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Genetic Variants Associated with Breast Cancer Risk: Comprehensive Field Synopsis, Meta-Analysis, and Epidemiologic Evidence

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SUMMARY

Background—Over 1,000 reports have been published during the past two decades on associations between genetic variants in candidate genes and breast cancer risk. Results have been generally inconsistent. We conducted literature searches and meta-analyses to provide a field synopsis of the current understanding of the genetic architecture of breast cancer risk.

Methods—Systematic literature searches for candidate gene association studies of breast cancer risk were conducted in two stages using PubMed on or before February 28, 2010. A total of 24,500 publications were identified, of which, 1,059 were deemed eligible for inclusion. Meta-analyses were conducted for 279 genetic variants in 128 candidate genes or chromosomal loci that had a minimum of three data sources available. Variants with significant associations by meta-analysis were assessed using the Venice criteria and scored as having strong, moderate, or weak cumulative evidence for an association with breast cancer risk.

Findings—Fifty-one variants in 40 genes showed statistically significant associations with breast cancer risk. Cumulative epidemiologic evidence for an association with breast cancer risk was graded as strong for 10 variants in six genes (*ATM*, *CASP8*, *CHEK2*, *CTLA4*, *NBN*, and *TP53*), moderate for four variants in four genes (*ATM*, *CYP19A1*, *TERT*, and *XRCC3*), and weak for 37 additional variants. Additionally, in meta-analyses that included a minimum of 10,000 cases and 10,000 controls, convincing evidence of no association with breast cancer risk was identified for 45 variants in 37 genes.

Interpretation—While most genetic variants evaluated in previous candidate gene studies showed no association with breast cancer risk in meta-analyses, 14 variants in 9 genes were found to have moderate to strong evidence for an association with breast cancer risk. Further evaluation of these variants is warranted.

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AUTHOR CONTRIBUTIONS

BZ conducted literature searches, data extraction, and analyses. ABF assessed data quality. BZ and ABF drafted the manuscript with substantial contributions from WZ. WZ reviewed results and provided guidelines for presentation and interpretation. All authors contributed to the revision of the manuscript.

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INTRODUCTION

Breast cancer is a multifactorial disease caused by complex inherited and environmental factors (1). To date, genetic studies have identified and confirmed four rare high-penetrance genes (*BRCA1*, *BRCA2*, *TP53* and *PTEN*), four rare moderate-penetrance genes (*CHEK2*, *ATM*, *BRIP1* and *PALB2*), and approximately 20 common low-penetrance variants in 19 genes or loci that contribute to a woman's risk of breast cancer (Table 1) (2–12). Virtually all of the common genetic risk variants were identified from recent genome-wide association studies (GWAS). While this list represents the culmination of our current understanding of the genetic architecture of breast cancer, together, these genes and loci are estimated to account for only 28% of the inherited causes of the disease (11).

Despite the prominence and growing body of results from GWAS, candidate-gene association studies remain the most prevalent type of investigation to identify common breast cancer susceptibility alleles. More than 1,000 candidate-gene breast cancer association studies have been published in the last two decades, which have evaluated more than 7,000 genetic variants (webappendix, page 1). While some of these variants may represent true associations with breast cancer risk, many more are false-positive associations which fail to replicate among additional study populations. Determining if associations are real has generally been conducted by examining the totality of the epidemiologic evidence in conjunction with biological plausibility, in the form of a meta-analysis. While most previous meta-analyses focus on one variant, or variants within one gene, recent meta-analyses have begun to increase in size and scope (13, 14). Additionally, guidelines for the assessment of cumulative evidence for genetic associations, which have become known as the Venice criteria, have been set forth by the Human Genome Epidemiology Network Working Group (15, 16).

Given the plethora of candidate-gene association studies, the necessity for replication across studies to identify markers truly associated with disease risk (17–19), and the criteria provided to evaluate genetic associations with disease, this study was undertaken in an attempt to evaluate all candidate-gene association studies in the field of breast cancer, conduct meta-analyses for variants with sufficient data available, and provide a field synopsis on our current understanding of the genetic architecture of breast cancer risk.

METHODS

All methodology was drawn from guidelines proposed by the Human Genome Epidemiology Network for the systematic review of genetic association studies (15, 16, 20, 21).

Study Eligibility, Criteria and Literature Searches

Studies were eligible to be included if they met the following criteria. First, publications must have been either online or in peer-review journals, in the English language, on or before February 28, 2010. Second, the study design must be a case-control, cohort, or cross-sectional association study conducted on humans. Third, breast cancer cases must have been diagnosed by pathological and/or histological examination. Fourth, the study must have provided sufficient information such that the genotype frequencies for both breast cancer cases and controls could be determined. High penetrance germline mutations in known breast cancer susceptibility genes, such as *BRCA1*, *BRCA2*, *PTEN*, and *TP53* were not included in this meta-analysis. Because GWAS-identified variants have been convincingly replicated by multiple studies, they also were not included in this meta-analysis.

To identify all relevant publications, we employed a two-stage search strategy (Figure 1). First, PubMed was queried with the terms ‘breast cancer AND association’ to find all studies published prior to August 31, 2009 that included associations with breast cancer. This search yielded 11,699 publications, which were screened by title and abstract, or a full text review if necessary, to identify 799 publications that met our eligibility criteria; these publications included variants within 404 candidate genes or chromosomal loci. Second, targeted monthly searches of PubMed between September 01, 2009 and February 28, 2010 were conducted using the 404 candidate genes or chromosomal loci, for example ‘SHBG’ or ‘rs6259’ in conjunction with ‘breast cancer’ as query terms. General monthly searches between September 01, 2009 and February 28, 2010 were also conducted using the term ‘breast cancer’. Finally, the references of all included studies were screened, as well as reference lists from review and meta-analyses; the PubMed option ‘Related Articles’ was also used to search for additional potential publications. These three components of our second stage search strategy identified a total of 12,831 publications, of which 260 met our eligibility criteria; these included variants within 117 additional candidate genes or chromosomal loci. Thus, a total of 24,500 publications were screened by title, abstract, or full text if necessary, to identify a total of 1,059 eligible publications including 521 candidate genes or chromosomal regions and 2,787 genetic variants.

Data Extraction and Preparation

Data were extracted by the first author (BZ) and checked by the second author (ABF). In the case of sequential or multiple publications of the same or overlapping data, only the publication that reported results from the largest or most recent analysis was included. Publications with completely redundant information were not included (N=57). If a publication included multiple source or study populations, data was extracted separately if possible. Data extracted from each eligible publication included first author, year published, PMID number, study design, method of case selection, matching factors if applicable, source population, ethnicity of participants, inclusion criteria of cases and controls, mean ages of cases and controls, sample size, genes, variants, major and minor alleles, genotype counts for cases and controls, Hardy-Weinberg Equilibrium (HWE) among controls, genotyping methods used, whether these methods had been validated, and whether genotyping was conducted in a blinded manner. Specifically, case selection was classified as population-based, hospital-based, or mixed. Ethnicity was classified as either African, Asian (East Asian descent), Caucasian (European descent), or other (including mixed) based on the ethnicity of at least 80% of the study population (22). If ethnicity was not reported, we considered the ethnicity of the source population based on the country in which the study was conducted (22). The most current gene names (<http://preview.ncbi.nlm.nih.gov/gene/>) and variant accession numbers (<http://www.ncbi.nlm.nih.gov/snp/>) were used according to respective NCBI databases (23). For variants without accession numbers, the most commonly used name, such as nucleotide position (i.e. 7271T>G) or protein residue (i.e. Val2424Gly) was used. Minor and major alleles of variants among populations of specific ethnicities were determined according to dbSNP (<http://www.ncbi.nlm.nih.gov/snp/>). Genetic variants from publications were checked for inversion of major and minor alleles; if the reported MAF was different from that in dbSNP by 20% or greater, the authors were contacted (N=7). Additionally, if reported alleles differed from those in dbSNP, authors were contacted (N=10). Responses were received and issues were resolved for six and seven publications, respectively, so these studies were included. Further, authors were contacted for 26 publications that were initially ineligible due to insufficient information for data extraction; responses were received for five queries, so these publications were included. Information on genes and variants from the 21 publications without sufficient information to be included in our meta-analyses is available in the webappendix (pages 6–16). Thus, 1,059 eligible publications had sufficient data available for extraction and meta-analysis inclusion.

