

Candidate Genetic Modifiers for Breast and Ovarian Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

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Abstract

Background: *BRCA1* and *BRCA2* mutation carriers are at substantially increased risk for developing breast and ovarian cancer. The incomplete penetrance coupled with the variable age at diagnosis in carriers of the same mutation suggests the existence of genetic and nongenetic modifying factors. In this study, we evaluated the putative role of variants in many candidate modifier genes.

Methods: Genotyping data from 15,252 *BRCA1* and 8,211 *BRCA2* mutation carriers, for known variants ($n = 3,248$) located within or around 445 candidate genes, were available through the iCOGS custom-designed array. Breast and ovarian cancer association analysis was performed within a retrospective cohort approach.

Results: The observed *P* values of association ranged between 0.005 and 1.000. None of the variants was significantly associated with breast or ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers, after multiple testing adjustments.

Conclusion: There is little evidence that any of the evaluated candidate variants act as modifiers of breast and/or ovarian cancer risk in *BRCA1* or *BRCA2* mutation carriers.

Impact: Genome-wide association studies have been more successful at identifying genetic modifiers of *BRCA1/2* penetrance than candidate gene studies. *Cancer Epidemiol Biomarkers Prev*; 24(1); 308–16. ©2014 AACR.

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Introduction

Germline *BRCA1* or *BRCA2* mutations substantially increase the risk of developing breast and ovarian cancer over those of the general population (1). The penetrance is incomplete and combined with the observed variability in age at cancer diagnosis in carriers of identical mutations, suggests the existence of genetic and/or environmental modifying factors. Direct evidence for genetic modifiers of breast and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers has been provided

through genome-wide association studies (GWAS; ref. 2). In parallel, multiple variants in candidate genes that affect *BRCA1* or *BRCA2* protein expression, act along the same biologic pathways, or physically interact with *BRCA1* or *BRCA2* proteins have been evaluated as putative modifiers of *BRCA1/2* mutations (reviewed in ref. 3). However, only a handful of these factors were confirmed and independently validated as "true modifiers" (4). The aim of the present study was to assess the putative modifier effect of 3,248 sequence alterations in 445

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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Table 1. Description of the 17 projects included in the study

