Common Breast Cancer-Predisposition Alleles Are Associated with Breast Cancer Risk in \textit{BRCA1} and \textit{BRCA2} Carriers

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Please cite this article in press as: Antoniou et al., Common Breast Cancer-Predisposition Alleles Are Associated with Breast Cancer Risk in \textit{BRCA1} and \textit{BRCA2}. The American Journal of Human Genetics (2008), doi:10.1016/j.ajhg.2008.02.008
Germline mutations in \( \text{BRCA1} \) and \( \text{BRCA2} \) confer high risks of breast cancer. However, evidence suggests that these risks are modified by other genetic or environmental factors that cluster in families. A recent genome-wide association study has shown that common alleles at single nucleotide polymorphisms (SNPs) in \( \text{FGFR2} \) (rs2981582), \( \text{TNRC9} \) (rs3803662), and \( \text{MAP3K1} \) (rs889312) are associated with increased breast cancer risks in the general population. To investigate whether these loci are also associated with breast cancer risk in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers, we genotyped these SNPs in a sample of 10,358 mutation carriers from 23 studies. The minor alleles of SNP rs2981582 and rs889312 were each associated with increased breast cancer risk in \( \text{BRCA2} \) mutation carriers (per-allele hazard ratio [HR] = 1.32, 95% CI: 1.20–1.45, \( p_{\text{trend}} = 1.7 \times 10^{-8} \) and HR = 1.12, 95% CI: 1.02–1.24, \( p_{\text{trend}} = 0.02 \) but not in \( \text{BRCA1} \) carriers. rs3803662 was associated with increased breast cancer risk in both \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers (per-allele HR = 1.13, 95% CI: 1.06–1.20, \( p_{\text{trend}} = 5 \times 10^{-3} \) in \( \text{BRCA1} \) and \( \text{BRCA2} \) combined). These loci appear to interact multiplicatively on breast cancer risk in \( \text{BRCA2} \) mutation carriers. The differences in the effects of the \( \text{FGFR2} \) and \( \text{MAP3K1} \) SNPs between \( \text{BRCA1} \) and \( \text{BRCA2} \) carriers point to differences in the biology of \( \text{BRCA1} \) and \( \text{BRCA2} \) breast cancer tumors and confirm the distinct nature of breast cancer in \( \text{BRCA1} \) mutation carriers.

### Introduction

\( \text{BRCA1} \) (MIM 113705) and \( \text{BRCA2} \) (MIM 600185) mutations confer high risks of breast and other cancers. A meta-analysis of mutation-positive families identified through population-based studies of breast or ovarian cancer estimated the risk of breast cancer by age 70 years to be 65% and 45% for \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers, respectively.\(^1\) Although the pattern of risk was similar, the absolute magnitude of risk in that study was lower than in previously published studies based on families with multiple affected individuals, in particular for \( \text{BRCA2} \) mutation carriers.\(^2\) The breast cancer risks in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers have also been found to vary by the age at diagnosis and the type of cancer (unilateral breast cancer, contralateral breast cancer, or ovarian cancer) in the index patient.\(^1,3,4\) Such observations are consistent with the hypothesis that breast cancer risks in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers are modified by other genetic or environmental factors that cluster in families.\(^1,3\) Further evidence of genetic modifiers of risk comes from segregation-analysis models that have quantified the extent of variability in the risk of breast cancer in mutation carriers in terms of a polygenic-modifying variance.\(^5,6\) In addition, Begg et al.\(^3\) demonstrated significant between-family variation in risk.

A number of studies have evaluated associations between genetic variants and breast cancer risk in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers\(^7,9\), but apart from a recent CIMBA (Consortium of Investigators of Modifiers of \( \text{BRCA1/2} \) study that found evidence of association among \( \text{BRCA2} \) mutation carriers who are rare homozygotes for a single nucleotide polymorphism (SNP) in \( \text{RAD51} \), no other such associations have been reliably identified.\(^9\) A recent genome-wide association study in breast cancer identified five common susceptibility alleles that are associated with an increased risk of breast cancer in the general population.\(^10\) To address whether these polymorphisms are also associated with the risk of breast cancer in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers, we typed the three SNPs with the strongest evidence of association in \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers from the CIMBA study.\(^7\)

