doi:10.4149/neo_2015_038

Assessing the interactions between the associations of common genetic variants on 2q35 and 16q12 with breast cancer risk

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Received March 14, 2014 / Accepted August 27, 2014

Genome-wide association studies (GWAS) have identified 2q35 and 16q12 as breast cancer (BC) susceptibility loci. However, the association between the two polymorphisms and BC remains controversial and inconsistent. We therefore performed a more precise estimation of these relationships by meta-analysing the currently available evidence from the literature. The PubMed, Ovid, Medline and Web of Science databases were searched. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strengths of the associations. Thirty studies, including 106,312 cases and 140,939 controls, were identified. Overall, significantly elevated breast cancer risk was associated with the A allele of 2q35 rs13387042 when all studies were pooled into the meta-analysis (OR 1.11, 95%CI 1.07-1.15). Additionally, the T allele of 16q12 rs3803662 was associated with significantly increased breast cancer risk (OR 1.20, 95%CI 1.16-1.24). When stratifying for ethnicity, significantly increased risks were found among Caucasians, Asians and mixed ethnicities for both rs13387042 and rs3803662. For rs13387042, an association was observed for both estrogen receptor-positive (ER+) (OR 1.14, 95%CI 1.11-1.17) and ER-negative (ER-) disease (OR 1.05, 95%CI 1.01-1.09) and for progesterone receptor-positive (PR+) (OR 1.16, 95%CI 1.12-1.19) and PR-negative (PR-) disease (OR 1.07, 95%CI 1.03-1.12). Similarly, a stronger association was observed for rs3803662 with ER+ tumors (OR 1.23, 95%CI 1.13-1.32) compared with ER- tumors (OR 1.08, 95%CI 0.97-1.20), and the same condition occurred for the polymorphism with PR+ tumors (OR 1.26, 95%CI 1.02-1.55) versus with PR- tumors (OR 1.15, 95%CI 0.90-1.46). When stratified by BRCA mutation status, a stronger association was observed with BRCA2 carriers (OR 1.23, 95%CI 1.05-1.44) than BRCA1 carriers (OR 1.09, 95%CI 1.04-1.15). In conclusion, this meta-analysis demonstrated that the A allele of 2q35 rs13387042 and the T allele of 16q12 rs3803662 are risk factors associated with increased breast cancer susceptibility.

Key words: rs13387042, rs3803662, estrogen receptor, progesterone receptor, breast cancer, meta-analysis

Breast cancer is one of the most common cancers and the primary cause of deaths of women in the world [1]. It is estimated that approximately 1.15 million new cases occur every year [2]. Researchers have reached a consensus that the environment and genetic factors may affect the susceptibility to cancer; however, the mechanism is still not understood. Breast cancer is nearly twice as common in first-degree relatives of women with the disease as in relatives of women without this history, suggesting an important role of inherited susceptibility [3]. Common variants of genes involving breast carcinogenesis-related pathways are candidate loci for cancer susceptibility [4]. Breast cancer may also be attributable to mutations in high-penetrant genes such as BRCA1 and BRCA2. However, these alleles are associated with only a small fraction of breast cancer [5]. In recent years, several genome-wide association studies have been conducted and have identified some genetic susceptibility loci that are associated with breast cancer risk. Stacey et al. [6] identified that rs13387042 at chromosome 2q35 and rs3803662 at chromosome 16q12 were associated with breast cancer. In another study, Easton et al. [7] also found rs3803662 as a risk factor for breast cancer. Although the common variants on chromosomes 2q35 and 16q12 that confer susceptibility to breast cancer have been independently replicated by subsequent studies, the results were generally

inconsistent and inconclusive. Hence, we performed this meta-analysis of the published studies to clarify the inconsistencies and derive a more precise estimation of the association between the two polymorphisms and breast cancer.

Materials and methods

Search strategy. The literature included in our analysis was selected from the PubMed, Ovid, Medline, and Web of Science databases using the terms "2q35" or "rs13387042", "16q12" or "rs3803662", "polymorphism" or "variation" and "breast cancer". All potentially eligible studies published before the end of April 2013 were retrieved, and their reference lists were hand searched to find other relevant publications. Of the studies with overlapping data that were published by the same investigators, only the most recent study was included; for republished studies, only the one with the largest sample numbers was selected. All studies included in this meta-analysis were published in English and included the full text.

Studies were included if they met the following criteria: (1) evaluation of the 2q35 rs13387042 and 16q12 rs3803662 polymorphisms and breast cancer risk, (2) independent case-control studies or cohort studies, (3) sufficient available data to estimate an odds ratio (OR) with its 95% confidence interval (95%CI), and (4) in line with the Hardy-Weinberg equilibrium (HWE) in controls of the same ethnicity (P<0.01 was eligible); a deviation from the HWE was allowed in a mixed population. The major exclusion criteria were as follows: (1) no control population, and (2) no available genotype frequency.

Data extraction and quality assessment. Two investigators independently reviewed and extracted information from all eligible publications. Disagreement was resolved by discussion when there was a conflict. For each study, the following data were extracted: first author's surname, year of publication, country, ethnicity, source of control, Hardy-Weinberg equilibrium (HWE) status, estrogen receptor (ER) status, progesterone receptor (PR) status, total number of cases and controls, and inclusion of genotype frequency in cases and controls (Table S1). Studies with different ethnic groups were considered individual studies in this analysis.

Data analysis. Odds ratios with 95%CIs were used to assess the strength of the association between the 2q35 rs13387042, 16q12 rs3803662 polymorphism and breast cancer risk. The meta-analysis examined the associations between the following: (1) the allele contrast model, (2) the homozygote codominant model, (3) the heterozygote codominant model, (4) the dominant model, and (5) the recessive model. In addition, subgroup analyses were conducted based on ethnicity, ER status, and PR status. Chi-square-based Q-tests were performed to check the heterogeneity among different studies [8]. When heterogeneity existed (P<0.10), the random-effects model (the DerSimonian and Laird method) was used to estimate the summarised OR [9]; otherwise, we conducted the fixed-effects model (Mantel and Haenszel method) [10]. Sensitivity analyses were conducted to assess the stability of the results, which means that a single study in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the overall OR. Publication bias was assessed by Egger's test [11] and Begg's funnel plot [12]. P values less than 0.05 were considered statistically significant. The STATA version 12.0 (Stata Corp, College Station, TX) was used to perform all analyses.