Statistical Analysis

All statistical tests in this study were two-tailed and P values ≤ 0.05 were considered statistically significant unless stated otherwise. Statistical analyses were conducted with Stata, version 11.0 (Stata Corporation, College Station, TX). For meta-analysis of any variant, a minimum of three data sources was required; this decision was made to stabilize the heterogeneity test statistic (I^2), and to ensure that sensitivity analyses could be conducted. Eligible publications included a total of 2,787 genetic variants, of which 279 had at least three data sources for meta-analysis. For common variants ($MAF \geq 5\%$), effects associated with minor alleles were evaluated. Because major and minor alleles can be reversed in populations of different ethnicities, averaged MAFs across studies may be greater than 50%; when this occurred, the minor allele among Caucasians was used as the minor allele in all analyses. For copy number variations (CNVs), mitochondrial (mtDNA) polymorphisms, and phenotype traits, the less prevalent variant or trait was evaluated for associated effects unless otherwise stated. Hardy-Weinberg equilibrium (HWE) among controls of each study was assessed by Fisher's exact test to compare observed and expected genotype frequencies (24). Estimates of association with cancer risk were evaluated by odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using the random-effects method of DerSimonian and Laird (25). For common genetic variants, allelic, dominant, and recessive models were computed; for rare variants, CNVs, mtDNA polymorphisms, and phenotype traits, only the appropriate dominant or recessive model was employed unless stated otherwise. Analyses stratified by ethnicity were conducted whenever data permitted; a minimum of three data sources were required for these ethnicity specific meta-analyses. To minimize false negative errors, of variants that showed no evidence of associations with breast cancer risk in meta-analyses, only those with a minimum of 10,000 cases and 10,000 controls were selected for presentation.

Evaluation of our meta-analysis results included test of heterogeneity, sensitivity analyses, and examination for bias. Heterogeneity between studies was assessed by Cochran Q statistic and P value < 0.10 indicated statistically significant heterogeneity of studies within meta-analyses (26). We also used the I^2 metric to quantify the heterogeneity (27). Generally, the I^2 values less than 25% correspond to mild heterogeneity, and values between 25% and 50% correspond to moderate heterogeneity, whereas values greater than 50% correspond to large heterogeneity between studies. Sensitivity analyses were conducted to assess the robustness and examine the results of our meta-analyses for possible bias. For variants with significant findings, firstly, the first published or first positive report, defined as the earliest study to publish a significant association ($P \leq 0.05$), was excluded, then all small studies (< 500 cases) were excluded, and finally, for common variants, all studies in which controls were not in HWE ($P \leq 0.05$) were excluded. Potential publication bias was evaluated by symmetry of funnel plots of effect sizes versus standard errors; Begg's test was used to identify significant asymmetry (28). Bias due to results from small studies was evaluated by modified Egger tests which corrects for potential type I errors (29). An excess of significant findings was evaluated by the method of Ioannidis and Trikalinos (30) for each individual meta-analysis, as well as for groups of meta-analyses, defined by significance of association with breast cancer risk, degree of heterogeneity (large or not), or ethnicity (Caucasian, Asian, or other). P values < 0.10 were considered statistically significant in the modified Egger test and the test for excess of significant findings.

Assessment of Cumulative Evidence

We applied the Venice criteria to all significant associations identified by meta-analysis in our report to evaluate the epidemiologic credibility of each (15, 16). Credibility was defined as strong, moderate, or weak, based on grades of 'A', 'B', or 'C' in three categories: amount of evidence, replication of the association, and protection from bias (15, 16). Amount of

evidence was graded by the sum of test alleles or genotypes among both cases and controls in the meta-analysis; 'A' for over 1,000, 'B' for 100 to 1,000, and 'C' for less than 100. Caution was taken when applying this criterion to very rare variants ($MAF \leq 0.5\%$), as scores of 'A' are unobtainable. Replication was graded by the heterogeneity statistic; 'A' for $I^2 < 25\%$, 'B' for I^2 between 25% and 50%, and 'C' for $I^2 > 50\%$. Protection from bias was graded as 'A' if there was no observable bias and bias was unlikely to explain the presence of the association, 'B' if bias could be present or could explain the presence of the association, or 'C' if bias was evident or was likely to explain the presence of the association. Assessment of protection from bias also included consideration of the magnitude of the association; a score of 'C' was assigned to an association with a summary OR < 1.15 unless the association had been replicated prospectively by multiple studies with no evidence of publication bias. Thus, the cumulative epidemiologic evidence of statistically significant associations in meta-analyses were considered to be strong if all three grades were 'A', moderate if all three grades were either 'A' or 'B', or weak, if any grades were 'C'.

Role of the Funding Source

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RESULTS

Meta-Analyses of Associations with Breast Cancer Risk

A total of 1,059 publications including 521 genes or chromosomal loci and 2,787 variants were eligible to be included in our analysis (Figure 1). The majority (91%, $N=961$) of these reports were published since 2000, with the highest number published in 2008 ($N=154$) (webappendix, page 1). The average number of variants analyzed per publication was consistently less than five until 2005, and then dramatically increased, reaching a maximum of 15.6 in 2008. The median and mean sample size of cases included in the 1,059 publications was 461 and 1,037, respectively (range: 26–35,331). The median and mean sample size of controls was 503 and 1,261, respectively (range: 24–37,214). Meta-analyses were conducted for 279 genetic variants (235 common and 44 rare) in 128 candidate genes or chromosomal loci that had a minimum of three data sources available (webappendix, pages 2–5). The average pooled sample size of the 279 meta-analyses was 14,952 (range: 616–92,701); each meta-analysis included an average of 8.6 independent studies (range: 3–61). Common variants ($MAF \geq 5\%$) included synonymous SNPs ($N=14$), nonsynonymous SNPs ($N=95$), intronic or intragenic SNPs ($N=33$), SNPs in 5' or 3' UTRs ($N=68$), mitochondrial (mtDNA) polymorphisms ($N=9$), short tandem repeats (STR) or microsatellite polymorphisms ($N=10$), copy number variations (CNVs) ($N=2$), phenotypes ($N=3$), and one frameshift polymorphism. Rare variants ($MAF < 5\%$) included nonsynonymous SNPs or mutations ($N=27$), truncating or splice-junction mutations ($N=6$), intronic or intragenic SNPs ($N=3$), SNPs in 5' or 3' UTRs ($N=2$), mtDNA polymorphisms ($N=4$), and one STR and CNV each.

