

Common Breast Cancer Susceptibility Alleles and the Risk of Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers: Implications for Risk Prediction

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Abstract

The known breast cancer susceptibility polymorphisms in *FGFR2*, *TNRC9/TOX3*, *MAP3K1*, *LSP1*, and 2q35 confer increased risks of breast cancer for *BRCA1* or *BRCA2* mutation carriers. We evaluated the associations of 3 additional single nucleotide polymorphisms (SNPs), rs4973768 in *SLC4A7/NEK10*, rs6504950 in *STXBP4/COX11*, and rs10941679 at 5p12, and reanalyzed the previous associations using additional carriers in a sample of 12,525 *BRCA1* and 7,409 *BRCA2* carriers. Additionally, we investigated potential interactions between SNPs and assessed the implications for risk prediction. The minor alleles of rs4973768 and rs10941679 were associated with increased breast cancer risk for *BRCA2* carriers (per-allele HR = 1.10, 95% CI: 1.03–1.18, $P = 0.006$ and HR = 1.09, 95% CI: 1.01–1.19, $P = 0.03$, respectively). Neither SNP was associated with breast cancer risk for *BRCA1* carriers, and rs6504950 was not associated with breast cancer for either *BRCA1* or *BRCA2* carriers. Of the 9 polymorphisms investigated, 7 were associated with breast cancer for *BRCA2* carriers (*FGFR2*, *TOX3*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7*, 5p12, $P = 7 \times 10^{-11} - 0.03$), but only *TOX3* and 2q35 were associated with the risk for *BRCA1* carriers ($P = 0.0049$, 0.03, respectively). All risk-associated polymorphisms appear to interact multiplicatively on breast cancer risk for mutation carriers. Based on the joint genotype distribution of the 7 risk-associated SNPs in *BRCA2*

mutation carriers, the 5% of *BRCA2* carriers at highest risk (i.e., between 95th and 100th percentiles) were predicted to have a probability between 80% and 96% of developing breast cancer by age 80, compared with 42%

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to 50% for the 5% of carriers at lowest risk. Our findings indicated that these risk differences might be sufficient to influence the clinical management of mutation carriers. *Cancer Res*; 70(23); 9742–54. ©2010 AACR.

Introduction

Pathogenic mutations in *BRCA1* and *BRCA2* confer elevated risks of breast and ovarian cancer. Cancer risk estimates have been found to vary by the age at diagnosis and the cancer site of the proband that led to the family ascertainment (1–3). Studies have demonstrated significant variation in the breast cancer risks between families that segregate mutations in *BRCA1* and *BRCA2*, according to the strength of family history (2, 4). Such evidence suggests that genetic or other factors that cluster in families could modify the cancer risks conferred by *BRCA1* and *BRCA2* mutations.

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Note: Supplementary data for this article are available at Cancer Research Online (<http://cancerres.aacrjournals.org/>).

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Direct evidence of such modifiers of risk has been demonstrated through recent large-scale association studies conducted by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA; ref. 5). These studies evaluated common genetic variants (single nucleotide polymorphisms; SNPs) that have been shown to be associated with breast cancer risk for women from the general population through genome-wide association studies (GWAS; refs. 6–9). The CIMBA studies suggest that of the 6 variants investigated so far (rs2981582 in *FGFR2*, rs3803662 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs13281615 on 8q24, and rs13387042 on 2q35), only the *TOX3* and 2q35 polymorphisms were associated with breast cancer risk for *BRCA1* mutation carriers. Five of the polymorphisms, all but the variant in the 8q24 region, were associated with breast cancer risk for *BRCA2* mutation carriers. The estimated relative risk for the 8q24 SNP was consistent with that for the general population, but was not statistically significant.

Since these investigations, 11 other breast cancer susceptibility variants have been identified through GWAS (10–14) including 3 SNPs, rs4973768 in *SLC44A7/NEK10*, rs6504950 in *STXBP4/COX11*, and rs10941679 on 5p12. To evaluate whether these 3 polymorphisms are also associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers we genotyped these polymorphisms in the CIMBA cohort. We also genotyped additional mutation carriers for the 6 polymorphisms previously investigated by CIMBA (6, 7). Here we present the updated results based on a larger number of female *BRCA1* and *BRCA2* mutation carriers. We also evaluated the evidence for interactions between the variants and the implications for risk prediction for *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Subjects

Female carriers of pathogenic mutations in *BRCA1* and *BRCA2* were recruited through the CIMBA initiative (5). Thirty-nine studies contributed data for mutation carriers who were successfully genotyped for 1 or more of the 9 SNPs investigated. The large majority of carriers were recruited through cancer genetics clinics offering genetic testing, and enrolled into national or regional studies. Some carriers were identified by population-based sampling of cases, and some by community recruitment (e.g., in Ashkenazi Jewish populations). Eligibility to participate in CIMBA is restricted to carriers of pathogenic *BRCA1* or *BRCA2* mutations who were 18 years or older at recruitment. 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 diagnoses; and age or date at bilateral prophylactic mastectomy. Information was also available on the country of residence, defined to be the

country of the clinic at which the carrier family was recruited to the study. Related women 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 (15). Women who self-reported as "nonwhite" and those who carried pathogenic mutations in both *BRCA1* and *BRCA2* were excluded from the current analysis. All carriers participated in clinical or research studies at the host institutions under ethically approved protocols. Further details of the CIMBA initiative can be found elsewhere (5).

