Breast and ovarian cancer risk prediction

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Outline

• Overview of breast and ovarian cancer risk models
• Independent validation studies
• CanRisk – tool description & features
• Ongoing & planned work
Identifying at-risk individuals and optimising clinical management

Genetic
Lifestyle
Hormonal
Reproductive
Family
History

Personalised Cancer Risks
Cancer Risk Stratification

Targeted Prevention and Early Detection

• Screening
  ➢ When? How often?

• Chemoprevention
  ➢ Who? When?

• Risk-reducing surgery
  ➢ When?

• Behaviour/lifestyle
CanRisk: Personalised cancer risks

- Breast Cancer
- Contralateral Breast
- Ovarian Cancer
- Mutation carrier probabilities
BOADICEA breast cancer model: comprehensive risk prediction

- Other unobserved genetic effects
- Lifestyle/hormonal/reproductive risk factors
- Breast tumour characteristics: ER/PR/HER2
- Population demographics

Lee et al, Genet Med 2019
Ovarian cancer model in CanRisk

- Other unobserved genetic effects
- Lifestyle/hormonal/reproductive risk factors
- Population demographics

Lee, Yang et al (submitted) medRxiv (2020)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast cancer model</th>
<th>Ovarian cancer model</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>BRCA2</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PALB2</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>CHEK2</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>ATM</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>RAD51C</td>
<td>✘</td>
<td>✓</td>
</tr>
<tr>
<td>RAD51D</td>
<td>✘</td>
<td>✓</td>
</tr>
<tr>
<td>BRIP1</td>
<td>✘</td>
<td>✓</td>
</tr>
</tbody>
</table>
Polygenic Risk Scores

• Breast and ovarian cancer

• Allows for any PRS provided distribution characteristics are known

• Adjusts residual family history effect automatically – no double counting

• Custom Options
  • Breast Cancer: 313 SNP PRS (and slight variations)  
    Mavaddat et al, AJHG 2019
  • Ovarian cancer: 36 SNP PRS  
    Dareng et al, (under review; medRxiv)
### Lifestyle, reproductive & hormonal risk factors & mammographic density

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Breast cancer model</th>
<th>Ovarian cancer model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>Parity</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Age at first live birth</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Menopause hormone therapy</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Height</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>Mammographic density</td>
<td>✓</td>
<td>✘</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>✘</td>
<td>✓</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>✘</td>
<td>✓</td>
</tr>
</tbody>
</table>

Also modify cancer risks for mutation carriers:

- e.g. OC use & ovarian cancer

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Lee et al Genet Med 2019
Lee et al (under review; medRxiv 2020)
Combining risk factors altogether: risk stratification example

NICE clinical management risk categories

Population risk  Moderate risk  High risk

Risk factors only
Genetics (SNPs, PRS) only
Combined – full model

Breast Cancer Risk by Age 80 (%)

Probability Density

15% 1.2%
Increased CBC risk entirely due to susceptibility defined in model
  ➢ Rare genetic variants
  ➢ PRS
  ➢ Family history
  ➢ Lifestyle/hormonal risk factors

CBC incidence: 50% of breast cancer incidence in standard model (1 breast at risk)
  ➢ As such – model-based prediction NOT based on CBC risk estimates

No other additional variation in risk considered
  • Treatment of the first cancer, e.g. particular hormonal therapy
  • Tumour pathology
Contralateral breast cancer risk interpretation on CanRisk
BOADICEA validation in prospective cohorts of unaffected women

- Generations study: “Population-based” study, age 23-75, UK

- KARMA study: Mammographic screening cohort screening, age 40-75, Sweden

- TRANSCAN: Unaffected women with BRCA1 and BRCA2 mutations (presented at the December UKCGG meeting)
Clinical validity: UK Generations (prospective) study

Observed vs Predicted 5 year-risks: family history, lifestyle, PRS (1,337 women, 619 with BC)

Women <50 years old
E/O = 0.97 (0.62-1.53)
AUC: 0.697 (0.641 - 0.752)

Women 50 years old and over
E/O = 1.09 (0.66-1.80)
AUC: 0.646 (0.609 - 0.682)

Polygenic Risk Scores & family history

Has a SNP array / Polygenic Risk Score (PRS), ever been run?