Using all available data, 29 variants within 20 genes (*ATM*, *CASP8*, *CHEK2*, *CTLA4*, *CYP19A1*, *ERCC2*, *ESR1*, *GSTM1*, *GSTT1*, *HSD17B1*, *IFNG*, *IGF1*, *LRTOMT*, *MTHFR*, *NBN*, *NUMA1*, *TP53*, *TYMS*, *VDR*, and *WRN*) were found to have statistically significant associations with breast cancer risk by meta-analysis (Table 2A). These meta-analyses included an average of 13.1 studies (range: 3–61) and 19,591 subjects (range: 721–92,701). Strong associations with breast cancer risk (ORs greater than two) were seen for two rare

truncating mutations (*ATM E1978X* and *NBN 657del5*), as well as for three rare variants in *CHEK2* (*IVS2+1G>A*, a CNV deletion (5.5kb), and *1100delC*). Moderate associations with breast cancer risk (ORs greater than 1.5) were seen for three common variants, including nonsynonymous polymorphisms in *CHEK2* (*rs17879961*) and *LRTOMT* (*rs673478*) and a short tandem repeat in *CYP19A1* ((TTTA)₁₀). All four *CHEK2* variants had associations with breast cancer risk at $P < 10^{-5}$, as did two common nonsynonymous SNPs (*CASP8 rs1045485* and *CTLA4 rs231775*) and one deletion polymorphism (*GSTM1*). Additional significant associations with breast cancer risk by meta-analysis were found for nine non-coding SNPs (*CASP8 rs6435074* and *rs6723097*, *ESR1 rs3020314*, *HSD17B1 rs676387*, *IFNG rs2430561*, *IGF1 rs6220*, *NUMA1 rs3018301*, *TP53 rs12947788* and *rs12951053*), five nonsynonymous SNPs (*ATM rs1800057*, *ERCC2 rs13181*, *MTHFR rs1801133*, *VDR rs731236*, and *WRN rs1346044*), one synonymous SNP (*ESR1 rs1801132*), one deletion (*GSTT1*), one insertion/deletion polymorphism (*TP53 rs17878362*), and one short tandem repeat (*TYMS*). Some meta-analyses included women of only one ethnicity, as all available data included only one ethnicity. Fourteen variants with significant associations with breast cancer risk were studied only among Caucasian women, one significantly associated variant had data available only among Asian women.

Seven additional variants were found to be significantly associated with breast cancer risk in meta-analyses stratified by ethnicity conducted with a minimum of three data sources (Table 2B). Among Caucasians, these analyses were conducted for 206 variants and included an average of 7.8 studies (range: 3–38) and 15,987 subjects (range: 1,194–81,172). Among Asians, these analyses were conducted for 49 variants and included an average of 5.0 studies (range: 3–14) and 5,688 subjects (range: 1,370–14,901). Three common nonsynonymous polymorphisms (*AURKA rs1047972*, *MTR rs1805087*, and *NQO1 rs1800566*) had evidence of associations with breast cancer risk among Caucasian women, but not among Asian women. Three common SNPs had associations with breast cancer risk among Asian women, including two nonsynonymous polymorphisms (*GSTP1 rs1695* and *XRCC3 rs861539*) and one intronic variant (*ESR1 rs2234693*); there was no evidence for associations with breast cancer risk among Caucasian women. One noncoding variant (*TNF rs1800629*) reached statistical significance for a protective effect only among Caucasian women, although the association did not seem to differ between Asian and Caucasian women. Instead, significance among all available data for this *TNF* variant seemed to be attenuated by including studies conducted among women of ethnicities other than Asian or European ancestries (data not shown).

All genetic models of association presented in Table 2 are from allelic contrasts, except where data did not permit, such as for rare variants. Among the 36 variants found to have a significant association with breast cancer risk, there was sufficient data to evaluate 26 under dominant and recessive models. Of these, the association with breast cancer risk was no longer statistically significant for 11 and 10 variants, respectively, when dominant and recessive effect models were employed. Although not significant in allelic contrasts, 15 additional common genetic variants were found to have significant associations with breast cancer risk using either dominant or recessive genetic effect models in meta-analyses (Table 3). Of these, the association with the largest magnitude was for a nonsynonymous SNP (*NCOA3 rs2230782*), while the most significant association was for a noncoding variant (*TERT rs2853669*). No additional significant associations were found in ethnicity-specific analyses using either dominant or recessive genetic models.

Table 4 presents evidence of no association between 45 genetic variants in 37 genes and breast cancer risk by meta-analysis. Variants were evaluated in at least three studies, with a minimum of 10,000 cases and 10,000 controls total, and provide solid evidence for a null association. While allelic associations are presented, no evidence of association with breast

cancer risk was seen for any of these variants in any model tested (allelic, dominant, and recessive).

Evaluation of Meta-Analyses

Of the 279 meta-analyses conducted with all available data (webappendix, pages 2–5), 50.2% (N=140) had little or no heterogeneity ($I^2 < 25\%$), 22.9% (N=64) had moderate heterogeneity ($25\% \leq I^2 \leq 50\%$), and 26.9% (N=75) had large heterogeneity ($I^2 > 50\%$). Notably, the rate of large study heterogeneity for the 29 variants presented in Table 2 was significantly lower than the remaining 250 variants (3% and 30%, respectively; Fisher's exact P value = 0.003). Of the 225 ethnicity specific meta-analyses, 49.3% (N=111) had little or no heterogeneity, 24.4% (N=55) had moderate heterogeneity, and 26.2% (N=59) had large heterogeneity. Of the 396 dominant and recessive model meta-analyses, 53.8% (N=213) had little or no heterogeneity, 21.5% (N=85) had moderate heterogeneity, and 24.7% (N=98) had large heterogeneity.

Sensitivity analyses were conducted for all 51 variants significantly associated with breast cancer risk, first by excluding the first published or first positive report, then by excluding small studies (<500 cases), and then for common variants, by excluding studies in which control genotype distributions were not in HWE. When the first published or first positive report was excluded, the association for 30 variants was no longer statistically significant. However, only six of these variants showed an OR alteration of more than 5% (allelic associations for *IFNG* rs2430561 and *LRTOMT* rs673478, a dominant association for *BARD1* rs1048108, and recessive associations for *IL10* rs1800896, *LEPR* rs1137101, and *NCOA3* rs2230782). When small studies were excluded, the significance of the associations with breast cancer risk was attenuated for 15 variants, but only five had a change of magnitude of more than 5% (allelic associations for *ERCC2* rs13181 and *TP53* rs17878362, and recessive associations for *LEPR* rs1137101, *NCOA3* rs2230782, and *XRCC1* rs25487). Sensitivity analyses excluding small studies could not be conducted for seven variants (*GNB3* rs5443, *IFNG* rs2430561, *IL10* rs1800896, *LRTOMT* rs673478, *MSH3* rs26279, *NQO1* rs1800566, and *NUMA1* rs3018301) because no studies in their meta-analyses included at least 500 cases. Nineteen meta-analyses with significant associations with breast cancer risk included data with control genotype frequencies that deviated from HWE. Exclusion of these data sources resulted in diminished statistical significance for three variants (*GSTP1* rs1695, *MTR* rs1805087 and *NUMA1* rs3018301 among Caucasians) but alteration of the magnitude of the association by more than 5% for only one of these variants (*NUMA1* rs3018301).

Evidence of publication bias was evaluated by funnel plots and Begg's tests; three variants showed evidence of possible publication bias (allelic association for *ERCC2* rs13181, *TNF* rs1800629 among Caucasians, and a recessive association for *XRCC1* rs25487). Modified Egger tests were used to evaluate possible bias due to small studies. Evidence of more conservative results from larger studies than smaller studies was found for five variants among analyses conducted among all available data (*CHEK2* CNV deletion and 1100delC, *ERCC2* rs13181, *GSTM1* deletion, and *LRTOMT* rs673478), two variants among Caucasians (*NQO1* rs1800566 and *TNF* rs1800629), and dominant and recessive associations for *BARD1* rs1048108 and *XRCC1* rs25487, respectively. Notably, for both *CHEK2* variants, removal of the small studies did not materially alter the results. Among all 279 meta-analyses conducted, evidence of excess studies with significant findings was detected for 42, of which only one was in the group of variants with nominally significant summary ORs for breast cancer risk (*MTHFR* rs1801133). When grouped by variants with or without nominally significant associations, evidence of excess studies with significant findings was seen only among those without nominally significant summary ORs ($P < 10^{-8}$). Alternately, evidence for excess studies with significant findings was found for all meta-analyses groups defined by either heterogeneity or ethnicity. Further, when evaluating all studies included in

our meta-analyses as a whole, the observed number of studies with significant findings greatly exceeded the number expected ($P < 10^{-8}$), suggesting the presence of biases in published candidate-gene association studies.

