symposium article

Genetic modifiers of cancer risk for BRCA1 and BRCA2 mutation carriers

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Germline mutations in BRCA1 and BRCA2 confer high risks of female breast and ovarian cancer. However, there is strong evidence that these risks are modified by other factors, including familial or genetic factors. Genome-wide association studies have identified several breast cancer genetic susceptibility variants in the general population that are also associated with breast cancer risk for mutation carriers. The patterns of association for these variants vary between BRCA1 and BRCA2 mutation carriers and this variation appears to be driven by their differential associations with breast cancer subtypes defined by estrogen receptor status. We review the latest evidence regarding genetic modifiers of cancer risk for female BRCA1 and BRCA2 mutation carriers emerging from candidate gene studies, variants found in genome-wide association studies (GWAS) to be associated with cancer risk in the general population and GWAS specifically in mutation carriers. We also discuss the implications of these findings for cancer risk prediction in these women. BRCA1 and BRCA2 mutation carriers could potentially be among the first groups of individuals for whom clinically applicable risk profiling could be developed using the common breast cancer susceptibility variants identified through GWAS.

introduction

Breast cancer and ovarian cancer are complex diseases, with both genetic and environmental factors involved in their etiology. While various hormonal and lifestyle factors have been identified as playing an important role in these two pathologies, many of them common to both [1–10], having a family history of disease is one of the strongest risk factors. Women with a first-degree relative affected with breast cancer are at an estimated twofold increased risk of breast cancer, compared with those with no family history [11]. Similarly, having a first-degree relative affected with ovarian cancer is associated with a threefold increased risk of ovarian cancer [8]. Several high-risk breast and ovarian cancer susceptibility variants have been identified to date, the most important in the context of genetic counseling being BRCA1 and BRCA2.

Female carriers of deleterious BRCA1 and BRCA2 mutations are predisposed to high lifetime risks of breast and ovarian cancer. They are also at increased risk of pancreatic and possibly other cancers, while male mutation carriers are at increased risk of prostate, breast and breast cancer, the latter particularly if the mutation is in BRCA2 [12, 13]. Initial estimates, based on studies of selected multiple-case families, indicated that by age 70, ~80% of carriers of mutations in BRCA1 and BRCA2 would develop breast cancer, and ~60% of BRCA1 mutation carriers and 30% of BRCA2 mutation carriers would develop ovarian cancer [14, 15]. However, lower average penetrance estimates were obtained by a meta-analysis of studies that sampled index patients independently of their family history: cumulative breast cancer risk to age 70 of 65% for BRCA1 mutation carriers and 45% for BRCA2 mutation carriers. The corresponding estimates for ovarian cancer were 39% and 11% for BRCA1 and BRCA2 mutation carriers, respectively [16, 17]. In addition, it has been reported that penetrance estimates vary between, and within, mutation carrier families, by age at onset of the index case and by the type of cancer in the index case [16, 18, 19]. These observations, as well as that of a possible increased risk of breast cancer for mutation-negative women from carrier families [20, 21] are consistent with the hypothesis that cancer risks in BRCA1 and BRCA2 mutation carriers are modified by other factors, at least some of them genetic. Further evidence for genetic modifiers of risk comes from studies of other phenotypes, such as mammographic density, which are associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers [22], but themselves have a strong genetic component [23]. Finally, segregation analysis studies have quantified the extent of genetic variation in breast cancer risk for BRCA1 and BRCA2 mutation carriers [17, 18] and demonstrated that models that allow for other genes to have a modifying effect on the breast cancer risks conferred by BRCA1 and BRCA2 mutations fit significantly better to familial data than models without a modifying component [17, 24].
This review focuses on common genetic polymorphisms that modify the risk of breast and ovarian cancer in female BRCA1 and BRCA2 mutation carriers, based on the current evidence, and on their implications for cancer risk prediction in these women. It also explores the value of studying genetic modifiers of breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers in identifying genetic variants associated with different disease subtypes in the general population.

common variants associated with breast cancer risk for mutation carriers

Common genetic modifiers of breast cancer risk for carriers of mutations in BRCA1 and BRCA2 have been identified in essentially three ways: studies of single nucleotide polymorphisms (SNPs) in candidate genes, studies of SNPs found in genome-wide association studies (GWAS) to be associated with breast cancer risk in the general population and GWAS carried out in mutation carriers.

