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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 (BC) susceptibility polymorphisms in *FGFR2, TNRC9/TOX3, MAP3K1,LSP1* and 2q35 confer increased risks of BC for *BRCA1* or *BRCA2* mutation carriers. We evaluated the associations of three additional 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 BC risk for *BRCA2* carriers (per-allele Hazard Ratio (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 BC risk for *BRCA1* carriers and rs6504950 was not associated with BC for either *BRCA1* or *BRCA2* carriers. Of the nine polymorphisms investigated, seven were associated with BC for *BRCA2* carriers (*FGFR2, TOX3, MAP3K1, LSP1*, 2q35, *SLC4A7*, 5p12, p-values:7×10^{-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 BC risk for mutation carriers. Based on the joint genotype distribution of the seven 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 BC by age 80, compared with 42-50% for the 5% of carriers at lowest risk. Our findings indicated that these risk differences may be sufficient to influence the clinical management of mutation carriers.

Keywords

BRCA1; *BRCA2*; genetic modifier; common variant; genome-wide association study; penetrance; genetic counseling

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 or the cancer site of the proband that led to the family ascertainment (1-3) and 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 may modify the cancer risks conferred by *BRCA1* and *BRCA2* mutations. 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(5)). These studies evaluated common genetic variants (single nucleotide polymorphisms, SNPs) , which have been shown to be associated with breast cancer risk in the general population through genome-wide association studies (GWAS) (6-9). The CIMBA results suggest that of the six 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 in the general population but was not statistically significant.

Since these investigations, eleven other breast cancer susceptibility variants have been identified through GWAS (10-14) including three SNPs rs4973768 in *SLC4A7/NEK10*, rs6504950 in *STXBP4/COX11* and rs10941679 on 5p12. To evaluate whether these three 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 six 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 of interactions between the polymorphisms and the implications for risk prediction in *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 (39) studies contributed data for mutation carriers who were successfully genotyped for one or more of the nine 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 old or over 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, which was defined to be the country of the clinic at which the carrier family was recruited to the study. 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(15). Women who self-reported as “non-white” 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 which 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 one or more of the SNPs and were therefore included in the analysis (Supplementary Table 1).

Statistical analysis

The aim of the analysis was to evaluate the association between each genotype and breast cancer risk. The phenotype of each individual was therefore defined by her age at diagnosis of breast cancer or her age at last follow-up. For this purpose, individuals 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. Since 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)(16). We

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therefore conducted the analysis by modelling 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 HRs 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 HRs 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 × 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(17). 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 and used calendar-year- and cohort-specific breast cancer incidence rates for *BRCA1* and *BRCA2* (4). Risk reducing salpingo-oophorectomy (RRSO) 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 in the associations after adjustment(6, 7). We used a robust variance-estimation approach to allow for the non-independence among 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 may influence the HR estimates. We therefore repeated our analysis by excluding mutation carriers diagnosed more than five 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(4)). We estimated the total proportion of the modifying variance due to all SNPs by adding the individual proportions, i.e. 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 carries had an eligible genotype for at least one of the nine SNPs and were included in the analysis (total 19,934 mutation carriers, Supplementary Table 1). Of these 9,933 had an observed genotype at all nine 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 individuals 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 three newly investigated polymorphisms in the *SLC4A7/NEK10*, 5p12, *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 a HR of 1.10 (95% CI: 1.03-1.18, p-trend=0.006). There was no evidence that this SNP was associated with breast cancer risk for *BRCA1*

mutation carriers (HR 1.03, p-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; Figures 1 and 2). Models which 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-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 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-trend=0.032). A model which assumed that the underlying model was dominant fitted equally well ($HR_{dominant}$=1.15, 95%CI: 1.04-1.27, p_{dom}=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-trend=.16). There was no evidence that the HRs vary across studies (p_{het}=0.33 and 0.77 for *BRCA1* and *BRCA2* respectively; Figures 1 and 2), or that the HRs vary with age for either *BRCA1* or *BRCA2* (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-trend=0.59) or *BRCA2* mutation carriers (per-allele HR=1.03, 95%CI:0.95-1.11, p-trend=0.47). The HRs did not vary significantly with age for either *BRCA1* (p=0.15) or *BRCA2* (p=0.59). There was no evidence of heterogeneity in the HR estimates between studies (p_{het}= 0.43 and 0.10 for *BRCA1* and *BRCA2* respectively, Figure 1 and 2).