Cumulative Epidemiologic Evidence

Assessment of the cumulative epidemiologic evidence for significant meta-analysis associations was conducted (Table 2 and Table 3); evidence was scored as strong, moderate, or weak based on grades of 'A', 'B', or 'C' for the total amount of evidence, replication of the association, and protection against bias, as specified by the Venice criteria (15, 16). Of the 51 variants with significant associations with breast cancer risk with P values ≤ 0.05 , grades of 'A' were given to 32, 43, and 14 variants for the amount of evidence, replication of the association, and protection from bias, respectively. Grades of 'B' were given to 13, four, and zero variants for these three respective criteria. Grades of 'C' were given to 37 variants for protection from bias, mainly due to the loss of significance that occurred after excluding the first study ($N=30$) and/or a small effect with breast cancer risk ($OR < 1.15$, $N=26$). Additional reasons for grades of 'C' for protection from bias were given for variants with meta-analyses that showed smaller studies having larger effects than larger studies ($N=7$), a loss of significance when studies with cases not in HWE were excluded ($N=3$), significant Begg's test indicating publication bias ($N=3$), and an excess of significant findings ($N=1$); these reasons were not exclusive. Only one and four variants were given grades of 'C' for amount of evidence and replication of the association, respectively. Ten variants received 'A' grades for all three criteria and can therefore be regarded to have strong cumulative epidemiologic evidence of an association with breast cancer risk, including *ATM* 5932G>T, *CASP8* rs1045485 and rs6723097, *CHEK2* IVS2+1G>A, rs17879961, 5.5 kb deletion, and 1100delC, *CTLA4* rs231775, *NBN* 657del5, and *TP53* rs17878362. Four variants received either an 'A' or 'B' grade in all three criteria, and were thus scored as having moderate evidence of an association, including *ATM* rs1800057, a short tandem repeat in *CYP19A1*, a recessive effect for *TERT* rs2853669, and an allelic association among Asian women for *XRCC3* rs861539. The remaining variants evaluated in our study received a 'C' grade in one or more criteria, and so despite an overall significant association with breast cancer risk by meta-analysis, were scored as having weak cumulative evidence of an association based on the Venice criteria. As proposed by the Human Genome Epidemiology Network (16), a few exceptions in scoring of the Venice criteria were made. One variant (*CASP8* rs1045485) was not penalized for its small summary effect ($OR < 1.15$), as it showed a very consistent association across studies that were specifically designed to evaluate it. Additionally, five variants (*ATM* 5932G>T, *CHEK2* IVS2+1G>A, 5.5 kb deletion, and 1100delC, and *NBN* 657del5) were not scored for the amount of evidence due to their very low frequency in the population ($< 0.5\%$).

DISCUSSION

This work represents the largest and most comprehensive assessment of the literature on the genetic architecture of breast cancer susceptibility conducted to date. Using methodology based on the guidelines for systematic reviews of genetic association studies proposed by the Human Genome Epidemiology Network (15, 16, 20, 21), we conducted a comprehensive field synopsis and meta-analysis of genetic variants and breast cancer risk. Statistically significant associations with breast cancer risk were found for 51 variants, including 17 that showed moderate to strong cumulative epidemiologic evidence for a true association. Additionally, meta-analyses with very large sample sizes (20,000 participants minimum), provided convincing evidence of no association with breast cancer risk for 45 variants in 37 genes.

Strong cumulative evidence for associations with breast cancer was found for six rare variants; four of which are in the tumor suppressor checkpoint kinase 2 (*CHEK2*) which initiates DNA repair after double-strand breakage (31–33). The four *CHEK2* variants with strong evidence include the *1100delC* truncating mutation at codon 381 in exon 10, a nonsynonymous polymorphism in exon 3 (*I157T*, *rs17879961*), a truncating mutation in exon 3 (*IVS2+1G>A*), and a 5.5 kb deletion that includes exons 9 and 10. Due to protein truncations, *1100delC*, *IVS2+1G>A*, and the 5.5 kb deletion have kinase deficient molecules, while the minor allele of SNP *I157T* results in a *CHEK2* protein with normal kinase activity but binding and phosphorylating downstream substrates is deficient (31–35). The increased risks of breast cancer associated with these variants ranged from 1.52 (1.31–1.77) for *I157T* (*rs17879961*), to 3.10 (2.59–3.71) for *1100delC*; the association with breast cancer for this variant is well established. Notably, the *CHEK2* 5.5 kb deletion is the first low-penetrance large deletion variation to be confirmed to have a highly significant association with breast cancer risk specific in Caucasian women from Eastern European (36–38).

Our meta-analyses revealed two additional rare variants with strong evidence of association with breast cancer risk. A rare truncating variant (*E1978X*) in the ataxia-telangiectasia mutated (*ATM*) gene was associated with a very large increase in breast cancer risk by a meta-analysis of four studies (OR: 4.56, 95% CI: 1.35–15.42) among Caucasian women. The *ATM* gene encodes a protein kinase involved in the monitoring and double-strand DNA repair (39, 40). A rare five base pair deletion in exon 6 (*657del5*) of the *NBN* gene (previously known as *NBS1*) showed a significant association with breast cancer risk (OR 2.42, 95% CI: 1.54–3.80) based on seven published studies among Caucasians. The *NBN* gene encodes nibrin, a member of the MRE11/RAD50 double-strand break repair complex involved in cell-cycle checkpoint regulation (41); the rare deletion results in a truncated protein without full functionality.

Two of the four common SNPs that showed strong cumulative evidence for associations with breast cancer risk were located in the *CASP8* gene (also known as *FLICE* and *MCH5*, 2q33-q34), which is a member of the cysteine-aspartic acid protease family, and has an important role in apoptosis (42). A nonsynonymous SNP, *D302H* (*rs1045485*) in exon 9, was first reported to be associated with breast cancer risk by a large-scale candidate-gene association consortium analysis (43). Our meta-analysis of 17 data sources indicates a significant protective effect associated with the minor allele of this polymorphism (OR: 0.89, 95% CI: 0.85–0.93). This locus is not polymorphic among Asians, so this association is limited to Caucasians (43). Our meta-analysis also revealed strong evidence of an association with breast cancer risk for a second variant in the *CASP8* gene, an intronic SNP, *rs6723097*, that is located approximately 21 kb away from *D302H*. These two SNPs are in very weak linkage disequilibrium ($r^2=0.153$ among Caucasians based on HapMap LD release 27) (23), and thus these two variants may be independently associated with breast cancer risk. Notably, *rs6723097* is in high LD with *rs6435074*, another *CASP8* variant which was found to have weak cumulative evidence for an association with breast cancer risk.

Two additional common variants showing strong cumulative evidence for associations with breast cancer in meta-analyses were located in the *CTLA4* (also known as *CD152*) and *TP53* genes. The *CTLA4* variant, an exon 1 nonsynonymous SNP (*rs231775*) was associated with a moderate increase in breast cancer risk (OR: 1.25, 95% CI: 1.14–1.37) by meta-analysis of three studies conducted among Asian women. The variant results in a threonine to alanine substitution in the leader sequence of cytotoxic T-lymphocyte-associated protein 4, which transmits an inhibitory signal to T-cells and is thought to influence carcinogenesis via antitumor immunity (44). The SNP is proposed to enhance the inhibitory effect of CTLA4

on T-cell activation (45–47). Notably, this variant has also been associated with other cancer sites, including esophageal and lung cancer among Asians (45). No studies evaluating breast cancer risk and this SNP have been conducted among Caucasians. Finally, while rare germline mutations in the tumor suppressor *TP53* have been identified as high-penetrance breast cancer susceptibility alleles (48), in the current analyses, a common 16-bp insertion/deletion variant (*rs17878362*) in intron 3 was found to have strong evidence of a small effect on breast cancer risk. Women with the deletion were more likely to be breast cancer cases (OR: 1.15, 95% CI: 1.04–1.26) based on our meta-analysis of 12 studies. This association is supported by functional evidence that reduced levels of *TP53* mRNA were also associated with the deletion (49), and p53 is essential for initiating apoptosis or senescence in response to DNA damage (50).

