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Replication of genome-wide discovered breast cancer risk loci in the Cypriot population

Maria A. Loizidou[1], Andreas Hadjisavvas[1, 2§], John P. A. Ioannidis[3, 4, 5], Kyriacos Kyriacou[1]

[1] Department of EM / Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

[2] Brunel Institute for Cancer Genetics and Pharmacogenomics**,** Brunel University, Uxbridge, UB8 3PH, United Kingdom

[3] Department of Hygiene and Epidemiology, University of Ioannina School of Medicine and Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, 45110, Greece

[4] Center for Genetic Epidemiology and Modelling, Tufts University School of Medicine, Boston MA 02111, United States of America

[5] Department of Epidemiology, Harvard School of Public Health, Boston MA 02115, United States of America

[§] Corresponding author

Correspondence:

Dr A. Hadjisavvas, Department of Electron Microscope / Molecular Pathology, The Cyprus Institute of Neurology and Genetics, 6. International Airport Ave., Ayios Dometios, P.O.BOX 23462, 1683, Nicosia, CYPRUS

Telephone: +35722392739, Fax: +35722392641, E-mail: ahsavvas@cing.ac.cy

Abstract

Purpose: Genome-wide association studies (GWAS) have identified associations with robust statistical support for influencing breast cancer susceptibility. Most GWAS and replications have been conducted in Northern European populations and to a lesser extent in Asians, and Ashkenazi Jews. It is important to evaluate whether these variants confer risk across different populations and also to assess the magnitude of risk conferred. The aim of this study was to evaluate previously GWAS-identified breast cancer risk variants in the Cypriot population.

Methods: Eleven GWAS-discovered single nucleotide polymorphisms (SNPs) were analyzed for association with breast cancer in 1,109 Cypriot female breast cancer patients and 1,177 healthy female controls.

Results: Four of the eleven SNPs evaluated were found to be nominally significantly associated ($P<0.05$) with breast cancer risk in the Cypriot population. Based on estimated power, five associations would be expected to be nominally significant. The correlation coefficient of effect sizes (per-allele odds ratio) between the Cypriot population and the original GWAS populations where these SNPs had been discovered, was 0.58 ($P=0.064$), while allele frequencies were very similar ($r=0.88$, $P<0.001$).

Conclusions: Overall, we show modest concordance for breast cancer GWAS-discovered alleles and their effect sizes in the Cypriot population. The effects sizes of GWAS-discovered SNPs need to be verified separately in different populations.

Keywords: breast cancer; Cyprus; GWAS replication; SNP

Introduction

Breast cancer is the most common cancer in women in developed countries [1]. Genetic factors play an important role in both sporadic and familial breast cancer [2-4]. In the mid 1990s, the two major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, were identified [5-6]. Inherited mutations in these high-penetrance genes explain only a small fraction of the familial risk for the disease [7] and attempts to localize additional highly penetrant breast cancer susceptibility genes have failed [8]. This led to the suggestion that the remaining breast cancer susceptibility is polygenic in nature and that multiple low penetrance alleles, each conferring a small risk, are involved [9-10]. In the last few years, a new harvest of breast cancer susceptibility alleles has emerged using genome-wide association studies (GWAS). Scanning common variants in an agnostic fashion, these studies have identified several new associations with robust statistical support for influencing breast cancer susceptibility [11-18]. Between 2007 and 2009, a total of eleven breast cancer susceptibility loci in or near genes such as *FGFR2*, *MAP3K1*, *LSP1*, *TOX3* (formerly known as *TNRC9*), *COX11* and at 1p11.2, 2q35, 3p24, 6q25.1, 6q22.23 and 8q24.21, were discovered [19]. Newer and larger GWAS efforts continue to yield additional risk loci [20].

The majority of breast cancer GWAS and replications published to-date have been conducted in Northern European populations [11-13,17-18,15] and to a lesser extent in Asians [16] and Ashkenazi Jews [14]. It is important to assess whether these variants confer risk across different populations and also to assess the magnitude of risk conferred [21].

The aim of this study was to evaluate previously GWAS-identified breast cancer risk variants in the Cypriot population using a case-control design. The Cypriot population belongs to the wider Caucasian family, but it is genetically distinct from other Caucasian populations and substantially different from Northern European populations [22]. In this report, a total of eleven genetic variants were examined for their association with breast cancer risk.