Genotyping

Genotyping was performed using either the iPLEX or Taqman platforms. To ensure genotyping consistency, all genotyping centers were required to adhere to the CIMBA genotyping quality control criteria that are described in detail in Appendix 1 (Supplementary Material). After excluding samples that failed quality control, 19,934 unique mutation carriers (12,525 *BRCA1*, 7,409 *BRCA2*) from 39 studies had an observed genotype for 1 or more of the SNPs and were included in the analysis (Supplementary Table S1).

Statistical analysis

The aim of the analysis was to evaluate the association between each genotype and breast cancer risk. The phenotype of each woman was defined by her age at diagnosis of breast cancer or her age at last follow-up. For this purpose, women were censored at the age of the first breast cancer diagnosis, ovarian cancer diagnosis, or bilateral prophylactic mastectomy or the age at last observation. Mutation carriers censored at ovarian cancer diagnosis were considered unaffected. Because mutation carriers were not sampled randomly with respect to their disease status, standard methods of survival analysis (such as Cox regression) may lead to biased estimates of the hazard ratios (HR; ref. 16). We, therefore, conducted the analysis by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described (15). The effect of each SNP was modeled either as a per-allele HR (multiplicative model) or as separate HR for heterozygotes and homozygotes, and these were estimated on the log scale. Where there was evidence of deviation from the multiplicative model, dominant and recessive models were also fitted. The HR were assumed to be independent of age (i.e., we used a Cox proportional hazards model). The assumption of proportional hazards was tested by adding a "genotype \times age" interaction term to the model to fit models in which the HR changed with age. Analyses were carried out using the pedigree analysis software MENDEL (17). We examined between-study heterogeneity by comparing the models that allowed for study-specific log-HR against models in which the same log-HR was assumed to apply to all studies. All analyses were stratified by study group and country of residence and used calendar year and cohort-specific breast cancer incidences for *BRCA1* and *BRCA2* (4). Risk reducing salpingo-oophorectomy was not considered in the analysis as it is not expected to be associated with the underlying SNP genotype (i.e., it is not a confounder) and previous analyses

of these SNPs suggested no marked effect on the associations after adjustment (6, 7). We used a robust variance-estimation approach to allow for the nonindependence of related carriers (18).

To investigate whether our results were influenced by any of our assumptions we performed additional sensitivity analyses. If any of the SNPs were associated with disease survival, the inclusion of prevalent cases could influence the HR estimates. We therefore repeated our analysis by excluding mutation carriers diagnosed more than 5 years prior to the age at recruitment into the study.

We further investigated for interactions between the SNPs and estimated the absolute risk of developing breast cancer based on the joint distribution of all SNPs that were significantly associated with risk for either *BRCA1* or *BRCA2* mutation carriers. Details of these methods are described in Appendix 2.

The proportions of the modifying variance explained by the set of associated SNPs were estimated by $\ln(c)/\sigma^2$, where c is the estimated coefficient of variation in incidences associated with SNP (19, 20) and σ^2 is the estimated modifying variance (1.32 and 1.73 for *BRCA1* and *BRCA2* mutation carriers, respectively; ref. 4). We estimated the total proportion of the modifying variance due to all SNPs by adding the individual proportions, that is, by assuming that the loci combined multiplicatively.

Results

After the exclusions described in the methods section, a total of 12,525 *BRCA1* and 7,409 *BRCA2* mutation carriers had an eligible genotype for at least 1 of the 9 SNPs and were included in the analysis (total 19,934 mutation carriers, Supplementary Table S1). Of these, 9,933 had an observed genotype for all 9 SNPs. Subjects were followed until the first breast cancer diagnosis (10,546), ovarian cancer diagnosis (1,981), or bilateral prophylactic mastectomy (567). The remaining subjects were censored at the age they were last observed (6,840). Only subjects censored at a breast cancer diagnosis were assumed to be affected in the analysis. Table 1 summarizes the key characteristics of this CIMBA cohort.

The results for the 3 newly investigated polymorphisms in the *SLC4A7/NEK10*, 5p12, and *STXBP4/COX11* regions are shown in Table 2. rs4973768 in *SLC4A7/NEK10* was associated with breast cancer risk for *BRCA2* mutation carriers, where each copy of the minor allele was estimated to confer an HR of 1.10 (95% CI: 1.03–1.18, $P_{\text{trend}} = 0.006$). There was no evidence that this SNP was associated with breast cancer risk for *BRCA1* mutation carriers (HR 1.03, $P_{\text{trend}} = 0.26$). There was no evidence of heterogeneity in the study HR estimates ($P = 0.08$ and 0.66 for *BRCA1* and *BRCA2*, respectively; Figs. 1 and 2). Models that allowed for an age-dependent HR did not fit better than the models with a constant HR ($P = 0.72$ and 0.93 for *BRCA1* and *BRCA2*, respectively).

