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Confirmation of 5p12 as a susceptibility locus for progesterone-receptor-positive, lower grade breast cancer

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Abstract

Background—The single nucleotide polymorphism 5p12-rs10941679has been found to be associated with risk of breast cancer, particularly estrogen receptor (ER)-positive disease. We aimed to further explore this association overall, and by tumor histopathology, in the Breast Cancer Association Consortium.

Methods—Data were combined from 37 studies, including 40,972 invasive cases, 1,398 cases of ductal carcinoma in situ (DCIS) and 46,334 controls, all of white European ancestry, as well as 3,007 invasive cases and 2,337 controls of Asian ancestry. Associations overall and by tumor invasiveness and histopathology were assessed using logistic regression.

Results—For white Europeans, the per-allele odds ratio (OR) associated with 5p12-rs10941679 was 1.11 (95% confidence interval [CI] =1.08–1.14, $P=7\times10^{-18}$) for invasive breast cancer and 1.10 (95%CI=1.01–1.21, $P=0.03$) for DCIS. For Asian women, the estimated OR for invasive disease was similar (OR=1.07, 95%CI=0.99–1.15, $P=0.09$). Further analyses suggested that the association in white Europeans was largely limited to progesterone receptor (PR)-positive disease (per-allele OR=1.16, 95%CI=1.12–1.20, $P=1\times10^{-18}$ versus OR=1.03, 95%CI=0.99–1.07, $P=0.2$ for PR-negative disease; P-heterogeneity=2×10^{-7}); heterogeneity by estrogen receptor status was not observed ($P=0.2$) once PR status was accounted for. The association was also stronger for lower-grade tumors (per-allele OR [95%CI]=1.20 [1.14–1.25], 1.13 [1.09–1.16] and 1.04 [0.99–1.08] for grade 1, 2 and 3/4, respectively; P–trend=5×10^{-7}).

Conclusion—5p12 is a breast cancer susceptibility locus for PR-positive, lower gradebreast cancer.

Impact—Multi-centre fine-mapping studies of this region are needed as a first step to identifying the causal variant or variants.

Keywords

Breast cancer; SNP; susceptibility; disease subtypes

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Introduction

Genome-wide association studies (GWAS) have identified several single-nucleotide polymorphisms (SNPs) associated with breast cancer risk. Key to these findings, and to the more precise estimation of the associated relative risks, has been their replication in large independent case-control series. SNPs in or close to the genes *LSP1*, *MAP3K1*, *FGFR2*, *TOX3*, *MRPS30*, *COX 11*, *MRPS30*, and *SLC4A7*, and in chromosomal regions 8p24 and 2q35 have all been replicated in the Breast Cancer Association Consortium (BCAC) (1–4)

An Icelandic GWAS and replication study of 5,028 breast cancer cases and 32,090 controls revealed multiple signals in the 5p12 chromosomal region (5). The most strongly associated SNP was rs10941679, the minor G allele being associated with an estimated per-allele odds ratio (OR) of 1.19 (95% confidence interval [CI]=1.11–1.26, $P=2.9\times10^{-11}$). The authors reported that the increased risk was particularly marked for estrogen receptor (ER)-positive disease (N=2,726 cases, per-allele OR=1.27, 95%CI=1.19–1.35, $P=2.5\times10^{-12}$; *P*-heterogeneity=0.004) (5). In addition, our previous breast cancer GWAS reported evidence of an association with another SNP on 5p12, rs981782 ($P=9\times10^{-6}$), based on data from 23,408 cases and 24,636 controls from 21 BCAC studies (2). The Icelandic-led study evaluated both these SNPs in multivariable models and observed that only 5p12-rs10941679 was independently associated with breast cancer risk (5). This SNP was not among those genotyped in the first phase of our previous GWAS (2).

The aims of the present study were to estimate the relative risk of breast cancer associated with 5p12-rs10941679 in a much larger case-control series comprising studies participating in the BCAC, to evaluate its independence of any association with 5p12-rs981782, and to assess associations by disease subtypes defined by histopathology.