### Material and Methods

#### Study Sample

Eligibility was restricted to female carriers who had pathogenic mutations in \( \text{BRCA1} \) or \( \text{BRCA2} \) and were 18 years old or older. Twenty-three different studies submitted information on mutation carriers (Table 1). Information collected included the year of birth; mutation description, including nucleotide position and base change; age at last follow-up; ages at breast and ovarian cancer diagnosis; and age or date at bilateral prophylactic mastectomy. Information was also available on the country of residence, which was defined to be the country of the clinic at which the carriers were recruited (some studies included carriers from several countries). Related individuals were identified through a unique family identifier. Women were included in the analysis if they carried mutations that were pathogenic according to generally recognized criteria.\(^7\) (Breast Cancer Information Core, BIC). All carriers participated in clinical and research studies at the host institutions under IRB-approved protocols. Further details of the CIMBA initiative can be found elsewhere.\(^7\)

#### Genotyping

All centers included at least 2% of the samples in duplicate, no template controls in every plate, and a random mixture of affected and unaffected carriers. Samples that failed in two or more of the SNPs genotyped were excluded from the analysis. A study was included in the analysis only if the call rate was over 95% after samples that failed at multiple SNPs had been excluded. The concordance between duplicates had to be at least 98%. To further validate the accuracy of genotyping across centers, we required all groups to genotype 95 DNA samples from a standard test plate for all three SNPs. If the genotyping was inconsistent for more than one sample in the test plate, the study was excluded from the analysis of that SNP. Based on these criteria, four studies were excluded from the analysis of rs2981582, and three studies were excluded from the analysis of rs3803662. As an extra genotyping quality-control check, we also evaluated deviation from Hardy-Weinberg equilibrium (HWE) among unrelated subjects separately for each SNP and study. Two studies gave HWE p values of 0.02 and 0.001. Examination of the cluster plots for these SNPs did not reveal any unusual patterns, and these studies were therefore included in the analysis. The genotype frequencies among unrelated individuals for all other studies and SNPs were consistent with HWE.

#### Statistical Analysis

After the above exclusions, a total of 10,358 unique \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers had an observed genotype for at least...
one of the three polymorphisms (6,791 BRCA1 carriers; 3,557 BRCA2 carriers; and ten BRCA1 and BRCA2 carriers; Table 1). Individuals were classified according to their age at diagnosis of breast cancer or their age at last follow-up. For this purpose, individuals were censored at the age of the first breast cancer diagnosis (n = 5,489), ovarian cancer diagnosis (n = 975), or bilateral prophylactic mastectomy (n = 340) or the age at last observation (n = 3,554). Only individuals censored at breast cancer diagnosis were assumed to be affected (Table 2). Mutation carriers were censored at ovarian cancer diagnosis and were considered unaffected. We ignored data on breast cancer occurrence after an ovarian cancer because the risk of breast cancer may be affected by the treatment for ovarian cancer, and the recording of a second breast cancer may be inaccurate in a woman with advanced ovarian cancer.

We performed additional sensitivity analyses to investigate whether any bias could be introduced in our results as a result of our assumptions. If the SNPs under study were associated with disease survival in carriers, the estimated HRs might be affected by the inclusion of prevalent cases. We therefore performed

