Current application of genetic variants to clinical management

Predicting Risk Of Cancer At Screening

Prof D Gareth Evans
Breast cancer cumulative risk UK population and Asia
Breast cancer risk in general population

Targeted screening and prevention based on risk

BRCA1/2
TP53
polygenes

Single
Low risk

Risk reducing Surgery*

MRI screening

Targeted prevention strategies

Lifetime risk of breast cancer

<table>
<thead>
<tr>
<th>Duration</th>
<th>Lifetime risk of breast cancer</th>
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<tbody>
<tr>
<td>2</td>
<td>No genetic predisposition</td>
</tr>
<tr>
<td>6</td>
<td>Low risk</td>
</tr>
<tr>
<td>10</td>
<td>Single</td>
</tr>
<tr>
<td>20</td>
<td>polygenes</td>
</tr>
<tr>
<td>40</td>
<td>BRCA1/2</td>
</tr>
<tr>
<td>60</td>
<td>TP53</td>
</tr>
<tr>
<td>80</td>
<td></td>
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</table>

Remove From NBSP 55-60%

NBSP 8-80% risk; 40-45% of population

55-60% of women

*optional
Breast Cancer

- 4-5% due to high risk genes (Claus 1994, Newman 1989)
- 27% have a hereditary element from twin studies (Peto & Mack)
- Only about 13% of breast cancer accounted for.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk &gt;4 BC&lt;60</th>
<th>Familial BC</th>
<th>All BC</th>
<th>Lifetime risk</th>
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<tbody>
<tr>
<td>BRCA1</td>
<td>50%</td>
<td>6%</td>
<td>1.7%</td>
<td>60-85%</td>
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<tr>
<td>BRCA2</td>
<td>30%</td>
<td>6%</td>
<td>1.5%</td>
<td>50-85%</td>
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<tr>
<td>TP53</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>?8%</td>
<td>90-100%</td>
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<tr>
<td>ATM</td>
<td>?1-5%</td>
<td>3%</td>
<td>1-5%</td>
<td>20%</td>
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<tr>
<td>PTEN</td>
<td>0%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>60%</td>
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<tr>
<td>STK11</td>
<td>0%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>40%</td>
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</table>
Proportion of familial breast cancer 2014

- BRCA1: 54%
- BRCA2: 19%
- TP53/STK11/CDH1/PTEN: 11%
- CHEK2/ATM: 9%
- GWAS SNPs: 1%
- BRIP/PALB: 1%
- Other: 5%
Figure 4. Cumulative Risk of Breast Cancer among BRCA2 Mutation Carriers by Combined FGFR2 and TNRC9 Genotype under a Multiplicative Model for the Joint Effects of the Loci
The combined FGFR2 and TNRC9 genotypes are as follows: FGFR2 = GG, GA, or AA; TNRC9 = CC, CT, or TT. “Average” represents the cumulative breast cancer risk over all possible modifying effects among BRCA2 mutation carriers born after 1950. The minor allele frequencies for the FGFR2 and TNRC9 SNPs were assumed to be 0.39 and 0.26, respectively.
Cumulative breast cancer risks for BRCA2 by combined genotype distribution at SNPs rs2981582 in FGFR2, rs3803661 in TOX3/TNRC9, rs889312 in MAP3K1, rs3817198 in LSP1, rs13387042 in 2q35 region, rs4773768 rs10941679
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.
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
**Prediction Of Cancer At Screening (PROCAS)**

- **Distribution of VAS density scores**
  - Bar chart showing the number of participants across different VAS density score ranges.
  - Categories include 0-10%, 11-20%, 21-30%, 31-40%, 41-50%, 51-60%, 61-70%, 71-80%, 81-90%, 91-100%.

- **10 year breast cancer risk**
  - Bar chart indicating the percentage of PROCAS participants across different risk categories.
  - Categories range from 0-1% to 8%.

- **Offer interventions**

- **SNP**
  - DNA sequence information.

- **Cuzick et al Lancet 2014**
  - Reference to research publication.

- **Harvie et al BJN 2013**
  - Another reference to research publication.
Distribution of 10 year risk scores (%)

First 10,000 recruits

95 women at ≥8% risk

PROCAS Sept 2011
<table>
<thead>
<tr>
<th>SNP</th>
<th>gene</th>
<th>rs</th>
<th>risk</th>
<th>RA</th>
<th>F</th>
<th>weight 0</th>
<th>weight 1</th>
<th>weight 2</th>
<th>0 freq</th>
<th>1 freq</th>
<th>2 freq</th>
<th>RR</th>
<th>W*F</th>
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<td>1.03</td>
<td>1.47</td>
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<td>49</td>
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<td>1.32</td>
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<td>48</td>
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<td>0.86</td>
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</table>
Comparison of standard risk factors with 18 SNPs on DNA testing 993 samples