Results

Search results and methodological quality of the included studies. There were 35 studies as a result of the search and screening. During the extraction of data, 5 articles were excluded because they did not provide the allele frequencies needed for the OR calculations. Therefore, a total of 30 studies, with 106,312 cases and 140,939 controls, were finally included [6, 13-41]. For the rs13387042 polymorphism, 21 studies were available, including 71,537 cases and 92,697 controls. For the rs3803662 polymorphism, 25 studies were available, including 69,127 cases and 95,954 controls. The main characteristics of the identified studies are summarised in Table 1.

Association between the rs13387042 polymorphism and BC. The main results of this meta-analysis are listed in Table 2. Overall, significantly elevated breast cancer risk was associated with the rs13387042 polymorphism when all studies were pooled into the meta-analysis (OR 1.11, 95%CI 1.07-1.15). The corresponding results can be observed in the other models (the homozygote codominant model: OR 1.22, 95%CI 1.15-1.29; the heterozygote codominant model: OR 1.12 95%CI 1.09-1.15; the dominant model: OR 1.16 95%CI 1.13-1.20; the recessive model: OR 1.13 95%CI 1.05-1.22) (Table 2). In the analysis stratified by ethnicity, ORs of 1.15 (95%CI 1.13-1.18) and 1.12 (95%CI 1.03-1.23) were calculated for rs13387042 among Caucasians and Asians, respectively. For mixed ethnicities, the OR for the Allele contrast model was 1.11 (95%CI 1.03-1.20), the OR for the homozygote codominant model was 1.14 (95%CI 1.08-1.21), the OR for the heterozygote codominant model was 1.15 (95%CI 1.07-1.24), the OR for the dominant model was 1.15 (95%CI 1.10-1.21), and the OR for the recessive model was 1.05 (95%CI 0.95-1.15) (Table 2, Figure 1). However, no significantly increased risk was found among Africans for all genetic models.

We further performed an analysis to test for differences in the associations of the polymorphism with breast cancer risk with respect to different prognostic factors. We compared estrogen receptor-positive (ER+) case subjects with estrogen receptor- negative (ER-) case subjects and, in a similar fashion, progesterone receptor-positive (PR+) case subjects with receptor-negative (PR-) case subjects. Stratification of tumors by ER status indicated that rs13387042 had a stronger association with ER+ tumors (OR 1.14, 95%CI 1.11-1.17) than ER-tumors (OR 1.05, 95%CI 1.01-1.09) (Figure 2). In addition, rs13387042 was associated with greater risk of PR+ tumors (OR 1.16, 95%CI 1.12-1.19) than PR- tumors (OR 1.07, 95%CI 1.03-1.12) (Figure 3).

Table 1. Characteristics of eligible studies in meta-analysis.

Studies	Year	Country	Ethnicity	Source	Cases	Controls	HWE of controls
rs13387042G>A							
Stacey et al.[6]	2007	Iceland, Sweden ,Spain and Holland	Caucasians	PB	4533	17513	NA
Milne et al.[13]	2009	Australia and United States	Caucasians	PB	28713	33708	0.672
Barnholtz-Sloan et al.[14]	2010	United States	Caucasians	PB	1230	1117	0.944
Hemminki et al.[15]	2010	German	Caucasians	PB	1415	1830	NA
Teraoka et al.[16]	2011	United States	Caucasians	Nested	704	1386	0.226
Slattery et al.[17]	2011	Southwestern United States	Caucasians	PB	1733	2041	0.062
Butt et al.[18]	2012	Sweden	Caucasians	Nested	685	1342	0.447
Ottini et al.[19]	2013	Italy	Caucasians	PB	413	745	0.734
Milne et al.[13]	2009	Southeast Asia	Asian	PB	2797	2261	0.868
Long et al.[20]	2010	China	Asian	PB	2951	3006	NA
Seuta et al.[21]	2011	Japan	Asian	PB	697	1394	NA
Lin et al.[22]	2012	China	Asian	HB	88	69	0.609
Dai et al.[23]	2012	China	Asian	HB	1771	1851	0.266
Kim et al.[24]	2012	Korea	Asian	PB	2257	2052	NA
Zheng et al.[25]	2009	African-American	African	PB	810	1784	NA
Barnholtz-Sloan et al.[14]	2010	United States	African	PB	742	657	0.995
Long et al.[26]	2013	African-American	African	PB	1230	2059	NA
Antoniou et al.[27]	2009	Different country	Mixed	Nested	7815	6675	<0.01
Muligan et al.[28]	2011	Europe, North America and Australia	Mixed	PB	7422	6102	<0.01
Harlid et al.[29]	2012	European	Mixed	Nested	3393	4837	0.01
Rinella et al.[30]	2013	Jewish	Mixed	PB	138	268	NA
rs3803662 C>T							
Stacey et al.[6]	2007	Iceland, Sweden ,Spain and Holland	Caucasians	PB	4554	17577	NA
Tapper et al.[31]	2008	European	Caucasians	HB	899	2980	NA
Mcinerney et al.[32]	2009	Ireland	Caucasians	PB	950	986	0.161
Barnholtz-Sloan et al.[14]	2010	United States	Caucasians	PB	1230	1118	0.591
Tamimi et al.[33]	2010	Sweden	Caucasians	PB	687	738	0.576
Latif et al.[34]	2010	British	Caucasians	HB	901	373	0.66
Gorodnova et al.[35]	2010	Russia	Caucasians	PB	140	174	0.294
Hemminki et al.[15]	2010	German	Caucasians	PB	1415	1830	NA
Teraoka et al.[16]	2011	Denmark and United States	Caucasians	Nested	703	1389	0.98
Slattery et al.[17]	2011	Southwestern United States	Caucasians	PB	1737	2042	0.55
Butt et al.[18]	2012	Sweden	Caucasians	Nested	695	1387	0.38
Ottini et al.[19]	2013	Italy	Caucasians	PB	412	745	0.741
Li et al.[36]	2009	China	Asian	HB	291	291	0.47
Long et al.[15]	2010	China	Asian	PB	6345	3795	NA
Liang et al.[37]	2010	China	Asian	PB	1025	1046	0.603
Seuta et al.[16]	2011	Japan	Asian	PB	697	1394	NA
Han et al.[38]	2011	Korea	Asian	HB	3285	3494	0.317
Kim et al.[24]	2012	Korea	Asian	PB	2257	2052	NA
Barnholtz-Sloan et al.[14]	2010	United States	African	PB	740	657	0.654
Garcia-Closas et al.[39]	2008	European or Asian	Mixed	Nested	16739	25026	<0.01
Antoniou et al.[40]	2008	Different country	Mixed	Nested	5092	4457	0.756
Campa et al.[41]	2011	United States and Europe	Mixed	PB	8305	11595	0.0001
Muligan et al.[28]	2011	Europe, North America and Australia	Mixed	PB	6346	5522	0.73
Harlid et al.[29]	2012	European	Mixed	Nested	3544	5018	0.28
Rinella et al.[30]	2013	Jewish	Mixed	PB	138	268	NA