candidate gene studies

Several common polymorphisms in candidate genes have been investigated as potential modifiers of breast cancer risk for BRCA1 and BRCA2 mutation carriers. These studies have concentrated largely on genes thought to be functionally relevant to the disease or to interact functionally with BRCA1 and/or BRCA2. Many positive associations have been reported, but all have either failed to replicate [25–30] or require definitive replication in larger studies [31]. The only exceptions to this have been RAD51-135G→C and CASP8-D302H. The RAD51 polymorphism has been studied previously as a candidate risk modifier in mutation carriers based on the fact that the RAD51 protein interacts directly with both BRCA1 and BRCA2 [19, 32, 33]. An analysis by the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) [34] found that BRCA2 mutation carriers who have two copies of the ‘C’ allele at this locus have a threefold increased breast cancer risk compared with carriers with two copies of the ‘G’ allele [35]. In a separate study, the CIMBA investigated the polymorphism in the apoptosis-related gene CASP8 because it was found to be associated with reduced breast cancer in the general population, following initial positive findings from candidate gene association studies [36]. Results indicate that the minor allele of CASP8-D302H confers a reduction in breast cancer risk for BRCA1 mutation carriers that is similar in magnitude [per-allele hazard ratio (HR) 0.85] [37] to the reduction in risk for the general population (per-allele HR 0.88; Tables 1 and 2).

SNPs found by GWAS to be associated with breast cancer risk in the general population

Until recently, attention has been focused on SNPs with clear statistical evidence of association (P < 10^{-7}) with breast cancer risk in the general population as potential modifiers of risk in BRCA1 and BRCA2 mutation carriers. To date, 18 such loci have been identified, all but one (CASP8-D302H) by GWAS [36, 38–46]. Results for these SNPs in the general population are summarized in Table 1. These variants are generally common [minor allele frequency (MAF) ≥0.13] and have relatively small associated per-allele odds ratio (OR, all <1.30). Many of these SNPs are more strongly associated with estrogen receptor (ER)-positive disease than ER-negative disease. This observation is likely related to the fact that all but one of the published studies have been based on predominantly sporadic breast cancer cases of white European ancestry, a large majority (70%–80%) of which have ER-positive disease.

Such variants have been considered potential modifiers of breast cancer risk for BRCA1 and BRCA2 mutation carriers. To investigate this, the CIMBA has studied such loci in its large collection of BRCA1 and BRCA2 mutation carriers. Results have been published for six of these polymorphisms and these are summarized in Table 2. Two SNPs have been found to be associated with the risk of breast cancer for BRCA1 mutation carriers, rs3803662 in the TOX3/TNRC9 region and rs13387042 in 2q35 [49, 50]. On the other hand, five of the six polymorphisms studied were associated with breast cancer risk for BRCA2 mutation carriers [49, 50] (Table 2). The strongest evidence of association was for a polymorphism in the FGFR2 gene (P = 2 x 10^{-8}), for which each copy of a minor allele was estimated to confer an HR of 1.32. Of the six polymorphisms studied, only 8q24-rs13281615 was not significantly associated with breast cancer risk for BRCA2 mutation carriers, but the HR estimate (1.06) was similar to the per-allele OR estimate in the general population (1.08) [39]. This analysis was based on ~5400 BRCA2 mutation carriers and it may be that much larger samples are required to detect such effects reliably.

These results indicate that the GWAS-identified susceptibility SNPs for the general population are differentially associated with risk for BRCA1 and BRCA2 mutation carriers. BRCA1 and BRCA2 mutations are associated with different breast tumor characteristics. While mutations in both genes are associated with the development of higher grade tumors [51], breast cancers in BRCA2 mutation carriers are otherwise broadly similar to those diagnosed in the general population, which are predominantly ER positive. In contrast, breast cancers in BRCA1 mutation carriers have a distinct morphology, more often have a ‘basal’ phenotype [52, 53] and are predominantly ER negative. Lakhani et al. [54] estimated that 90% of breast cancers in BRCA1 mutation carriers are ER negative, compared with 35% for BRCA2 mutation carrier cases. Figure 1 summarizes for GWAS-identified SNPs, the associations observed in BRCA1 and BRCA2 mutation carriers, and the associations with ER-positive and ER-negative breast cancer in the general population. The pattern of association of these SNPs for mutation carriers, by gene, is consistent with that for breast cancer defined by ER status in the general population. That is, SNPs associated with the risk of ER-negative disease tend to be associated with risk for carriers of mutations in BRCA1, whereas those associated with ER-positive disease in the general population, which constitute the majority of the susceptibility variants identified to date by GWAS, tend to be associated with risk for carriers of mutations in BRCA2. It has therefore been suggested that the differences in the associations of these SNPs with breast cancer risk for BRCA1 versus BRCA2 mutation carriers could be explained by the differential effects of the underlying causal...
Table 2. SNPs associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers

<table>
<thead>
<tr>
<th>Gene/region</th>
<th>SNP</th>
<th>No. carriers</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>% Variance explained</th>
<th>References</th>
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<tr>
<td></td>
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SNPs identified through candidate gene studies
- **RAD51**: rs1801320
  - 5778 carriers
  - 1.59 (0.96–2.63)
  - 0.07
  - 3 × 10^{-5}
  - 91
  - 1.21
  - [36]

SNPs identified by GWAS
- **FGFR2**: rs2981522
  - 1.02 (0.95–1.09)
  - 0.9
  - 3263
  - 1.32
  - [48]

SNPs identified through GWAS carried out in mutation carriers
- **C19orf62**: rs18170
  - 8363 carriers
  - 1.26 (1.17–1.35)
  - 2 × 10^{-9}
  - 1.3
  - [53]

**Table 1.** SNPs associated with breast cancer risk in the general population

<table>
<thead>
<tr>
<th>Locus-SNP</th>
<th>Gene(s)</th>
<th>Freq.</th>
<th>OR (overall)</th>
<th>P (het)</th>
<th>OR (ER+)</th>
<th>OR (ER-)</th>
<th>References</th>
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<tbody>
<tr>
<td>10p14-rs1045485</td>
<td>CASP8</td>
<td>0.13</td>
<td>0.88</td>
<td>0.2</td>
<td>0.90</td>
<td>0.93</td>
<td>[36]</td>
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<tr>
<td>10q21-rs1011790</td>
<td>CDKN2A, CDKN2B</td>
<td>0.17</td>
<td>1.09</td>
<td>0.2</td>
<td>1.09</td>
<td>1.00</td>
<td>[46]</td>
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<tr>
<td>10p15-rs2380205</td>
<td>ANKRD16, FBXO18</td>
<td>0.43</td>
<td>0.9</td>
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<td>0.94</td>
<td>0.04</td>
<td>[46]</td>
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<td>10q21-rs10995190</td>
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<td>0.15</td>
<td>0.86</td>
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<td>0.83</td>
<td>0.91</td>
<td>[46]</td>
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<tr>
<td>10q22-rs704010</td>
<td>ZMIZ1</td>
<td>0.39</td>
<td>1.07</td>
<td>0.9</td>
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<td>11q13-rs614367</td>
<td>intergenic</td>
<td>0.15</td>
<td>1.15</td>
<td>0.2</td>
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aPer-allele hazard ratio (HR) unless specified otherwise.

bP-value for test of association.

cProportion of the polygenic modifying variance explained [49].

dHR for genotype CC versus GG.

eHR under a dominant model.

GWAS, genome-wide association studies; SNP, single nucleotide polymorphism.
variants on the development of ER-defined subtypes of disease [49, 50].