Materials and Methods

Thirty-seven studies from Europe, North America, Australia, and Asia participated in genotyping for the present study via the BCAC, contributing a total of 41,243 invasive breast cancer cases, 1,406 cases of ductal carcinoma in-situ (DCIS) and 46,621 controls of white European origin and 3,082 invasive cases and 2,402 controls of Asian origin. All 37 studies genotyped 5p12-rs10941679. Seven studies also genotyped 5p12-rs981782 in a total of 8,247 invasive cases and 10,363 controls, all of European origin. Fourteen of the 37 participating studies had already genotyped 5p12-rs981782 in white Europeans as part of the previously published study (2). Descriptions of studies are provided in Supplemental Table 1 and final sample sizes are presented in Supplemental Table 2.

All studies provided information on disease status and self-reported race/ethnicity for all subjects and age at diagnosis for cases. All but five studies (BIGGS, FBCS, HUBCS, RBCS and UCIBCS) also provided age at data collection for controls. “Selected cases” were a subset of 7,128 invasive cases selected for inclusion or oversampled by nine studies because they had bilateral breast cancer, a family history of breast cancer and/or other characteristics that suggested they were at increased genetic risk (all cases from BBCS, FBCS, GC-HBOC, kConFab/AOCS, MBCSG, NC-BCFR, OFBCR and RBCS and 211 cases from CNIO-BCS,

see Supplemental Table 1). ER and progesterone receptor (PR) status were provided for a subset of cases, respectively, as were human epidermal growth factor receptor 2 (HER2) status and other histological features including axillary node status and tumor grade, size, and morphology (see Supplemental Table 3). This histopathology information was generally abstracted from medical reports.

Subjects who reported having ethnicity other than white European were excluded, with the exception of those from the three Asian studies, for which only subjects of Asian origin were included. Only subjects from studies that genotyped at least 30 cases of DCIS were included in the analyses of risk of DCIS. All subjects gave written informed consent, where applicable, and each study was approved by the relevant local institutional review boards.

Most studies carried out genotyping using Taqman nuclease assay (Taqman®), with reagents designed by Applied Biosystems as Assays-by-Design™ and genotyping performed using the ABI PRISM 7900HT, 7700 or 7500 Sequence Detection Systems according to manufacturer's instructions. Three studies used Sequenom's MassARRAY system and iPLEX technology (Sequenom, San Diego, CA, USA), with oligonucleotides design carried out according to the guidelines of Sequenom and performed using MassARRAY Assay Design software (version 3.1). The method used by each study is identified in Supplemental Table 2. All studies complied with BCAC genotyping quality control (QC) standards by including at least 2% of samples in duplicate and a common set of 93 CEPH DNAs used by the HapMap Consortium (HAPMAPPT01, Coriell Institute for Medical Research, Cambden, NJ).

Statistical Methods

Departure from Hardy-Weinberg equilibrium (HWE) was tested for in controls from each centre using Pearson/s χ^2 test (1df). The association of each SNP with breast cancer risk was assessed by estimating genotype-specific and per-allele ORs using logistic regression, adjusted for study. The exclusion of studies for which the age of controls was not known and the additional adjustment for age (in 5-year categories and as a continuous covariate) made no substantial difference to the results. Between-study heterogeneity in ORs was assessed using a likelihood ratio test (LRT) comparing the model with interaction terms for the per-allele log-OR by study to the model with no interaction terms. Differences in ORs by ethnicity (white European, Asian) and age (<40, 40–49, 50–59, 60–69, ≥70 years) were evaluated using a similar LRT, the latter modeled as a linear trend by fitting the median age for each of the defined categories.