NA not available, HB hospital-based, PB population-based, Nested nested case–control study, HWE Hardy–Weinberg equilibrium

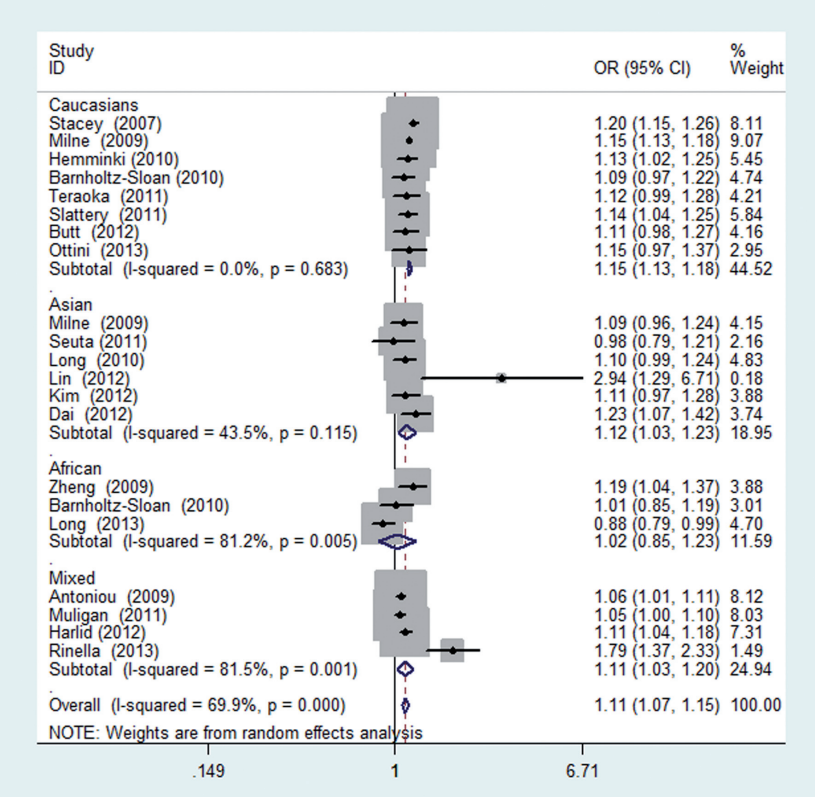

Figure 1. Forest plot from the meta-analysis of breast cancer risk and 2q35 rs13387042 polymorphism

Association between the rs3803662 polymorphism and BC. The main results of the associations between the rs3803662 polymorphism and BC are listed in Table 3. In the overall analysis, the risk allele of rs3803662 was significantly associated with increased breast cancer (the allele contrast model: OR 1.20, 95%CI 1.16-1.24; the homozygote codominant model: OR 1.38, 95%CI 1.27-1.50; the heterozygote codominant model: OR 1.16 95%CI 1.10-1.21; the dominant

Table 2. Meta-analysis of the 2q35 rs13387042 polymorphism on breast cancer risk

Study groups	N	Allele contrast model	Homozygote codominant model	Heterozygote codominant model	Dominant model	Recessive model
		(A vs G)	(AA vs GG)	(GA vs GG)	(GA+AA vs GG)	(AA vs GG+GA)
		OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph
Total	21	1.11(1.07-1.15) 0.000	1.22(1.15-1.29) 0.094	1.12(1.09-1.15) 0.045	1.16(1.13-1.20)0.810	1.13(1.05-1.22)0.000
Ethnicity						
Caucasian	8	1.15(1.13-1.18) 0.683	1.30(1.25-1.36)0.948	1.10(1.06-1.14) 0.969	1.17(1.13-1.21) 0.980	1.22(1.18-1.26)0.907
Asian	6	1.12(1.03-1.23) 0.115	1.59(1.07-2.36) 0.513	1.17(0.97-1.42) 0.112	1.22(0.98-1.51)0.059	1.55(1.04-2.30)0.581
African	3	1.02(0.85-1.23) 0.005	1.08(0.70-1.66) -	1.10(0.71-1.71) -	1.09(0.71-1.66) -	0.99(0.80-1.23) -
Mixed	4	1.11(1.03-1.20) 0.001	1.14(1.08-1.21) 0.486	1.15(1.07-1.24) 0.139	1.15(1.10-1.21)0.627	1.05(0.95-1.15)0.015
ER status						
ER+	5	1.14(1.11-1.17)0.187	1.26(1.16-1.36)0.312	1.11(0.98-1.27)0.040	1.16(1.04-1.29)0.096	1.18(1.09-1.28)0.215
ER-	5	1.05(1.01-1.09)0.046	1.14(0.95-1.36) 0.057	1.14(0.94-1.38)0.007	1.13(0.97-1.33)0.030	1.07(0.90-1.28)0.007
PR status						
PR+	3	1.16(1.12-1.19)0.350	1.31(1.23-1.40)0.584	1.20(0.95-1.52)0.033	1.25(1.04-1.52)0.076	1.26(1.20-1.32)0.959
PR-	3	1.07(1.03-1.12)0.086	1.11(0.85-1.44)0.140	1.06(0.83-1.35)0.094	1.88(1.33-2.64)0.004	1.14(1.06-1.21)0.365

