Mavaddat, N; Pharoah, PD; Michailidou, K; Tyrer, J; Brook, MN; Bolla, MK; Wang, Q; Dennis, J; Dunning, AM; Shah, M; Luben, R; Brown, J; Bojesen, SE; Nordestgaard, BG; Nielsen, SF; Flyger, H; Czene, K; Darabi, H; Eriksson, M; Peto, J; Dos-Santos-Silva, I; Dudbridge, F; Johnson, N; Schmidt, MK; Broeks, A; Verhoef, S; Rutgers, EJ; Swerdlow, A; Ashworth, A; Orr, N; Schoemaker, MJ; Figueroa, J; Chanock, SJ; Brinton, L; Lissowska, J; Couch, FJ; Olson, JE; Vachon, C; Pankratz, VS; Lambrechts, D; Wildiers, H; Van Ongeval, C; van Limbergen, E; Kristensen, V; Grenaker Ahns, G; Nord, S; Borresen-Dale, AL; Nevanlinna, H; Muranen, TA; Ai tamokki, K; Blomqvist, C; Chang-Claude, J; Rudolph, A; Seibold, P; Flesch-Janys, D; Fasching, PA; Haeblerle, L; Ekici, AB; Beckmann, MW; Burwinkel, B; Marme, F; Schneeweiss, A; Sohn, C; Trentham-Dietz, A; Newcomb, P; Titus, L; Egans, KM; Hunter, DJ; Lindstrom, S; Tamimi, RM; Kraft, P; Rahman, N; Turnbull, C; Renwick, A; Seal, S; Li, J; Liu, J; Humphreys, K; Benitez, J; Pilar Zamora, M; Arias Perez, JJ; Menendez, P; Jakubowska, A; Lubinski, J; Jaworska-Bieniek, K; Durka, K; Bogdanova, NV; Antonenokva, NN; Drk, T; Anton-Culver, H; Neuhausen, SL; Ziegas, A; Bernstein, L; Devilee, P; Tollemara, RA; Seynaeve, C; van Asperen, CJ; Cox, A; Cross, SS; Reed, MW; Khursnutdinova, E; Bermisheva, M; Prokofyeva, D; Takhi rova, Z; Meindl, A; Schmutzler, RK; Sutter, C; Yang, R; Schramm, P; Bremer, M; Christlensen, H; Park-Simon, TW; Hillemanns, P; Gunel, P; Truong, T; Menegaux, F; Sanchez, M; Radice, P; Peterslongo, P; Manoukian, S; Pensotti, V; Hopper, JL; Tsimiklis, H; Apicella, C; Southey, MC; Brauch, H; Brinning, T; Ko, YD; Sigurdson, AJ; Doody, MM; Hamann, U; Torres, D; Ulmer, HU; Frsti, A; Sawyer, EJ; Tomlinson, I; Kerin, MJ; Miller, N; Andrulis, IL; Knight, JA; Glendon, G; Marie Mulligan, A; Chenevix-Trench, G; Balleine, R; Giles, GG; Mihe, RL; McLean, C; Lindblom, A; Margolin, S; Haiman, CA; Henderson, BE; Schumacher, F; Le Marchand, L; Eilber, U; Wang-Gohrke, S; Hooning, MJ; Hollestelle, A; Barn den Ouweland, AM; Koppert, LB; Carpenter, J; Clarke, C; Scott, R; Mannermaa, A; Kataja, V; Kosma, VM; Hartikainen, JM; Brenner, H; Arndt, V; Stegmaier, C; Karina Dieffenbach, A; Winqvist, R; Pylks, K; Jukkola-Vuorinen, A; Grip, M; Offit, K; Vijai, J; Robson, M; Rau-Murthy, R; Dwek, M; Swann, R; Annie Perkins, K; Goldberg, MS; Labreche, F; Dumont, M; Eccles, DM; Tapper, WJ; Rafiq, S; John, EM; Whittemore, AS; Slager, S; Yannoukakos, D; Tolan, AE; Yao, S; Zheng, W; Halverson, SL; Gonzalez-Neira, A; Pita, G; Rosario Alonso, M; Hove, N; Herrero, D; Tessier, DC; Vincent, D; Baccetti, F; Luccarini, C; Baynes, C; Ahmed, S; Maranian, M; Healey, CS; Simard, J; Hall, P; Easton, DF; Garcia-Closas, M (2015) Pre
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Prediction of Breast Cancer Risk Based on Profiling With Common Genetic Variants

Breast cancer is the most common cancer among Western women, with approximately 1.67 million cases diagnosed annually worldwide (1). Strategies such as endocrine risk-reducing medication and early detection by breast cancer screening can reduce the burden of disease but have disadvantages including side effects, overdiagnosis, and increased cost (2–4). Stratification of women according to the risk of developing breast cancer could improve risk reduction and screening strategies by targeting those most likely to benefit (5–8).