**GWAS in BRCA1 and BRCA2 mutation carriers**

The evidence from the studies described above indicates that genetic variants that modify breast cancer risk for BRCA1 mutation carriers may differ from those for BRCA2 carriers or for non-carriers. This led investigators to search for genetic loci associated with breast cancer for BRCA1 and BRCA2 mutation carriers through separate GWAS in each of the two groups using the CIMBA collection. Initial results have so far been reported for the BRCA1 mutation carrier GWAS as part of a fast replication two-stage experiment [48]. Two SNPs at locus 19p13 were independently associated with breast cancer risk. Based on the combined analysis of stages 1 and 2, each copy of the minor allele of SNP rs8170 was associated with an estimated HR of 1.26 [95% confidence interval (CI) 1.17–1.35], whereas each copy of the ‘C’ allele at SNP rs2363956 was associated with reduced breast cancer risk (HR 0.84; 95% CI 0.80–0.89). Modelling the joint effects of all significant SNPs in the region revealed that the most parsimonious model was one that included the effects of both rs8170 and rs2363956 (2df \(P = 10^{-13}\)), indicating that the association signal could be driven by a variant that is correlated with both these polymorphisms. SNP imputation analysis in the 19p13 region, using data from the 1000 genomes project data as reference, revealed a series of correlated SNPs with smaller \(P\) values. Fine-mapping of the region based on direct genotyping is underway, as is a large-scale replication of findings from stage 1. A population-based case–control study of these polymorphisms revealed that neither was associated with the overall risk of breast cancer (Table 1). However, when cases were stratified by ER status, both SNPs were found to be associated with the risk of ER-negative disease (Table 1) and the magnitude and direction of the associations were similar to those observed for BRCA1 mutation carriers. Both SNPs were also associated with triple-negative [ER-, PR- and human epidermal growth factor receptor 2 (HER2)-negative] disease in the population-based study, which is consistent with the observation that the majority of breast tumors in BRCA1 mutation carriers exhibit a triple-negative phenotype [48]. SNP rs8170 is located within the C19orf62 gene, which encodes mediator of Rap80 interactions and targeting 40 kDa (MERIT40), a protein that interacts with BRCA1 in a protein complex. Further research is required to characterize the function of this locus.

**common variants associated with ovarian cancer risk for mutation carriers**

Although a number of small studies have evaluated candidate genes as ovarian cancer risk modifiers [28], to date, no genetic modifiers of ovarian cancer risk for BRCA1 and BRCA2 mutation carriers have been definitively identified. Studies of ovarian cancer risk modifiers are challenging because of the smaller number of mutation carriers diagnosed with ovarian cancer compared with breast cancer and therefore small studies tend to be underpowered to detect modifying effects reliably. In fact, only one SNP has been observed to be associated with ovarian cancer risk in the general population at a high level of statistical significance (\(P < 10^{-7}\)) [55]. The minor allele of 9p22-rs3814113, with a frequency of 32%, was associated with protection from ovarian cancer (per-allele OR 0.82). This association was stronger for serous tumors (OR 0.77), which are the most common histological subtype of ovarian cancer. This SNP is therefore a potential modifier of ovarian cancer risk for BRCA1 and BRCA2 mutation carriers, both of which also
tend to develop serous tumors [56], although this is yet to be evaluated. Further ovarian cancer GWAS and combined analysis studies are underway and are likely to yield additional common susceptibility SNPs. As for breast cancer, additional studies of less common disease subtypes may also prove to be fruitful in this regard. These could also provide good candidates as potential modifiers of ovarian cancer risk for BRCA1 and BRCA2 mutation carriers and future studies will aim to investigate these. Evaluation of SNPs as ovarian cancer risk modifiers as part of the GWAS in mutation carriers is also currently ongoing.

**Implications for cancer risk prediction for mutation carriers**

Individually, the common modifying polymorphisms are associated with modest relative risks of breast cancer (HR ≤ 1.32, Table 2). Evidence from published studies to date indicates that these combine multiplicatively, with no evidence of statistical interaction [49, 50]. The combined relative risks can therefore be much larger, depending on the number of risk alleles that a mutation carrier has, and this may have implications for their clinical utility in terms of breast cancer risk prediction. For example, based on the combined relative risk associated with the FGF2 and TOX3/TNRC9 polymorphisms, the absolute risk of developing breast cancer by age 80 for BRCA2 mutation carriers varies from 54% for those with no risk alleles (representing 20% of BRCA2 mutation carriers) to 82% for those with two copies of risk alleles at both loci (representing 1% of BRCA2 mutation carriers) [50].

The power of SNP profiles to predict breast cancer risk in the general population is currently limited because the SNPs identified to date explain only a small proportion of the total genetic variation in risk [57–59]. Nevertheless, risk profiles based on currently established susceptibility variants may have a role in the delivery of effective screening programs, and predictive power is expected to improve as more susceptibility loci are identified [57, 60]. Figure 2A shows the predicted absolute risk of developing breast cancer in the general population by risk category, as determined by risk profiling based on the allele frequencies and associated relative risk estimates for the 18 established susceptibility polymorphisms (Table 1), and assuming that these combine multiplicatively on the risk scale. The 5% of women in the general population at lowest risk are expected to have an absolute lifetime risk of ≤5.7%, compared with an absolute lifetime risk of ≥19% for the 5% at highest risk.