ORs specific to disease subtypes defined by ER, PR and HER2 status (positive, negative), by combinations of these markers, and by axillary node status (none, ≥1 affected), tumor grade (1, 2, ≥3), tumor size (≤10, 11–20, >20mm) and tumor morphology (ductal, lobular), were estimated for white Europeans using polytomous logistic regression with control status as the reference outcome. Heterogeneity in the OR by subtypes was tested for by applying polytomous logistic regression to cases-only, treating the number of minor alleles as the outcome and restricting, for each explanatory variable, the beta coefficient for the comparison of 2 to 0 minor alleles to be double that for the comparison of 1 to 0 minor alleles. This is equivalent to modeling a log-additive per-allele OR and allows multiple

tumor markers to be modeled simultaneously. Linear trends were tested for grade by fitting values 1, 2, and 3, and for size by fitting the median value, for the defined categories, respectively. Enrichment of the risk allele in "selected cases" was assessed using the likelihood ratio test comparing polytomous logistic regression models with and without the per-allele OR constrained to be equal for selected and unselected cases, relative to controls (1df). We minimised bias in the estimation of OR by repeating all analyses after excluding "selected cases". All statistical tests were two-sided. The term "genome-wide" statistically significant is taken to imply $p<10^{-7}$; otherwise "statistically significant" implies $p<0.05$. All analyses were carried out using Stata: Release 10 (6).

Meta-analyses were carried out using *metan* command based on log-transformed OR estimates and their 95%CI from different reports.

Results

Minimum genotype concordance of 98% for duplicate samples and 95% for the CEPH samples was observed in all studies, as were minimum genotype calls of 97% for both SNPs in cases and controls. Evidence of departure from HWE was observed for 5p12-rs10941679 in controls from two studies (FBCS [P = 0.02] and HABCS [P=0.005], Supplemental Table 2); for both studies, cluster plots were double-checked visually and determined to be of high quality, and all their genotype data were therefore included in the final analysis.

Thirty-four studies successfully genotyped 5p12-rs10941679 in a total of 40,972 invasive breast cancer cases (7,037 of which were selected for increased genetic risk), 1,398 DCIS cases, and 46,334 controls of white European origin. Genotypes were also obtained for this SNP for 3,007 cases and 2,337 controls of Asian origin recruited by three studies. A total of 8,213 invasive cases and 10,340 controls were successfully genotyped for 5p12-rs981782 by seven studies. Previously published data for this SNP were included from 14 studies to obtain genotypes for both SNPs in 5p12 for 23,548 invasive cases and 28,142 controls, all of white European origin. Genotype counts by study are provided in Supplemental Table 4.

The minor G allele of 5p12-rs10941679 was less frequent in white European women (26%) than in Asian women (49%). Estimated ORs, for invasive breast cancer and DCIS, and by ethnicity, are presented in Table 1. The genotype-specific OR estimates were consistent with a log-additive model for white Europeans. The per-G-allele OR estimate was 1.12 (95%CI=1.10–1.15, $P=6\times10^{-24}$), and there was no evidence of heterogeneity in the OR among studies overall (P=0.1) or among studies of Asians (P=0.3), studies of white Europeans that included "selected cases" (P=0.3) or studies of white Europeans without "selected cases" (P=0.2) (Figure 1). This association was maintained at genome-wide statistical significance when SNP 5p12-rs981782 was included as a covariate in the logistic regression model (OR=1.11, 95%CI=1.09–1.15, $P=6\times10^{-13}$). For 5p12-rs10941679 the estimated per-G-allele OR for DCIS was similar to that for invasive disease (OR=1.10, 95%CI=1.01–1.21, P=0.03). The per-G-allele OR for invasive breast cancer did not appear to be different for Asian women (P-heterogeneity=0.3), but the estimate was lower and not statistically significant (1.07; 95%CI=0.99–1.15, P=0.09). All further analyses were based on white European women only.

We observed weak evidence that the G allele of 5p12-rs10941679 was enriched in "selected cases" (P=0.06). The estimated per-allele OR was 1.18 (95%CI=1.11–1.24, $P=1\times10^{-8}$) when comparing cases selected for increased genetic risk to controls from the same studies and 1.11 (95%CI=1.08–1.14, $P=7\times10^{-18}$) when they were excluded. There was evidence of an increase in the per-allele OR associated with 5p12-rs10941679 with age (P=0.01), with estimates of 1.10 (95%CI=1.01–1.19), 1.08 (95%CI=1.02–1.15), 1.14 (95%CI=1.09–1.19), 1.12 (1.07–1.17) and 1.16 (95%CI=1.06–1.26) for white European women aged <40, 40–49, 50–59, 60–69 and ≥70, respectively. This trend was also observed when age was modeled in years (P=0.02), with an estimated interaction OR of 1.02 (95%CI=1.00–1.04) per G allele, per 10-year increase in age. The same trend was observed after excluding "selected cases" (interaction OR=1.02, 95%CI=1.00–1.05, P=0.03).