Both genetic and lifestyle factors are implicated in the aetiology of breast cancer. Women with a history of breast cancer in a first-degree relative are at approximately two-fold higher risk than women without a family history (9). Rare high-risk mutations particularly in the BRCA1 and BRCA2 genes explain less than 20% of the two-fold familial relative risk (FRR) (10) and account for a small proportion of breast cancer cases in the general population. Low frequency variants conferring intermediate risk, such as those in CHEK2, ATM, and PALB2, explain 2% to 5% of the FRR. Genome-wide association studies (GWAS) have led to the discovery of multiple common, low-risk variants (single nucleotide polymorphisms [SNPs]) associated with breast cancer risk (11), many of which are differentially associated by estrogen receptor (ER) status (12,13). Recently, new risk-associated variants have been identified in a large-scale replication study conducted by the Breast Cancer Association Consortium (BCAC) as part of the Collaborative Oncological Gene-Environment Study (COGS). SNPs were genotyped in over 40 000 breast cancer cases and 40 000 control women, using a custom array (iCOGS). This experiment increased the number of SNPs robustly associated with breast cancer from 27 to more than 70 and identified additional variants specific to ER-negative breast cancer (14–17).

Risks conferred by SNPs are not sufficiently large to be useful in risk prediction individually. However, the combined effect of multiple SNPs could achieve a degree of risk discrimination that is useful for population-based programmes of breast cancer prevention and early detection (8,18). In this report, we investigated the value of using 77 breast cancer-associated single nucleotide polymorphisms (SNPs) for risk stratification, in a study of 33 673 breast cancer cases and 33 381 control women of European origin. We tested all possible pair-wise multiplicative interactions and constructed a 77-SNP polygenic risk score (PRS) for breast cancer overall and by estrogen receptor (ER) status. Absolute risks of breast cancer by PRS were derived from relative risk estimates and UK incidence and mortality rates.

**Results:** There was no strong evidence for departure from a multiplicative model for any SNP pair. Women in the highest 1% of the PRS had a three-fold increased risk of developing breast cancer compared with women in the middle quintile (odds ratio [OR] = 3.36, 95% confidence interval [CI] = 2.95 to 3.83). The ORs for ER-positive and ER-negative disease were 3.73 (95% CI = 3.24 to 4.30) and 2.80 (95% CI = 2.26 to 3.46), respectively. Lifetime risk of breast cancer for women in the lowest and highest quintiles of the PRS was 5.2% and 16.6% for a woman without family history, and 8.6% and 24.4% for a woman with a first-degree family history of breast cancer.

**Conclusions:** The PRS stratifies breast cancer risk in women both with and without a family history of breast cancer. The observed level of risk discrimination could inform targeted screening and prevention strategies. Further discrimination may be achievable through combining the PRS with lifestyle/environmental factors, although these were not considered in this report.
effects of the 77 SNPs on overall breast cancer risk, as well as
on the risk of ER-positive and ER-negative disease separately. We
estimated absolute risks of developing breast cancer for different
levels of the PRS, accounting for the competing risk of mortality
from other causes. Effect sizes were confirmed in one large study
(pKARMA) that was not part of any SNP discovery set. We discuss
the degree of breast cancer risk stratification obtained in women
with and without a family history of breast cancer.

Methods

Study Subjects and Genotyping

Study participants for the primary analyses (set 1) were 89 049
women of European origin participating in 41 studies in BCAC. All
studies were approved by the relevant institutional review boards,
and all individuals gave written informed consent. Samples were
genotyped using a custom Illumina iSelect array (iCOGS) compris-
ing 211 155 SNPs (15). For some analyses, a further 72 014 women
in BCAC genotyped for the relevant SNPs in earlier experiments
were included (set 2). For PRS analyses (67 054 women), studies
that oversampled breast cancer cases with a family history (21
995 women) were excluded. Supplementary Tables 1–3 (available
online) show study designs and numbers of breast cancer cases
and control women included.