The 5p12 SNP rs10941679 was also associated with breast cancer risk for *BRCA2* mutation carriers (2df $P = 0.022$ and $P_{\text{trend}} = 0.032$). Although the HR estimate for the heterozygote carriers of the minor allele was greater than the risk for the homozygote carriers, there was no significant evidence that the

Table 1. Summary characteristics for the 19,934 eligible *BRCA1* and *BRCA2* carriers used in the analysis

Characteristic	<i>BRCA1</i>		<i>BRCA2</i>	
	Unaffected	Breast cancer	Unaffected	Breast cancer
Number	5,989	6,536	3,399	4,010
Person-years follow-up	255,973	268,566	150,499	150,499
Median age at censure (IQR)	42 (34–51)	40 (35–47)	43 (34–53)	43 (37–50)
Age at censure, <i>N</i> (%)				
<30	851 (14.2)	565 (8.6)	485 (14.3)	185 (4.6)
30–39	1,707 (28.5)	2,584 (39.5)	898 (26.4)	1,254 (31.3)
40–49	1,812 (30.3)	2,275 (34.8)	908 (26.7)	1,507 (37.6)
50–59	1,042 (17.4)	833 (12.7)	629 (18.5)	741 (18.5)
60–69	393 (6.6)	219 (3.4)	310 (9.1)	252 (6.3)
70+	184 (3.1)	60 (0.9)	169 (5.0)	71 (1.8)
Year of birth, <i>N</i> (%)				
Before 1920	36 (0.6)	44 (0.7)	30 (0.9)	40 (1.0)
1920–1929	146 (2.4)	212 (3.2)	108 (3.2)	176 (4.4)
1930–1939	388 (6.5)	532 (8.1)	245 (7.2)	437 (10.9)
1940–1949	833 (13.9)	1,349 (20.6)	427 (12.6)	902 (22.5)
1950–1959	1,294 (21.6)	1,945 (29.8)	685 (20.2)	1,145 (28.9)
1960 and later	3,292 (55.0)	2,454 (37.6)	1,904 (56.0)	1,310 (32.7)

Abbreviation: IQR, interquartile range.

heterogeneity model (separate HR parameter for heterozygote and homozygotes) fit better than the multiplicative model for the effect of the minor allele of this SNP ($P = 0.07$). Under the multiplicative model, the per-allele HR was estimated to be 1.09 (95% CI: 1.01–1.19, $P_{\text{trend}} = 0.032$). A model that assumed that the underlying model was dominant fitted equally well ($HR_{\text{dominant}} = 1.15$, 95% CI: 1.04–1.27, $P_{\text{dominant}} = 0.008$). The 5p12 polymorphism was not associated with breast cancer for *BRCA1* mutation carriers (HR = 0.96, 95% CI: 0.90–1.02, $P_{\text{trend}} = 0.16$). There was no evidence that the HR vary across studies ($P_{\text{het}} = 0.33$ and 0.77 for *BRCA1* and *BRCA2*, respectively; Figs. 1 and 2), or that the HR vary with age for either *BRCA1* or *BRCA2* mutation carriers ($P = 0.45$ and 0.37, respectively).

The *STXBP4/COX11* SNP rs6504950 was not associated with breast cancer risk for either *BRCA1* (per-allele HR = 1.02, 95% CI: 0.96–1.08, $P_{\text{trend}} = 0.59$) or *BRCA2* mutation carriers (per-allele HR = 1.03, 95% CI: 0.95–1.11, $P_{\text{trend}} = 0.47$). The HR did not vary significantly with age for either *BRCA1* ($P = 0.15$) or *BRCA2* ($P = 0.59$) mutation carriers. There was no evidence of heterogeneity in the HR estimates between studies ($P_{\text{het}} = 0.43$ and 0.10 for *BRCA1* and *BRCA2*, respectively; Figs. 1 and 2).

To investigate whether our results may have been biased by the inclusion of prevalent cancers we repeated the analysis after excluding carriers diagnosed with breast or ovarian cancer more than 5 years prior to their recruitment into the study (i.e., long-term survivors). Individuals from studies in which the date/age at recruitment was not provided were also excluded from this analysis. The results for all 3 SNPs are summarized in Supplementary Table S2. The HR estimates were very similar to the analysis that included prevalent cancers. However, the P values were larger and the 5p12 SNP was no longer significantly associated with breast cancer

risk ($P_{\text{trend}} = 0.13$, $P_{\text{dominant}} = 0.05$) possibly due to the smaller number of mutation carriers included in this analysis.

The updated results for SNPs, rs2981582 in *FGFR2*, rs3803662 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSPI*, rs13281615 in 8q24, and rs13387042 in 2q35, which include additional mutation carriers genotyped since they were originally published, are shown in Table 3. The sample size increase varied from 1,347 to 1,840 mutation carriers for the latest published SNPs in *LSPI*, 8q24, and 2q35 and from 3,413 to 3,854 mutation carriers for SNPs in *FGFR2*, *TOX3/TNRC9*, and *MAP3K1*. The pattern of associations of these SNPs with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers were similar to that found from the previously published CIMBA analyses, with the same SNPs significantly associated at the 5% level (6, 7). In the combined set of *BRCA1* mutation carriers, only the *TOX3/TNRC9* and 2q35 polymorphisms were associated with risk ($P_{\text{trend}} = 0.0049$ and 2df $P = 0.01$, respectively). In contrast, 5 of the 6 SNPs were associated with the risk of developing breast cancer in the combined set of *BRCA2* mutation carriers. The most significant association was for the *FGFR2* polymorphism ($P_{\text{trend}} = 6.8 \times 10^{-11}$) in which each copy of the minor allele was estimated to confer an HR of 1.30 (95% CI: 1.20–1.40), followed by *TOX3/TNRC9* (per-allele HR = 1.17, 95% CI: 1.07–1.27, $P_{\text{trend}} = 0.00029$). These 2 SNPs had the largest increase in sample size since the previous analysis, and the significance of each association was correspondingly greater ($P_{\text{trend}} = 1.7 \times 10^{-8}$ and 0.009 in the previous analysis for *FGFR2* and *TOX3/TNRC9*, respectively). The significance of associations between the other SNPs (*LSPI*, *MAP3K1*, 2q35) and breast cancer risk for *BRCA2* mutation carriers were similar to those reported previously (Table 3). The 8q24 SNP

