Risk estimation and stratified screening: Is this the way forward?

Predicting Risk Of Cancer At Screening

D Gareth Evans
Potential risk factors* & factors to be investigated* for inclusion in a model

Breast cancer risk in general population

- Targeted screening and prevention based on risk
  - BRCA1/2
  - TP53
  - Polygenes
- Single Low risk
  - No genetic predisposition
  - MRI screening
  - Risk reducing Surgery*
- Lifetime risk of breast cancer

*optional
Family History & Genetics

- Number of affected family members, and age of developing breast cancer.
- BRCA1 & BRCA2 gene mutations
- Genetic variants – currently >100 known genetic variants that can increase the risk of breast cancer by between 5-30%
Proportion of familial breast cancer 2016

- BRCA1: 42%
- BRCA2: 9%
- TP53/STK11/CDH1/PTEN: 11%
- CHEK2/ATM: 1%
- GWAS SNPs: 5%
- BRIP/PALB: 1%
- Other: 31%
Breast Density

- Increased breast density increases risk of breast cancer.
- After family history and age this is the largest risk factor.
- Breast density is assessed from mammograms.
- There are a number of different methods for assessing breast density, but these methods need validating.
Mammographic Density

Dense breast

Lifet ime risk
25%

Non dense breast

Lifet ime risk
4%
Aims of the PROCAS study

- To determine whether it is feasible to incorporate personal breast cancer risk prediction into NHS BSP
- Alter mammographic screening interval based on each woman’s personal risk of cancer
- Introduce preventive measures for women who are high risk
PROCAS Summary

- 60,000 women, who attend NHS BSP in Greater Manchester will take part.

- Information on lifestyle and family history will be collected from a study questionnaire.

- Breast density assessments will be carried out.

- 10,000 of the 60,000 women will have genetic testing.

- This information will be incorporated to predict each woman’s individual breast cancer risk
Breast Density

- Breast density results will be obtained from 2 mammograms (Y1 and Y3) for each woman.

- We will use a number of breast density assessment methods and determine which is best for use within NHS BSP.
PROCAS Study Questionnaire

Collects information on:

- Family history
- Age at menarche
- Parity
- Age at first full term pregnancy
- Age menopause
- HRT use
- BMI
- Alcohol intake
- Exercise
DNA testing

- Carried out at Withington Community Hospital
- Participants provided with a saliva sample collection kit
- Collect sample (approx 5 min) seal and post to laboratory
- Laboratory extract DNA
- St Mary’s Hospital, Manchester carry out analysis to look for genetic variants
DNA testing

- 10,000 participants will be invited to have DNA testing
- Laboratory extract DNA
- St Mary’s Hospital, Manchester
- carry out analysis to look for
- genetic variants
- 10,000 recruited
Invitation letter sent

Consent taken & questionnaire completed

Mammogram 1 performed

OPTIONAL - DNA sample collected (10,000/60,000)

Initial risk calculation (Tyrer-Cuzick)

High risk & selection of low risk women informed of risk (if opted to receive risk information)

Mammogram 2 performed

Breast density results, questionnaire results & DNA results (if applicable) combined to give re-adjusted risk score
Recruitment

Number recruited 01/03/2015 – 57,432

- Uptake year 1: 35%
- Uptake year 2: 43%
- Uptake year 3: 37%
- Uptake year 4: 47%

- Year 2 uptake amongst first attendees aged 47-52: 52%

- Uptake when study staff present 60%
PRediction Of Cancer At Screening (PROCAS)

Distribution of VAS density scores

Number of participants

0-10% 11-20% 21-30% 31-40% 41-50% 51-60% 61-70% 71-80% 81-90% 91-100%

VAS density score

% of PROCAS participants

0-1% 1-<2% 2-<3% 3-<4% 4-<5% 5-<8% ≥8%

10 year breast cancer risk

Offer interventions

Cuzick et al Lancet 2014
Harvie et al BJN 2013
Tyrer-Cuzick risk in 53594 women in NHSBSP
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<th>SNP</th>
<th>gene</th>
<th>risk</th>
<th>RA</th>
<th>freq weight 0</th>
<th>weight 1</th>
<th>weight 2</th>
<th>0 freq</th>
<th>1 freq</th>
<th>2 freq</th>
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<td>16</td>
<td>48</td>
<td>36</td>
<td>0.86</td>
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10 year 18 SNP risks with MD adjusted TC in 9346 women
Correlation SNPs to T-C RR