While the estimated relative risks associated with the susceptibility SNPs identified to date for mutation carriers are of similar magnitude to those for the same SNPs in the general population, their combined relative risks translate to much larger differences in the absolute risk of developing breast cancer for mutation carriers, because of their already elevated average risk of the disease. This is demonstrated by comparison of Figure 2A with Figure 2B, the latter showing the predicted absolute risk for developing breast cancer for BRCA2 mutation carriers, using the same 18 SNP profile. Not all of these 18 SNPs have been investigated in BRCA2 mutation carriers, and so it should be noted that Figure 2B gives the maximum potential risk discrimination that could be achieved assuming that all currently known breast cancer susceptibility alleles are also associated with the same relative risks of breast cancer for BRCA2 mutation carriers. Results obtained so far from the evaluation in BRCA2 mutation carriers of GWAS hits from the general population indicate that this may well be the case [49, 50]. According to this model, the 5% of the BRCA2 mutation carriers at lowest risk are predicted to have a lifetime breast cancer risk of ≤47%, compared with a lifetime risk of ≥89% for the 5% at highest risk. Such differences in absolute risk could potentially be informative in the genetic counseling process. Based on only the six SNPs that have been investigated in mutation carriers (Table 2) a more restricted risk range is predicted [49, 50].

As discussed previously, fewer of these SNPs have been found to be associated with breast cancer risk for BRCA1 mutation carriers. However, as more associations are identified through the ongoing BRCA1 mutation carrier GWAS, a similar separation in risk by SNP profile can be expected for these women at already high risk of breast cancer. In addition, it

![Figure 2](image-url)
appears reasonable to expected that genetic variants identified through GWAS restricted to ER-negative or triple-negative breast cancer, or through GWAS carried out in populations in which ER-negative disease is more common (such as the Asian and black populations) [44] may also be relevant for risk prediction in BRCA1 mutation carriers.

disclosures
The authors declare no conflict of interest.

references

conclusions
GWAS to discover breast cancer susceptibility variants in the general population and, to a lesser extent candidate gene studies, have led to the identification of several genetic loci that modify breast cancer risk for BRCA1 and BRCA2 mutation carriers. However, the currently established modifier loci explain only a small proportion of the genetic variation in breast cancer risk in these women (2.2% in BRCA1 and 5.2% in BRCA2 mutation carriers, Table 2), indicating that additional modifiers of risk remain to be identified. Because the effect sizes are expected to be relatively small, studies with large numbers of mutation carriers will be required to identify such variants reliably [61]. Given the rarity of mutations in BRCA1 and BRCA2, this will be possible only through continued recruitment of mutation carriers as well as collaboration through international initiatives like the CIMBA. Initial results from the published GWAS of BRCA1 mutation carriers demonstrate that additional genetic modifiers of risk can be identified by applying this approach specifically to mutation carriers, and the large-scale replication stages of GWAS in both groups of mutation carriers are therefore eagerly anticipated. Furthermore, they indicate that GWAS targeted at specific breast cancer subtypes may also identify additional breast cancer susceptibility variants. In particular GWAS of BRCA1 mutation carriers may identify alleles associated with ER-negative disease and/or relevant to the development of basal tumors. Differences in the associations of the modifying polymorphisms with breast cancer risk for BRCA1 and BRCA2 mutation carriers are likely to reflect differences in the biology of tumor development in these two groups of women at high risk of breast cancer. The identification of such polymorphisms could therefore lead to a better understanding of the etiology of tumors in mutation carriers and also to the development of effective and more specific therapies for breast cancer in mutation carriers.

In contrast to the general population, the modest effect sizes associated with susceptibility polymorphisms for mutation carriers could translate into clinically relevant differences in the absolute risks of developing the disease, particularly when combined with those of other established risk factors in mutation carriers, such as mammographic density [22] and mutation position [12, 62]. This indicates that BRCA1 and BRCA2 mutation carriers may be two of the first groups of individuals for whom clinical applications could be developed using the common cancer susceptibility variants.

acknowledgements
ACA is a Cancer Research UK Senior Cancer Research Fellow.