To investigate whether our results may have been biased by the inclusion of prevalent cancers we repeated the analysis after excluding those who were 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 three SNPs are summarised in Supplementary Table 2. The HR estimates were very similar to the analysis which included prevalent cancer patients. However, the p-values were larger and the 5p12 SNP was no longer significantly associated with breast cancer risk (p-trend=0.13, p-dominant=0.05) 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 *LSP1*, 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 1347 to1840 mutation carriers for the latest published SNPs in *LSP1*, 8q24 and 2q35 and from 3413 to 3854 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 seen in 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-trend=0.0049 and 2df p=0.01 respectively). In contrast, five of the six 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-trend=6.8×10^{-11}) in which each copy of the minor allele was estimated to confer a 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-trend=0.00029). These two SNPs had the largest increase in sample size since the previous analysis, and the significance of each association was correspondingly greater (p-trend=1.7×10^{-8} and 0.009 in the

previous analysis for *FGFR2* and *TOX3/TNRC9* respectively). The significance of associations between the other SNPs (*LSP1, MAP3K1*, 2q35) and breast cancer risk for *BRCA2* mutation carriers were similar to those reported previously (Table 3). The 8q24 SNP was not associated with breast cancer risk for *BRCA2* mutation carriers (per-allele HR=1.06 95%CI 0.98-1.13, p-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 confidence intervals. 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 3). 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 seven SNPs associated with *BRCA2* breast cancer risk (p≥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 and 95th percentile HRs were 1.9, 1.3 and 3.0 respectively. Figure 3B translates the combined HRs 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%, (5% and 95% 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 seven associated SNPs. The risk of developing breast cancer by age 50 for the 5% of the mutation carriers at lowest risk is between 10-13%, compared with 29-47% 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 for each SNP (all nine) in population-based studies (Supplementary Figure 1). The predicted combined HR and cumulative risks based on the median, the 5% and 95% 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 nine breast cancer susceptibility polymorphisms identified through genome wide association studies, for their associations with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers. Of the three new polymorphisms investigated, the *SLC4A7/NEK10* and 5p12 SNPs were associated with breast cancer risk for *BRCA2* mutation carriers. In each case, 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 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 a HR for breast cancer in *BRCA2* mutation carriers similar to the odds ratio estimated from population based studies as our confidence interval includes the 0.95 OR 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 cancer patients in the analysis.

We have also incorporated newly-recruited mutation carriers in the analysis of the six SNPs that we previously investigated (*FGFR2, TNRC9/TOX3, MAP3K1, LSP1*, 8q24 and 2q35) (6, 7). The conclusions from these analyses were qualitatively similar to those previously reported, but there were some differences in the estimated HRs for the risk associated SNPs. With the exception of *TOX3/TNRC9* in *BRCA2*, the HRs 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 HRs, 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 HRs. However, previous analyses of these SNPs, that 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 nine SNPs and breast cancer risk differed substantially between *BRCA1* and *BRCA2* mutation 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* ($p = 3\times10^{-6}$), *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 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 (while BRCA2 tumors are predominantly ER-positive)(25). More specifically, these two SNPs were the only SNPs associated significantly with breast cancer expressing basal markers [Garcia-Closas, personal communication], the predominant subtype of breast cancer in *BRCA1* carriers. The 5p12 and *SLC4A7/NEK10* SNPs analyzed in the current study also conferred higher relative risks for ER-positive disease, consistent with this hypothesis(10, 11). Our results therefore provide further evidence for the distinct nature of the *BRCA1*related breast tumors. Overall, the seven 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, while 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.