![Graph showing correlation between SNP and TC risk]
Venn diagram of overlap of highest 10% risk from 1000 women with SNP, Tyrer-Cuzick score and VAS density
## Stage of cancer by MD adjusted risk category

### Age and BMI adjusted MD

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Number</th>
<th>% of popul</th>
<th>BCs</th>
<th>% with BC</th>
<th>LN+ve</th>
<th>High Stage 2/3</th>
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<tbody>
<tr>
<td>High &gt;8%</td>
<td>1314</td>
<td>2.6%</td>
<td>52</td>
<td>4.0%</td>
<td>9/38  (24%)</td>
<td>18/47 (38%)</td>
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<tr>
<td>Mod 5-7.9%</td>
<td>4654</td>
<td>9.1%</td>
<td>160</td>
<td>3.4%</td>
<td>21/121 (17.3%)</td>
<td>42/144 (29%)</td>
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<tr>
<td>Above ave 3.5-4.9%</td>
<td>8339</td>
<td>16.3%</td>
<td>222</td>
<td>2.7%</td>
<td>39/165 (23.6%)</td>
<td>54/197 (27.5%)</td>
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<tr>
<td>Average 2-3.5%</td>
<td>22001</td>
<td>42.9%</td>
<td>402</td>
<td>1.8%</td>
<td>64/312 (20.5%)</td>
<td>98/363 (27%)</td>
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<tr>
<td>Below average 1-2%</td>
<td>14272</td>
<td>27.8%</td>
<td>176</td>
<td>1.2%</td>
<td>22/133 (16.5%)</td>
<td>35/155 (22.5%)</td>
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<tr>
<td>Low &lt;1%</td>
<td>684</td>
<td>1.3%</td>
<td>3</td>
<td>0.4%</td>
<td>1/3 (33%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Above vs below average-</td>
<td>11.7%</td>
<td>3.6%</td>
<td>P&lt;0.0001</td>
<td>19% v 17% p=0.18</td>
<td>31.5%v23% p=0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** P values indicate statistical significance.
Effects of risk on stage

- 60/191 (31.5%) >mod/high risk stage 2a-3;
- 36/158 (23%) below average stage 2a-3; p=0.09
- 59/5968 = 10 per 1000 stage 2a-3 >average risk
- 36/14956 = 2.4 per 1000 stage 2a-3 average or lower risk  p<0.0001  <-<0.6 per 1000 p.a
- 36957/50627 (71%) at average or below
Calibration T-C and Gail model

Brentnall et al Breast Cancer Res 2016
Breast density and residual by time of diagnosis since enrolment.
T-C Density and SNPs in PROCAS
9346 women 439 cancers

Bar chart showing proportions of women in different T-C density groups with breast cancer (BC). The groups are:
- Low <1%
- 1-2%
- Average 2-3.5%
- 3.5-5%
- Moderate 5-8%
- High 8%+

The chart indicates the percentage of women within each group.
T-C + Density + SNPs in PROCAS Risks 9346 women
Calibration of SNP18
Distribution of 10 year breast cancer and 439 incident breast cancers in PROCAS

N = 9346

- % of women
- % 10 year risk

- TC alone
- %BC
- TCMDSNP
- %BC2

35% of pop get 51% of cancers
But 60% of high stage cancers
Effects of risk on stage

- 33/116 (28.5%) >mod/high risk stage 2a-3;
- 36/158 (23%) below average stage 2a-3; p=0.09
- 33/1668 = 20 per 1000 stage 2a-3 >average risk
- 13/2796 = 4.6 per 1000 stage 2a-3 average or lower risk  p<0.0001  -1 per 1000 p.a c.f 4 per 1000
Cancers found on interval screen in high risk