Materials and Methods

Study subjects

The subjects included in the current study are drawn from the *MASTOS* study, a population-based case-control study of breast cancer in Cyprus. Blood samples were collected between 2004 and 2006 from 1109 female breast cancer patients diagnosed between 40-70 years old and 1177 unrelated healthy controls of the same age range as the cases. No matching was performed. Cases participating in the study were women who were previously diagnosed with breast cancer between January 1999 and December 2006. The majority of cases (n=981) were ascertained from the Bank of Cyprus Oncology Centre that operates as a referral centre and offers treatment and follow-up for 80-90% of all breast cancer cases diagnosed in Cyprus. The rest of the patients (n=128), were recruited at the Oncology Departments of the Nicosia, Limassol, Larnaca and Paphos district hospitals. The control group consisted of healthy women who were participating in the National program for breast cancer screening with the use of mammography. Volunteers were enrolled in the study during the same calendar period as the cases, from the 4-district mammography screening centers that operate in Cyprus. Eligible controls were women with no previous history of breast cancer who had a negative mammography result. All study

participants, both cases and controls, were of Greek Cypriot Caucasian origin. The participation rate of cases and controls was very high covering around 98% of eligible cases and controls who were approached to participate and provide DNA. Breast cancer cases were verified by reviewing histological reports. The study protocol was approved by the National Bioethics Committee of Cyprus. All participants provided written informed consent.

SNP Selection and Genotyping

We selected and genotyped 11 SNPs that had been associated with increased risk of breast cancer in at least one publication using the genome-wide significance threshold of $p<5x10^{-8}$ as of the end of 2009 [23]. These include rs2981582 in *FGFR2*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs3803662 in *TOX3*, rs6504950 in *COX11*, rs11249433 at 1p11.2, rs13387042 at 2q35, rs4973768 at 3p24, rs2180341 at 6q22.23, rs2046210 at 6q25.1 and rs13281615 at 8q24.21.

Genotyping was performed using the Taqman SNP genotyping assays from Applied Biosystems Inc. (ABI). Each assay was carried out using 10 ng genomic DNA in a 5 μl reaction using Taqman Universal PCR Master Mix (ABI), forward and reverse primers, and FAM and VIC-labelled probes purchased from Applied Biosystems (ABI Pre-Designed assays). All assays were carried out in 384-well plates. The fluorescence profile was read on an ABI PRISM 7900HT instrument and the results analyzed with Sequence Detection Software (ABI). For quality control, 96 random samples were genotyped in duplicate and had identical genotyping assignments. Investigators were blinded as to whether samples were duplicates, cases or controls. The order of the DNA samples on 384-well plates was randomized in order to ensure

the same study conditions for samples from cases and controls. Genotyping call rates ranged from 96 to 99% and duplicate concordance rates were 100%.

Data Analysis

Hardy Weinberg equilibrium (HWE) was assessed in the control samples by applying an exact test. Deviation from HWE was considered nominally statistically significant at the $P < 0.05$ level.

Genotype frequency differences between cases and controls were tested using unconditional logistic regression without any adjustments. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated under the log-additive model, using the major allele in the Cypriot control population as reference. ORs thus represent the risk conferred per copy of the minor allele. Secondary analyses examined also recessive and dominant models of inheritance.

Pearson's correlation coefficient (r) was used to estimate the correlations in minor allele frequencies between our study, HapMap CEU population [24] and the GWAS population where each SNP was first discovered. The overall correlation between ORs in the Cypriot population and the GWAS population where each SNP was first discovered was also calculated.

The power of the study to detect ORs similar to those previously found in the GWAS, given the allele frequencies observed in the Cypriot population, was estimated at alpha value of 0.05.

Statistical analyses were run in SNPStats [25] for HWE and logistic regressions, PS [26] for power calculations, and Stata, version 10.1 (College Station, TX), for correlation analyses. *P*-values for association are two-tailed and not adjusted for multiple comparisons, since this is a replication effort for associations that already have robust statistical support. Design and reporting follow the STREGA guidance [27].

Results

Table 1 shows the allele frequencies in cases and controls for the 11 SNPs which were genotyped in this study and genotype frequencies appear in Supplementary Table 1. Genotype distributions of controls at each locus were consistent with HWE (Supplementary Table 1).

Four of the eleven breast cancer–associated SNPs discovered in GWAS (i.e. rs2981582, rs889312, rs13387042 and rs2046210) were statistically significantly associated with breast cancer risk in this study at *P* less than 0.05 (Table 1). All associations were of very modest magnitude, and the largest OR association observed in the Cypriot population was with the G allele of rs889312, located in the *MAP3K1* gene (OR=1.18 per copy of risk allele).