Each polymorphism was estimated to confer 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 highest 5% of the risk distribution had a HR of 2.64 (95%CI: 1.83-3.80, $p=2.3\times10^{-7}$) 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 RRs from population studies, and the quantile-specific risk estimates were similar, indicating that the HRs were not exaggerated due to overfitting. Since 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 effects of the seven 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 counselling 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 5^{th} percentile of risk distribution will have lifetime risk of developing the disease of 23% and those at the 95^{th} percentile will have a lifetime risk of almost 100%(4). This analysis suggests that much greater improvements in risk profiling of carriers could be realised 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 effect results in substantial risk differences in absolute risk among SNP genotype categories. Such differences could inform genetic counselling and may 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 individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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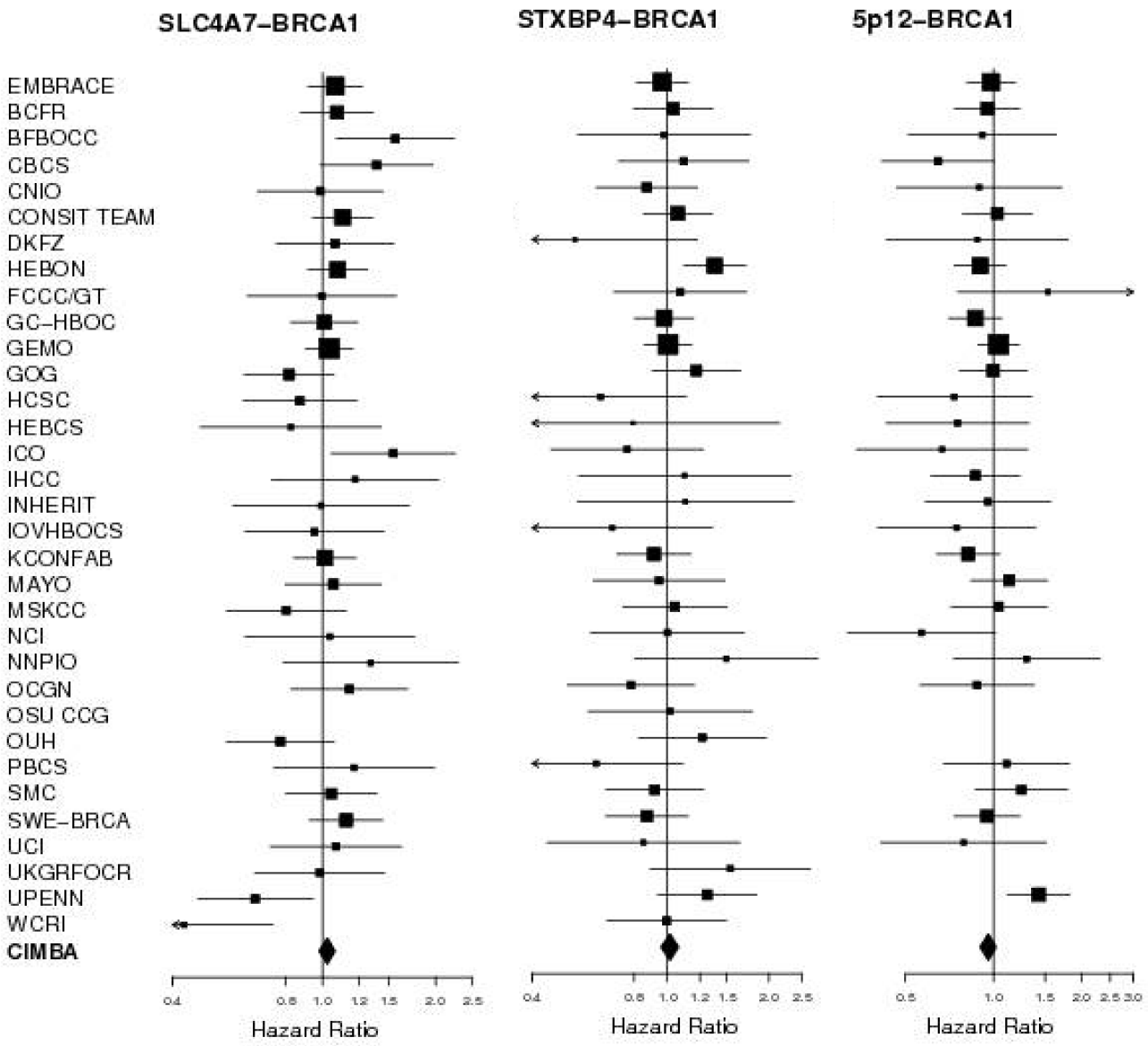

Figure 1.

Study specific per-allele HR estimates for *BRCA1* 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% confidence intervals.