Table 2. Genotype frequencies by disease status and hazard ratio estimates

Mutation/gene	Genotype	Unaffected (%)	Affected (%)	HR	95% CI	P	
SLC4A7/NEK10 rs4973768	<i>BRCA1</i>	CC	1,249 (25.8)	1,380 (25.4)	1.00		
		CT	2,440 (50.4)	2,706 (49.7)	1.00	0.92–1.09	
		TT	1,155 (23.8)	1,353 (24.9)	1.06	0.96–1.17	
		2df test					0.40
		Per allele			1.03	0.98–1.08	0.26
	<i>BRCA2</i>	CC	735 (26.4)	782 (23.2)	1.00		
		CT	1,359 (48.8)	1,651 (49.0)	1.11	0.98–1.25	
		TT	689 (24.8)	937 (27.8)	1.22	1.06–1.40	
		2df test					0.024
		Per allele			1.10	1.03–1.18	0.0064
STXBP4/COX11 rs6504950	<i>BRCA1</i>	GG	2,613 (53.5)	2,953 (53.4)	1.00		
		GA	1,915 (39.2)	2,179 (39.4)	1.01	0.94–1.10	
		AA	357 (7.3)	385 (7.2)	1.04	0.90–1.19	
		2df test					0.86
		Per allele			1.02	0.96–1.08	0.59
	<i>BRCA2</i>	GG	1,556 (55.3)	1,808 (53.2)	1.00		
		GA	1,054 (37.5)	1,351 (39.7)	1.07	0.97–1.19	
		AA	203 (7.2)	242 (7.1)	0.99	0.82–1.20	
		2df test					0.36
		Per allele			1.03	0.95–1.11	0.47
5p12 rs10941679	<i>BRCA1</i>	AA	2,490 (56.3)	2,991 (56.7)	1.00		
		AG	1,626 (36.8)	1,929 (36.6)	0.97	0.89–1.05	
		GG	304 (6.9)	351 (6.7)	0.90	0.77–1.04	
		2df test					0.34
		Per allele			0.96	0.90–1.02	0.16
	<i>BRCA2</i>	AA	1,535 (59.2)	1,809 (55.4)	1.00		
		AG	900 (34.7)	1,264 (38.7)	1.16	1.04–1.29	
		GG	156 (6.0)	190 (5.8)	1.05	0.85–1.30	
		2df test					0.022
		Per allele			1.09	1.01–1.19	0.032
	Dominant			1.15	1.04–1.27	0.0083	

was not associated with breast cancer risk for *BRCA2* mutation carriers (per-allele HR = 1.06, 95% CI: 0.98–1.13, $P_{\text{trend}} = 0.13$), but the number of additional *BRCA2* mutation carriers included in this analysis was only 628, and the 95% CI still included the estimated relative risk in population-based studies. For all SNPs except *TNRC9/TOX3*, the inclusion of newly genotyped mutation carriers resulted in somewhat attenuated HR estimates, but narrower CI. The dominant model remained the most parsimonious model for the 2q35 SNP for both *BRCA1* and *BRCA2* carriers.

We evaluated all pairwise interactions between the SNPs that were associated with breast cancer risks for *BRCA1* and *BRCA2* separately (Supplementary Table S3). There was no evidence of any departure from a log-additive model for the *TOX3/TNRC9* and 2q35 SNPs on the breast cancer risk for *BRCA1* mutation carriers ($P = 0.22$) or for any pairwise combination of the 7 SNPs associated with *BRCA2* breast cancer risk ($P \geq 0.07$).

Figure 3A shows the distribution of the combined HR across the 7 SNPs associated with breast cancer for *BRCA2* mutation carriers, based on the estimates from the CIMBA sample and assuming that all SNPs interact multiplicatively. The HR varied from 1 for *BRCA2* mutation carriers who were homozygous for the protective allele at all loci, to 5.75 for those who were homozygous for the risk allele at all loci. The median, 5th percentile HR, and 95th percentile HR were 1.9, 1.3, and 3.0, respectively. Figure 3B translates the combined HR into absolute risks of developing breast cancer by age 80. The estimated risk of developing breast cancer by 80 for *BRCA2* mutation carriers varies from 42% to 96%. The median cumulative breast cancer risk is 64% (5th and 95th percentile risk 50% and 80%, respectively). Figure 4 shows the age-specific cumulative risks of developing breast cancer in *BRCA2* mutation carriers by the combined genotype distribution at the 7 associated SNPs. The risk of developing breast cancer by age 50 for the 5% of the