N number of involved studies; Ph P value of Q test for heterogeneity test

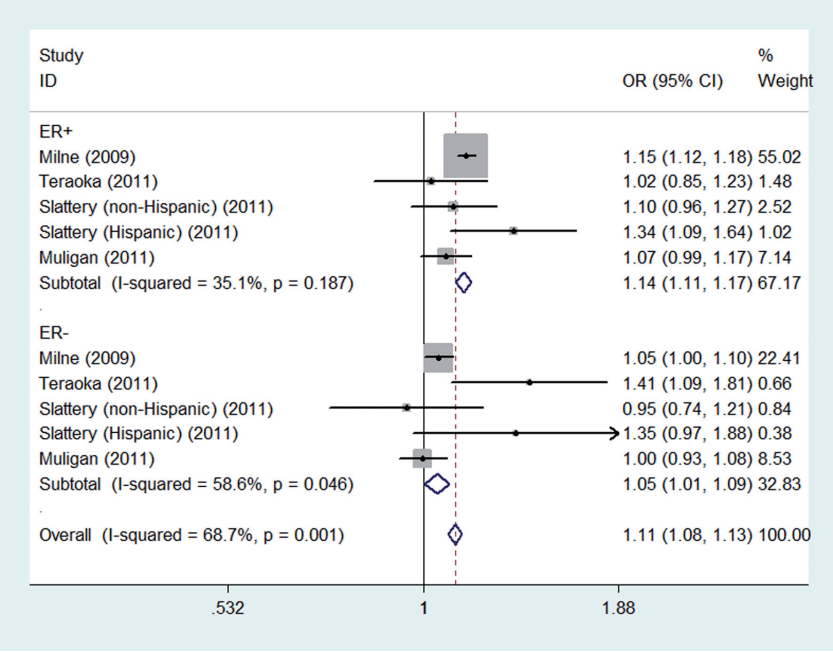

Figure 2. Per-allele odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between 2q35 rs13387042 and breast cancer risk by ER status

model: OR 1.20, 95%CI 1.14-1.27; the recessive model: OR 1.29, 95%CI 1.21-1.37) (Table 3). When stratifying for ethnicity, significantly increased risks were found among Caucasians and mixed ethnicities for all genetic models; however, no significantly increased risk was found for Africans. For Asians, the OR for the Allele contrast model was 1.19 (95%CI 1.12-1.26), the OR for the homozygote codominant model was 1.18 (95%CI 0.84-1.65), the OR for the heterozygote codominant model was 1.11 (95%CI 0.90-1.36), the OR for the dominant model was 1.16 (95%CI 0.93-1.46), and the OR for the re-

Table 3. Meta-analysis of the 16q12 rs3803662 polymorphism on breast cancer risk

Study groups	N	Allele contrast model	Homozygote codominant model	Heterozygote codominant model	Dominant model	Recessive model
		(T vs C)	(TT vs CC)	(CT vs CC)	(CT+TT vs CC)	(TT vs CC+CT)
		OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph	OR (95 % CI) Ph
Total	25	1.20(1.16-1.24) 0.000	1.38(1.27-1.50)0.000	1.16(1.10-1.21)0.002	1.20(1.14-1.27) 0.000	1.29(1.21-1.37)0.008
Ethnicity						
Caucasian	12	1.24(1.17-1.32) 0.002	1.53(1.30-1.79)0.067	1.18(1.06-1.31)0.023	1.24(1.11-1.38)0.007	1.40(1.24-1.59)0.258
Asian	6	1.19(1.12-1.26)0.065	1.18(0.84-1.65)0.018	1.11(0.90-1.36)0.136	1.16(0.93-1.46) 0.064	1.18(1.00-1.40) 0.110
African	1	0.96(0.83-1.11) –	0.92(0.68-1.25) -	0.97(0.74-1.27) -	0.95(0.74-1.23) -	0.94(0.74-1.19) -
Mixed	6	1.18(1.12-1.25)0.000	1.40(1.27-1.53)0.007	1.16(1.10-1.23)0.007	1.20(1.13-1.28) 0.001	1.31(1.22-1.41) 0.066
ER status						
ER+	8	1.23(1.13-1.32)0.009	1.60(1.40-1.84)0.156	1.25(1.18-1.34)0.334	1.30(1.20-1.42)0.140	1.41(1.26-1.57)0.235
ER-	8	1.08(0.97-1.20)0.009	1.23(0.97-1.56)0.036	1.15(1.09-1.23)0.446	1.12(1.00-1.25)0.118	1.19(0.98-1.44)0.087
PR status						
PR+	4	1.26(1.02-1.55) 0.010	1.67(1.11-2.49) 0.028	1.29(1.00-1.65)0.084	1.36(1.03-1.81)0.023	1.39(1.03-1.88)0.064
PR-	4	1.15(0.90-1.46)0.093	1.43(0.85-2.42)0.086	1.15(0.92-1.43)0.809	1.15(0.43-3.10)0.540	1.26(0.75-2.13)0.030
BRCA mutations						
BRCA1	3	1.09(1.04-1.15)0.877	1.20(1.06-1.36)0.923	1.09(1.02-1.17)0.912	1.11(1.04-1.19)0.889	1.15(1.02-1.30)0.947
BRCA2	3	1.23(1.05-1.44)0.020	1.39(1.07-1.81)0.137	1.25(1.02-1.54)0.032	1.29(1.05-1.60)0.017	1.25(1.08-1.46)0.379