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Table 1. Number of BRCA1 and BRCA2 Mutation Carriers by Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA1 and BRCA2</th>
<th>Genotyping platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBRACE</td>
<td>U.K. and Eire</td>
<td>658</td>
<td>471</td>
<td>3</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>Spanish National Cancer Centre (CNIO)</td>
<td>Spain</td>
<td>167</td>
<td>205</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Deutsches Krebsforschungszentrum (DFKZ)</td>
<td>Germany</td>
<td>122</td>
<td>50</td>
<td>0</td>
<td>Taqman, MALDI-TOF MS, Biplex</td>
</tr>
<tr>
<td>Fox Chase Cancer Center (FCCC)</td>
<td>U.S.A.</td>
<td>50</td>
<td>41</td>
<td>1</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers (GEMO)</td>
<td>France</td>
<td>1102</td>
<td>554</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)</td>
<td>Germany</td>
<td>568</td>
<td>280</td>
<td>3</td>
<td>BIORAD iCycler</td>
</tr>
<tr>
<td>Hospital Clinico San Carlos (HSC)</td>
<td>Spain</td>
<td>90</td>
<td>78</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Helsinki Breast Cancer Study (HBCS)</td>
<td>Finland</td>
<td>102</td>
<td>104</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT BRCA)</td>
<td>Quebec- Canada</td>
<td>72</td>
<td>82</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>iConFab</td>
<td>Australia</td>
<td>426</td>
<td>353</td>
<td>0</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>Modifiers and Genetics in Cancer (MAGIC)</td>
<td>U.S.A.</td>
<td>683</td>
<td>378</td>
<td>1</td>
<td>Taqman</td>
</tr>
<tr>
<td>MAYO</td>
<td>U.S.A.</td>
<td>108</td>
<td>54</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Milan Breast Cancer Study Group (MBCSG)</td>
<td>Italy</td>
<td>251</td>
<td>135</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>National Cancer Institute (NCI)</td>
<td>U.S.A.</td>
<td>147</td>
<td>50</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>National Israeli Cancer Control Center (NICCC)</td>
<td>Israel</td>
<td>283</td>
<td>160</td>
<td>1</td>
<td>Taqman</td>
</tr>
<tr>
<td>Ontario Cancer Genetics Network (OGCN)</td>
<td>Canada</td>
<td>195</td>
<td>143</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Odense University Hospital(OUH)</td>
<td>Denmark</td>
<td>106</td>
<td>0</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>Pisa Breast Cancer Study (PBGS)</td>
<td>Italy</td>
<td>54</td>
<td>30</td>
<td>0</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>Sheeba Medical Centre (SMC) - Tel Hashomer</td>
<td>Israel</td>
<td>283</td>
<td>101</td>
<td>0</td>
<td>Taqman</td>
</tr>
<tr>
<td>SWE-BRCA</td>
<td>Sweden</td>
<td>426</td>
<td>127</td>
<td>0</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>Med-SQuaD</td>
<td>Czech Republic</td>
<td>138</td>
<td>37</td>
<td>0</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>University of Pennsylvania (UPENN)</td>
<td>U.S.A.</td>
<td>271</td>
<td>124</td>
<td>1</td>
<td>iPLEXb</td>
</tr>
<tr>
<td>HEReditary Breast and Ovarian study Netherlands (DNA-HEBON)</td>
<td>The Netherlands</td>
<td>489</td>
<td>0</td>
<td>0</td>
<td>iPLEXb</td>
</tr>
</tbody>
</table>

Total: 6791 3557 10

a Coordinating center.

b Indicates that samples were genotyped at a central location (Queensland Institute of Medical Research).
Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>BRCA1*</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unaffected</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>Number</td>
<td>10,358</td>
<td>3300</td>
<td>3501</td>
</tr>
<tr>
<td>Person-years follow-up</td>
<td>440,252</td>
<td>140,541</td>
<td>14,2734</td>
</tr>
<tr>
<td>Median age at censure (IQR)</td>
<td>41 (34–49)</td>
<td>41 (33–50)</td>
<td>40 (34–46)</td>
</tr>
</tbody>
</table>

Age at Censure, N (%)

< 30
1222 (10.8) 499 (15.1) 320 (9.1) 196 (12.5) 107 (5.4)
30–39
3436 (33.2) 958 (28.7) 1416 (40.5) 243 (28.1) 619 (31.2)
40–49
3305 (31.9) 946 (28.7) 1200 (12.1) 228 (14.5) 731 (36.9)
50–59
1683 (16.3) 584 (17.7) 423 (12.1) 295 (18.7) 381 (19.2)
60–69
562 (5.4) 208 (6.3) 109 (3.1) 135 (8.6) 110 (5.5)
70+
250 (2.4) 105 (3.2) 33 (0.9) 77 (4.9) 35 (1.8)

Year of Birth, N (%)

< 1920
92 (0.9) 25 (0.8) 32 (0.9) 20 (1.3) 15 (0.8)
1920–1929
383 (3.7) 93 (2.8) 140 (4.0) 48 (3.0) 102 (5.1)
1930–1939
963 (9.3) 246 (7.4) 335 (9.6) 138 (8.8) 264 (12.3)
1940–1949
2066 (20.0) 511 (15.5) 936 (23.9) 228 (14.5) 491 (24.8)
1950–1959
2913 (28.1) 804 (24.4) 1122 (32.0) 368 (23.4) 619 (31.2)
1960+
3741 (36.0) 1221 (36.1) 1036 (29.6) 772 (49.0) 512 (25.8)