The other seven SNPs were not associated with breast cancer risk in our study. For three of the seven SNPs (rs4973768, rs6504950 and rs2180341) the point estimates of the ORs were in the opposite direction than previously described and one other SNP (rs11249433) had OR=1.00 in the Cyprus population.

Evaluation of the 11 SNPs under recessive and dominant models of inheritance did not show lower p-values for the association for any of the SNPs, with the exception of rs2180341 that was marginally associated with breast cancer risk in a recessive model (OR=1.36; *P*=0.054). P-values were also lower with the recessive rather than log-additive model for rs889312, and rs2046210 and they were nominally significant with both models.

The correlation coefficients of effect sizes (per-allele OR) and minor allele frequencies between the Cypriot and the GWAS populations are r=0.58 (p=0.064) and 0.88 (p<0.001) respectively (Figure 1). Similarly, the Pearson correlation coefficient in minor allele frequencies between the Cypriot and the CEU Hapmap population is 0.83 (p=0.001).

The power of our study (1,109 case patients and 1,177 control subjects) to detect ORs similar to those previously found, given the allele frequencies observed in the Cypriot population ranges from 8% for rs6504950 to 97% for rs2180341, at alpha value of 0.05 (see Figure 1). By summing the power estimates for all SNPs to detect the respective ORs previously seen in GWAS, it is estimated that if ORs were identical in the Cypriot population, our study would be expected to have found five nominally statistically significant associations among the eleven tested. This is not significantly different from the 4 nominally significant associations that we observed.

Discussion

GWAS in Europeans [11-13,17-18,15] and other populations [16,14] have recently identified and confirmed new genetic variants associated with breast cancer. However, it is recognized that the prevalence of breast cancer as well as the allele frequencies differ across populations. It is therefore important to understand the effect of the GWAS discovered markers in women of other ethnicities.

This is the first study in Cypriot women that has systematically evaluated breast cancer susceptibility loci recently identified through GWAS. Of the eleven SNPs evaluated, four (rs2981582, rs889312, rs13387042, rs2046210) were found to be nominally significantly associated with breast cancer risk in the Cypriot population. The effect estimates of these four SNPs are in the same direction as previously reported in the original studies. Based on estimated power, five associations would be expected to be nominally significant among the eleven tested , if the effects were of the same magnitude as seen in the GWAS– not very inconsistent with the four statistically significant associations actually observed.

The strongest association was found for rs889312, for which there was an 18% elevated risk of breast cancer with each risk allele. The per-allele OR in the current study for this SNP was slightly higher than that estimated in the original GWAS. This enrichment could be due to modification by other risk factors, such as gene-gene or gene environment interactions or differences in LD pattern. Alternatively, it could be a chance finding, given that the 95% CI for that SNP goes as low as 1.04. The other three SNPs were, in general, weakly associated with the risk of breast cancer, with

each allele conferring elevated risks of 15% or lower. These modest effects are consistent with what GWAS have also shown for these SNPs.

Seven previously identified risk SNPs were not associated with breast cancer risk in the Cypriot population (*P* values ranged from 0.066 to 0.88). For the majority of these SNPs, limited power is the most likely explanation for the null associations observed. However, this study was well-powered (97% estimated power) to detect the effect of rs2180341, recently identified following a GWAS in the Ashkenazi Jewish genetic isolate [14]. This association was validated in a subsequent replication analysis of independent cohorts of cases and controls of both Ashkenazi Jewish as well as non-Jewish, predominantly European American, populations [28] . It is noted that the aggregated analysis of European breast cancer cases and controls showed a significant association in all modes of analysis, with the strongest association signal assuming the recessive model [28]. Under the recessive model, rs2180341 was marginally associated with breast cancer risk in the Cypriot population. Most GWAS-discovered SNPs fit best to a log-additive model, most likely due to power considerations [29-30]. However, for some SNPs, alternative models of inheritance may also apply and would be interesting to compare such models in different populations.

For four of the SNPs, the point estimates were not in the same direction in the Cyprus population versus the GWAS populations. Two of these SNPs (rs4973768 and rs11249433) have been previously found to be stronger with estrogen receptor (ER) positive than with ER negative breast cancer [17-18]. We have not evaluated tumor pathology in our study. It is possible that the presence of an excess of ER negative cases in our sample, may have masked the effects of these SNPs.