Project	Rationale for testing SNPs as risk modifiers for breast cancer and ovarian cancer in <i>BRCA</i> -mutation carriers	Number of SNPs included	Reference
1	Previous data suggested that irradiation response genes whose expression is associated with <i>BRCA1</i> and <i>BRCA2</i> mutation status are enriched for the presence of common genetic modifiers of breast cancer risk.	18	Walker LC et al. Evidence for SMAD3 as a modifier of breast cancer risk in <i>BRCA2</i> mutation carriers. <i>Breast Cancer Res</i> 2010;12:R102.
2	X chromosome SNPs shown to be associated with risk of breast cancer in the CGEMS breast cancer study were considered.	11	Hunter DJ et al. A genome-wide association study identifies alleles in <i>FGFR2</i> associated with risk of sporadic postmenopausal breast cancer. <i>Nat Genet</i> 2007;39:870-4.
3	Previous data suggested that the "del" allele of rs3834129 was associated with increased breast cancer risk in <i>BRCA1</i> -mutation carriers.	1	Catucci I et al. The <i>CASP8</i> rs3834129 polymorphism and breast cancer risk in <i>BRCA1</i> mutation carriers. <i>Breast Cancer Res Treat</i> 2011;125:855-60.
4	Search for risk modifiers of <i>BRCA1</i> 5382insC-mutation carriers was performed by a pooled GWAS in 124 women diagnosed with breast cancer (<45 years) and 119 unaffected controls (>50 years at last follow-up) from Poland. The highest-ranked SNPs from the pooled GWAS were selected.	137	None
5	The proposed SNPs are related to genes in regulatory T-cell (Treg) and myeloid-derived suppressor cell (MDSC) pathways. Both pathways play a role in cancer immunosuppression.	2,637	Schreiber RD et al. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. <i>Science</i> 2011;331:1565-70.
6	The proposed SNPs were associated with breast density. These SNPs were tested only as modifier of breast cancer risk.	72	Steude JS et al. Mammographic density and matrix metalloproteinases in breast tissue. <i>Cancer Microenviron</i> 2010;3:57-65. Guo YP et al. Growth factors and stromal matrix proteins associated with mammographic densities. <i>Cancer Epidemiol Biomarkers Prev</i> 2001;10:243-8. Verheus M et al. Common genetic variation in the <i>IGF-1</i> gene, serum <i>IGF-1</i> levels and breast density. <i>Breast Cancer Res Treat</i> 2008;112:109-22. Diorio C et al. Genetic polymorphisms involved in insulin-like growth factor (<i>IGF</i>) pathway in relation to mammographic breast density and <i>IGF</i> levels. <i>Cancer Epidemiol Biomarkers Prev</i> 2008;17:880-8. Diorio C et al. Vitamin D pathway polymorphisms in relation to mammographic breast density. <i>Cancer Epidemiol Biomarkers Prev</i> 2008;17:2505-8.
7	SNPs or (SNPs in) genes were considered according to following criteria: (i) affecting circadian rhythms; (ii) interacting with <i>CLOCK</i> ; (iii) involved in binding <i>IGF-1</i> to binding proteins; (iv) in progesterone receptor gene and previously found associated with BC and OvC risk; (v) related to disease treatment.	20	Hoffman AE et al. <i>CLOCK</i> in breast tumorigenesis: genetic, epigenetic, and transcriptional profiling analyses. <i>Cancer Res</i> 2010;70:1459-68. Kelemen LE et al. Genetic variation in stromal proteins decorin and lumican with breast cancer: investigations in two case-control studies. <i>Breast Cancer Res</i> 2008;10:R98. Patel AV et al. <i>IGF-1</i> , <i>IGFBP-1</i> , and <i>IGFBP-3</i> polymorphisms predict circulating <i>IGF</i> levels but not breast cancer risk: findings from the Breast and Prostate Cancer Cohort Consortium (BPC3). <i>PLoS One</i> . 2008;3:e2578.
8	All these SNPs are located in selenoprotein genes and are involved in selenium metabolism; selenium is known to be associated with cancer risk.	11	Ostergaard MZ et al. Interactions between genes involved in the antioxidant defence system and breast cancer risk. <i>Br J Cancer</i> 2006;95:525-31. Méplan C et al. Association between Polymorphisms in Glutathione Peroxidase and Selenoprotein P Genes, Glutathione Peroxidase Activity, HRT Use and Breast Cancer Risk <i>PLoS One</i> . 2013;8:e73316. Udler M et al. Common germline genetic variation in antioxidant defense genes and survival after diagnosis of breast cancer. <i>J Clin Oncol</i> 2007;25:3015-23. Sutherland A et al. Polymorphisms in the selenoprotein S and 15-kDa selenoprotein genes are associated with altered susceptibility to colorectal cancer. <i>Genes Nutr</i> 2010;5:215-23.
9	Previous data suggested that the rs1045485 SNP modified disease penetrance of breast and ovarian cancer in <i>BRCA1</i> mutation carriers.	1	Engel C et al. Association of the variants <i>CASP8</i> D302H and <i>CASP10</i> V410I with breast and ovarian cancer risk in <i>BRCA1</i> and <i>BRCA2</i> mutation carriers. <i>Cancer Epidemiol Biomarkers Prev</i> 2010;19:2859-68.
10	The proposed SNPs are located within the <i>PARP1</i> gene that plays a key role in the repair of DNA single-strand breaks.	3	Gonçalves A et al. Poly(ADP-ribose) polymerase-1 mRNA expression in human breast cancer: a meta-analysis. <i>Breast Cancer Res Treat</i> 2011;127:273-81.
11	SNPs were considered because of observations based on evidences of recent positive selection and presence in the same genomic region of genes, (i) coding for <i>BRCA1</i> interacting proteins; (ii) involved in cancer or breast cancer; (iii) involved in DNA damage response and interacting with <i>TP53</i> .	13	Voight BF et al. A map of recent positive selection in the human genome. <i>PLoS Biol</i> 2006; 4:e72. Lappalainen T et al. Genomic landscape of positive natural selection in Northern European populations. <i>Eur J Hum Genet</i> 2010;18:471-8.