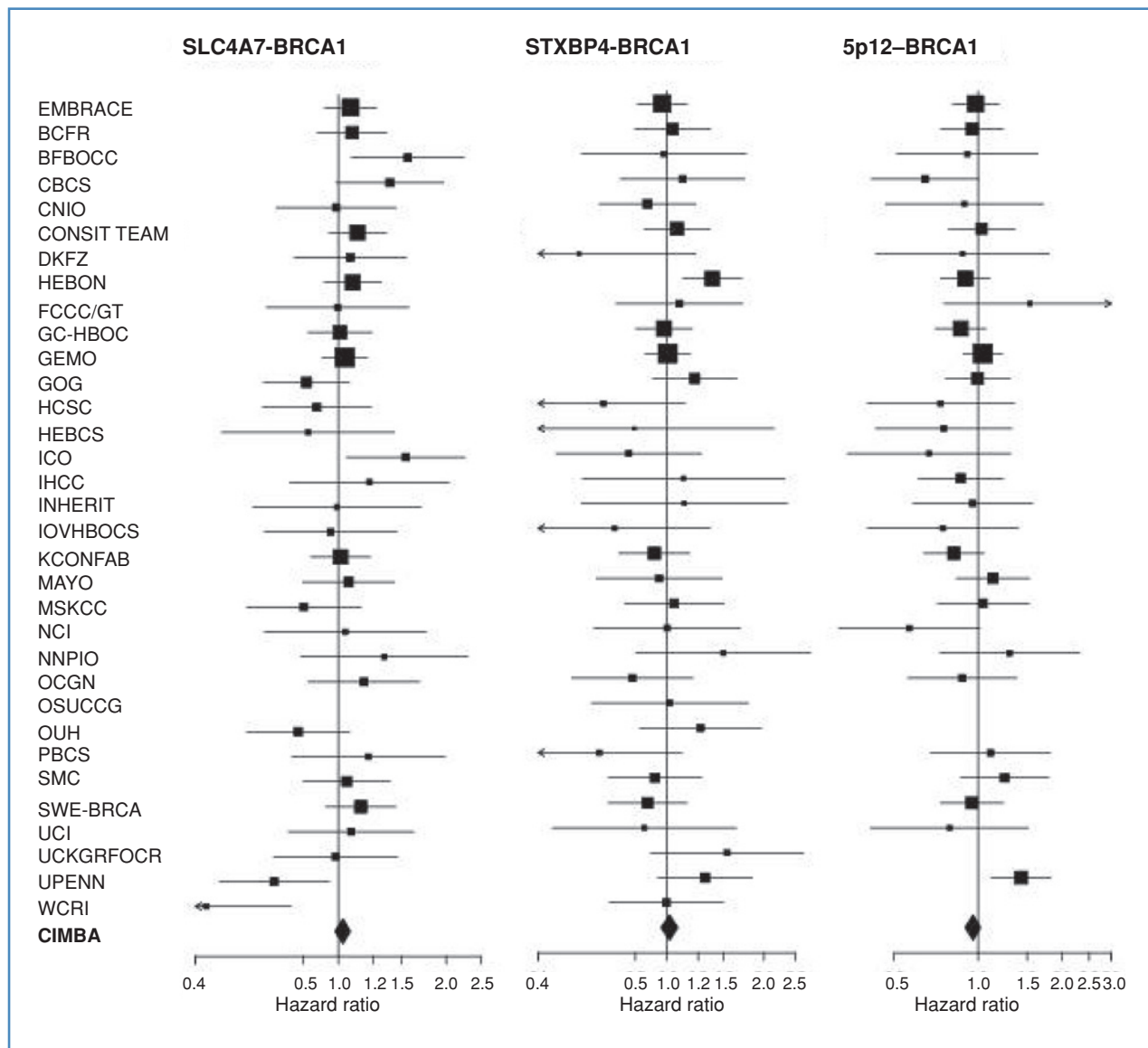


Figure 1. Study-specific per-allele HR estimates for *BRCA1* mutation carriers for SNPs: rs4973768 in *SLC4A7/NEK10*, rs6504950 in *STXPB4/COX11*, and rs10941679 in the 5p12. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% CI.

mutation carriers at lowest risk is between 10% and 13%, compared with 29% to 47% for the 5% of the mutation carriers at highest risk. For comparison, we computed the cumulative risks using a risk score based on the published per-allele odds ratios (OR) for each SNP (all 9) in population-based studies (Supplementary Figure S1). The predicted combined HR and cumulative risks based on the median, the 5th and 95th percentiles of the genotype distribution were similar to those based on the CIMBA estimates.

The average risk of developing breast cancer for *BRCA1* mutation carriers by age 80 was previously estimated to be approximately 66% (4). Based on the combined *TOX3/TNRC9-2q35* genotype distribution, 13% of *BRCA1* mutation carriers who were homozygous for the protective allele at both loci will have a risk of developing breast cancer of 61%,

compared with 72% for the 2% of the *BRCA1* mutation carriers who have the at-risk genotype at both loci.

Discussion

We have investigated 9 breast cancer susceptibility variants identified through GWAS, for their associations with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers. Of the 3 new polymorphisms investigated, the *SLC4A7/NEK10* and 5p12 SNPs were associated with breast cancer risk for *BRCA2* mutation carriers. For each SNP, the per-allele HR was similar to the published relative risks in population-based studies. For *BRCA1* mutation carriers, neither SNP showed an association with breast cancer risk, and in each case the 95% CI for the HR