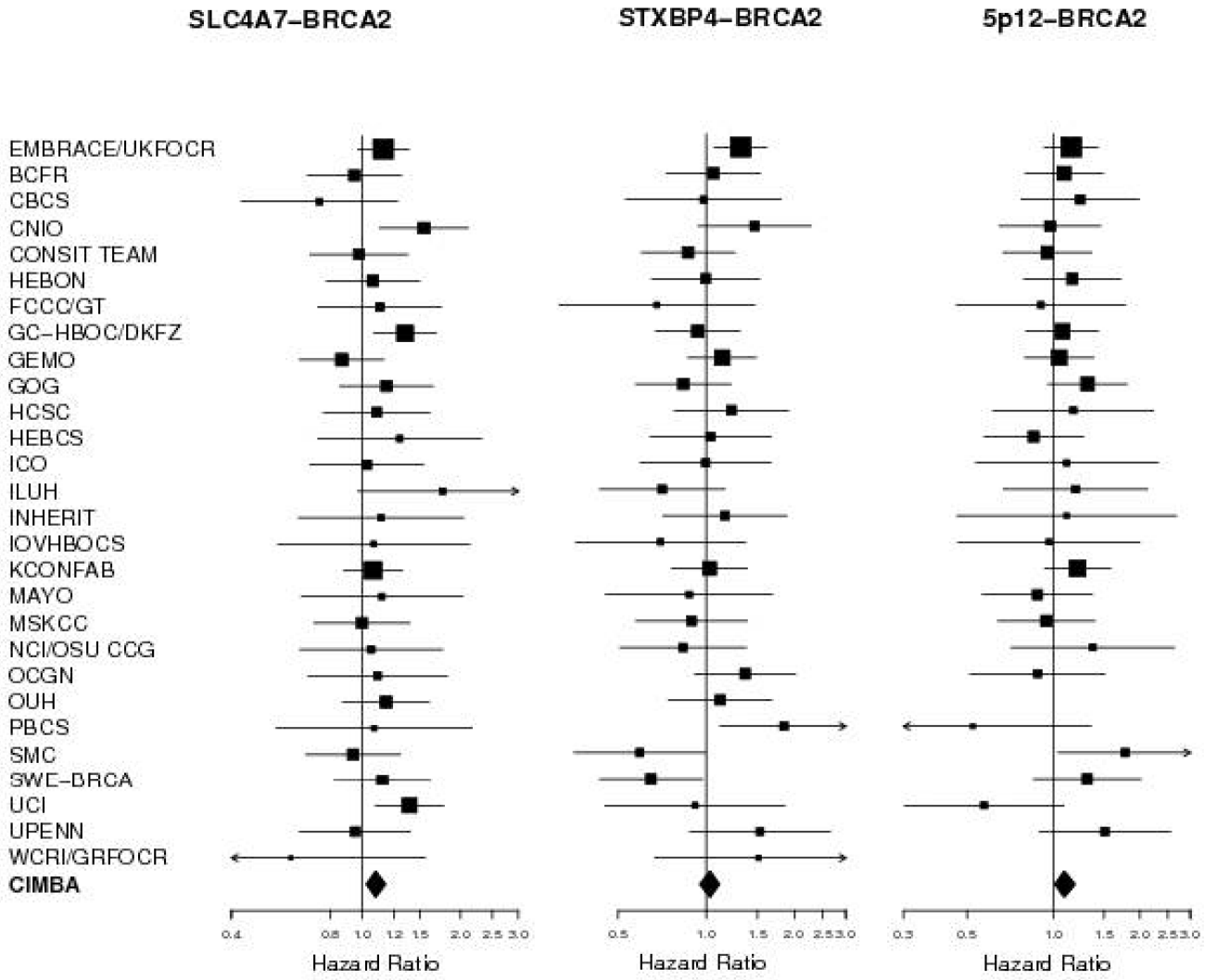

Figure 2.

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% confidence intervals.

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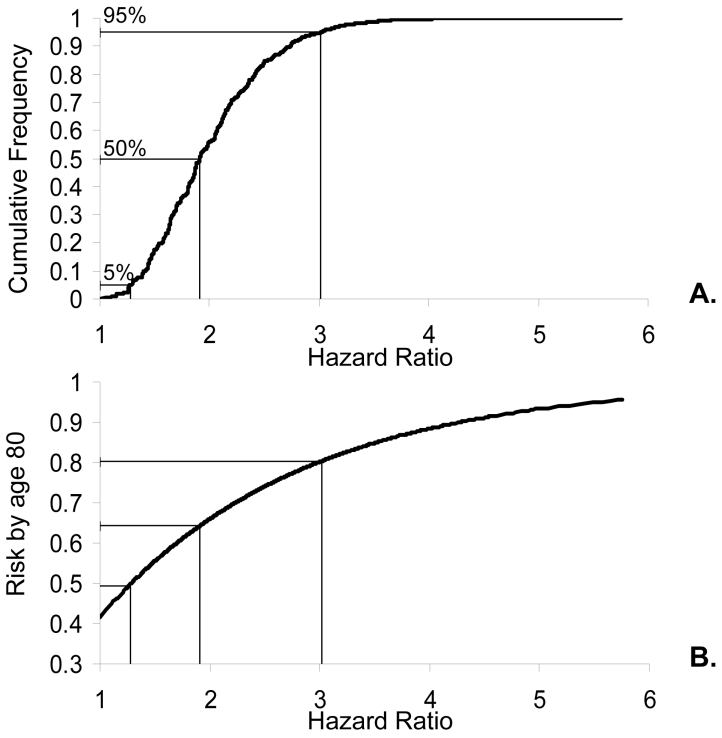