Analyses were based primarily on variants reported to be
associated (at \( P < 5 \times 10^{-8} \)) by COGS or previous publications, with
either breast cancer overall or ER-negative disease. SNPs and
regions included are summarized in Supplementary Table 4
(available online).

Statistical Methods

Tests for pair-wise SNP*SNP interactions (departures from a
multiplicative model) were carried out using logistic regression,
with breast cancer as the outcome. The two SNPs were each
coded as a categorical variable (ie, fitting a separate parameter
for heterozygous and risk-allele homozygous genotypes), while
the interaction term (SNP1*SNP2) was included as continuous
covariate. All analyses were adjusted for study and seven prin-
cipal components (PC) to account for population substructure
(15). Additional interaction tests used are described in the
Supplementary Methods (available online).

To investigate the association between breast cancer risk and
the combined effects of 77 SNPs, a PRS was derived for each indi-
vidual using the formula:

\[
PRS = \beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k
\]

where \( \beta_k \) is the per-allele log odds ratio (OR) for breast cancer
associated with the minor allele for SNP \( k \), and \( x_k \) the number
of alleles for the same SNP (0, 1, or 2), and \( n = 77 \) is the total number
of SNPs. Thus, the PRS summarizes the combined effect of the
SNPs, ignoring departures from a multiplicative model (18). SNPs
and corresponding odds ratios used in derivation of PRSs are
summarized in Supplementary Table 4 (available online).

Logistic regression models were used to estimate the odds
ratios for breast cancer by percentile of the PRS, with the mid-
dle quintile category (40th to 60th percentile) as the reference.
Observed odds ratios for breast cancer by percentile of the PRS
were compared with predicted odds ratios under a multiplica-
tive polygenic model of inheritance. Modification of the PRS by
age or by family history of breast cancer in a first-degree rela-
tive was evaluated by fitting additional interaction terms in the
model. All tests of statistical significance were two-sided. The
thresholds for statistical significance are indicated below.

The absolute risk of overall breast cancer, ER-positive and
ER-negative breast cancer for individuals in each risk category,
was calculated taking into account the competing risk of dying
from other causes apart from breast cancer. Approximate con-
fidence limits for the absolute risk were derived from the vari-
cance-covariance matrix of the log (relative risk) parameters in
the logistic regression analysis. Detailed methods are provided
in Supplementary Methods (available online).

Results

Pairwise Multiplicative SNP*SNP Interaction
Analyses

Data on 46 450 breast cancer cases and 42 599 controls
from 41 studies were included in the interaction analyses

<table>
<thead>
<tr>
<th>Type of breast cancer</th>
<th>Case-control analyses</th>
<th>Case-only analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS</td>
<td>OBS/EXP</td>
</tr>
<tr>
<td>All SNPs</td>
<td></td>
<td>( n = 3080 ) SNP pairs</td>
</tr>
<tr>
<td>All breast cancers</td>
<td>44</td>
<td>1.43</td>
</tr>
<tr>
<td>ER-positive</td>
<td>43</td>
<td>1.40</td>
</tr>
<tr>
<td>ER-negative</td>
<td>35</td>
<td>1.13</td>
</tr>
<tr>
<td>Unlinked SNPs</td>
<td></td>
<td>( n = 2556 ) SNP pairs</td>
</tr>
<tr>
<td>All breast cancers</td>
<td>35</td>
<td>1.37</td>
</tr>
<tr>
<td>ER-positive</td>
<td>38</td>
<td>1.49</td>
</tr>
<tr>
<td>ER-negative</td>
<td>30</td>
<td>1.17</td>
</tr>
</tbody>
</table>

\( \dagger \) 46 450 breast cancer cases and 42 599 control women
were included in the analysis of all breast cancers. 27 074 breast cancer cases were included in the analysis
of ER-positive disease and 7413 breast cancer cases were included in the analysis of ER-negative disease. \( n = \) number of single nucleotide polymorphism (SNP) pairs
tested; OBS = number of tests observed with \( P_{\text{uncorrected}} < .01 \); OBS/EXP = number of tests observed with \( P_{\text{uncorrected}} < .01 \) divided by the number of positive tests expected
by chance, given the number of SNP pairs tested; SNP = single nucleotide polymorphism.

\( \dagger \) Only results of SNP pairs not strongly associated in the control population (\( P_{\text{uncorrected}} > .01 \) in control-only analyses) were included in the counts.

\( \ddagger \) \( P \) value for difference between observed and expected numbers of tests, assuming each test is independent and that, under the null hypothesis, the observed
number of statistically significant tests follows a poisson distribution. The statistical test was two-sided.