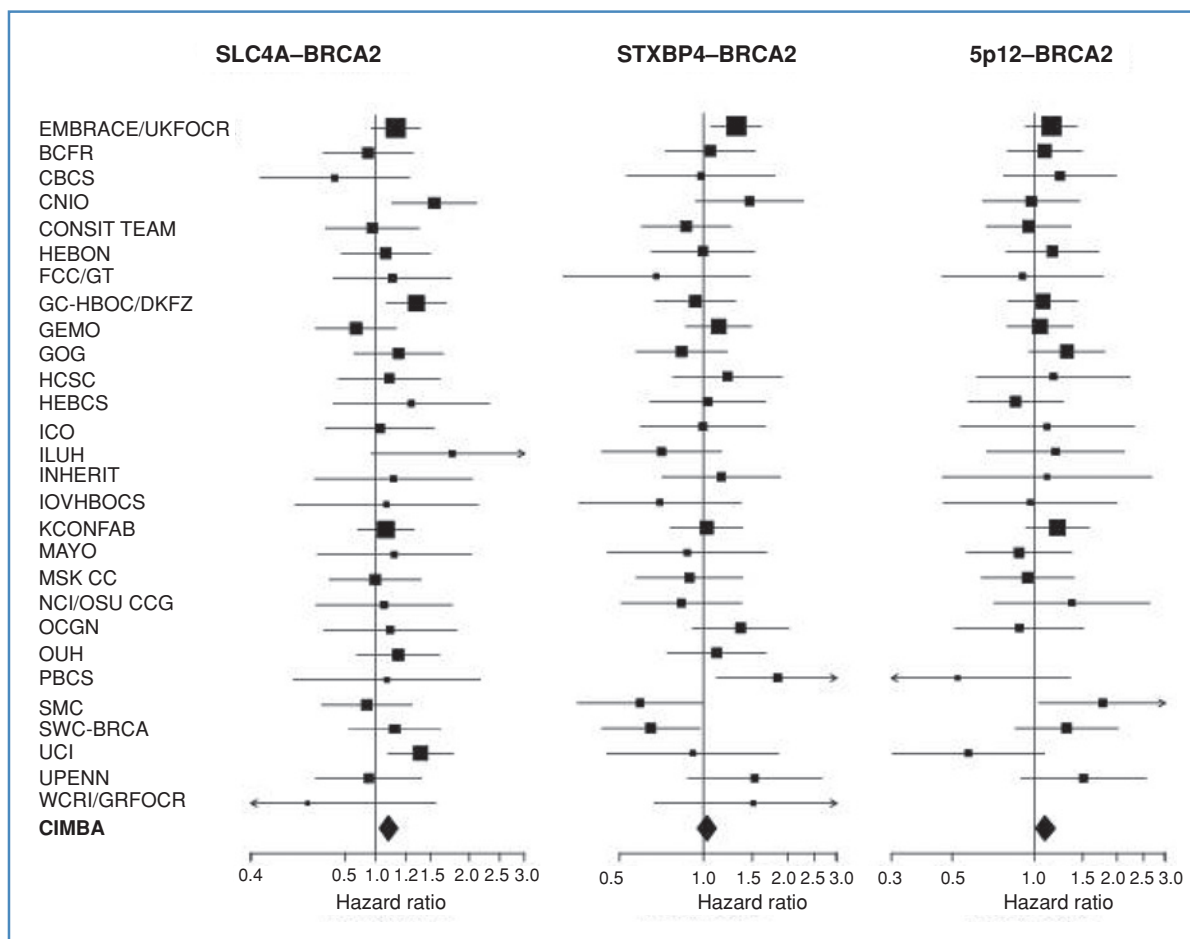


Figure 2. Study-specific per-allele HR estimates for *BRCA2* mutation carriers for SNPs: rs4973768 in *SLC4A7/NEK10*, rs6504950 in *STXBP4/COX11*, and rs10941679 in the 5p12. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% CI.

excluded the published point estimate for the general population. The *STXBP4/COX11* SNP was not associated with breast cancer risk for either *BRCA1* or *BRCA2* mutation carriers. However, we cannot rule out that this SNP confers an HR for breast cancer in *BRCA2* mutation carriers similar to the OR estimated from population-based studies as our CI includes that estimate (10). Given the magnitude of the effect in population-based studies, the current CIMBA sample of *BRCA2* mutation carriers would have limited power to detect such an association (power of 31% at a 0.05 significance level). The estimated effects were not materially altered by inclusion of prevalent breast cancers in the analysis.

We have also incorporated newly recruited mutation carriers in the analysis of the 6 SNPs that we previously investigated (*FGFR2*, *TNRC9/TOX3*, *MAP3K1*, *LSPL*, 8q24, and 2q35; refs. 6, 7). The conclusions from these analyses were qualitatively similar to those previously reported, but there were some differences in the estimated HR for the risk associated SNPs. With the exception of *TOX3/TNRC9* in *BRCA2*, the HR were somewhat attenuated, perhaps reflecting a "winner's curse" effect (i.e., HR overestimation) in the original investigation (21). The addition of new samples strengthened the

associations for the *FGFR2* and *TOX3/TNRC9* SNPs, which are the SNPs with largest estimated HR, but the association *P* values increased marginally for the other SNPs.

We focused on the associations of these SNPs with the risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers. For this purpose, individuals who developed ovarian cancer first, were censored at the ovarian cancer diagnosis and were assumed to be unaffected in the analysis. If any of these polymorphisms were associated with ovarian cancer risk, this could potentially lead to biased estimates of the breast cancer HR. However, previous analyses of these SNPs, which excluded mutation carriers who developed ovarian cancer, yielded similar HR estimates to the analysis that included these carriers (6). Moreover, there is no evidence from population-based studies of ovarian cancer that any of these SNPs are associated with ovarian cancer risk in the general population (22, 23). A separate CIMBA study to estimate the effects of these polymorphisms on ovarian cancer risk for mutation carriers, assessed within a competing risks analysis framework is currently ongoing.