N number of involved studies; Ph P value of Q test for heterogeneity test

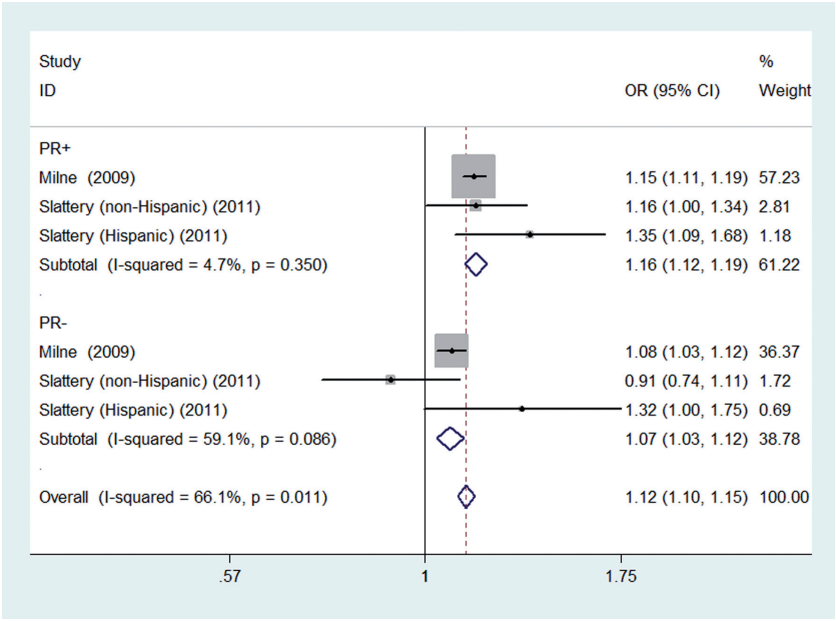

Figure 3. Per-allele odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between 2q35 rs13387042 and breast cancer risk by PR status

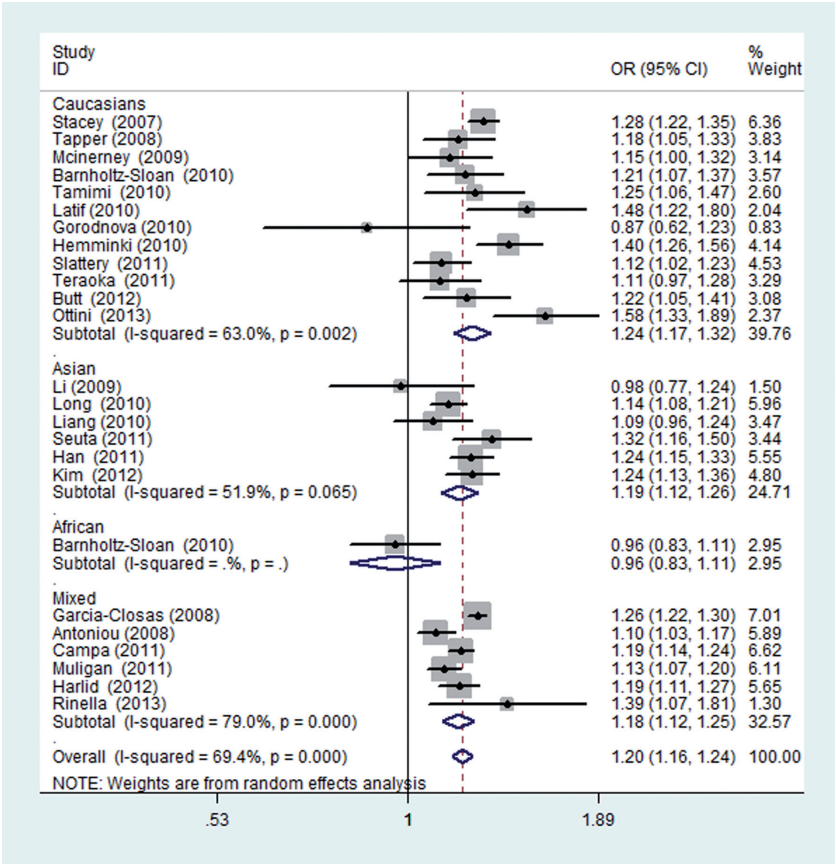

Figure 4. Forest plot from the meta-analysis of breast cancer risk and 16q12 rs3803662 polymorphism

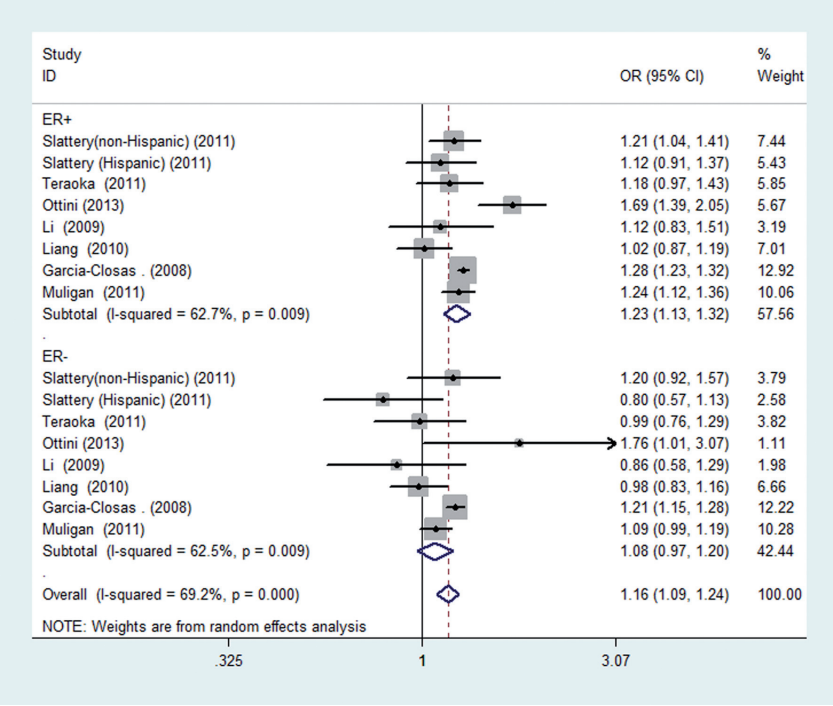

Figure 5. Per-allele odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between 16q12 rs3803662 and breast cancer risk by ER status

cessive model was 1.18 (95%CI 1.00-1.40) (Table 3, Figure 4). When stratified by ER status, a stronger association was observed for the polymorphism and ER+ tumors (OR 1.23, 95%CI 1.13-1.32) compared to ER- tumors (OR 1.08, 95%CI 1.97-1.20) (Figure 5). Similarly, a stronger association was observed for the polymorphism with PR+ tumors (OR 1.26, 95%CI 1.02-1.55) versus PR- tumors (OR 1.15, 95% CI 0.90-1.46) (Figure 6). When stratified by BRCA mutation status, a stronger association was observed with BRCA2 carriers (OR 1.23, 95%CI 1.05-1.44) than BRCA1 carriers (OR 1.09, 95%CI 1.04-1.15) (Figure 7).