(Continued on the following page)

Table 1. Description of the 17 projects included in the study (Cont'd)

Project	Rationale for testing SNPs as risk modifiers for breast cancer and ovarian cancer in BRCA-mutation carriers	Number of SNPs included	Reference
12	Steroid hormones such as estrogens play an important role in the etiology of breast cancer contributing to tumor growth by promoting cell proliferation. SNPs in candidate genes involved in sex steroid metabolism were considered. The SNPs were tested also as breast cancer risk modifiers considering estrogen receptor status of BRCA-mutation carriers (see Supplementary Table S3).	139	Labrie F et al. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. <i>Endocr Rev</i> 2003;24:152-82.
13	<i>RAD51C</i> is a breast cancer gene. SNPs located within, or in close proximity to <i>RAD51C</i> were selected.	17	Meindl A et al. Germline mutations in breast and ovarian cancer pedigrees establish <i>RAD51C</i> as a human cancer susceptibility gene. <i>Nat Genet</i> 2010;42:410-4.
14	The highest-ranked SNPs from a GWAS based on 700 hereditary breast cancer cases and 1,200 controls were selected.	142	None
15	SNP rs2981582 in <i>FGFR2</i> is strongly associated with risk of breast cancer and acting as a risk modifier in <i>BRCA2</i> mutation carriers. Rs2981582 may also influence the risk of ovarian cancer among <i>BRCA1/2</i> -mutation carriers. This SNP was tested only as modifier of ovarian cancer risk.	1	Easton DF et al. Genome-wide association study identifies novel breast cancer susceptibility loci. <i>Nature</i> 2007;447(7148):1087-93. Hunter DJ et al. A genome-wide association study identifies alleles in <i>FGFR2</i> associated with risk of sporadic postmenopausal breast cancer. <i>Nat Genet</i> 2007;39: 870-4. Antoniou AC et al. Common breast cancer predisposition alleles are associated with breast cancer risk in <i>BRCA1</i> and <i>BRCA2</i> mutation carriers. <i>Am J Hum Genet</i> 2008;82:937-48.
16	The rs10895068 SNP in the promoter of the progesterone receptor (<i>PR</i>) gene (+331G/A) has been reported to be associated with endometrial cancer risk. Our previous study in 220 patients from BC and OC families showed a marginal association of the +331A allele with OC risk. This SNP was tested only as modifier of ovarian cancer risk.	1	Vivo ID et al. A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. <i>Proc Natl Acad Sci U S A</i> 2002;99:12263-68. Romano A et al. Impact of two functional progesterone receptor polymorphisms (<i>PRP</i>): +331G/A and <i>PROGINS</i> on the cancer risks in familial breast/ovarian cancer. <i>Open Cancer J</i> 2007;1:1-8.
17	The proposed SNPs were selected according to the hypothesis that different levels of expression of the remaining normal allele in <i>BRCA2</i> mutation carriers may be associated with variable penetrance of <i>BRCA2</i> mutations.	24	Maia AT et al. Effects of <i>BRCA2</i> cis-regulation in normal breast and cancer risk amongst <i>BRCA2</i> mutation carriers. <i>Breast Cancer Res</i> 2012;14:R63.

candidate genes on breast/ovarian cancer risk in 23,463 *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Recruitment and data collection

All study participants were women, >18 years old, carrying a deleterious germline mutation in either *BRCA1* or *BRCA2*. DNA samples and phenotypic data were submitted by 54 study centers participating in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA; ref. 5). Recruitment strategies, clinical, demographic, and phenotypic data collected from each participant, and quality control procedures, have previously been reported (4, 5). All study participants took part in research studies at the parent institutions under ethically approved protocols as detailed (4, 5).

Sequence variants genotyped

DNA samples were genotyped using the custom Illumina iCOGS array which included 211,155 SNPs as previously described (<http://www.nature.com/icogs/primer/cogs-project-and-design-of-the-icogs-array/>; ref. 6). We report results from 3,248 SNPs from 445 candidate genes proposed by 17 PIs (= projects). The rationale for selecting the SNPs or genes as candidate cancer risk modifiers in *BRCA1* and *BRCA2* mutation carriers is shown in Table 1. The list of SNPs included in the study and their gene location (if any) are provided in Supplementary Table S1. Genotyping quality control procedures were carried out as reported elsewhere (6).