The associations between the 9 SNPs and breast cancer risk differed substantially between *BRCA1* and *BRCA2* muta-

Table 3. Hazard ratio estimates for previously published associations using additional mutation carriers

Mutation/SNP	Including newly recruited mutation carriers				Original analysis (6, 7)			
	Unaffected/ affected	HR ^a	95% CI	P ^b	Unaffected/ affected	HR ^a	95% CI	P ^b
<i>FGFR2</i> rs2981582								
<i>BRCA1</i>	3,822/4,446	1.03	0.97–1.09	0.31	2,874/3,154	1.02	0.95–1.09	0.60
<i>BRCA2</i>	2,160/2,716	1.30	1.20–1.40	6.8 × 10 ⁻¹¹	1427/1836	1.32	1.20–1.45	1.7 × 10 ⁻⁸
<i>TOX3/TNRC9</i> rs3803662								
<i>BRCA1</i>	3,911/4,492	1.09	1.03–1.16	0.0049	3,031/3,263	1.11	1.03–1.19	0.0043
<i>BRCA2</i>	2,135/2,679	1.17	1.07–1.27	0.00029	1,426/1,829	1.15	1.03–1.27	0.009
<i>MAP3K1</i> rs889312								
<i>BRCA1</i>	4,152/4,404	0.99	0.93–1.05	0.63	3,272/3,469	0.99	0.93–1.06	0.86
<i>BRCA2</i>	2,282/2,840	1.10	1.01–1.19	0.022	1,557/1,967	1.12	1.02–1.24	0.020
<i>LSP1</i> rs3817198								
<i>BRCA1</i>	4,480/5,383	1.05	0.99–1.11	0.11	4,203/4,781	1.05	0.99–1.11	0.090
<i>BRCA2</i>	2,636/3,266	1.14	1.06–1.23	0.00079	2404/3030	1.16	1.07–1.25	0.00028
8q24 rs13281615								
<i>BRCA1</i>	4,730/5,498	1.00	0.95–1.05	0.93	4,254/4,762	1.00	0.94–1.05	0.88
<i>BRCA2</i>	2,723/3,338	1.06	0.98–1.13	0.13	2,408/3,025	1.06	0.98–1.14	0.15
2q35 rs13387042								
<i>BRCA1</i>	4,554/5,383				4,268/4,763			
Heterozygotes		1.14	1.04–1.25			1.18	1.07–1.30	
Homozygotes		1.05	0.94–1.16			1.08	0.97–1.21	
2df test				0.010				0.003
Per allele		1.02	0.96–1.07	0.57		1.03	0.98–1.09	0.24
Dominant		1.11	1.01–1.21	0.026		1.14	1.04–1.25	0.0047
<i>BRCA2</i>								
<i>BRCA2</i>	2,646/3,300				2,407/3,042			
Heterozygotes		1.16	1.03–1.32			1.21	1.06–1.37	
Homozygotes		1.11	0.97–1.28			1.12	0.97–1.31	
2df test				0.048				0.015
Per allele		1.05	0.98–1.13	0.17		1.06	0.98–1.14	0.14
Dominant		1.15	1.02–1.29	0.021		1.18	1.04–1.33	0.0079

^aPer allele Hazard Ratio unless specified

^bMultiplicative model unless specified

tion carriers. Seven of the polymorphisms were associated with the risk of developing breast cancer for *BRCA2* mutation carriers (*FGFR2*, *TOX3/TNRC9*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7/NEK10*, 5p12). However, despite the larger sample size for *BRCA1* carriers, only *TOX3/TNRC9* and 2q35 were associated with the risk of breast cancer for *BRCA1* mutation carriers. Significant differences in the HR between *BRCA1* and *BRCA2* were observed for *FGFR2* ($P = 3 \times 10^{-6}$), *MAP3K1* ($P = 0.03$), and 5p12 ($P = 0.01$). We have previously suggested that such differences could be explained by the differential effects of these SNPs by tumor subtype, specifically by estrogen receptor (ER) status. Analyses by the Breast Cancer Association Consortium have indicated that many of the susceptibility loci confer higher relative risks for ER-positive disease, with weaker or absent association for ER-negative disease (24). Interestingly, the *TOX3* and 2q35 SNPs, which exhibit associations for *BRCA1* carriers, show the strongest evidence for association with ER-negative breast cancer risk in the general population, consistent with

the observation that *BRCA1* tumors are predominantly ER-negative whereas *BRCA2* tumors are predominantly ER-positive (25). More specifically, these 2 SNPs were the only SNPs associated significantly with breast cancer expressing basal markers (M. Garcia-Closas, personal communication), the predominant subtype of breast cancer in *BRCA1* carriers. The 5p12 and *SLC4A7/NEK10* SNPs analyzed in this study also conferred higher relative risks for ER-positive disease, consistent with this hypothesis (10, 11). Therefore, our results provide further evidence for the distinct nature of the *BRCA1* related breast tumors. Overall, the 7 SNPs associated with breast cancer risk for *BRCA2* mutation carriers were estimated to account for approximately 4% of the genetic variability of breast cancer in *BRCA2*, whereas the *TOX3/TNRC9* and 2q35 were estimated to account for 0.4% of the genetic variability in breast cancer risk in *BRCA1*. The estimated contribution to *BRCA1* breast cancer risk variability is slightly lower than previously estimated (7), as a result of the attenuated HR estimates in the present analysis.