Results from analyses by breast cancer subtypes defined by histopathological features are presented in Tables 2 and 3. The number of cases from each study for which this information was available is presented in Supplemental Table 3. We observed strong evidence that the per-allele OR associated with 5p12-rs10941679 differed by ER status, PR status and ER/PR combined (all $P<10^{-5}$, Table 2). When ER and PR status were modeled together in the case-only analysis only the association with PR status was maintained ($P=6\times10^{-4}$, compared to P=0.2 for ER status). The OR estimates by combined ER/PR status were consistent with the heterogeneity being present by PR rather than ER status. Furthermore, heterogeneity in the OR by PR status was observed when only cases with ER-positive disease were considered (P=0.005), but not by ER status when only cases with PR-positive disease were considered (P=0.8). After excluding "selected cases", the per-G-allele OR estimates were 1.03 (95%CI=0.99–1.07, P=0.2) for PR-negative disease and 1.16 (95%CI=1.12–1.20, $P=1\times10^{-18}$) for PR-positive disease. We observed no further heterogeneity by HER2 status (P=0.3). The trend of increasing per-allele OR with age remained apparent when only the risk of PR-positive disease was considered (interaction OR=1.03, 95%CI=1.00–1.06, P=0.05).

There was also clear evidence that 5p12-rs10941679 was more strongly associated with the risk of lower-grade breast cancer ($P=5\times10^{-7}$, Table 3). When grade and PR status were modeled together in a case-only analysis, evidence of heterogeneity was observed for both tumor characteristics (P<0.002). After excluding "selected cases", the per-G-allele OR estimates were 1.20 (95%CI=1.14–1.25), OR=1.13 (95%CI=1.09–1.16) and OR=1.04 (95%CI=0.99–1.08) for grade 1, 2 and 3/4 disease, respectively). Further restriction to PR-positive cases gave consistent results [OR=1.22 [95%CI=1.14–1.30], OR=1.15 [95%CI=1.10–1.20] and OR=1.07 [95%CI=1.00–1.15], respectively). We also assessed the association of 5p12-rs10941679 with risk of different grades of DCIS and, while based on limited data (N=210, 102 and 124 cases with grade 1, 2 and 3 DCIS, respectively), the per-allele OR estimates were consistent with the trend observed for invasive disease (OR=1.33 [95%CI=0.88–2.02], OR=1.08 [95%CI=0.78–1.49] and OR=0.98 [95%CI=0.72–1.33] for grade 1, 2 and 3 DCIS, respectively). There was no evidence of heterogeneity in per-G-allele OR by nodal status, tumor size or tumor type.

Further to our previous report of a possible association with breast cancer risk of variant rs981782, also in 5p12, we genotyped this SNP in an additional 8,213 invasive cases and

10,340 controls from studies participating in the BCAC and found no evidence of association (per-G-allele OR=0.97, 95%CI=0.93–1.02, *P*=0.2, Table 4). When we added in data for participants genotyped as part of the previous study (2), to give a combined total of 23,548 invasive cases and 28,142 controls of white European origin, the per-G-allele OR estimate was 0.95 (95%CI=0.92–0.97, $P=2\times10^{-5}$). The MAF for controls genotyped using Taqman, iPlex and the GWAS SNP-array (2) were similar (0.47, 0.45 and 0.50, respectively). This possible association was attenuated, but still nominally statistically significant, when 5p12-rs10941679 was also included in the logistic regression model (OR=0.97, 95%CI=0.94–0.99, *P*=0.007). The per-allele OR estimate for each SNP adjusted for the other was unchanged after excluding "selected cases". The estimated linkage disequilibrium coefficient (r^2) between the two SNPs was 0.04, both across all white European subjects genotyped (N=52,506) and for controls only (N=28,142).