Sensitivity analyses. Influence analysis was performed to assess the influence of each individual study on the pooled OR by the sequential removal of individual studies. No individual study significantly affected the pooled ORs, as the results show (Figure S1, S2).

Publication bias. Both Begg's funnel plot and Egger's test were conducted to estimate the publication bias of the articles. The shape of the funnel plot for the polymorphisms was symmetric (Figure S3, S4), which indicated no evidence of publication bias for rs13387042 and rs3803662.

Discussion

The pathogenesis of the carcinogenesis and progression of BC is still not understood. However, previous evidence suggests that it is a polygenic disease that is also related to environmental factors. Recently, GWAS have discovered that the common variations rs13387042 at 2q35 and rs3803662 at 16q12 were associated with BC risk, as described above. However, limitations, such as small size, ethnic differences, and BC subtype, of the studies made the results inconsistent. Therefore, a meta-analysis was performed to explore the heterogeneity of the polymorphisms and more precisely assess the effect of the polymorphisms on BC risk.

Our analysis showed that the 2q35 rs13387042 G>A and 16q12 rs3803662 C>T polymorphisms were significantly correlated with increased BC risk. The A allele of the 2q35 rs13387042 variant and T allele of the 16q12 rs3803662 C>T variant were low- penetrant risk factors for developing BC. In the analysis stratified by ethnicity, significantly increased risk was found among Caucasians, Asians and mixed ethnicities. However, no significantly increased risk was found among Africans. Some points may be responsible for this result. For the rs13387042 polymorphism, the frequencies of the risk allele differed from 0.510 in Caucasians [6] to 0.060 in the Chinese population [17]. For the rs3803662 polymorphism, the frequency of risk for the T allele varied markedly between ethnicities, from 0.341 in European-Americans to 0.530 in Japanese-Americans [31]. So, ethnic differences might contribute to the inconsistent results. Furthermore, a polymorphism may affect the BC risk by combining with another nearby variance, and the pattern of the interaction could differ for different ethnicities. In addition, the particular lifestyles of the

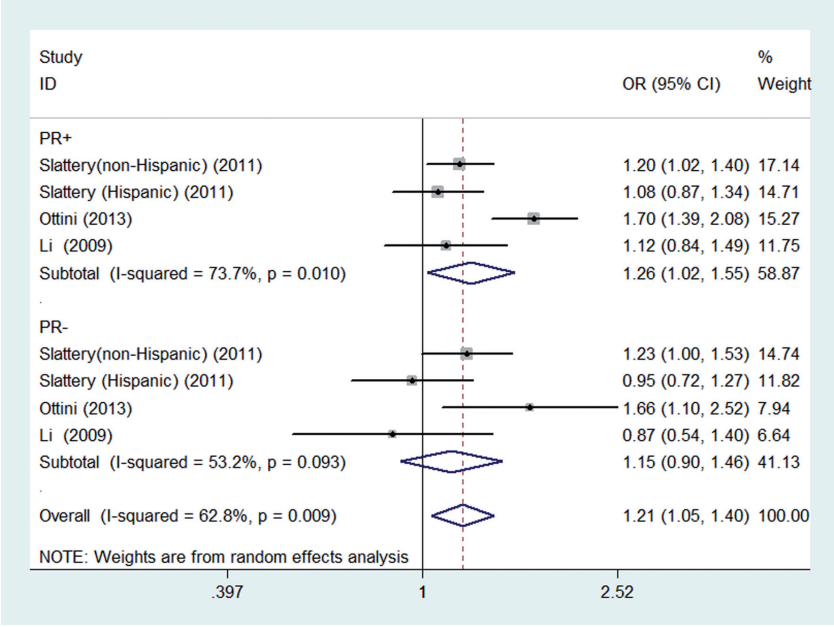

Figure 6. Per-allele odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between 16q12 rs3803662 and breast cancer risk by PR status

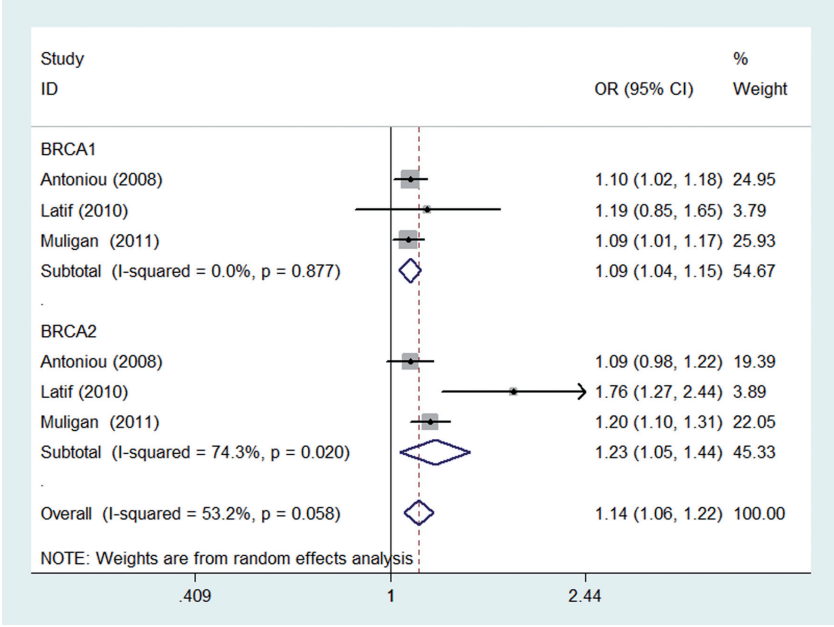

Figure 7. Per-allele odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between 16q12 rs3803662 and breast cancer risk by BRCA mutation

different populations might contribute to the result. Furthermore, the number of studies among the African population was limited, resulting in no sufficient statistical power to show slight effects, thus larger sample size studies are warranted to further validate the ethnic differences in the effect of the polymorphism on BC risk.

The previous studies on 2q35-rs13387042 and 16q12-rs3803662 suggested that the association risk was confined to ER+ tumors [6]. However, in our results, both 2q35 and 16q12 were associated with ER+ tumors and ER- tumors. The difference is that the association for ER+ breast cancer seems to be stronger than that for ER- breast cancer. Similar risks

were observed when the results were stratified by PR status. Because the ER and PR statuses are the major markers of breast cancer subtype, these observations suggested that inherited risk variants of these subtypes might vary. Although this observation has no immediate clinical significance, this result provides clues to the biological mechanisms underpinning tumor heterogeneity, which may ultimately lead to improved prevention and treatment.