\( \|$ Some SNPs were linked, as described in the Supplementary Methods (available online).

\( \|$ Only the most statistically significant SNP from each group of linked SNPs were included in these analyses.
Association Between PRS and Breast Cancer Risk

As predicted by the polygenic, multiplicative model, the number of breast cancer risk alleles and the 77-SNP PRS approximated a normal distribution for both breast cancer cases and control women (Figure 1). The odds ratios for developing breast cancer by percentiles of the PRS, compared with women in the middle quintile (40th to 60th percentile) are shown in Figure 2A. The observed odds ratios were similar to the odds ratios predicted under a polygenic multiplicative model; the 95% confidence interval (CI) included the predicted odds ratio at all points except the 80th to 90th percentile (Figure 2A; Supplementary Table 8, available online). For women in the lowest 1% of the PRS distribution, the estimated odds ratio compared with women in the middle quintile was 0.32 (95% CI = 0.25 to 0.40). By contrast, for women in the highest 1% of the PRS distribution, the estimated OR compared with women in the middle quintile was 3.36 (95% CI = 2.95 to 3.83, P = 7.5x10^-10). When PRS were derived separately for ER-positive and ER-negative disease, the corresponding odds ratios were 3.73 (95% CI = 3.24 to 4.30) and 2.80 (95% CI = 2.26 to 3.46), respectively (Figure 2, B and C). The log OR per unit standard deviation of the PRS was 0.44 (95% CI = 0.42 to 0.46) for overall breast cancer, 0.49 (95% CI = 0.47 to 0.51) for ER-positive, and 0.37 (95% CI = 0.34 to 0.40) for ER-negative disease (Table 3). A validation analysis including only one large study (pKARMA) that was not part of any SNP discovery analyses found similar odds ratio estimates to those in the remaining studies, except for the 60% to 80% and 90% to 95% categories, for which estimates were higher in pKARMA (Table 4; Supplementary Table 9, available online). The log OR per unit SD was also similar for pKARMA alone (log OR per unit SD = 0.4).

The associations between PRS and breast cancer in different age groups are summarized in Table 3 and Supplementary Figure 2 (available online). There was a statistically significant interaction between PRS and age, the association between PRS and breast cancer risk decreasing with age (Table 3).

A family history of breast cancer in one or more affected first-degree relatives was reported by 18.5% of breast cancer cases and 11.1% of control women. The odds ratio for family history was attenuated from 1.81 to 1.68 (12.6% attenuation) after adjusting for the PRS (Table 2). At younger ages (<40 years), there was less attenuation (from 2.90 to 2.76, 4.6% attenuation) (Table 2). The joint effects of the PRS and family history were largely consistent with a multiplicative model (Pinteraction = .34 for the interaction between the PRS and family history; data not shown); however, we observed a stronger effect of family history for women at the lowest 1% of the PRS (Supplementary Table 10, available online).

The discriminative accuracy of the PRS, as measured by the C-statistic, was 0.622 (95% CI = 0.619 to 0.627); discrimination was...
Table 4. Validation analyses in the pKARMA study*

<table>
<thead>
<tr>
<th>Percentile of PRS, %</th>
<th>All studies in iCOGS excluding pKARMA</th>
<th>pKARMA only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR† (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>0.29 (0.23 to 0.37)</td>
<td>0.48 (0.28 to 0.83)</td>
</tr>
<tr>
<td>&gt;1–5</td>
<td>0.42 (0.37 to 0.47)</td>
<td>0.48 (0.36 to 0.63)</td>
</tr>
<tr>
<td>5–10</td>
<td>0.55 (0.50 to 0.61)</td>
<td>0.58 (0.45 to 0.74)</td>
</tr>
<tr>
<td>10–20</td>
<td>0.65 (0.60 to 0.70)</td>
<td>0.68 (0.57 to 0.81)</td>
</tr>
<tr>
<td>20–40</td>
<td>0.80 (0.76 to 0.85)</td>
<td>0.81 (0.71 to 0.94)</td>
</tr>
<tr>
<td>40–60</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>60–80</td>
<td>1.18 (1.12 to 1.24)</td>
<td>1.35 (1.19 to 1.54)</td>
</tr>
<tr>
<td>80–90</td>
<td>1.48 (1.39 to 1.57)</td>
<td>1.56 (1.34 to 1.82)</td>
</tr>
<tr>
<td>90–95</td>
<td>1.69 (1.56 to 1.82)</td>
<td>2.05 (1.70 to 2.47)</td>
</tr>
<tr>
<td>95–99</td>
<td>2.20 (2.03 to 2.38)</td>
<td>2.12 (1.73 to 2.59)</td>
</tr>
<tr>
<td>&gt;99</td>
<td>2.81 (2.43 to 3.24)</td>
<td>3.06 (2.16 to 4.34)</td>
</tr>
</tbody>
</table>