Discussion

This analysis of 40,972 invasive cases and 46,334 controls from 37 studies definitively confirms the 5p12-rs10941679 as a breast cancer susceptibility locus in white European women. After excluding cases selected for increased genetic susceptibility, we estimated an OR for white European women of 1.11 per G allele (95%CI=1.08–1.14). This association was independent of a possible association with 5p12-rs981782 and appeared to be stronger for older women.

The estimated OR for Asian women (3,007 cases and 2,337 controls) was consistent with that for European women, but the confidence limits were too wide to demonstrate a definite association (OR=1.07, 95%CI=0.99–1.15). The Shanghai Breast Cancer Study also estimated a per-G-allele OR of 1.07 (95%CI=0.99–1.15) using data from 2,950 cases and 2,986 controls (7). Assessed together, these two large studies suggest that 5p12-rs10941679 is associated with increased breast cancer risk in Asian women (meta-analysis OR=1.07 (95%CI=1.02–1.13, *P*=0.01), although even larger studies will be required to precisely estimate the corresponding OR.

The initial paper on 5p12-rs10941679, based on 6,145 cases and 33,016 controls, reported a larger per-G-allele OR for breast cancer in general of 1.19 (95%CI=1.11–1.28) (5). This larger initial estimate probably reflects "winner's curse" whereby the estimated OR in the study discovering the association tends to be overestimated (8). Stacey et al. (5) also reported that the increased risk associated with 5p12-rs10941679 was limited to ER-positive disease and consistent results have been observed in other studies (7, 9). We replicated this finding, but our larger sample size enabled us to carry out a more detailed analysis that revealed a stronger association with PR-positive disease (per-G-allele OR=1.16, 95%CI=1.12–1.20). The heterogeneity in the OR by ER status appeared to be driven by the correlation between ER and PR status. Furthermore, we have established that the association is also stronger for lower grade tumors in general, and lower grade PR-positive tumors specifically. Stacey et al. (5), also noted a possibly larger OR for lower grade tumors, but not after ER-status was taken into account. This multifaceted heterogeneity has also been observed for 10q26-rs2981582, which appears to be associated with increased risk of lower grade ER-positive tumors (10).

In our previous GWAS, we observed that the minor G allele of 5p12-rs981782 in the same region was associated with reduced risk of breast cancer. The estimated per-G-allele OR for white European women was 0.94 (95%CI=0.91–0.97, $P=9\times10^{-6}$), based on data from 20,649 cases of invasive breast cancer and 22,578 controls from 19 studies participating in the replication stages (2 and 3) (2). We did not replicate this association in the present study of 8,247 cases and 10,363 controls, but our result (OR=0.97, 95%CI=0.93–1.02, *P*=0.2) was not inconsistent with the existence of a modest protective effect. Reeves et al. (11) studied 5p12-rs981782 in 10,306 cases and 10,309 controls from the Million Women Study and estimated a per-G-allele OR of 0.94 (95%CI=0.91–0.98, *P*=0.003). Stacey et al. (5) also evaluated this SNP in 5,028 cases and 32,090 controls and reported the corresponding OR to be 0.96 (95%CI=0.92–1.01, *P*=0.1). The Cancer Genetic Markers of Susceptibility (CGEMS) project studied SNP 5p12-rs4866929, which is in high linkage disequilibrium with 5p12-rs981782 ($r^2=0.96$), in a total of 5,692 cases and 5,576 controls and obtained an OR estimate of 0.97 (95%CI=0.91–1.03, *P*=0.4) (3, 9). When combined together in a meta-analysis, these results for 5p12-981782 (excluding those from CGEMS) give an estimated OR of 0.95, 95%CI=0.93–0.97, $P=5\times10^{-8}$), suggesting that this SNP is associated with a modest reduction in breast cancer risk.