For rs3803662, when stratified by the BRCA mutation carrier status, a stronger association was observed with BRCA2 carriers than BRCA1 carriers. This result is consistent those from previous studies. The breast cancer risk for BRCA1 and BRCA2 mutation carriers has been estimated to be between 40% and 80% by age 70 [42-44]. More studies must be performed to uncover the mechanism behind the rs3803662 polymorphism in the BRCA mutation and BC.

2q35-rs13387042 is located in a 90-kb region of high linkage disequilibrium that contains neither known genes nor non-coding RNAs. Trinucleotides repeat containing 9 (TNRC9) is a gene located at chromosome 16q12, and several polymorphisms, including rs3803662, have been identified in this gene. Although their functions are uncertain, the two polymorphisms are newly described risk factors for breast cancer. Thus, functional studies in this region are likely to lead to a better understanding of the mechanisms of carcinogenesis and progression of breast cancer.

The advantage of the study is its much larger sample size, and it summarises the latest studies on the association between rs13387042, rs3803662 and BC. The qualities of case-control studies meet our inclusion criterion. Furthermore, the lack of publication bias indicates that the entire pooled result should be unbiased. In addition, we also performed analyses to test for differences in the associations of the polymorphism with breast cancer risk with respect to different hormone receptor statuses, and we analysed the correlation between the BRCA mutation at rs3803662 and BC susceptibility, which has never been explored. However, the limitation in this meta-analysis should be attended. First, the studies in our analysis on Caucasians were more numerous than those of other ethnicities, so the statistical power for the other ethnicities is limited. Second, our results were based on unadjusted estimates, and we were unable to adjust them using possible confounders such as age, smoking, menopausal status, alcohol consumption and other lifestyle risk factors.

In summary, our meta-analysis demonstrated that both rs13387042 and rs3803662 were associated with increased risk of BC, particularly in Caucasian and Asian populations. Due to the limitations of studies of African-descent populations, further studies including a wider spectrum of subjects are needed to investigate the role of these variants in these populations.

Supplementary information is available in the online version of the paper.

Acknowledgements: We gratefully acknowledge support from the National Natural Science Foundation (81472485, 81072057, 11271163/A0117).

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doi:10.4149/neo_2015_038

Supplementary Information

Assessing the interactions between the associations of common genetic variants on 2q35 and 16q12 with breast cancer risk

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Supplementary Figure

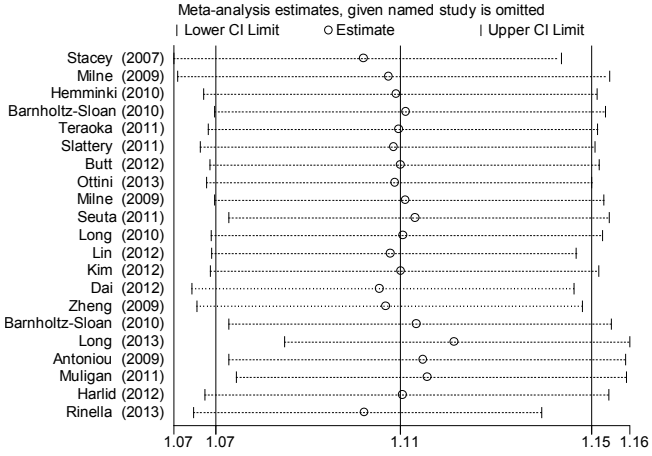

Figure S1 Influence analysis of the individual dataset for 2q35 rs13387042 polymorphism
This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate the pooled OR when the left study is omitted in this meta-analysis. The two ends of the dotted lines represent the 95 % CI.

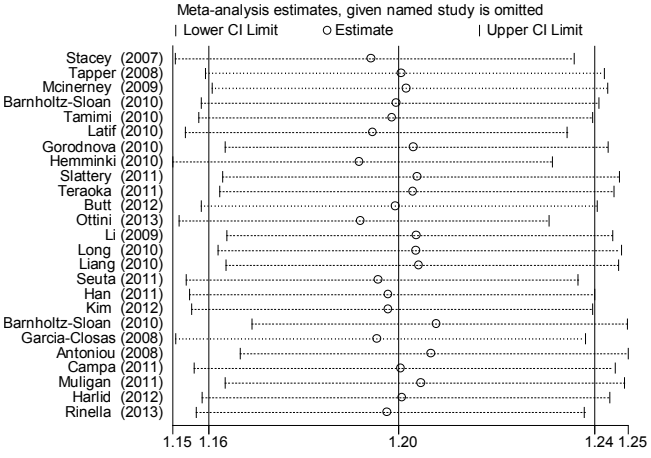

Figure S2 Influence analysis of the individual dataset for 16q12 rs3803662 polymorphism
This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate the pooled OR when the left study is omitted in this meta-analysis. The two ends of the dotted lines represent the 95 % CI.

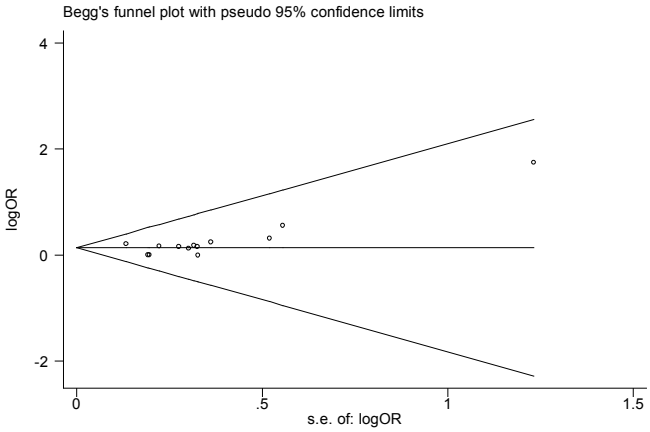

Figure S3 Begg's funnel plot of publication bias test for the 2q35 rs13387042 polymorphism
Each point represents a separate study for the indicated association. The vertical axis represents log [OR] and the horizontal axis means the standard error of log [OR]. Horizontal line and sloping lines in funnel plot represent random-effect summary OR and expected 95 % CI for a given standard error, respectively. Area of each circle represents the contribution of each study to the pooled OR.