Risk-Reducing Salpingo-Oophorectomy (RRSO)

No RRSO 6613 (63.8) 2,032 (61.6) 2369 (67.7) 928 (59.0) 1284 (64.7)
RRSO 577 (5.6) 318 (9.6) 85 (2.4) 119 (7.6) 55 (2.8)
Missing 3168 (30.6) 950 (28.8) 1047 (29.9) 527 (33.4) 644 (32.5)

IQR: Interquartile range.

*a Includes the ten females who have mutations in both BRCA1 and BRCA2.

Our analyses are complicated by the fact that BRCA1 and BRCA2 mutation carriers are not randomly sampled with respect to their disease status. Many carriers are sampled through families seen in genetic clinics. The first tested individual in a family is usually someone diagnosed with cancer at a relatively young age. Such study designs therefore tend to lead to an oversampling of affected individuals, and standard analytical methods such as Cox regression might lead to biased estimates of the risk ratios.13 For example, consider an individual affected at age 50. In a standard analysis of a cohort study, the SNP genotype for the individual will be compared with those of all individuals at risk at age 50. This analysis leads to consistent estimates of the HR estimates. However, in the present design, mutation carriers are already selected on the basis of disease status (where affected individuals are oversampled). If standard cohort analysis were applied to these data, it would cause affected individuals at age 50 to be compared to unaffected carriers selected on the basis of their future disease status. If the genotype is associated with the disease, the risk estimate will be biased to zero because too many affected individuals (in whom the at-risk genotype is overrepresented) are included in the comparison group. Simulation studies have shown that this effect can be quite marked.13

To correct for this potential bias, we analyzed the data within a survival analysis framework by modelling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes. A detailed description of the retrospective-likelihood approach has been published.9 The effect of each SNP was modeled either as a per-allele HR or as separate HRs for heterozygotes and homozygotes. The HRs were assumed to be independent of age (i.e., we used a Cox proportional-hazards model). We verified the assumption of proportional hazards by examining the Kaplan-Meier estimates of the survival functions by genotype and by subsequently adding a genotype × age interaction term to the model in order to fit models in which the HR changed with age. Analyses were carried out with the pedigree-analysis software MENDEL.14 Under this approach, the baseline age-specific incidence rates in the Cox proportional-hazards model are chosen such that the overall breast cancer incidence rates, averaged over all genotypic categories, agree with external estimates of BRCA1 and BRCA2 incidence rates.6 We examined between-study heterogeneity by comparing the models that allowed for study-specific log-hazard ratios against models in which the same log-hazard ratio was assumed to apply to all studies. All analyses were stratified by study group and country of residence (where numbers were sufficiently large) and used calendar-year- and cohort-specific
breast cancer incidence rates for BRCA1 and BRCA2. The risk of breast cancer in compound BRCA1 and BRCA2 mutation carriers was assumed to be that for BRCA1 mutation carriers. We used a robust variance-estimation approach to allow for the nonindependence among related carriers. To evaluate the combined robust variance-estimation approach to allow for the nonindependence among related carriers.

\[ \text{HR} = \frac{\text{Risk in mutation carriers}}{\text{Risk in unaffected}} \]

Results

Results are shown in Table 3. SNP rs2981582 in FGFR2 was associated with breast cancer risk in the combined sample of BRCA1 and BRCA2 mutation carriers (p trend = 0.0001). However, when BRCA1 and BRCA2 carriers were analyzed separately, the association was restricted to BRCA2 mutation carriers (p trend = 2 × 10^{-8}), and there was no evidence of an association among BRCA1 carriers (p trend = 0.6; p = 1.3 × 10^{-5} for the difference in the estimates between BRCA1 and BRCA2 carriers). The estimated effect among BRCA2 mutation carriers was consistent with a multiplicative model in which each copy of the disease allele conferred a hazard ratio (HR) of 1.32 (95% CI: 1.20–1.45) (Figure 1). There was some suggestion that the HRs might differ between studies for BRCA1 (p = 0.03), but there was no evidence of heterogeneity for BRCA2 (p = 0.11).