Figure 3.

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 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.

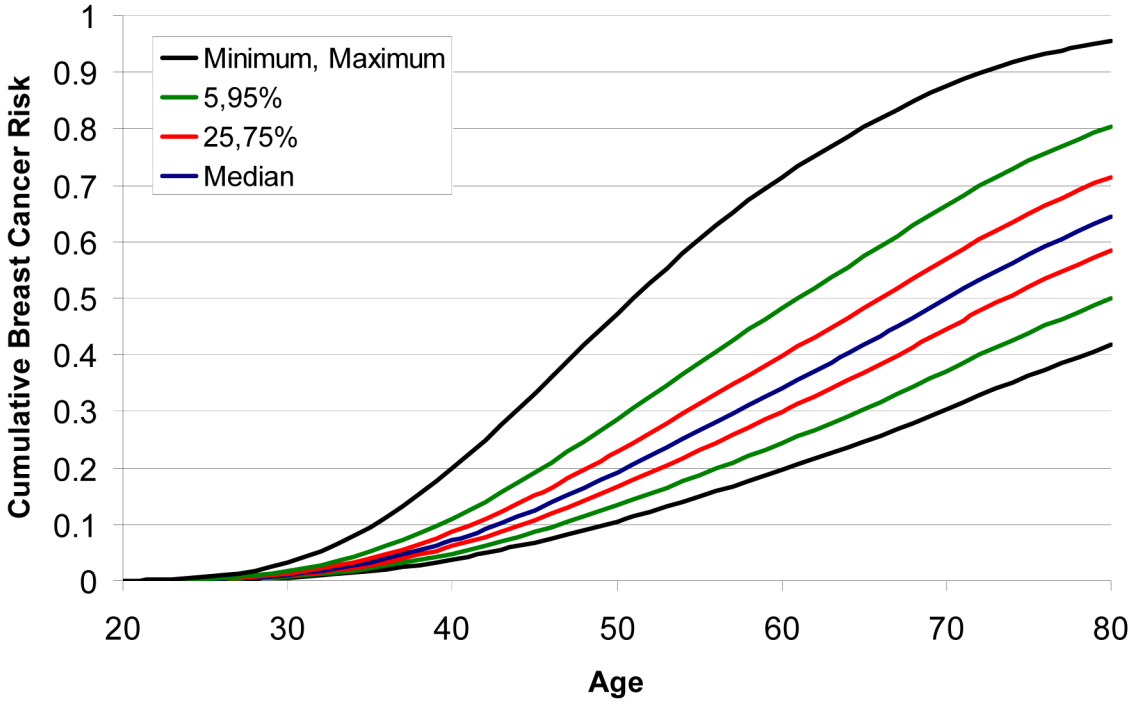

Figure 4.
Age specific cumulative breast cancer risks for *BRCA2* mutation carriers by percentiles of the combined genotype distribution at SNPs rs2981582 in *FGFR2*, rs3803662 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs13387042 in 2q35 region, rs4973768 in *SLC4A7/NEK10* and rs10941679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