* Comparison of effect sizes ( odds ratios) by percentile of the polygenic risk score (PRS) in pKARMA (not included in the discovery set) and in all other studies ( included in the discovery set). The pKARMA study comprises 4553 breast cancer cases and 5537 control women. Only single nucleotide polymorphisms (SNPs) that reached genome-wide statistical significance in a meta-analysis of iCOGS and previous combined genome-wide association studies were included in the risk score, and the effect sizes for each SNP were estimated using iCOGS database minus pKARMA (Supplementary Table 9, available online). PRS = polygenic risk score; OR = odds ratio.† Odds ratios are for different percentiles of the polygenic PRS relative to the middle quintile (40% to 60%) of the PRS.

Similar when restricted to pKARMA alone, with an area under the curve of 0.615 (95% CI = 0.608 to 0.616) (data not shown).

Absolute Risks of Developing Breast Cancer by Levels of PRS

The estimated risk of developing breast cancer by age 80 years for women in the lowest and highest 1% of the PRS was 3.5% (95% CI = 2.6% to 4.4%) and 29.0% (95% CI = 24.9% to 33.5%), respectively (Figure 3A). For the lowest and highest quintiles of the PRS, the risk was 5.3% (95% CI = 5.1% to 5.7%) and 17.2% (95% CI = 16.1% to 18.1%), respectively (data not shown). The corresponding risks of developing ER-positive disease were 4.1% and 15.7% for women in the lowest and highest quintiles, respectively, of the ER-positive PRS (averaged over all ER-negative PRS categories), whereas the highest lifetime risk for ER-negative disease was 2.4% (women in the highest quintile of ER-negative PRS and average ER-positive risk) (Figure 3). Lifetime risk of breast cancer for women in the lowest and highest quintiles of the PRS were 5.2% and 16.6% for a woman without family history and 8.6% and 24.4% for a woman with a first-degree family history of breast cancer (Figure 4).

We estimated the 10-year absolute risk of breast cancer at different ages and evaluated the age at which women at different levels of the PRS reach a threshold of 2.4%, which corresponds to the average 10-year risk of breast cancer for women age 47 years. This threshold was reached at 32 years for women whose PRS is above the 99th percentile of the PRS, and 57 years for women in the 20th to 40th percentiles of the PRS, and was never reached for women in lower percentiles (Figure 3D). As expected, lifetime risks were higher, and the ages at which the 2.4% threshold was reached were lower for women with a family history of breast cancer (Figure 4).

Discussion

In this report, we evaluated the degree of breast cancer risk stratification that can be attained in women of European ancestry using data for 77 common genetic variants, summarized as a PRS. Our results show that the PRS stratifies breast cancer risk in women without family history and refines genetic risk in women with a family history of breast cancer.

The PRS we used (sum of the minor alleles weighted by the per-allele log OR) is the most efficient, assuming that SNP odds ratios combine multiplicatively (ie, no interactions on a log-additive scale) (18). Evaluation of pairwise SNP interactions showed that this was a reasonable assumption. Although no individual interactions could be established, we observed an excess of multiplicative interactions at P less than .01. This could be the result of underlying population stratification not accounted for by principal components adjustment or reflect the presence of multiple interactions too weak to be established individually. A recent study also found no evidence for interactions among SNPs with weaker evidence for main effects (19). Although we did not test for higher order interactions among SNPs, consistency between empirical and predicted odds ratios assuming multiplicative effects suggests that across all possible multivariate interactions the overall effect is close to multiplicative.

The 77-SNP PRS was associated with a larger effect than previously reported for a 10-SNP PRS (20). For example, our odds ratio for breast cancer for women in the highest compared with the middle quintile was 1.82 (95% CI = 1.73 to 1.90) vs 1.44 (95% CI = 1.35 to 1.53) for the 10-SNP PRS (20). A potential concern is that the PRS was constructed using iCOGS data that were, in part, the basis for discovery of many of the loci. This could lead to some upward bias in the odds ratio estimates (winner’s curse); however, analyses based on a large study (pKARMA) that was not part of any discovery set obtained similar estimates indicating that any winner’s curse effect is likely to be small.