10 year breast cancer risk

% of PROCAS participants

10 year breast cancer risk

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

Tyrer-Cuzick
SNP
Comparison of standard risk factors with 18 SNPs on DNA testing 993 samples.
10 year 18 SNP risks in 6954 women
10-yr risk @50 using classical factors (TC), SNP18 the 67 iCOGS SNPs (SNP67), and both combined (TC + SNP67).
Correlation SNPs to T-C RR

SNP

T/C risk

0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00
Venn diagram of overlap of highest 10% risk from 993 women with SNP, Tyrer-Cuzick score and VAS density.
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
- 200/202 attended next mammogram p<0.0001 compared to usual re-attendance of
A polygenic risk score (PRS) for each women based on 77 SNPs

Analyses included women of European origin:

33,673 cases : 21,365 ER+ and 5,738 ER-
33,381 controls

\[
PRS = \sum_{j=1}^{n} b_j x_j = b_1 x_1 + b_2 x_2 + \ldots + b_n x_n
\]

- \(b_j\) per-allele log (OR) for risk allele at locus \(j\) from logistic regression adjusted for study and 7 PCs
- \(x_j\) number of risk alleles at at locus (0, 1 or 2)
- \(n\) number of loci included in the risk score

Mavaddat E et al for BCAC, Under Review
Current PRS can stratify women with and without family history by genetic risk

10-year risk of breast cancer by percentiles of 77-SNP polygenic score by family history of breast cancer

With family history

Without family history

2.4% risk threshold

Mavaddat E et al for BCAC, Under Review
FHC resource

10,500 women screened

**Breast cancer**
- 533 BC (93 at referral)
- 438 BC
- 245 in women in prog.
- 193 in women discharged
- DNA on 424 women
- 129 BRCA carriers
- 200 BRCA negative

**Controls**
- 1200
- Matched
- Age
- Type of mammogram
FHRisk recruitment

• Cohort study
  4,394 questionnaires received

• Case control study
  312 cases and 953 controls recruited
FH Risk Feedback

- 1200 women already advised on SNP scores
- RR <0.5 advised should (have) protect
- RR 0.5-2.0 may not have affected risk
- RR >2 likely to (have) increase(d) risk
Validation in BRCA1/2

- FGFR2, Tox3, MAP3K, 2q, 1p11.2, SLC4A7, 6q25.1, LSP1, 5p12 –BRCA2
- Tox3, 2q, 6q25.1 –BRCA1
Validation in BRCA1/2

- Use all 18 validated SNPs
- Initially with Turnbull weightings
- Then with Antoniou weightings
- Then adding non validated SNPs
Validation in BRCA1/2

- 445 BRCA2 carriers, 280 had developed breast cancer.
- 480 BRCA1 patients, 269 developed breast cancer.
<table>
<thead>
<tr>
<th>SNPs</th>
<th>Gene</th>
<th>Mean RR upper quintile</th>
<th>Mean RR lower quintile</th>
<th>Hazard Ratio upper to lower</th>
<th>Actual Hazard ratio from Cox analysis</th>
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<tbody>
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<td>0.224</td>
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Nelson-Aalen cumulative hazard estimates - Turnbull weightings

BRCA2
BRCA2 Antoniou weightings 9 SNPs

Nelson-Aalen cumulative hazard estimates

![Graph showing Nelson-Aalen cumulative hazard estimates for different groups labeled group_9snps = 1 to group_9snps = 5 over analysis time ranging from 20 to 80.](image_url)
BRCA2 Antoniou weightings 9 SNPs + unvalidated

Nelson-Aalen cumulative hazard estimates - BRCA2 carriers

Analysis Time

High risk - Group 1
Group 2
Group 3
Group 4
Low risk - Group 5

High risk - Group 1
Group 2
Group 3
Group 4
Low risk - Group 5

Analysis Time
Uptake BRRM in unaffected non mutation carriers

- 50% of BRCA1/2 carriers quoted 60-85% risk have surgery by 5 years

- 211/3515 (6%) of unaffected high risk women session 2

- 51/798 (6%) of women at 40-45% had RRM

- 45/1815 (2.5%) of High (33-39%) risk had RRM

- 16/902 (1.8%) of high moderate 25-32% had RRM

P <0.005

Evans et al CEBP 2009
SNPs in Prognosis

- A number of SNPs have been validated as prognostic markers
- Covered by Gillian Mitchell
Conclusions

- BRCA2 - 9 validated SNPs have good correlation but could be improved by additional SNPs
- BRCA2 SNPs ready for prime time
- Can use to guide RRM advice
- BRCA1 not good correlation

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 Dawe

- Email: PROCAS.Study@uhsm.nhs.uk
The PROCAS team

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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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- Helen Byers
- Dr Bronwyn Kerr
- Tara Clancy

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- Ms Victoria Rose

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- Dr Katherine Haynes

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