Ethnicity-specific associations identified by meta-analysis included both variants that only had data available among women of one ethnicity, and variants with significant associations only in ethnicity stratified analyses. More significant associations with candidate genes were identified among European women than other ethnicities, primarily because the vast majority of studies have been conducted among Europeans. Ethnicity-specific disease associations may arise from differences in genetic LD structure across populations or due to other unknown environmental or genetic contributors. Additional evaluation of these variants among women of different ethnic populations is warranted. In addition to the 10 variants that had strong cumulative evidence of an association with breast cancer risk, four had moderate evidence, including rare variants in the *ATM* and *CYP19A1* genes among all women, a common polymorphism with a recessive effect in the *TERT* gene, and a common nonsynonymous SNP in the *XRCC3* gene among Asian women. Additional investigation of these seven variants is also warranted.

Although identifying variants significantly associated with breast cancer risk is interesting, an equally important goal of meta-analysis is to reveal genetic variants that show no evidence of an association to a high degree of certainty. Forty-five variants in 37 genes were not associated with breast cancer risk in meta-analyses of 20,000 subjects minimum. These meta-analyses had greater than 93 and 97% power to detect additive associations of 1.10 for variants with MAFs of 15% or 20%, respectively. Therefore, continued evaluation of the main effects of these variants in epidemiologic studies with a similar sample size is unlikely to be fruitful.

Limitations of this field synopsis must be addressed. Although an exhaustive search of the literature was performed, it is likely that some publications were overlooked. Reports in languages other than English were not included, and publications without resolvable genotype counts could not be incorporated. However, these should comprise a minority of the total work investigating breast cancer associated variants, and including these studies should not alter the overall results of this large-scale meta-analysis. Analyses were not conducted for all variants ever evaluated in relation to breast cancer, but rather only for those with a minimum of three data sources. Genotype counts and crude estimates of effect were used in these meta-analyses, rather than adjusted estimates of the association. Further, we did not evaluate gene-gene or gene-environment interactions. While these analyses may be interesting and informative, finding concordance in definitions of exposure variables and uses of covariates across studies is challenging, and thus these interaction analyses were beyond the scope of the current report; additional investigation in these areas is needed. Heterogeneity was commonly observed in the 279 meta-analyses conducted. Although we could remove some variability by conducting ethnicity specific analyses, other sources of heterogeneity were not examined, such as tumor types or estrogen receptor status. Most publications do not report associations by subtypes of breast cancer; future research that evaluates associations by breast tumor type is needed. Multiple comparisons may be another

potential concern. Including different genetic effect models and ethnicity-specific analyses, a total of 982 meta-analyses were performed; a Bonferroni corrected P value threshold for significance would be 5×10^{-5} . Five variants with strong epidemiologic evidence have p -values that surpass this threshold. However, this P value is overly conservative, as many of the tests conducted were not independent. Further, we sought to summarize and evaluate existing associations, rather than to identify new associations. Using a P value significance threshold of 0.05 reduced the possibility of type II errors. Most importantly, variants with significant associations with breast cancer were graded as having strong, moderate, or weak cumulative evidence based on the Venice criteria (15,16), so the interpretation of a result should not be determined by its P value alone. In line with this, eight of the 10 variants with strong epidemiologic evidence had P values $\leq 10^{-4}$. Finally, we found that the Venice criteria (15, 16) were more suitable for common variants than rare variants. To earn an “A” grade for amount of evidence, a variant with a MAF of 0.5% would require at least 100,000 subjects; no meta-analyses conducted to date were that large. Therefore, we propose amendments for the Venice criteria to include a minimum of three homogeneous sources, a more stringent P value, the incorporation of biological evidence, and consideration of the minor allele frequency.

Both new large studies and meta-analyses of existing studies are needed to identify disease associated genetic variants. The consistency of the association, a major criterion for evaluating causality in epidemiologic studies can not be readily assessed in a single study, particularly the one conducted in a single population. There are some differences in genetic architectures across ethnic groups, and thus some variants may be associated with disease risk in one population but not in others. Further, a variant may show heterogeneity of effect by ethnicity due to gene-gene and gene-environment interactions, and so conducting research among different populations is needed to uncover these differences. On the other hand, meta-analyses may suffer from publication bias and further, these analyses could be limited by data available from published studies that are conducted using different protocols. Nevertheless, meta-analyses are an important tool to evaluate the consistency of study findings, assess cumulative evidence from previous studies, and provide clues and guidelines for future studies.

It has been 20 years since the mapping of the breast-ovarian cancer susceptibility gene *BRCA1* to chromosome 17 (51). Recent GWAS have provided strong evidence for 19 common loci as breast cancer susceptibility variants (2–12). These common loci, along with germline mutations in *BRCA1* and other known breast cancer susceptibility genes, explain only 28% of the heritability of the disease (11). Most GWAS have been conducted among women of European ancestries; future studies in other populations are likely to identify additional variants. Increased coverage of genetic variation in new SNP arrays used in GWAS are also likely to identify additional breast cancer susceptibility variants. Although GWAS is a powerful tool to uncover common genetic variants for breast cancer and other complex diseases, candidate gene studies remain useful to test *a priori* hypotheses and confirm associations with breast cancer risk for genetic variants selected based on strong biological evidence. In this large-scale, comprehensive meta-analysis, we identified 14 genetic variants that showed strong or moderate evidence of associations with breast cancer risk; further investigation of these variants is warranted. Notably, all ten variants with strong cumulative epidemiologic evidence retained significance for an association with breast cancer risk regardless of genetic model employed, and eight of ten have functional data in the literature supporting a role in breast cancer susceptibility. In addition, we identified 45 variants in 37 genes that convincingly showed no evidence of association with breast cancer risk. Our meta-analyses summarize the current state of the literature of breast cancer susceptibility genetic architecture, and provide useful data for designing future studies to evaluate genetic factors for breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 1

Summary of Established Genetic Factors Associated with Breast Cancer Risk

A: High- and moderate-penetrance breast cancer susceptibility genes			
Gene	Variants	Relative Risk	Population Frequency (%)
<i>BRCA1</i>	Multiple mutations	>10	0.1
<i>BRCA2</i>	Multiple mutations	>10	0.1
<i>TP53</i>	Multiple mutations	>10	<0.1
<i>PTEN</i>	Multiple mutations	>10	<0.1
<i>ATM</i>	Truncating and missense mutations	2–4	<0.5
<i>CHEK2</i>	1100delC	2–5	0.7
<i>BRIP1</i>	Truncating mutations	2–3	0.1
<i>PALB2</i>	Truncating mutations	2–5	<0.1

