Incorporating low-risk alleles for accuracy in Breast Cancer risk

ESMO – Hereditary Cancer Genetics 26-27 April Lugano

Name
Dr Marc Tischkowitz  MD PhD

Reader in Medical Genetics, Department of Medical Genetics
Honorary Consultant, East Anglian Medical Genetics Service
DISCLOSURE OF INTEREST

I have no conflicts to declare
COMBINED GWAS, ICOGS AND ONCOARRAY DATA
~123,000 cases and ~106,000 controls of European ancestry

Total: 170 loci, P<5x10^-8
OncoArray: 75 novel loci ~18% of Familial Relative Risk

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
COMBINED SNP ASSOCIATIONS

Polygenic Risk Scores (PRS)

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

SNPs combine multiplicatively on risk scale
313- SNP POLYGENIC RISK SCORE

Breast Cancer Association Consortium (BCAC)

94,094 breast cancer cases and 75,017 control women

PRS normally distributed in both cases and controls

Explains 20% of Familial Risk

Mavaddat et al JNCI 2015 Mavaddat et al, AJHG 2019
SNPS IN BREAST CANCER RISK PREDICTION

313 breast SNPs
Common
Identified by GWAS
Individually confer a minimal alteration in risk
Can increase or decrease risk
Mechanism of action for most is unknown

Mavaddat et al, AJHG 2019
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%

1%
Potential for transformative risk stratification

% of population

95%

4%

1%

Risk factors

Age at menarche
Parity
Age at first birth
HRT
BMI
Benign disease
Alcohol use
Family history

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

% of population

% of breast cancer cases

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

- 95% of population
- 4% of breast cancer cases
- 1% of breast cancer cases
- 87% of breast cancer cases
- 9% of breast cancer cases
- 4% 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% Near Population
- 4% Raised Risk
- 1% High Risk

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

% of breast cancer cases

Risk factors
- 87% Near Population
- 9% Raised Risk
- 4% High Risk

Risk factors+
- Mammographic Density+
- All genetics
- 95% Near Population
- 4% Raised Risk
- 1% High Risk
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

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%

Risk factors + Mammographic Density + All genetics
- Near Population: 87%
- Raised Risk: 25%
- High Risk: 23%
**PRS VS FAMILY HISTORY**

**PRS at the 10th centile**

Lifetime risk at age 20

Number of first degree relatives affected with BC at 50

**PRS at 90th centile**

Number of first degree relatives affected with BC at 50
What about SNPs in Breast Cancer risk prediction?

- BC 50-80%, OC (B1) 30-50% (B2) 10-20%
- RRM 6% uptake if risk <50% vs ~50% uptake if risk >50%
- **BRCA2** carriers OC risk:
  10th percentile of OC PRS = 6% vs 19% at 90th percentile

---

**A**

![](breast_cancer_risk_BRCa1.png)

**B**

![](ovarian_cancer_risk_BRCa2.png)
BOADICEA

The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) is a computer program that is used to calculate the risks of breast and ovarian cancer in women based on their family history. It is also used to calculate the probability that they are carriers of cancer-associated mutations in the BRCA1 or BRCA2 gene. To access BOADICEA, all you need is a BOADICEA user account, which you can set up online in a minutes here.

You can access two different versions of the BOADICEA program using the links in the menu to the left:

(i) BWA v3 considers the explicit effects of BRCA1 and BRCA2 mutations;

(ii) BWA v4 Beta considers the explicit effects of BRCA1, BRCA2, PALB2, CHEK2 and ATM mutations.

This tool is provided for research use only. The BOADICEA software is at an early stage of development and is provided “as is” (ie. it is not error-free). BOADICEA is designed for research use only and is not designed for providing information on which to base clinical decisions. BOADICEA has not been approved for use by any regulatory authority.