TNRC9 SNP rs3803662 was associated with an increased risk of breast cancer in both BRCA1 and BRCA2 mutation carriers (p trend = 0.004 and 0.009, respectively; joint p trend = 0.00005). The per-allele HR was estimated to be 1.11 (95% CI: 1.03–1.19) for BRCA1 carriers and 1.15 (95% CI: 1.03–1.27) for BRCA2 carriers (p = 0.6 for the difference in the BRCA1 and BRCA2 per-allele HR estimates). There was no evidence of heterogeneity in the HRs among studies (BRCA1: p = 0.67; BRCA2: p = 0.63; Figure 2).

There was no evidence that SNP rs889312 in MAP3K1 was associated with breast cancer risk in the combined sample of BRCA1 and BRCA2 mutation carriers or in BRCA1 carriers alone (p trend = 0.29 and 0.86, respectively). However, BRCA2 mutation carriers who carried a copy of the minor allele of this SNP were at increased risk of breast cancer (per-allele HR = 1.12, 95% CI: 1.02–1.24; p trend = 0.02). There was some evidence of heterogeneity in the HRs between studies for BRCA2 (p = 0.02) but not for BRCA1 (p = 0.06) mutation carriers (Figure 3). We also investigated whether the HRs change with age by including an age × genotype interaction term in the model.

There was no significant evidence that HRs vary by age for any of the variants.

If these SNPs were associated with disease survival in carriers, the estimated HRs might be affected by the inclusion of prevalent cancer cases. We therefore repeated our analysis after excluding cancer cases diagnosed more than five years prior to their study recruitment. A total of 7,027 BRCA1 and BRCA2 mutation carriers were eligible for this analysis (2,523 affected; 4,504 unaffected). The estimated per-allele HRs among BRCA2 mutation carriers were virtually unchanged for the FGFR2 SNP rs2981582 (per-allele HR 1.37 (95% CI: 1.22–1.54; p trend = 2 × 10^{-7}) and the MAP3K1 SNP rs889312 (HR: 1.11, 95% CI: 0.98–1.25, p trend = 0.11), but slightly higher for the TNRC9 SNP rs3803662 (BRCA1: 1.17 (95% CI:1.06–1.28, p trend = 0.001; BRCA2: 1.24 (95% CI: 1.10–1.41, p trend = 0.0008; BRCA1 and BRCA2 combined p trend = 9 × 10^{-7}).

Risk-reducing salpingo-oophorectomy (RRSO) reduces the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. To investigate whether allowance for RRSO alters our results in any way, we repeated the analysis after censoring the BRCA1 and BRCA2 mutation carriers at the time of surgery. Because information on RRSO was missing for approximately 30% of the carriers, we performed this analysis by first including all carriers in the analysis and assuming that carriers with no RRSO information did not have the surgery; we then repeated the analysis after including only carriers with data on RRSO as previously described. When all BRCA1 and BRCA2 mutation carriers were included in this analysis, the HRs and significance test results were very similar to results of the analysis in which no censoring at RRSO took place (Table S1 in the Supplemental Data). When carriers with no information on RRSO were excluded, the sample size was reduced from 10,358 to 7,190. The estimated HRs remained virtually identical to those in the primary analysis, although the p values were increased, because of a reduced sample size (Table S1; rs2981582 in BRCA2: p trend = 6 × 10^{-6}, rs3803662 in BRCA1, BRCA2 and combined: p trend = 0.03, 0.02, 0.001 respectively; rs889312 in BRCA2: p trend = 0.16).

BRCA1 and BRCA2 mutations are also associated with increased risks of ovarian cancer. Carriers who had developed ovarian cancer were included in our analyses as unaffected. A possible bias could have been introduced if these SNPs were associated with ovarian cancer risk. Although there is no evidence of such an association in the general population (American Society of Human Genetics meeting 2007, San Diego, USA, Abstract 428), we repeated our analyses by excluding the 975 mutation carriers who were censored at an ovarian cancer diagnosis. The estimated HRs were unchanged (Table S2).