B: Low-penetrance loci associated with breast cancer risk identified by genome-wide association studies			
Locus	Variant	OR (95% CI) ¹	MAF (%) ²
<i>1p11/NOTCH2/FCGR1B</i>	<i>rs11249433</i>	1.14 (1.10–1.19)	39
<i>2q35</i>	<i>rs13387042</i>	1.20 (1.14–1.26)	50
<i>3p24/SLC4A7/NEK10</i>	<i>rs4973768</i>	1.11 (1.08–1.13)	46
<i>5p12/MRPS30</i>	<i>rs4415084</i>	1.16 (1.10–1.21)	40
	<i>rs10941679</i>	1.19 (1.13–1.26)	24
<i>5q11/MAP3K1</i>	<i>rs889312</i>	1.13 (1.10–1.16)	28
<i>6q22/ECHDC1/RNF146</i>	<i>rs2180341</i>	1.41 (1.25–1.59)	21
<i>6q25/ESR1/C6orf97</i>	<i>rs2046210</i>	1.29 (1.21–1.37)	35
<i>8q24</i>	<i>rs13281615</i>	1.08 (1.05–1.11)	40
<i>9p21/CDKN2A/2B</i>	<i>rs1011970</i>	1.09 (1.04–1.14)	17
<i>10p15/ANKRD16/FBXO18</i>	<i>rs2380205</i>	0.94 (0.91–0.98)	43
<i>10q21/ZNF365</i>	<i>rs10995190</i>	0.86 (0.82–0.91)	15
<i>10q22/ZMIZ1</i>	<i>rs704010</i>	1.07 (1.03–1.11)	39
<i>10q26/FGFR2</i>	<i>rs2981582</i>	1.26 (1.23–1.30)	38
	<i>rs1219648</i>	1.27 (1.18–1.36)	40
<i>11p15/LSP1</i>	<i>rs3817198</i>	1.07 (1.04–1.11)	30
<i>11q13</i>	<i>rs614367</i>	1.15 (1.10–1.20)	15
<i>14q24/RAD51L1</i>	<i>rs999737</i>	0.89 (0.85–0.93)	24
<i>16q12/TOX3/LOC643714</i>	<i>rs3803662</i>	1.28 (1.21–1.35)	27
	<i>rs4784227</i>	1.25 (1.20–1.31)	24
<i>17q22/COX11</i>	<i>rs6504950</i>	0.95 (0.92–0.97)	27
<i>19p13/ABHD8/ANKLE1/C19orf62</i>	<i>rs2363956</i>	0.80 (0.74–0.87)	47

¹ Odds ratio and 95% confidence interval from original report of association with breast cancer risk² Minor allele frequency

Table 2

Genetic Variants Showing Significant Associations with Breast Cancer Risk at $P \leq 0.05$ in Meta-Analyses

Gene	Variant	Comparison ¹	Frequency (%) ²	Ethnicity	Number Evaluated			Breast Cancer Risk		Heterogeneity		Venice Criteria Grade ³		Cumulative Evidence of Association ⁴
					Studies	Cases	Controls	OR (95% CI)	P	P value	I ²			
A: Associations identified by analyses of all available data														
ATM	5932G>T (E1978X)	Carriers vs. noncarriers	0.05	Caucasian *	4	6,593	3,793	4.56 (1.35–15.42)	0.015	1.000	0	× A A	+++	
ATM	rs1800057 (Pro1054Arg)	(CG+GG) vs. CC	5.06	All ancestries	9	4,998	6,122	1.20 (1.01–1.44)	0.038	0.466	0	B A A	++	
CASP8	rs1045485 (Asp302His)	C vs. G	13.29	Caucasian *	17	18,382	19,419	0.89 (0.85–0.93)	4.65×10 ^{−8}	0.992	0	A A A	+++	
CASP8	rs6435074 (A34767C)	A vs. C	25.72	Caucasian *	3	2,677	3,093	1.12 (1.03–1.22)	0.010	0.865	0	A A C	+	
CASP8	rs6723097 (A35438C)	A vs. C	36.33	Caucasian *	3	2,610	3,040	1.16 (1.07–1.25)	1.91×10 ^{−4}	0.997	0	A A A	+++	
CHEK2	IVS2+1G>A	Carriers vs. noncarriers	0.39	Caucasian *	5	9,970	7,526	3.07 (2.03–4.63)	9.82×10 ^{−8}	0.707	0	× A A	+++	
CHEK2	rs17879961 (I157T)	Carriers vs. noncarriers	4.19	Caucasian *	8	13,311	10,817	1.52 (1.31–1.77)	4.76×10 ^{−8}	0.324	14	A A A	+++	
CHEK2	Deletion	Carriers vs. noncarriers	0.30	Caucasian *	5	10,543	8,447	2.53 (1.61–3.97)	6.33×10 ^{−5}	0.419	0	× A A	+++	
CHEK2	1100delC	Carriers vs. noncarriers	0.49	All ancestries	47	41,791	50,910	3.10 (2.59–3.71)	<10 ^{−20}	0.315	8	× A A	+++	
CTLA4	rs231775 (Thr17Ala)	A vs. G	38.54	Asian *	3	2,214	2,288	1.25 (1.14–1.37)	1.59×10 ^{−6}	0.676	0	A A A	+++	
CYP19A1	(TTTA)10	R10 vs R7	1.76	All ancestries	13	7,979	8,564	1.53 (1.05–2.22)	0.027	0.044	45	B B A	++	
ERCC2	rs13181 (Lys751Gln)	C vs. A	34.62	All ancestries	33	15,843	16,827	1.13 (1.05–1.22)	0.002	0.000	76	A C C	+	
ESR1	rs3020314 (C5029T)	C vs. T	31.73	Caucasian *	3	5,189	5,614	1.12 (1.06–1.18)	1.09×10 ^{−4}	0.535	0	A A C	+	
ESR1	rs1801132 (Pro325Pro)	G vs. C	23.83	All ancestries	14	10,836	14,685	0.95 (0.90–1.00)	0.038	0.297	14	A A C	+	
GSTM1	Deletion	Null vs. present	48.64	All ancestries	61	21,289	24,850	1.11 (1.06–1.18)	8.86×10 ^{−5}	0.003	36	A B C	+	
GSTT1	Deletion	Null vs. present	23.37	All ancestries	43	16,518	19,423	1.11 (1.03–1.20)	0.006	0.005	40	A B C	+	
HSD17B1	rs676387 (C-150A)	A vs. C	27.13	Caucasian *	3	11,794	14,205	1.05 (1.00–1.09)	0.050	0.278	22	A A C	+	
IFNG	rs2430561 (T874A)	A vs. T	43.32	All ancestries	3	324	397	1.25 (1.01–1.54)	0.039	0.691	0	B A C	+	
IGF1	rs6220 (C84864T)	T vs. C	29.50	All ancestries	3	6,213	7,192	1.06 (1.00–1.11)	0.048	0.656	0	A A C	+	
LRTOMT	rs673478 (G-239A)	C vs. T	4.51	Caucasian *	3	607	587	1.53 (1.07–2.18)	0.020	0.683	0	B A C	+	
MTHFR	rs1801133 (Ala222Val)	T vs. C	32.24	All ancestries	46	21,696	27,229	1.04 (1.00–1.07)	0.041	0.115	21	A A C	+	
NBN	657del5	Carriers vs. noncarriers	0.36	Caucasian *	7	7,082	9,504	2.42 (1.54–3.80)	1.18×10 ^{−4}	0.736	0	× A A	+++	
NUMA1	rs3018301 (G-510A)	A vs. G	5.17	Caucasian *	3	606	590	1.45 (1.03–2.03)	0.033	0.911	0	B A C	+	
TP53	rs12947788 (T72C)	T vs. C	8.61	Caucasian *	3	4,357	5,224	1.11 (1.01–1.23)	0.033	0.568	0	A A C	+	