For any BOADICEA inquiry please contact Alex Cunningham (apc40@medschl.cam.ac.uk) or Antonis Antoniou (eca20@medschl.cam.ac.uk).

https://drive.google.com/open?id=1YZR8YiT451E2e6cv2AlyP9VLYdcglp9
The changing paradigm of diagnostic testing for germline mutations in cancer genetics

Strong FHx
Clear ascertainment
Targeted testing
Genotype correlates with Phenotype
High penetrance

Incidental Finding
Panels, Exomes, Tumour Sequencing
Weak/unknown correlation with phenotype
Lower Penetrance?
Clinical implications less clear
Acknowledgements

Ambry Genetics, US: Holly Laduca, Jill Dolinsky
Cancer Research Initiatives Foundation, Cancer Research Malaysia: Teo Soo Hwang, Patsy Ng Pei Sze
Central Manchester University Hospitals, UK: Gareth Evans
Charles University in Prague, Czech Rep: Marketa Janatova
Children's Hospital of Eastern Ontario, Canada: Eva Tomiaik, Kathleen Claes
City of Hope, US: Susan Neuhansen, Jeffery Weitzel
Curie Institute, France: Fabienne Lesueur, Marianne Dedier, Claude Houdayer
Ghent University Hospital, Belgium: Kim De Leeneer, Bruce Poppe, Kathleen Claes
Inherited Cancer Registry, US: Tuya Pal, Kelly Metcalfe
Istituto Nazionale Tumori, Italy: Paolo Peterlongo, Paolo Radice
Kepler University Hospital Linz, Austria: Florian Obermair
Lund University, Sweden: Hans Ehrencreuna
Mayo Clinic, Rochester, US: Fergus J. Couch
McGill University, Canada: William D. Foulkes
Mercy Hospital Oklahoma City, US: Sharon Nall, Julie Beasley
MSKCC, US: Jonine Bernstein (WECARE), Mark Robson
National Cancer Center Singapore: Ann S.G. Lee, Peter Ang
National Centre for Scientific Research Demokritos, Greece: Fiorentia Fostira, Drakoulis Yannoukakos
Ovarian Cancer Association Consortium, US: Starr Guzman, Ellen Goode
Peter MacCallum Cancer Centre, Melbourne, Australia: Paul A James
QIMR Berghorfer Institute, Australia: Georgia Chenevix-Trench
Royal Melbourne Hospital, Australia: Alison H. Trainer
Samuel Lunenfeld Research Institute, Canada: Irene Andruis
Sylvester Comprehensive Cancer Center, University of Miami, US: Sophia George
The CHUM Department of Genetic Medicine, Canada: Zaki el Haflaf
The University of Vermont Cancer Center, US: Wendy McKinnon
University Hospital Vall d'Hebron, Spain: Orland Diez Gibert
University in Leipzig, Germany: Christoph Engel
University of Cambridge, UK: Antonis C. Antoniou, Xin Yang, Goska Leslie, Alicja Doroszuk, James Whitworth, Eamonn Maher, Douglas Easton, Paul Pharoah
University of Chicago, US: Sarah Nielsen, Fumi Olopade
University of Cologne, Germany: Rita Schmutzler, Eric Hahnen
University of Copenhagen, Denmark: Thomas V. O. Hansen
University of Helsinki, Finland: Tuomas Heikkinen, Sofia Khan, Kristiina Aittomäki, Heli Nevanlinna
University of Melbourne, Australia: Zhi L. Teo, John L. Hopper, Melissa C. Southey (kConFab), Tu Nguyen-Dumont
University of Miami, US: Rachel Silva-Smith
University of Oulu, Finland: Katri Pylkäs, Jukka S Moilanen, Robert Wirgvis
University of Pennsylvania, US: Susan Domchek
University of Rome, Italy: Laura Ottini
University of Southern California, US: Gruber Stephen, Culver Julie, Idos Gregory
University of Utah, US: Saundra S Buys, David E. Goldgar
Vilnius University Hospital, Lithuania: Ramunas Janavicius
VU Medical Center, Netherlands: Muriel Adank
Further Reading:

**Gene-panel sequencing and the prediction of breast-cancer risk.**

**Cancer genetics, precision prevention and a call to action**
Clare Turnbull, Amit Sud, Richard S. Houlston
Nature Genetics 2018 50(9) 1212-1218