
<th></th>
<th>Noncarriers</th>
<th>CHEK2*1100delC carriers</th>
</tr>
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<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRS^a</strong></td>
<td>1.58 (1.55–1.62)</td>
<td>1.59 (1.21–2.09)^b</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;1.0E-10</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Percentile of PRS, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.52 (0.48–0.56)</td>
<td>0.52 (0.16–1.74)</td>
</tr>
<tr>
<td>20–40</td>
<td>0.78 (0.72–0.84)</td>
<td>0.72 (0.28–1.88)</td>
</tr>
<tr>
<td>40–60</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>60–80</td>
<td>1.25 (1.16–1.34)</td>
<td>0.93 (0.39–2.25)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.92 (1.80–2.06)</td>
<td>2.03 (0.86–4.78)</td>
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| **Note:** | Referent |

Muranen et al, Genet Med (2016)
Combined effects of genetic, lifestyle/hormonal factors

• Studies of PRS x Lifestyle/hormonal factors ongoing

• SNP x Lifestyle/hormonal factors

  ➢ Multiplicative model plausible

Nickels et al Plos Genet (2013); Campa et al, JNCI 2011; Rudolph et al BCR 2015; Rudolph et al IJC (2015); Vachon et al JNCI (2015); Maas et al JAMA Oncol (2016)
Potential for transformative risk stratification

% of population

Risk factors

95%

4%

1%

NICE Guidelines (CG164):
- Near Population (risk:<17%)
- Raised Risk (risk:17-30%)
- High Risk (risk: ≥30%)
Potential for transformative risk stratification

NICE Guidelines (CG164):
- Near Population (risk:<17%)
- Raised Risk (risk:17-30%)
- High Risk (risk: ≥30%)

% of population

Risk factors

- Age at menarche
- Parity
- Age at first birth
- HRT
- BMI
- Benign disease
- Alcohol use
- Family history
Potential for transformative risk stratification

NICE Guidelines (CG164):
- Near Population (risk:<17%)
- Raised Risk (risk:17-30%)
- High Risk (risk: ≥30%)

% of population

% of breast cancer cases
Potential for transformative risk stratification

NICE Guidelines (CG164):
- Near Population (risk:<17%)
- Raised Risk (risk:17-30%)
- High Risk (risk: ≥30%)

% of population
- Risk factors: 95% (4% near, 1% raised, 1% high)
- Risk factors + Mammographic Density + All genetics: 83% (12% near, 5% raised, 5% high)

% of breast cancer cases
- 87% (9% near, 4% raised, 4% high)
Potential for transformative risk stratification

% of population

- Risk factors
  - Near Population: 95%
  - Raised Risk: 4%
  - High Risk: 1%

- Risk factors + Mammographic Density + All genetics
  - Near Population: 83%
  - Raised Risk: 12%
  - High Risk: 5%

% of breast cancer cases

- Near Population
  - Risk factors: 87%
  - Risk factors + Mammographic Density + All genetics: 52%

NICE Guidelines (CG164):
- Near Population (risk:<17%)
- Raised Risk (risk:17-30%)
- High Risk (risk: ≥30%)
# Breast cancer risk assessment tools

## TABLE 2. Breast Cancer Risk Assessment Tools Used in Clinical Practice: Components and Assumptions

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Gail</th>
<th>Claus</th>
<th>BRCAPRO</th>
<th>IBIS</th>
<th>BOADICEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>YES (descriptive)</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td><strong>BRCA1, BRCA2 mutations</strong></td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Common low-risk alleles</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Intermediate-high risk mutations (<strong>CHEK2, PALB2, ATM, etc.</strong>)</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES**</td>
</tr>
<tr>
<td>Residual non-BRCA1/2 familial aggregation</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES†</td>
<td>YES; dominant 3rd gene</td>
</tr>
<tr>
<td><strong>BRCA1/2 breast cancer pathology associations</strong></td>
<td>NO</td>
<td>NO</td>
<td>YES†</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td><strong>BRCA1/2 risk modification by family history</strong></td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Variants of uncertain significance</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Predicting estrogen receptor (ER)-specific risks</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Mammographic density</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Hormonal, lifestyle, and reproductive risk factors</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES†</td>
<td>NO</td>
</tr>
<tr>
<td>Other cancers (nonbreast or ovarian cancer)</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Predicting second cancer risks (contralateral breast, ovarian cancer)</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

*Kurian, Antoniou & Domchek, 2016 ASCO Educational handbook*
Genetic variants in existing breast cancer risk tools

- **BRCA1, BRCA2 mutations**
  - BRCAPRO, IBIS, BOADICEA

- **Common genetic variants – SNPs**
  - No tool incorporating SNPs & risk factors available for clinical use
  - Improved performance of existing algorithms (e.g. IBIS, BOADICEA, Gail) Dite et al (2015); Brentnall et al (2014); Darabi et al (2012)
  - Consistency in modeling joint genetic & lifestyle/hormonal factors required
  - **BPC3 model** (Maas et al 2016)

- **Truncating variants in moderate/high risk genes (PALB2, CHEK2, ATM)**
  - BOADICEA Lee et al Genet Med (2016)
• BRCA₁, BRCA₂, polygenic (unobserved genetic effects)
• Family history breast, ovarian prostate, pancreatic cancer
• Tumour characteristics - ER/PR/HER₂/Cytokeratin markers
• Population, ethnicity, year of birth

Intermediate risk variants? PALB₂, CHEK₂, ATM
BRCA1, BRCA2, PALB2, ATM and CHEK2 average breast cancer risks in BOADICEA

Lee et al, Genet in Med 2016
Risks are family history specific

Lee et al, Genet in Med 2016

No affected relatives

Mother with BC at age 40
Negative predictive testing

Breast cancer risk

Age

Proband in untested family

Population risk

Lee et al, Genet in Med 2016
Negative predictive testing

Proband in untested family
Mother BRCA1-positive, proband BRCA1-negative
Population risk

Breast cancer risk

Age

Lee et al, Genet in Med 2016
Negative predictive testing

- Proband in untested family
- Mother BRCA1-positive, proband BRCA1-negative
- Mother ATM-positive, proband ATM-negative
- Population risk

Age vs. Breast cancer risk

Lee et al., Genet in Med 2016
BOADICEA: Beta v.4
https://pluto.srl.cam.ac.uk/cgi-bin/bd4/v4beta14/bd.cgi

Lee et al, Genet in Med 2016
Future directions

- Large scale sequencing: all known/suspected breast cancer genes
- Integrate with in-silico and functional data -> comprehensive risk model
- Interpretation of gene variants and provide risk estimates
- Acceptability and utility of comprehensive gene panel testing in the clinical genetics context.

https://bridges-research.eu

2015
• Gain insights into the aetiology underlying the heterogeneity of breast cancer

• Understand how disease heterogeneity, combined with germline genetics, other risk factors, influence clinical outcome.

• Implementation of breast cancer risk stratification
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