To evaluate the potential combined effects of the two most significant SNPs on breast cancer risk in BRCA2 mutation carriers, we fitted a multiplicative model (log additive, 2 degrees of freedom [df]) for the effects of the FGFR2 SNP rs2981582 and TNRC9 SNP rs3803662 and compared this against a fully saturated model in which
a separate parameter was fitted for each \textit{FGFR2-TNRC9} combined genotype (8 df). The HR estimates for all nine genotypes under the multiplicative and fully saturated models are shown in Table 4. The HRs were remarkably similar under the two models, and there was no significant evidence that the fully saturated model fit better than the multiplicative model \((\chi^2 = 4.48, \text{df} = 6, \text{p-value}:0.61)\). Under the multiplicative model, the highest HR was 2.26 for carriers who were homozygotes for the risk allele at both loci in comparison to \textit{BRCA2} carriers who did not have any risk alleles. Based on the minor allele frequencies of the \textit{FGFR2} and \textit{TNRC9} SNPs in the general population, approximately 36% of the \textit{BRCA2} mutation carriers will have HRs in excess of 1.5 in comparison to the 20% of
carriers who will have no copies of the disease allele at either FGFR2 or TNRC9.

**Discussion**

Our results provide strong evidence that SNP rs2981582 in FGFR2 is associated with breast cancer risk in BRCA2 mutation carriers and that SNP rs3803662 in TNRC9 is associated with breast cancer risk in both BRCA1 and BRCA2 mutation carriers. With our sample size, we can rule out a comparable involvement of rs2981582 in the breast cancer risk for BRCA1 mutation carriers. These results were unaltered when we accounted for survival bias and risk-reducing salpingo-oophorectomy or when we included ovarian cancer cases as unaffected in the analysis. There was no evidence of heterogeneity in the HRs between studies. The evidence of association with SNP rs889312 in MAP3K1 was weaker and was restricted to BRCA2 mutation carriers. For all three SNPs, the estimated HRs in BRCA2 carriers were very similar to the corresponding estimated odds ratios (OR) for breast cancer derived from data from large population-based case-control studies\(^6\) (per-allele ORs: 1.26, 1.20 and 1.13 for rs2981582 [FGFR2], rs3803662 [TNRC9], and rs889312 [MAP3K1], respectively). Based on the per-allele HR estimates, the frequencies of the risk alleles in the general population\(^6\) and recent estimates of the genetic variance of the breast cancer risks in BRCA1 and BRCA2 mutation carriers (“modifying variance”) derived from breast cancer segregation analyses\(^6\), the TNRC9 SNP is predicted to account for approximately 0.5% of the BRCA1 modifying variance. The SNPs in FGFR2, TNRC9, and MAP3K1 are estimated to account for 2.8% of the BRCA2 modifying variance.
It has been reported that more than 90% of BRCA1 breast cancer tumors are estrogen receptor (ER) negative, whereas BRCA2 breast cancer tumors have an ER distribution similar to that in the general population, in which the majority are ER positive. A recent Breast Cancer Association Consortium study found that the FGFR2 SNP rs2981582 was more strongly associated with ER-positive breast cancers than ER-negative tumors (OR: 1.31 versus 1.08, respectively). The same study found that the TNRC9 SNP rs3803662 was associated with the risk of both ER-positive and ER-negative breast cancers, which is again consistent with our results. Therefore, our results are consistent with the hypothesis that the SNPs modify the risk of breast cancer to a similar, relative extent in carriers for either BRCA2 or (in the case of TNRC9 rs3803662) BRCA1 and noncarriers.

Table 4. HR Estimates for the Combined Genotypes of SNPs in FGFR2 and TNRC9 among BRCA2 Carriers under a Multiplicative Model and under a Fully Saturated Model