It is less clear whether the association between 5p12-rs981782 and breast cancer risk is independent of the effect marked by 5p12-rs10941679. In contrast to the findings of Stacey et al. (5), in the present study (23,548 cases and 28,142 controls) the evidence of association for 5p12-rs981782 remained after adjusting for 5p12-rs10941679 (*P*=0.007), although the effect was slightly attenuated. Furthermore, the correlation between these two SNPs was too weak ($r^2=0.04$, N=52,506) for the association seen with 5p12-r981782 to be due to confounding by 5p12-rs10941679. However, it remains possible that these two associations are driven by a variant correlated with both SNPs. Stacey et al. (5) found that a third SNP nearby, 5p12-rs4415084 was associated with breast cancer risk, independently of 5p12-rs10941679 ($r^2=0.51$ between the two SNPs). Multi-centre fine-mapping studies of this region are needed to obtain the samples sizes required to identify the causal variant or variants behind these multiple small signals.

As discussed by Stacey et al. (5), 5p12-rs10941679 resides between two genes: *MRPS30*, which encodes the smaller 28S subunit of the mitochondrial ribosome and has pro-apoptotic properties (12), and *FGF10*, a fibroblast growth factor which is amplified in around 10% of breast cancers (13), although there is a recombination hotspot separating this SNP from *FGF10*. Therefore, as for the vast majority of low-penetrance breast cancer susceptibility loci identified by GWAS, an implicated gene or functional mechanism remains to be elucidated.

A potential limitation of our study was that information on tumor histopathology was not available for all cases and, where it was, these data were predominantly abstracted from medical records, rather than being obtained through a standardised pathology review. Thus some misclassification may have been present and this may have attenuated some associations with tumor phenotype. However the strong association with PR and ER status suggests that this effect was minimal, at least for the features examined here.

In conclusion, 5p12-rs10941679 is a confirmed marker of breast cancer susceptibility. In white European women it is associated with increased risk of lower-grade, PR-positive tumors. These findings suggest that commonly collected tumor characteristics other than ER status can be used to identify subtypes of breast cancer with distinct etiology, and that large collaborative studies are required to identify the genetic contributions specific to each of these.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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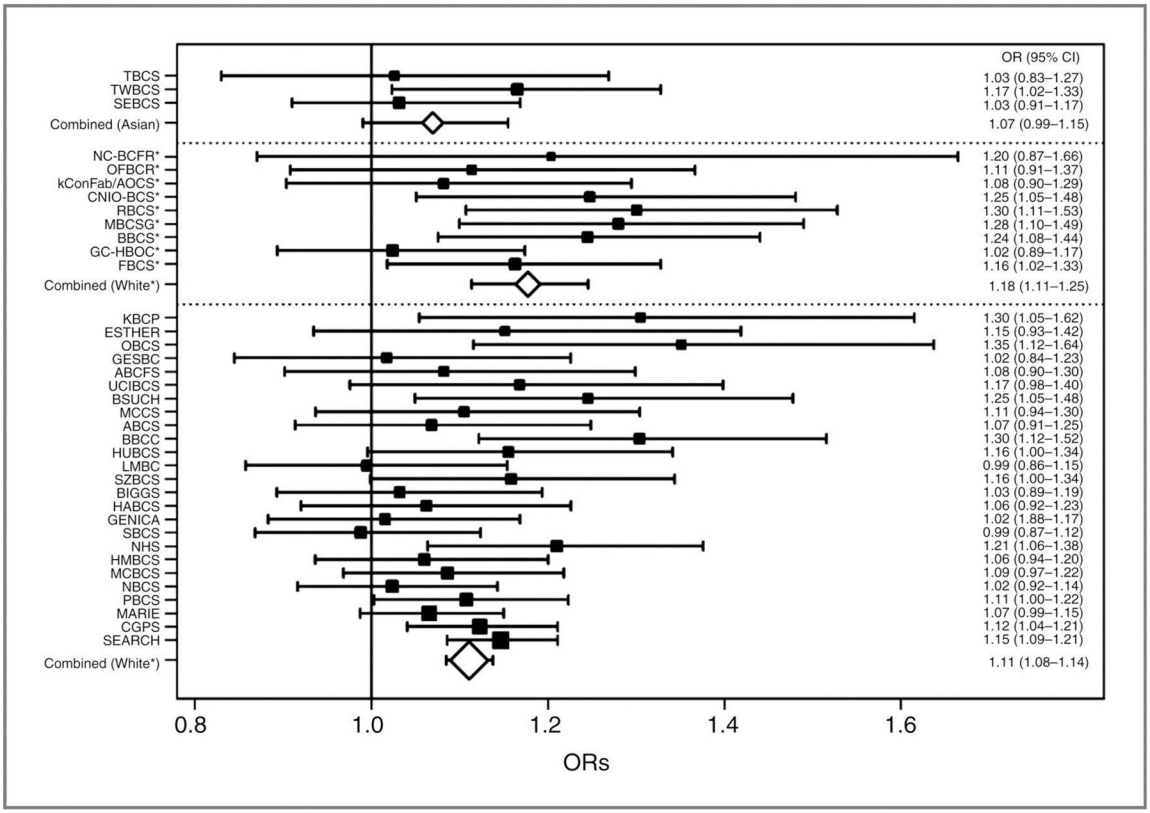