There has been little evidence of differences by age in the per-allele odds ratio for individual SNPs. However, we observed a small but statistically significant decrease in odds ratio for PRS with increasing age. As expected, the odds ratio for family history was reduced after adjustment for the PRS. This attenuation (~12.6%) was consistent with the estimated fraction of the two-fold FRR explained by the 77-SNPs under a polygenic risk model (15). The joint effects of PRS and family history were consistent with a multiplicative model. A stronger FRR was observed for women at the lowest percentile of the PRS, but this was based on small numbers and requires confirmation. The degree of attenuation of the family history odds ratio was lower below age 40 years, as a result of the higher FRR at young ages, suggesting that rarer genetic variants may be more important at young ages.

We calculated the absolute risk of developing breast cancer for women at different levels of genetic risk according to the PRS. The lifetime risk for women below the first and above the 99th percentile of the PRS was 3.5% (95% CI = 2.6% to 4.4%) and 29.0% (95% CI = 24.9% to 33.5%), respectively. UK NICE guidelines recommend enhanced surveillance for women with a family history with lifetime risk of developing breast cancer over 17% (21). Figure 3 indicates that the PRS alone could identify approximately 8% of all women in the UK population at this level of risk, regardless of family history or other risk factors; approximately 17% of all breast cancer cases in the population would be expected to occur among these women. By contrast, the low absolute risk of breast cancer among women at the lowest end of the risk distribution raises the possibility that such women might be recommended more limited surveillance. Women at different levels of the PRS reach the same 10-year risk threshold at different ages, supporting the notion that using SNP profiles rather than age alone as a criterion to offer routine mammographic screening could lead to more effective screening programs (6). The utility of such an approach
would, however, depend on the acceptability of risk-based surveillance, together with health economic considerations.

Prediction of subtype-specific breast cancer should also be informative for prevention (4). Recently updated NICE guidelines include recommendations to use endocrine treatments (tamoxifen and raloxifene) for primary prevention of breast cancer for women at moderate to high risk (21). These guidelines are based on risk of overall breast cancer for women with a family history of breast cancer. However, because these drugs prevent only ER-positive tumours, risk estimates incorporating the ER-positive PRS could better define the subset of women most likely to benefit. Our sample was derived from studies in Europe, North America, and Australia and restricted to women of European origin. While the results should be widely applicable in these populations, additional studies will be required to develop and validate genetic profiles for other populations, in particular Asian and African populations, where SNP associations, background incidence rates and distribution of tumour characteristics are substantially different.

Our analysis summarized family history in terms of a single binary variable, but familial risk of breast cancer also depends on the number of affected and unaffected relatives and their ages. Risk prediction algorithms that combine full family history data with a polygenic component perform better than simpler models (22). It is possible to incorporate the current PRS into family-history based models for breast cancer, such BOADICEA, to improve genetic risk prediction (23).

The COGS project includes the largest set of breast cancer studies with both phenotype and genotype information, and our analysis utilized by far the largest number of SNPs with confirmed associations with breast cancer, including all SNPs discovered to date. Further refinement of the risk stratification should be possible through incorporating additional SNPs exhibiting evidence for association, but not at formal genome-wide

![Figure 1](image-url)

Figure 1. Distribution of the number of breast cancer risk alleles (A) and polygenic risk score residuals after adjusting the polygenic risk score (PRS) for study and seven principal components (B), in 33,673 breast cancer cases and 33,381 control women of European origin. The PRS approximated a normal distribution in both breast cancer cases and control women. The mean PRS was 0.69 for breast cancer cases and 0.49 for control women. PRS residuals are standardized Pearson’s residuals calculated after regression of the score on seven principal components.
Figure 2. Association between the polygenic risk score (PRS) and breast cancer risk in women of European origin for (A) all breast cancers, (B) estrogen receptor (ER)-positive disease, and (C) ER-negative disease. Odds ratios are for different percentiles of the PRS relative to the middle quintile (40% to 60%) of the PRS. Odds ratios and 95% confidence intervals are shown. Regular lines denote the observed estimates, and dotted lines the theoretical estimates under a multiplicative polygenic model with a standard deviation of the PRS of 0.45 for all breast cancer, 0.50 for ER-positive breast cancer, and 0.38 for ER-negative breast cancer, as derived from the estimated effect sizes and allele frequencies/haplotype frequencies for each locus. PRS = polygenic risk score.
Some limitations of this study should be noted. Although the study was extremely large, the numbers of breast cancer cases and control women were still too limited to provide precise estimates of relative risks in the extremes of the PRS (for example, the highest 1%). Numbers were also limited to explore exercise estimates of relative risks in the extremes of the PRS (for cases and control women were still too limited to provide precise estimates of the combined effects of multiple SNPs and the PRS act multiplicatively, target ing intermediate or high risk (23)). We estimated the C-statistic for the PRS to be 0.62. Assuming that the multiplicative model is correct, the C-statistic would increase to 0.66 with the addition of the lifestyle risk factors. If modifiable risk factors and the PRS act multiplicatively, targeting public health interventions to women at higher genetic risk should result in a larger absolute risk reduction. For example, the decision to prescribe hormone replacement therapy might be guided by the PRS (28). Similar considerations would apply to risk-reducing interventions such as preventive medication and oophorectomy.