<table>
<thead>
<tr>
<th>FGFR2/TNRC9 Genotype</th>
<th>HR Multiplicative Model</th>
<th>HR Fully Saturated Model</th>
<th>Predicted Genotype Distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG/CC</td>
<td>1.00</td>
<td>1.00</td>
<td>20.4</td>
</tr>
<tr>
<td>GG/CT</td>
<td>1.16</td>
<td>1.05</td>
<td>14.3</td>
</tr>
<tr>
<td>GG/TT</td>
<td>1.35</td>
<td>1.23</td>
<td>2.5</td>
</tr>
<tr>
<td>GA/CC</td>
<td>1.29</td>
<td>1.25</td>
<td>26.1</td>
</tr>
<tr>
<td>GA/CT</td>
<td>1.50</td>
<td>1.44</td>
<td>18.3</td>
</tr>
<tr>
<td>GA/TT</td>
<td>1.75</td>
<td>1.72</td>
<td>3.2</td>
</tr>
<tr>
<td>AA/CC</td>
<td>1.67</td>
<td>1.41</td>
<td>8.3</td>
</tr>
<tr>
<td>AA/CT</td>
<td>1.94</td>
<td>2.08</td>
<td>5.9</td>
</tr>
<tr>
<td>AA/TT</td>
<td>2.26</td>
<td>2.08</td>
<td>1.0</td>
</tr>
</tbody>
</table>

a Multiplicative model, per-allele HRs. FGFR2: 1.29 (95% CI: 1.17–1.43); TNRC9: 1.16 (95% CI: 1.04–1.30).
b Assuming a minor allele frequency of 0.39 for FGFR2 (rs rs2981582) and 0.26 for TNRC9 (rs rs3803662).

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risk of 55% or greater by age 70. If further such risk alleles are identified (for example, through additional genome scans), the proportion of carriers for whom the risk can be modified substantially will increase. These risks might also be affected by other factors, including family history, mutation type, and lifestyle risk factors, and future studies should aim to investigate these effects.

Supplemental Data

Two additional tables are available online at http://ajhg.org/.

Acknowledgments

A.C.A., K.A.P., and the CIMBA data management are funded by Cancer Research-UK. D.F.E. is a principal research fellow of Cancer Research-UK. We thank Ellen Goode for organizing the distribution of the standard DNA plates.

**CIMBA Collaborating Centres:**

German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC). GC-HBOC is supported by a grant of the German Cancer Aid (grant 107054) and the Center for Molecular Medicine Cologne (grant TV93) to R.K.S.

Hospital Clinico San Carlos (HCSC). T.C. is funded by FMMA/06 and RTICC06/0003/0021 HCSC-Spain.

Helsinki Breast Cancer Study (HEBCS). HEBCS was supported by the Academy of Finland (110663), Helsinki University Central Hospital Research Fund, the Sigrid Juselius Fund, and the Finnish Cancer Society. We thank Tuomas Heikkinen for his contribution in the molecular analyses and Kristiina Aittomäki, Kirsimari Alta-
article was supported by revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services. Support was also given by the National Institutes of Health through grant #1U01 CA 86389. Henry Lynch’s work is partially funded through the Charles F. and Mary C. Heider Chair in Cancer Research, which he holds at Creighton University. The hereditary cancer registry at City of Hope (J.W.) is supported in part by a General Clinical Research Center grant (M01 RR 00043) awarded by the NIH to the City of Hope National Medical Center, Duarte, California.

**Mayo Clinic Study (MAJO).** The Mayo Clinic study was supported by the Breast Cancer Research Foundation (BCRF), U.S. Army Medical Research and Materiel Command (W81XWH-04-1-0588), the Mayo Clinic Breast Cancer SPORE (PS0-CA116201), and NIH grant CA122340 to F.J.C. We wish to thank Noralane Lindor and Linda Wadum for their contributions.

**Milan Breast Cancer Study Group (MBCSG).** MBCSG is supported by Fondazione Italiana per la Ricerca sul Cancro (FIRC, Special Project “Hereditary tumors”). MBCSG acknowledges Marco Pierotti of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy and Bernardo Bonanni of the Istituto Europeo di Oncologia, Milan, Italy.

**Modifier Study of Quantitative Effects on Disease (Mod-SQuaD).** C.I.S. is partially supported by a Susan G. Komen Foundation Basic. Clinical, and Translational Research Grant (BCTR0402923). Research Project of the Ministry of Education, Youth and Sports of the Czech Republic No. MSM0021620808 to Michal Zikan, Zdenek Kleibl, and Petr Pohrliech. We acknowledge the contributions of Michal Zikan, Petr Pohrliech and Zdenek Kleibl (Department of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University Prague, Czech Republic) and Lenka Foretova, Machakova Eva, and Lukesova Miroslava (Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic).