Figure 1. Association of 5p12-rs10941679 with risk of invasive breast cancer, by study

Per-allele odds ratios (OR) and 95% confidence intervals (CI), with studies grouped into those that recruited Asian women and white European women. The latter group is further divided into those including “selected cases” likely to be at higher genetic risk (marked by an asterisk) and those with unselected cases. The area of the box/diamond is inversely proportional to the standard error of the log OR estimate.

Table 1

SNP 5p12-rs10941679 and risk of breast cancer

Group/invasiveness/genotype	Controls, N (%)	Cases, N (%)	OR (95%CI)	*P*
White European women				
Invasive disease (34 studies)				
AA	25,622 (55)	21,241 (52)	1.00	
AG	17,668 (38)	16,671 (41)	1.14 (1.11–1.17)	9×10^{-19}
GG	3,044 (6.6)	3,060 (7.5)	1.22 (1.15–1.29)	2×10^{-12}
per G-allele			1.12 (1.10–1.15)	6×10^{-24}
Adjusted for 5p12-rs981782*				
AA	15,648 (56)	12,243 (52)	1.00	
AG	10,684 (38)	9,598 (41)	1.14 (1.10–1.18)	2×10^{-11}
GG	1,810 (6.4)	1,707 (7.3)	1.19 (1.11–1.28)	3×10^{-6}
per G-allele			1.11 (1.09–1.15)	6×10^{-13}
White European women				
DCIS (15 studies)				
AA	14,187 (55)	726 (52)	1.00	
AG	9,733 (38)	578 (41)	1.17 (1.04–1.31)	0.009
GG	1,662 (6.5)	94 (6.7)	1.10 (0.88–1.38)	0.4
per G-allele			1.10 (1.01–1.21)	0.03
Asian women				
Invasive disease (3 studies)				
AA	612 (26)	765 (25)	1.00	
AG	1,155 (49)	1,460 (49)	1.03 (0.90–1.18)	0.6
GG	570 (24)	782 (26)	1.14 (0.98–1.33)	0.09
per G-allele			1.07 (0.99–1.15)	0.09

OR, odds ratio; CI, confidence interval; DCIS, ductal carcinoma in situ

*SNP 5p12-981782 included under a codominant model (2df), based on data on both variants available from 19 studies, including previously published data on 5p12-rs198782 (2).