Some limitations of this study should be noted. Although the study was extremely large, the numbers of breast cancer cases and control women were still too limited to provide precise estimates of relative risks in the extremes of the PRS (for example, the highest 1%). Numbers were also limited to explore the effects at very young ages, and estimates were less precise for ER-negative disease. There was heterogeneity among the effects at very young ages, and estimates were less precise for ER-negative disease. There was heterogeneity among the effects at very young ages, and estimates were less precise for ER-negative disease.

The risk discrimination provided by the genetic profile, summarised in the PRS and family history, should be further improved by combining, with lifestyle risk factors, benign breast disease, and mammographic density (24,25,28). Although we did not consider lifestyle factors explicitly in this dataset, other large studies have found no good evidence for interactions between common susceptibility SNPs and lifestyle factors for breast cancer, suggesting that SNPs generally combined multiplicatively (26,27). Darabi et al. (25) estimated a C-statistic of 0.60 for lifestyle risk factors including mammographic density. By comparison, we estimated the C-statistic for the PRS to be 0.62. Assuming that the multiplicative model is correct, the C-statistic would increase to 0.66 with the addition of the lifestyle risk factors. If modifiable risk factors and the PRS act multiplicatively, targeting public health interventions to women at higher genetic risk should result in a larger absolute risk reduction. For example, the decision to prescribe hormone replacement therapy might be guided by the PRS (28). Similar considerations would apply to risk-reducing interventions such as preventive medication and oophorectomy.

Figure 3. Cumulative and 10-year absolute risks of developing breast cancer for women of European origin by percentiles of the polygenic risk score (PRS). Cumulative absolute risk of developing breast cancer for (A) all breast cancers, (B) estrogen receptor (ER)–positive disease, and (C) ER-negative disease by percentiles of the PRS, and 10-year absolute risk of developing breast cancer for (D) all breast cancers, (E) ER-positive disease, and (F) ER-negative disease. Note different scales and PRS categories in the different panels. The red line shows the 2.4% risk threshold corresponding to the risk for women age 47 years who were eligible for screening, calculated as described in the Supplementary Methods (available online). Absolute risks were calculated using the PRS relative risks estimated as described in the Supplementary Methods (available online), and breast cancer incident rates and mortality from other causes obtained from the UK National Office for Statistics. For subtype-specific disease, the absolute risk for women in a particular PRS category for ER-positive disease and another PRS category for ER-negative disease were calculated. Information on proportions of tumors by ER status was obtained from the West Midlands Registry.

statistical significance, together with variants in genes conferring intermediate or high risk (15). The risk discrimination provided by the genetic profile, summarised in the PRS and family history, should be further improved by combining, with lifestyle risk factors, benign breast disease, and mammographic density (24,25,28). Although we did not consider lifestyle factors explicitly in this dataset, other large studies have found no good evidence for interactions between common susceptibility SNPs and lifestyle factors for breast cancer, suggesting that SNPs generally combined multiplicatively (26,27). Darabi et al. (25) estimated a C-statistic of 0.60 for lifestyle risk factors including mammographic density. By comparison, we estimated the C-statistic for the PRS to be 0.62. Assuming that the multiplicative model is correct, the C-statistic would increase to 0.66 with the addition of the lifestyle risk factors. If modifiable risk factors and the PRS act multiplicatively, targeting public health interventions to women at higher genetic risk should result in a larger absolute risk reduction. For example, the decision to prescribe hormone replacement therapy might be guided by the PRS (28). Similar considerations would apply to risk-reducing interventions such as preventive medication and oophorectomy.