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Table 1

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

Characteristic	BRCA1		BRCA2	
	Unaffected	Breast Cancer	Unaffected	Breast Cancer
Number	5989	6536	3399	4010
Person-Years follow-up	255973	268566	150499	150499
Median Age at Censure (IQR*)	42 (34-51)	40 (35-47)	43 (34-53)	43 (37-50)
Age at Censure, N (%)				
<30	851 (14.2)	565 (8.6)	485 (14.3)	185 (4.6)
30-39	1707 (28.5)	2584 (39.5)	898 (26.4)	1254 (31.3)
40-49	1812 (30.3)	2275 (34.8)	908 (26.7)	1507 (37.6)
50-59	1042 (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, N (%)				
<1920	36 (0.6)	44 (0.7)	30 (0.9)	40 (1.0)
1920-29	146 (2.4)	212 (3.2)	108 (3.2)	176 (4.4)
1930-39	388 (6.5)	532 (8.1)	245 (7.2)	437 (10.9)
1940-49	833 (13.9)	1349 (20.6)	427 (12.6)	902 (22.5)
1950-59	1294 (21.6)	1945 (29.8)	685 (20.2)	1145 (28.9)
1960+	3292 (55.0)	2454 (37.6)	1904 (56.0)	1310 (32.7)

*IQR: Interquartile Range

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Table 2

Genotype frequencies by disease status and Hazard Ratio estimates

Mutation/Gene	Genotype	Unaffected (%)	Affected(%)	HR	95% CI	p-Value
SLC4A7/NEK10 rs4973768						
BRCA1	CC	1249 (25.8)	1380 (25.4)	1.00		
	CT	2440 (50.4)	2706 (49.7)	1.00	0.92-1.09	
	TT	1155 (23.8)	1353 (24.9)	1.06	0.96-1.17	
	2df test					0.40
	Per Allele			1.03	0.98-1.08	0.26
BRCA2	CC	735 (26.4)	782 (23.2)	1.00		
	CT	1359 (48.8)	1651 (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						
BRCA1	GG	2613 (53.5)	2953 (53.4)	1.00		
	GA	1915 (39.2)	2179 (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
BRCA2	GG	1556 (55.3)	1808 (53.2)	1.00		
	GA	1054 (37.5)	1351 (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						
BRCA1	AA	2490 (56.3)	2991 (56.7)	1.00		
	AG	1626 (36.8)	1929 (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
BRCA2	AA	1535 (59.2)	1809 (55.4)	1.00		

Mutation/Gene	Genotype	Unaffected (%)	Affected(%)	HR	95% CI	p-Value
	AG	900 (34.7)	1264 (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

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Table 3

Hazard Ratio estimates for previously published associations using additional mutation carriers

	Including newly recruited mutation carriers				Original Analysis(6, 7)			
Mutation/SNP	**Unaffected/Affected**	**HR[a]**	**95% CI**	**p-value***	**Unaffected/Affected**	**HR[a]**	**95% CI**	**p-value***
FGFR2 rs2981582								
BRCA1	3822/4446	1.03	0.97-1.09	0.31	2874/3154	1.02	0.95-1.09	0.60
BRCA2	2160/2716	1.30	1.20-1.40	6.8×10^{-11}	1427/1836	1.32	1.20-1.45	1.7×10^{-8}
TOX3/TNRC9 rs3803662								
BRCA1	3911/4492	1.09	1.03-1.16	0.0049	3031/3263	1.11	1.03-1.19	0.0043
BRCA2	2135/2679	1.17	1.07-1.27	0.00029	1426/1829	1.15	1.03-1.27	0.009
MAP3K1 rs889312								
BRCA1	4152/4404	0.99	0.93-1.05	0.63	3272/3469	0.99	0.93-1.06	0.86
BRCA2	2282/2840	1.10	1.01-1.19	0.022	1557/1967	1.12	1.02-1.24	0.020
LSP1 rs3817198								
BRCA1	4480/5383	1.05	0.99-1.11	0.11	4203/4781	1.05	0.99-1.11	0.090
BRCA2	2636/3266	1.14	1.06-1.23	0.00079	2404/3030	1.16	1.07-1.25	0.00028
8q24 rs13281615								
BRCA1	4730/5498	1.00	0.95-1.05	0.93	4254/4762	1.00	0.94-1.05	0.88
BRCA2	2723/3338	1.06	0.98-1.13	0.13	2408/3025	1.06	0.98-1.14	0.15
2q35 rs13387042								
BRCA1	4554/5383				4268/4763			
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
BRCA2	2646/3300				2407/3042			
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

Mutation/SNP	Including newly recruited mutation carriers				Original Analysis(6, 7)			
	Unaffected/Affected	HR[a]	95% CI	p-value[*]	Unaffected/Affected	HR[a]	95% CI	p-value[*]
Dominant		1.15	1.02-1.29	0.021		1.18	1.04-1.33	0.0079

[*] Multiplicative model unless specified