<table>
<thead>
<tr>
<th>Age</th>
<th>Histology</th>
<th>Invasive/CIS</th>
<th>CIS</th>
<th>Size</th>
<th>Stage</th>
<th>Grade</th>
<th>LN</th>
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<td>51</td>
<td>IDC</td>
<td>invasive</td>
<td>no</td>
<td>15mm</td>
<td>1</td>
<td>II</td>
<td>0/9</td>
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<tr>
<td>63</td>
<td>IDC</td>
<td>invasive</td>
<td>no</td>
<td>28mm</td>
<td>2a</td>
<td>III</td>
<td>1/2</td>
</tr>
<tr>
<td>55</td>
<td>IDC</td>
<td>invasive</td>
<td>no</td>
<td>11mm</td>
<td>1</td>
<td>III</td>
<td>0</td>
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<tr>
<td>56</td>
<td>ILC</td>
<td>invasive</td>
<td>no</td>
<td>25mm</td>
<td>2a</td>
<td>II</td>
<td>0/1</td>
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<tr>
<td>54</td>
<td>IDC</td>
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<td>yes</td>
<td>7mm</td>
<td>1</td>
<td>I</td>
<td>0/2</td>
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</table>
PROCAS Risk Assessment

- First 50,000 women recruited
- 94.7% wished to know risk
- 0.5% indicated no preference
- 4.8% did NOT want to know
Intervention in those at high risk

- Women with a lifetime risk of 30%+ or
- 8% risk in 10 years
- are classified high risk by NICE
- All high risk women will be invited for a clinic visit
  a. If found after initial T-C assessment without MD/DNA
  b. If found after adding extra factors
- An equal number of low risk women will be invited
- Women can opt out of knowing risk on 2 occasions
  1. At consent
  2. When they receive a clinic appt
Risk appointments

High risk (8%+ 10 yr risk or 5%+ and >60% MD)

- Participants who are high risk: 815
- Participants who want to know their risk: 784
- Participants who have been invited for an appointment: 784
- Participants who have attended their risk appointment: 582 - 74%
- Participants who DNA’d their appointment: 10
- Participants who did not respond after two reminders: 132
- Participants who declined an appointment: 60

- 12/60 (20%) women entered IBIS2 and
- 5/25 (20%) in dietary studies
- 327/345 (95%) attended next mammogram p<0.001 compared to usual re-attendance of 84%
Risk appointments update

Low risk (<1.5% 10 year risk <10% MD)
- Participants who are low risk: 171
- Participants who want to know their risk: 150
- Participants who have been invited for an appointment: 192
- Participants who have attended their risk appointment: 105
- Participants who DNA’d their appointment: 6
- Participants who did not respond after two reminders: 56
- Participants who declined an appointment: 25

Reattendance at next invited NHSBSP visit -84% (64/76)

Evans et al Brit J Cancer 2016
Conclusions

- Breast cancer risk assessment is feasible in NHSBSP
- As many as 12-17% of the female population are at least moderate risk and entitled to consideration for:
  - Chemoprevention with tamoxifen
  - Annual mammography – 2.5%
- The great majority of women at moderate risk are unaware and/or that they are eligible for extra interventions
- 3 yearly mammography appears adequate 71% women at <3.5% MD adjusted 10-years risks
Conclusions

- SNPs are able to significantly add to breast cancer risk discrimination
- Can be used in a population and family history setting
- To risk stratify for screening and chemoprevention
Contacts

- Chief Investigator: Prof. Gareth Evans
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- Data Manager: Sarah Sampson

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The PROCAS team

Eileen and Chris who will be on the vans, and Stella and Julie who have been assisting us in the office.

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everyone counts staff awards

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- Dr Katherine Payne

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- Dr Emma Hurley
- Prof Anil Jain
- Dr Ursula Beetles
- Dr YY Lim
- Dr N Barr

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- Dr Jenny Diffey

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- Dr Bill Newman
- Dr Fiona Laloo
- Helen Byers
- Dr Bronwyn Kerr
- Tara Clancy

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- Dr Tony Moran

Others
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- Dr Adam Brentnall
- Dr Ruth Warren
- Prof Jane Wardle
- Helen Middleton-Price
- Wendy Watson

Central Manchester University Hospitals NHS Foundation Trust

creating a future without breast cancer

NHS National Institute for Health Research