The debate on public health utility and implementation of the PRS in clinical practice. Our work suggests that the PRS, particularly when used in combination with other risk factors, could help identify subsets of women at different levels of risk, for whom management would differ. The PRS may facilitate early detection of cancers in younger women and, importantly, identify individuals at risk of specific subtypes of breast cancer. Finally, there is potential for a stronger impact in modifying environmental factors in women at higher risk of breast cancer. Prospective analyses of the 77 SNP PRS, in combination with other risk factors, will be required to validate the overall accuracy of risk prediction. Such a comprehensive risk prediction...
algorithm could provide a powerful basis for stratified breast cancer prevention programs.

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Consortia Membership

Australian Ovarian Cancer Study Group

David D. Bosted, Adele C. Green, Georgia Chenexiv-Trench,Anna deFazio, Dorota Gertig, Penelope M. Webb.

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David Armer, Lesley Andrews, Yoland Antill, Shane Armitage, Rosemary Balleine, Agnes Bankier, Patti Bastick, John Beilby, Barbara Bennett, Ian Bennett, Anneke Blackburn, Michael Bogwitz, Meggan Brennan, Melissa Brown, Michael Buckley, Matthew Burgess, Jo Burke, Phyllis Butow, Ian Campbell, Alice Christian, Georgia Chenexiv-Trench, Christine Clarke, Alison Colley, Dick Cotton, Bronwyn Culling, Margaret Cummings, Sarah-Jane Dawson, Anna DeFazio, Martin Delatycki, Rebecca Dickson, Alexander Dobrovic, Tracy Dudding, Ted Edkins, Stacey Edwards, Gelareh Farshid, Susan Fawcett, Georgina Fenton, Michael Field, James Flanagan, Peter Fong, John Forbes, Stephen Fox, Juliet French, Claire Gaff, Mac Gardner, Mike Gattas, Graham Giles, Crantley Gill, Jack Goldblatt, Sian Greening, Scott Grist, Eric Haan, Marion Harris, Stewart Hart, Nick Hayward, Sue Healey, Louise Heiniger, John Hopper, Clare Hunt, Paul James, Rick Kefford, Alexa Kidd, Belinda Kiely, Judy Kirk, James Kollias, Yvonne Lakhani, Jennifer Leary, Geoff Lindeman, Lara Lipton, Liz Kiely, Judy Kirk, James Kollias, Jessika Koehler, Serguei Kovalenko, Tracy Dudding, Ted Edkins, Stacey Edwards, Gelareh Farshid, Susan Fawcett, Georgina Fenton, Michael Field, James Flanagan, Peter Fong, John Forbes, Stephen Fox, Juliet French, Claire Gaff, Mac Gardner, Mike Gattas, Graham Giles, Crantley Gill, Jack Goldblatt, Sian Greening, Scott Grist, Eric Haan, Marion Harris, Stewart Hart, Nick Hayward, Sue Healey, Louise Heiniger, John Hopper, Clare Hunt, Paul James, Rick Kefford, Alexa Kidd, Belinda Kiely, Judy Kirk, James Kollias, Jessika Koehler, Serguei Kovalenko, Sunil Lakhani, Jennifer Leary, Geoff Lindeman, Lara Lipton, Liz Lob, Graham Mann, Deborah Marsh, Bettina Meiser, Roger Milne, Gillian Mitchell, Shona O’Connell, Nick Pachter, Brian Patterson, Lester Peters, Kelly Phillips, Melanie Price, Lynne Purser, Tony Reeve, Edwina Rickard, Bridget Robinson, Barney Rudzki, Elizabeth Salisbury, Christobel Saunders, Joe Sambrook, Jodi Saulus, Robyn Sayer, Clare Scott, Elizabeth Scott, Rodney Scott, Adrienne Sexton, Raghwa Sharma, Andrew Shelling, Peter Simpson, Melissa Southey, Amanda Spurdle, Graeme Suthers, Pamela Sykes, Jessica Taylor, Ella Thompson, Heather Thorne, Sharron Townsend,
Alison Trainer, Kathy Tucker, Janet Tyler, Jane Visvader, Logan Walker, Paul Waring, Robin Ward, Bev Warner, Rachael Williams, Ingrid Winship, Mary Ann Young. *Peter MacCallum Cancer Center, Melbourne, Australia.

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