**National Cancer Institute study (NCI).** We acknowledge the contributions of Jeffrey Struweing and Marlin A Pineda from the Laboratory of Population Genetics. Greene and Struweing were supported by funding from the Intramural Research Program of the National Cancer Institute. Their data-collection efforts were supported by contracts NO2-CR-110195-50 and NO2-CR-65504 with Westat, Inc, Rockville, MD.

**Ontario Cancer Genetics Network (OCGN) study.** We thank Mona Gill for excellent technical assistance and acknowledge funding from Cancer Care Ontario and the National Cancer Institute of Canada with funds from the Terry Fox Run.

**Odense University Hospital (OUH) study.** The Danish Cancer Research Fund supported the Danish group at Odense University Hospital. Mads Thomassen is greatly acknowledged for performing the genotyping of the Danish samples.

**Pisa Breast Cancer Study (PBCS).** PBCS acknowledges AIRC the Italian Association for Cancer Research.

**University of Pennsylvania (UPENN) study.** K.L.N. is supported by the Breast Cancer Research Foundation (BCRF). S.M.D. is supported by QVC Network, the Fashion Footwear Association of New York, and the Marjorie B. Cohen Foundation.

**Sheeba Medical Center Study (SMC).** The Swedish BRCA1 and BRCA2 study (SWE-BRCA). SWE-BRCA collaborators: Per Karlsson, Margareta Nordling, Annika Bergman, and Zakaria Einbeigi, Gothenburg, Sahlgrenska University Hospital; Marie Stenmark-Askmaalm and Sigrun Liedgren, Linköping University Hospital; Åke Borg, Niklas Loman, Häkan Olsson, Ulf Kristofersson, Helena Jermström, and Katja Backenhorn, Lund University Hospital; Annika Lindblom, Brita Arver, Anna von Wachenfeldt, Annelie Liljegren, Gisela Barbany-Bustindza, and Johanna Rantalai, Stockholm, Karolinska University Hospital; Henrik Grönbek, Eva-Lena Stattin, and Monica Emanuelsson, Umeå University Hospital; Hans Bostrom, Richard Rosenquist Brandell, and Niklas Dahl, Uppsala University Hospital.

**Spanish National Cancer Centre (CNIO).** Thanks to Rosario Alonso, Alicia Barroso, and Guillermo Pita for their technical support. The samples studied at the CNIO were recruited by the Spanish Consortium for the Study of Genetic Modifiers of BRCA1 and BRCA2 (Spanish National Cancer Centre [Madrid], Sant Pau Hospital [Barcelona], Instituto Catalá d’Oncologia [Barcelona], Hospital Clinico San Carlos [Madrid], Valladolid University [Madrid], Cancer Research Centre [Salamanca], and Instituto Dexeus [Barcelona]) and the Instituto Demokritos. The work carried out at the CNIO was partly funded by grants from the Genome Spain, Mutual Madrileña and Marató Foundations.

**Deutsches Krebsforschungszentrum (DKFZ) study.** The DKFZ study was supported by the DKFZ. We thank Diana Torres and Muhammad A. Rashid for providing DNA samples and supplying data. We thank Antje Seidel-Renkert and Michael Gilbert for expert technical assistance.

**DNA-HEBON.** The following are DNA-HEBON collaborating centers, Netherlands. Coordinating center, Netherlands Cancer Institute, Amsterdam: Frans Hogervorst, Peggy Manders, Matti Rookus, Flora van Leeuwen, Laura van ’t Veer, and Senno Verhoef. Erasmus Medical Center, Rotterdam: Ans van den Ouweland, Margriet Collée, and Jan Klijn. Leiden University Medical Center, Leiden: Juiil Wijnen and Christi van Asperen. Radboud University Nijmegen Medical Center, Nijmegen: Marjolijn Lijtenberg and Nicoline Hoogerbrugge. VU University Medical Center, Amsterdam: Hans Gille and Hanne Meijers-Heijboer. University Hospital Maastricht, Maastricht: Kees van Roozendaal, Rien Blok, and Encarina Gomez-Garcia. The DNA-HEBON study is part of the HEBON study (HEReditary Breast and Ovarian study Netherlands) and is supported by Dutch Cancer Society grants NKI2004-3088 and NKI2007-3756.

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