- Upload a VCF (Variant Call Format) file
- Enter PRS values

Breast Cancer
- alpha: 0.44
- z-score: 0.1

Ovarian Cancer
- alpha
- z-score

Breast Cancer PRS:
54% of people in the population have a lower polygenic load.
46% of people in the population have a higher polygenic load.

lower polygenic risk
higher polygenic risk

Allowing exploring how risks could change if PRS available.
Guidance
Protocols for surveillance of women at very high risk of developing breast cancer
Updated 25 February 2021

Beverley Speight, Gareth Evans, Marc Tischkowitz
### Table of 10-Year Breast Cancer Risk(s)

Below are the calculated 10-year breast cancer risks based on the guidelines contained in the NHS protocol for surveillance of women at very high risk of developing breast cancer.

<table>
<thead>
<tr>
<th>Patient Age (years)</th>
<th>10-Year Breast Cancer Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>0.7</td>
</tr>
<tr>
<td>28</td>
<td>0.9</td>
</tr>
<tr>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>1.2</td>
</tr>
</tbody>
</table>
New features

• Disabling age and year of birth synchronization
  ➢ Proband
  ➢ Alive family members
  ➢ Allows for “retrospective” calculations & “censoring” at risk-reducing surgery
New features: PDF reports

Option to include table of family input data

Summary of Genetic Tests and Pathology

No genetic tests or pathology found in the family history.

Summary of Family and Age of Cancer Diagnoses

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>IndivID</th>
<th>FathID</th>
<th>MothID</th>
<th>Sex</th>
<th>MZtwin</th>
<th>Dead</th>
<th>Age</th>
<th>Yob</th>
<th>BC1</th>
<th>BC2</th>
<th>OC</th>
<th>PRO</th>
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<th>Ashkm</th>
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<td>m21</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>dwOW</td>
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<td>0</td>
<td>M</td>
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<td>0</td>
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<tr>
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<td>I21</td>
<td>F</td>
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Common query: higher risks for older mutation carriers than expected?

A worked example

61 year old `BRCA1` carrier
Common query: higher risks for older mutation carriers than expected?

A worked example

Kuchenbaecker et al JAMA 2017

<table>
<thead>
<tr>
<th>Age, During Follow-up, y</th>
<th>No. of Women Contributing in Age Category</th>
<th>No. of Person-Years</th>
<th>No. of Events</th>
<th>Incidence per 1000 Person-Years (95% CI)</th>
<th>Cumulative Risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRCA1 mutation carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>53</td>
<td>74.0</td>
<td>0</td>
<td>5.9 (3.4-10.1)</td>
<td>4 (2-7)</td>
</tr>
<tr>
<td>21-30</td>
<td>605</td>
<td>2222.5</td>
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<td>24 (21-29)</td>
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<tr>
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<tr>
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<td>61-70</td>
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<td>19</td>
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<tr>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>2276d</td>
<td>12356.1</td>
<td>269</td>
<td></td>
<td></td>
</tr>
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</table>

What is "expected"?

Incorrect calculation!

0.72 – 0.56 = 0.16

Ignores the fact the proband is unaffected
Common query: higher risks for older mutation carriers than expected?

A worked example

Kuchenbaecker et al JAMA 2017

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Conditional probability of being unaffected at 61:

Correct calculation:

\[
\frac{0.72 - 0.56}{1.0 - 0.56} = 0.36
\]
Common query: higher risks for older mutation carriers than expected?

A worked example

Conditional probability of being unaffected at 61:

- Correct calculation: $\frac{0.72 - 0.56}{1.0 - 0.56} = 0.36$

Same principles apply for: *PALB2, CHEK2* etc

Ovarian, contralateral breast cancer risks

CanRisk: ~38%
New features: Languages and notifications of changes

CanRisk v5
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
Welcome

NEW: 10-year breast cancer risks used in the NHS protocol for surveillance of women at very high risk can be enabled in the 'Preferences' window.

NEW: CanRisk tool for French, Dutch, German and Spanish speakers is available by selecting 'fr', 'nl', 'de' or 'es' from the top menu bar.

CanRisk Tool

- Load
- Save
- Reset
- Preferences

Input the information in any order by clicking on the blue bars. Please add as much information as possible. When a section is completed the bar will turn green. If some information is unknown, the bar will not turn green; this does not prevent risk calculation.

Personal Details
Lifestyle
Women's Health
Children
The CanRisk team (Cambridge)

Andrew Lee
Alex Cunningham
Tim Carver
Steph Archer
Doug Easton
Marc Tischkowitz
Fiona Walter
Acknowledgments

All study participants

University of Cambridge
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Jennifer Brooks

QIMR Berghofer
Georgia Chenevix-Trench

Cancer Research Malaysia
Soo Hwang Teo, Weang-Kee Ho

BCAC, CIMBA, IBCCS consortia

www.canrisk.org