Table 2

SNP 5p12-rs10941679 and risk of invasive breast cancer for white Europeans, by ER, PR and HER2 status

	N Participants		Log-additive Model		
	Cases	**Controls**	**OR (95%CI)**	***P***	**Case-only *P*-heterogeneity**
ER Status (29 studies)					
ER+	20,044	41,436	1.15 (1.12–1.19)	7×10^{-24}	
ER−	6,201	41,436	1.04 (0.99–1.08)	0.1	4×10^{-6}
PR Status (28 studies)					
PR+	14,557	40,577	1.16 (1.12–1.19)	8×10^{-20}	
PR−	7,744	40,577	1.04 (1.00–1.08)	0.08	5×10^{-7}
ER/PR Status (28 studies)					
ER+/PR+	13,517	40,577	1.16 (1.12–1.20)	3×10^{-19}	
ER+/PR−	3,104	40,577	1.06 (1.00–1.13)	0.04	
ER−/PR+	960	40,577	1.13 (1.02–1.26)	0.02	
ER−/PR−	4,558	40,577	1.02 (0.97–1.07)	0.5	6×10^{-6}
ER, PR and HER2 Status (16 studies)					
(ER+ or PR+)&HER2−	8,078	25,726	1.15 (1.10–1.20)	2×10^{-11}	
(ER+ or PR+)&HER2+	1,188	25,726	1.11 (1.02–1.22)	0.02	
ER−/PR−/HER2−	1,641	25,726	1.04 (0.95–1.12)	0.4	
ER−/PR−/HER2+	750	25,726	0.93 (0.83–1.05)	0.3	

OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR progesterone receptor; HER2, human epidermal growth factor receptor 2

Table 3

SNP 5p12-rs10941679 and risk of invasive breast cancer for white Europeans, by pathology characteristics

	N Participants		Log-additive Model		
	Cases	Controls	OR (95%CI)	*P*	Case-only *P*-heterogeneity*
Axillary node status (27 studies)					
Negative	16,566	39,148	1.12 (1.09–1.15)	3×10^{-13}	
Positive	9,762	39,148	1.13 (1.09–1.17)	1×10^{-10}	0.9
Grade (26 studies)					
1	5,032	38,601	1.20 (1.14–1.25)	1×10^{-13}	
2	12,204	38,601	1.13 (1.09–1.17)	1×10^{-12}	
3/4	7,802	38,601	1.04 (1.00–1.08)	0.05	5×10^{-7}
Size (19 studies)					
≤10mm	3,707	28,102	1.16 (1.09–1.22)	3×10^{-7}	
11–20mm	7,964	28,102	1.11 (1.07–1.16)	1×10^{-7}	
>20mm	6,823	28,102	1.11 (1.07–1.16)	1×10^{-6}	0.4
Morphology (26 studies)					
Ductal	20,283	38,447	1.12 (1.09–1.15)	2×10^{-15}	
Lobular	3,829	38,447	1.07 (1.02–1.13)	0.01	0.1

OR, odds ratio; CI, confidence interval

*For size and grade, a linear trend was tested by fitting the median values for each category as a continuous variable.

Table 4

SNP 5p12-rs981782 and risk of invasive breast cancer in white European women

Group/genotype	Controls, N (%)	Cases, N (%)	OR (95%CI)	*P*
Subjects genotyped for the present study (7 studies)				
AA	2,845 (28)	2,310 (28)	1.00	
AG	5,162 (50)	4,048 (49)	0.95 (0.89–1.02)	0.2
GG	2,333 (23)	1,855 (23)	0.94 (0.87–1.03)	0.2
per G-allele			0.97 (0.93–1.01)	0.2
Combined analysis* (19 studies)				
AA	7,815 (28)	6,890 (29)	1.00	
AG	14,056 (50)	11,626 (49)	0.93 (0.90–0.97)	0.001
GG	6,271 (22)	5,032 (21)	0.90 (0.86–0.95)	3×10^{-5}
per G-allele			0.95 (0.92–0.97)	2×10^{-5}
Adjusted for rs10941679* (19 studies)				
AA	7,815 (28)	6,890 (29)	1.00	
AG	14,056 (50)	11,626 (49)	0.95 (0.91–0.99)	0.02
GG	6,271 (22)	5,032 (21)	0.93 (0.89–0.98)	0.009
per G-allele			0.97 (0.94–0.99)	0.007

OR, odds ratio; CI, confidence interval

*based on white European subjects genotyped for 5p12-rs10941679 and 5p12-rs981782, including previously published data on the latter (2)