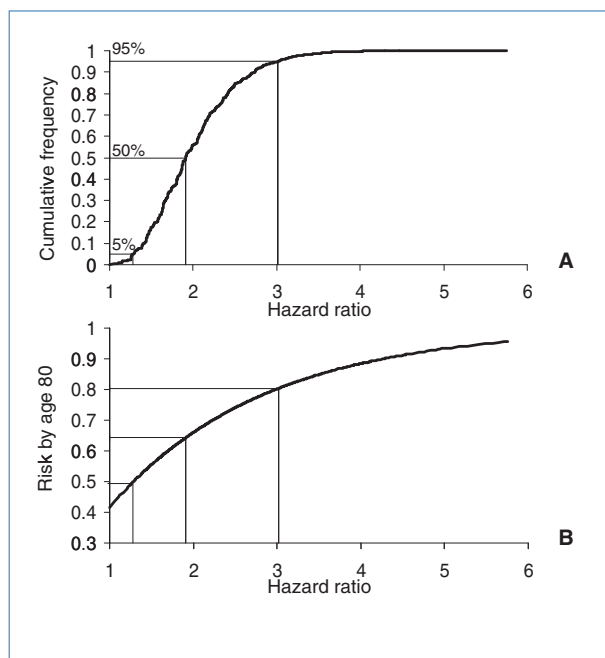


Figure 3. A, cumulative distribution function of the combined hazard ratio for breast cancer risk for *BRCA2* mutation carriers at SNPs: rs2981582 in *FGFR2*, rs3803662 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs13387042 in 2q35 region, rs4973768 in *SLC4A7/NEK10*, and rs10941679 in the 5p12 region (see Materials and Methods for definition of combined HR). B, predicted cumulative risk of developing breast cancer by age 80 for *BRCA2* mutation carriers by the combined HR at the above SNPs.

Each variant was estimated to be associated with a modest HR. The largest per-allele HR estimate was 1.30 for the *FGFR2* association for *BRCA2* mutation carriers. However, the combined effect of the susceptibility variants on risk can be much larger. Analysis of interactions between pairs of loci indicated that the combined effects were consistent with a multiplicative model. By defining a risk score based on this assumption, we estimated empirically that the

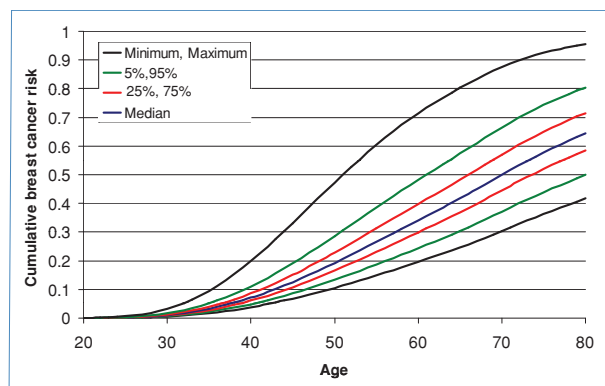


Figure 4. Age-specific cumulative breast cancer risks for *BRCA2* mutation carriers by percentiles of the combined genotype distribution at SNPs: rs2981582 in *FGFR2*, rs3803662 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs13387042 in 2q35 region, rs4973768 in *SLC4A7/NEK10*, and rs10941679 in the 5p12 region.

highest 5% of the risk distribution had an HR of 2.64 (95% CI: 1.83–3.80, $P = 2.3 \times 10^{-7}$) compared with the lowest 5%; this is very close to the predicted HR based on an assumed multiplicative model. We also conducted a similar analysis based on the estimated relative risks from population-based studies, and the quantile-specific risk estimates were similar, indicating that the HR were not exaggerated due to overfitting. Because we only considered pairwise interactions, it is possible that more complex interactions have been missed. However, given our results from the pairwise interactions and empirical score analysis, the multiplicative assumption seems plausible. A model with higher order interactions could lead to more powerful discrimination, but even with a study of this size there is insufficient power to fit higher order interactions reliably.

As *BRCA2* mutations confer elevated risks of breast cancer, the combined HR estimates translate to large differences in the absolute risk of developing breast cancer between genotypes. Based on the combined associations of the 7 SNPs we estimate that the 5% of *BRCA2* mutation carriers at lowest risk will have a lifetime risk of developing breast cancer of 50% or lower whereas the 5% at highest risk will have a lifetime risk of 80% or higher. Such differences in risk could potentially be informative for genetic counseling purposes for classifying *BRCA2* mutation carriers into different risk groups (26). A previous segregation analysis estimated that, based on the assumed distribution of modifiers of breast cancer risk, *BRCA2* mutation carriers at the 5th percentile of risk distribution will have lifetime risk of developing the disease of 23% and those at the 95th percentile will have a lifetime risk of almost 100% (4). This analysis suggests that much greater improvements in risk profiling of carriers could be realized in the future if further modifiers of risk are identified. In contrast to *BRCA2*, only a limited number of risk modifying polymorphisms have been identified for *BRCA1*. This could reflect the fact that GWAS have so far focused on breast cancer patients unselected for tumor subtypes. Ongoing GWAS in *BRCA1* mutation carriers and in ER-negative disease in the general population will be valuable in this respect.

In summary, our results indicate that the majority of the common breast cancer susceptibility variants identified through GWAS are associated with breast cancer risk for *BRCA2* mutation carriers, to a similar relative extent as in the general population. Their combined association results in substantial risk differences in absolute risk across SNP genotype categories. Such differences could inform genetic counseling and lead to improved management of mutation carriers. Future studies in both the general population and mutation carriers that include GWAS, denser genotyping, exome, and whole genome sequencing are likely to identify further variants associated with cancer risk for mutation carriers and will ultimately lead to more accurate risk prediction for these women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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