Gene	Variant	Comparison <i>I</i>	Frequency (%) ²	Ethnicity	Number Evaluated			Breast Cancer Risk		Heterogeneity		Venice Criteria Grade ³	Cumulative Evidence of Association ⁴
					Studies	Cases	Controls	OR (95% CI)	P	P value	I ²		
<i>TP53</i>	rs12951053 (T92G)	G vs. T	8.67	Caucasian *	3	4,349	5,247	1.12 (1.01–1.23)	0.027	0.618	0	A A C	+
<i>TP53</i>	rs17878362 (16bp Del/Ins)	Insertion vs. deletion	15.40	All ancestries	12	2,961	3,496	1.15 (1.04–1.26)	0.007	0.520	0	A A A	+++
<i>TPMS</i>	28-bp tandem repeat	2R vs. 3R	33.56	All ancestries	6	2,709	3,400	1.08 (1.00–1.17)	0.044	0.734	0	A A C	+
<i>VDR</i>	rs731236 (Ile352Met)	C vs. T	35.85	All ancestries	14	6,829	8,461	1.06 (1.00–1.12)	0.034	0.357	9	A A C	+
<i>WRN</i>	rs1346044 (Cys1367Arg)	C vs. T	14.16	All ancestries	3	2,747	3,555	1.14 (1.02–1.27)	0.019	0.330	10	A A C	+
B: Associations identified from additional analyses by ethnic group													
<i>AURKA</i>	rs1047972 (Val57Ile)	A vs. G	16.74	Caucasian	4	7,309	10,158	0.93 (0.88–0.98)	0.011	0.482	0	A A C	+
<i>ESR1</i>	rs2234693 (PvuII,T397C)	C vs. T	39.78	Asian	8	4,563	4,503	0.94 (0.89–1.00)	0.050	0.592	0	A A C	+
<i>GSTP1</i>	rs1695 (Ile105Val)	G vs. A	19.38	Asian	6	4,634	5,241	1.07 (1.00–1.15)	0.048	0.436	0	A A C	+
<i>MTR</i>	rs1805087 (Asp919Gly)	G vs. A	21.05	Caucasian	5	5,612	6,671	0.92 (0.86–0.99)	0.023	0.335	12	A A C	+
<i>NQO1</i>	rs1800566 (Pro187Ser)	T vs. C	16.58	Caucasian	5	1,488	1,695	1.27 (1.03–1.56)	0.023	0.049	58	A C C	+
<i>TNF</i>	rs1800629 (G-308A)	A vs. G	17.01	Caucasian	9	10,664	13,048	0.92 (0.87–0.96)	4.48×10 ⁻⁴	0.436	0	A A C	+
<i>XRCC3</i>	rs861539 (Thr241Met)	T vs. C	10.98	Asian	3	1,283	1,120	1.32 (1.08–1.60)	0.007	0.855	0	B A A	++

¹ Allelic contrast for common variants, or genetic comparison for rare variants; R = repeat

² Minor allele frequency for common variants, or population frequency of test group for rare variants

³ Venice Criteria grades are in the order of amount of evidence, replication of the association and protection from bias; five rare variants were not scored for amount of evidence (×)

⁴ Cumulative epidemiological evidence as graded by the Venice criteria as strong (+++), moderate (++) , or weak (+) for association with breast cancer risk

* Only Caucasian or Asian data was available for meta-analysis

Moderate linkage disequilibrium (LD) was found between *ESR1* rs3020314 and rs1801132 ; high LD was found between *CASP8* rs6435074 and rs6723097 ; perfect LD was found between *TP53* rs12947788 and rs12951053

Table 3

Additional Genetic Variants Showing an Association with Breast Cancer at $P \leq 0.05$ in Meta-Analyses Using Dominant or Recessive Models

Gene	Variant	Alleles ¹	MAF (%)	Number Evaluated			Allelic Contrasts			Best Genetic Model			Venice Criteria Grade ³	Cumulative Evidence of Association ⁴
				Studies	Cases	Controls	OR (95% CI)	P value	I ²	Model ²	OR (95% CI)	P value	I ²	
<i>BARID1</i>	rs1048108 (Pro24Ser)	T vs. C	35.52	4	6,155	6,499	0.90 (0.82–1.00)	0.058	60	DOM	0.87 (0.76–0.99)	0.040	58	+
<i>CHRI1</i>	rs7931342 (T14300292G)	T vs. G	48.76	3	8,093	8,490	0.96 (0.90–1.02)	0.147	42	REC	0.91 (0.85–0.98)	0.011	0	+
<i>CYP11B1</i>	rs1056836 (Leu432Val)	G vs. C	41.72	30	20,055	22,405	0.97 (0.92–1.01)	0.136	43	REC	0.93 (0.88–0.98)	0.006	0	+
<i>ESR1</i>	rs9340799 (A156751G)	G vs. A	32.68	19	16,535	27,162	0.97 (0.93–1.01)	0.126	28	REC	0.91 (0.85–0.98)	0.011	0	+
<i>GNB3</i>	rs5443 (Ser275Ser)	T vs. C	29.82	3	808	1,016	1.08 (0.93–1.24)	0.304	0	REC	1.44 (1.05–1.97)	0.023	0	+
<i>IGFBP3</i>	rs2854744 (C-202A)	A vs. C	48.12	20	28,352	38,550	0.98 (0.96–1.00)	0.114	0	REC	0.96 (0.93–1.00)	0.044	0	+
<i>IL1A</i>	rs17561 (Ala114Ser)	T vs. G	29.84	3	1,929	1,944	1.00 (0.80–1.25)	0.990	79	REC	1.27 (1.02–1.58)	0.031	0	+
<i>IL10</i>	rs1800896 (G-1082A)	G vs. A	46.91	4	1,124	1,218	1.17 (0.97–1.43)	0.105	59	REC	1.27 (1.02–1.58)	0.034	15	+
<i>LEPR</i>	rs1137101 (Gln223Arg)	A vs. G	33.37	5	1,851	2,074	1.46 (1.00–2.15)	0.051	90	DOM	1.46 (1.00–2.14)	0.050	80	+
<i>MSH3</i>	rs26279 (Ala1045Thr)	G vs. A	31.80	3	659	1,025	1.13 (0.97–1.31)	0.116	0	REC	1.37 (1.01–1.86)	0.044	0	+
<i>NCOA3</i>	rs2230782 (Gln586His)	C vs. G	8.19	3	3,252	3,871	0.95 (0.84–1.08)	0.439	0	REC	0.53 (0.30–0.95)	0.034	0	+
<i>POR</i>	rs10262966 (Gly5Gly)	G vs. A	22.63	3	1,038	877	1.12 (0.96–1.30)	0.143	0	REC	1.57 (1.04–2.36)	0.032	0	+
<i>PTGS2</i>	rs20417 (G-765C)	G vs. C	15.88	3	7,912	9,840	1.03 (0.95–1.11)	0.453	16	REC	1.20 (1.01–1.44)	0.039	0	+
<i>TERT</i>	rs2853669 (T-244C)	C vs. T	27.99	4	4,553	5,319	0.94 (0.89–1.01)	0.074	0	REC	0.76 (0.64–0.91)	0.002	22	++
<i>XRCC1</i>	rs25487 (Arg399Gln)	A vs. G	33.82	43	23,701	25,153	1.04 (1.00–1.09)	0.066	50	REC	1.10 (1.01–1.20)	0.027	48	+

¹ Minor vs. major allele (reference)

² Dominant (DOM) or recessive (REC) genetic effect models

³ Venice Criteria grades are in the order of amount of evidence, replication of the association, and protection from bias

⁴ Cumulative epidemiological evidence as graded by the Venice criteria as strong (+++), moderate (++), or weak (+) for association with breast cancer risk

Genetic Variants Showing No Association with Breast Cancer Risk in Meta-Analyses with Minimum Sample Sizes of 10,000 Cases and 10,000 Controls