Statistical analysis

Associations were evaluated within a retrospective cohort framework, by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes (4, 7). The associations between genotype and breast or ovarian cancer risk were assessed using the 1 d.f. score test statistic based on this retrospective likelihood while accounting for the non-independence among related individuals (8). All analyses were stratified by country of residence and used calendar-year and cohort-specific breast and ovarian cancer incidence rates for *BRCA1* and *BRCA2* mutation carriers. Details are provided elsewhere (2).

Results

A total of 23,463 mutation carriers were included (15,252 *BRCA1*, 8,211 *BRCA2* carriers), 12,127 with breast cancer (7,797 *BRCA1*, 4,330 *BRCA2* carriers), 3,093 with ovarian cancer (2,462 *BRCA1*, 631 *BRCA2* carriers), and 9,220 cancer-free carriers (5,788 *BRCA1*, 3,432 *BRCA2* carriers). All 3,248 SNPs were tested as genetic risk modifiers for both breast and ovarian cancer in *BRCA1* and *BRCA2* mutation carriers depending on the selection rationale (Table 1). For each SNP, the number of individuals with genotype data, minor allele frequencies, values of the χ^2 score test statistic, approximate HR estimates based on the score test statistic (7), overall *P* values, and retrospective likelihood HR are shown in Supplementary Table S2. Because project 12 was based on the hypothesis that estrogens contribute to breast cancer pathogenesis, these 139 SNPs were stratified by somatic estrogen receptor

Table 2. Observed and expected number of SNPs with *P* values <0.05 and <0.01

Category	Tumor	Number of SNPs tested ^a	Number of SNPs with <i>P</i> < 0.01 (expected)	Number of SNPs with <i>P</i> < 0.05 (expected)
<i>BRCA1</i>	BrCa	3,232	25 (32)	202 (162)
<i>BRCA1</i>	OvCa	3,160	13 (32)	146 (158)
<i>BRCA2</i>	BrCa	3,230	5 (32)	96 (161)
<i>BRCA2</i>	OvCa	3,157	6 (32)	131 (159)

^aNot all the 3,248 SNPs were tested in each category/tumor group.

status (Supplementary Table S3). None of the SNPs tested showed significant evidence of association with breast and/or ovarian cancer risk, as a single tested variant or after adjusting for multiple testing. Indeed, there were fewer associations at a nominal *P* < 0.05 or *P* < 0.01 than would be expected by chance (Table 2).

Discussion

In this study, there were no discernible effects for the genotyped SNPs on either breast or ovarian cancer risk in *BRCA1* or *BRCA2* mutation carriers. Despite the lack of evidence of association between these specific variants and breast/ovarian cancer risk for *BRCA1/BRCA2* mutation carriers, these genes may still modify cancer risk by other sequence alterations that are not represented on the iCOGS platform, by epigenetic alterations in gene expression, or in combination and interaction with other polymorphisms, that in concert have an overall effect on cancer risk.

In conclusion, the genotyped SNPs in the candidate modifier genes evaluated here have no major role in breast or ovarian cancer risk modification in either *BRCA1* or *BRCA2* mutation carriers. Our results suggest that a candidate gene approach where the selected SNPs have little a priori biologic plausibility is of limited value in identifying modifier genes, unlike agnostic genome-wide associations which have been more successful (8). Applying more advanced technologies (whole-exome/genome sequencing) and targeting phenotypically distinct mutation carriers may also offer further insights into modifier genes' identity.

Disclosure of Potential Conflicts of Interest

R.A. Eeles reports receiving commercial research grant from Janssen - Medical Education support to GU-ASCO meeting Feb. 2013 and has received speakers' bureau honoraria from Succinct Communications. R.L. Nussbaum has ownership interest (including patents) in Personalis and is consultant/advisory board member for Complete Genomics, Personalis, Invitae, and McDermott Will & Emery LLP. D.E. Goldgar has royalties from the University of Utah on *BRCA1* and *BRCA2* patents. P. Radice has received speakers' bureau honoraria from Regione Lombardia and is a consultant/advisory board member for Comitato Etico Cremona, Mantova e Lodi. J.E. Garber is a consultant/advisory board member for Pfizer and Novartis. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Epidemiological Study of BRCA1 and BRCA2 Mutation Carriers

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Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers

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BLOOD CANCER DISCOVERY

Candidate Genetic Modifiers for Breast and Ovarian Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

Paolo Peterlongo, Jenny Chang-Claude, Kirsten B. Moysich, et al.

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