The overall correlation between genetic effects (per-allele ORs) in the Cypriot and the GWAS populations is modest and not even nominally significant. Conversely, for the same variants, there is a very strong correlation in allele frequencies (correlation coefficient=0.88, $P<0.001$). This suggests that genuine differences may exist in the genetic effects. If so, then risk models built with these variants may give different results in different ethnicities [31].

As with any unrelated case-control genetic association study, population stratification and "cryptic relatedness" between subjects may be potential sources of bias in our study. Population stratification may occur when study participants are selected from subpopulations with a different prevalence of the phenotypes and genotypes. In order to avoid confounding from population stratification, we only enrolled women of self-verified Greek-Cypriot ancestry into the study. "Cryptic relatedness" between subjects leads to violation of the assumption of independent data points. The effect of "cryptic relatedness" is likely to be more important in inbred population isolates than in large out-bred populations [32]. Cyprus is a small island with less than a million population. Despite its small size, inbreeding is practically absent since consanguineous marriages are not permitted by law. Furthermore, in our study, all participants were unrelated minimizing potential bias due to relatedness.

The Cypriot population is a Caucasian-origin population. However, principal component analysis of samples from diverse regions of Europe shows substantial genetic diversity across different ethnicities that largely reflect the geographic distribution of populations [22]. In this regard, the Cypriot could be distinguished clearly from populations of neighboring countries and were quite distant on both

principal component dimensions from all Northern European sets [22]. The data of our study reinforce the need to replicate the GWAS discovered variants across different populations and ethnicities. The effects sizes of GWAS need to be verified separately in different populations, even when these populations are all under the Caucasian group.

Conclusions

In conclusion, we replicated four of the eleven regions identified as significantly associated with breast cancer from the GWAS, in a sample of Cypriot breast cancer cases and ethnically matched controls. The results of our study provide further support for the need to critically assess the generalizability of previously identified breast cancer associations and show the complexity of uniformly applying GWAS findings across different populations.

Competing interests

The authors declare that they have no competing interests.

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Fig. 1 Correlation of genetic effects and risk allele frequencies in GWAS populations vs. the Cypriot population. A) Genetic effects expressed in the ORs scale B) Risk allele frequencies. The data are shown by colored circles. The boxed number neighbouring each data point shows the estimated power (in %) at alpha value of 0.05 to detect the OR of the GWAS also in the Cypriot population, given the allele frequency observed in the Cypriot control subjects

Table 1. Allele frequencies in case patients and control subjects and odds ratio (OR) for previously identified risk SNPs

			Minor allele frequency				
SNP	**Genetic locus**	**Allele**[+]	**Control subjects**	**Case subjects**	**OR (95% CI)**	***P*-value**	**Reference**
rs2981582	10q26.13 / *FGFR2*	A / G	0.44	0.47	1.15 (1.03-1.30)	0.018	Easton et al. [11]
rs889312	5q11.2 / *MAP3K1*	C / A	0.29	0.33	1.18 (1.04-1.34)	0.01	Easton et al. [11]
rs13281615	8q24.21 / unknown	G / A	0.48	0.50	1.07 (0.95-1.20)	0.25	Easton et al. [11]
rs3817198	11p15.5 / *LSP1*	C / T	0.31	0.30	0.97 (0.86-1.10)	0.63	Easton et al. [11]
rs3803662	16q12.1 / *TOX3*	A / G	0.33	0.33	1.01 (0.89-1.14)	0.88	Easton et al. [11]
rs13387042	2q35 / unknown	G / A	0.45	0.41	0.85 (0.75-0.95)[*]	0.0051	Stacey et al. [12]
rs2180341	6q22.33 / *ECHDC1*	G / A	0.28	0.29	1.07 (0.93-1.21)	0.34	Gold et al. [13]
rs2046210	6q25.1 / unknown	A / G	0.41	0.44	0.94 (0.82-1.07)[*]	0.048	Zheng et al. [15]
rs11249433	1p11.2 / unknown	G / A	0.46	0.46	1.00 (0.89-1.12)	0.97	Thomas et al. [16]
rs4973768	3p24 / unknown	T / C	0.45	0.42	0.89 (0.79-1.01)	0.066	Ahmed et al. [17]
rs6504950	17q23 / *COX11*	A / G	0.26	0.25	0.94 (0.82-1.07)	0.33	Ahmed et al. [17]

[+] Tested allele / reference allele

[*] GWAS-described risk effect is for the major allele