Table 4

Gene	Variant	Comparison ¹	Frequency (%) ²	Number Evaluated			Breast Cancer Risk			Heterogeneity	
				Studies	Cases	Controls	OR (95% CI)	P value	P value	I ²	I ²
<i>ADH1B</i>	rs1042026 (A19107G)	G vs. A	28.93	9	11,381	15,573	0.99 (0.95–1.03)	0.617	0.375	7	7
<i>ATM</i>	rs1800054 (Ser49Cys)	(CG+GG) vs. CC	2.37	16	16,682	20,729	1.16 (0.95–1.41)	0.138	0.064	38	38
<i>AURKA</i>	rs2273535 (Phe31Ile)	A vs. T	31.96	16	19,709	24,646	1.03 (0.98–1.09)	0.277	0.001	61	61
<i>BD</i>	rs8190315 (Ser10Gly)	(GG+AG) vs. AA	3.41	11	13,783	14,272	1.05 (0.87–1.27)	0.607	0.093	38	38
<i>BRCA1</i>	rs1799950 (Gln356Arg)	C vs. T	7.72	9	11,280	19,210	1.00 (0.86–1.15)	0.949	0.001	70	70
<i>BRCA2</i>	rs144848 (Asn372His)	G vs. T	27.37	21	21,906	27,399	1.01 (0.98–1.04)	0.547	0.410	4	4
<i>CASP10</i>	rs13010627 (V410I)	A vs. G	6.07	28	29,904	32,870	1.02 (0.95–1.09)	0.609	0.005	46	46
<i>CASP8</i>	rs3834129 (–652 G/N del)	Deletion vs. non	43.41	16	13,254	13,639	0.96 (0.90–1.03)	0.233	0.001	62	62
<i>CCND1</i>	rs9344 (Pro241Pro)	A vs. G	50.53	14	12,846	13,118	1.04 (0.99–1.08)	0.115	0.179	26	26
<i>CDKN1A</i>	rs1801270 (Ser31Arg)	A vs. C	7.73	20	22,003	29,324	1.05 (0.95–1.15)	0.329	0.000	68	68
<i>COMT</i>	rs4680 (Val158Met)	A vs. G	47.01	41	27,433	34,787	0.98 (0.95–1.02)	0.339	0.022	33	33
<i>CYP17A1</i>	rs743572 (T–34C)	C vs. T	40.90	42	25,596	32,480	1.02 (0.99–1.05)	0.239	0.308	9	9
<i>CYP19A1</i>	rs10046 (C132810T)	C vs. T	48.27	8	12,122	17,607	1.03 (0.97–1.10)	0.279	0.023	57	57
<i>CYP1A1</i>	rs1048943 (Ile462Val)	G vs. A	8.44	27	12,332	17,182	1.06 (0.95–1.20)	0.299	0.000	64	64
<i>CYP1A1</i>	rs4646903 (T3801C)	C vs. T	19.36	26	10,568	14,542	1.00 (0.91–1.09)	0.956	0.000	61	61
<i>CYP1B1</i>	rs10012 (Arg48Gly)	G vs. C	28.63	9	10,821	12,597	1.03 (0.98–1.07)	0.255	0.511	0	0
<i>CYP1B1</i>	rs1056827 (Ala119Ser)	T vs. G	28.46	10	10,576	11,536	1.04 (0.97–1.11)	0.242	0.081	41	41
<i>CYP1B1</i>	rs1800440 (Asn453Ser)	G vs. A	17.48	11	11,311	13,410	0.99 (0.92–1.07)	0.826	0.098	38	38
<i>ERCC2</i>	rs1799793 (Asp312Asn)	A vs. G	32.99	22	13,994	13,868	0.98 (0.92–1.05)	0.635	0.000	67	67
<i>ERCC4</i>	rs744154 (G6068C)	C vs. G	27.24	28	29,136	31,799	1.00 (0.97–1.02)	0.882	0.492	0	0
<i>ESR2</i>	rs1256049 (Val328Val)	A vs. G	7.28	9	13,331	17,820	1.02 (0.94–1.09)	0.689	0.313	15	15
<i>ESR2</i>	rs4986938 (G39A)	A vs. G	34.33	10	13,346	19,153	0.97 (0.94–1.01)	0.104	0.739	0	0
<i>HSD17B1</i>	rs605059 (Ser312Gly)	G vs. A	47.25	11	13,987	17,066	0.98 (0.95–1.01)	0.196	0.480	0	0
<i>ICAM5</i>	rs1056538 (Val301Ile)	T vs. C	38.29	19	19,484	24,474	0.99 (0.95–1.03)	0.428	0.043	39	39
<i>IL6</i>	rs1800795 (G–174C)	C vs. G	38.50	9	10,885	18,602	1.02 (0.97–1.08)	0.545	0.294	17	17
<i>LIG4</i>	rs1805386 (Asp568Asp)	C vs. T	17.44	8	10,068	11,140	0.96 (0.91–1.02)	0.179	0.393	5	5
<i>MDM2</i>	rs2279744 (14+309T>G)	G vs. T	36.27	24	14,180	13,223	1.03 (0.98–1.08)	0.249	0.097	29	29

Gene	Variant	Comparison ¹	Frequency (%) ²	Number Evaluated			Breast Cancer Risk		Heterogeneity	
				Studies	Cases	Controls	OR (95% CI)	P value	P value	I ²
<i>MTHFR</i>	rs1801131 (Gln429Ala)	C vs. A	24.80	24	13,131	16,813	0.98 (0.94–1.03)	0.482	0.074	31
<i>NAT2</i>	Acetylation phenotype	Fast vs. slow	45.03	30	10,745	12,497	0.98 (0.92–1.05)	0.603	0.066	30
<i>NUMA1</i>	rs3750913 (Ala794Gly)	(CC+CG) vs. GG	5.63	16	16,182	18,908	1.08 (0.93–1.26)	0.332	0.008	52
<i>PGR</i>	rs1042838 (Val660Leu)	T vs. G	14.48	28	31,672	37,579	1.02 (0.98–1.07)	0.300	0.027	37
<i>PGR</i>	rs10895068 (G331A)	A vs. G	5.13	8	13,544	17,547	1.05 (0.97–1.15)	0.252	0.283	19
<i>PTGS2</i>	rs5275 (T8473C)	C vs. T	32.94	7	10,907	14,091	1.03 (0.98–1.07)	0.238	0.390	5
<i>PTGS2</i>	rs5277 (Val102Val)	G vs. C	15.04	3	10,583	12,607	0.97 (0.87–1.08)	0.598	0.027	72
<i>SHBG</i>	rs6259 (Asp356Asn)	A vs. G	12.28	7	10,092	12,663	0.98 (0.91–1.04)	0.452	0.321	14
<i>SOD2</i>	rs4880 (Val16Ala/Val-9Ala)	C vs. T	47.31	31	26,976	35,015	1.01 (0.97–1.05)	0.583	0.001	49
<i>TGFB1</i>	rs1800469 (C-509T)	T vs. C	34.85	11	12,125	15,273	1.00 (0.94–1.05)	0.889	0.056	44
<i>TGFB1</i>	rs1800470 (Leu10Pro)	C vs. T	40.30	32	20,125	27,269	1.01 (0.98–1.06)	0.461	0.049	31
<i>TNF</i>	rs361525 (A-417G)	A vs. G	4.82	30	31,996	34,887	1.01 (0.95–1.06)	0.851	0.479	0
<i>TP53</i>	rs1042522 (Arg72Pro)	C vs. G	29.63	52	31,484	35,113	0.98 (0.94–1.03)	0.446	0.000	62
<i>VDR</i>	rs1544410 (G63980A)	A vs. G	37.22	22	11,377	13,572	0.97 (0.93–1.03)	0.311	0.048	36
<i>VDR</i>	rs2228570 (Met1Arg/Lys/Thr)	T vs. C	37.64	19	12,349	16,707	1.05 (0.98–1.12)	0.159	0.000	67
<i>XRCC1</i>	rs1799782 (Arg194Trp)	T vs. C	8.50	20	10,414	10,796	0.98 (0.88–1.09)	0.682	0.012	47
<i>XRCC2</i>	rs3218536 (Arg188His)	G vs. A	7.78	15	17,932	18,738	0.96 (0.90–1.02)	0.192	0.298	14
<i>XRCC3</i>	rs1799796 (A17893G)	G vs. A	32.88	6	10,870	12,263	1.00 (0.92–1.08)	0.906	0.003	73

¹ Allelic contrast or phenotype trait for common variants, or genetic comparison for rare variants

² Minor allele frequency for common variants, or population frequency of test group for rare variants