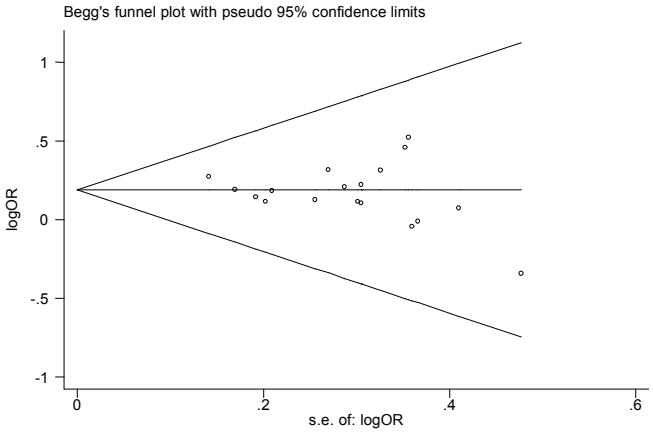

Figure S4 Begg's funnel plot of publication bias test for the 16q12 rs3803662 polymorphism
Each point represents a separate study for the indicated association. The vertical axis represents log [OR] and the horizontal axis means the standard error of log [OR]. Horizontal line and sloping lines in funnel plot represent random-effect summary OR and expected 95 % CI for a given standard error, respectively. Area of each circle represents the contribution of each study to the pooled OR.

Table S1 Genotypes and P values of rs13387042 and rs3803662 polymorphisms included in the meta-analysis

rs13387042 G>A											
First author	**Cases**					**Controls**					**P value**
	GG	GA	AA	G	A	GG	GA	AA	G	A	
Stacey				4143	4923				17618	17408	P<0.001with OR (95% CI) =1.20 (1.14-1.26)for at-risk allele
Milne	6016	13900	8797	25932	31494	7999	16803	8906	32801	34615	P value was NA;OR (95% CI) =1.28 (1.22-1.34)for AA
Hemminki				1217	1613				1684	1976	P<0.001 with OR (95% CI) = 1.33 (1.19–1.46)for at-risk allele
Barnholtz-Sloan	252	606	372	1110	1350	249	558	310	1056	1178	P value was NA; OR (95 % CI) = 0.93 (0.83–1.06) for at-risk allele
Teraoka	152	327	225	631	777	326	669	391	1321	1451	P=0.02with OR (95% CI) =1.19 (1.02-1.37)for at-risk allele
Slattery	448	840	445	1736	1730	601	974	466	2176	1906	P value was NA; OR (95 % CI)=1.11 (0.89-1.39)for AA
Butt	163	330	192	326	714	350	657	335	1357	1327	P value was NA; OR (95 % CI) =0.90 (0.79-1.03)for at-risk allele
Ottini	83	189	141	355	471	163	366	216	692	798	P=0.19with OR (95% CI) =1.13 (0.94–1.34)for AA
Milne	2247	513	37	5007	587	1844	395	22	4083	439	P value was NA;OR (95% CI) =1.37 (0.81-2.34)forAA
Seuta				1252	142				2498	290	P value was NA;OR (95% CI) =0.98 (0.79–1.23)for at-risk allele
Long				5194	708				5351	661	P=0.56with OR (95% CI) =1.03 (0.92-1.16)for at-risk allele
Lin	64	21	3	149	27	61	8	0	130	8	P value was NA; OR (95 % CI) =2.50 (1.03-6.07)for GA
Kim				4018	496				3694	410	P<0.001 with OR (95% CI) = 1.11 (0.96-1.28)for at-risk allele
Dai	1339	404	28	3082	460	1468	366	17	3302	400	P=0.037with OR (95% CI) =1.95 (1.04-3.66)for AA
Zheng				369	1251				928	2640	P=0.02with OR (95% CI) =1.20 (1.03–1.39)for at-risk allele
Barnholtz-Sloan	47	292	403	386	1098	45	254	358	344	970	P=0.882with OR (95 % CI) = 0.98 (0.82–1.17) for at-risk allele
Long				1875	585				3043	1075	P=0.011with OR (95% CI) =1.35 (0.98–1.87)for AA
Antoniou	1679	3959	2177	7317	8313	1633	3177	1865	6443	6907	P = 0.24 with HR (95 % CI) =1.03 (0.98–1.09)in BRCA1 cohort
Muligan	1639	3752	2031	7030	7814	1495	2935	1672	5925	6279	P = 0.48 with HR (95 % CI) =0.98 (0.91-1.04)in BRCA1 cohort
Harlid	796	1590	1007	3182	3604	1230	2328	1279	4788	4886	P=0.0019with OR (95% CI) =1.10 (1.04-1.17)for at-risk allele
Rinella				138	268				252	274	P<0.001 with OR (95% CI) = 1.80 (1.38-2.35)for at-risk allele

Table S1 Genotypes and P values of rs13387042 and rs3803662 polymorphisms included in the meta-analysis (continued)

rs3803662 C>T											
First author	**Cases**					**Controls**					**P value**
	CC	CT	TT	C	T	CC	CT	TT	C	T	
Stacey				6184	2924				25698	9456	P<0.001with OR (95% CI)=1.28 (1.21-1.35) for at-risk allele
Tapper				1276	522				4430	1530	P = 0.005 with OR (95% CI) = 1.19 (1.05–1.33)for at-risk allele
Mcinerney	486	382	82	1354	546	532	396	58	1460	512	P = 0.051 with OR (95% CI) = 1.15 (1.00–1.32) for at-risk allele
Barnholtz-Sloan	585	512	133	1682	778	589	440	89	1618	618	P value was NA; OR (95 % CI) = 1.25 (1.09–1.42) for at-risk allele
Tamimi	333	300	54	966	408	415	273	50	1103	373	P value was NA; OR (95 % CI) = 1.35 (0.89–2.03)for TT
Latif	422	395	84	1239	563	217	137	19	571	175	P = 0.31 with OR (95% CI) = 1.19 (0.85–1.57)in BRCA1 cohort
Gorodnova	74	50	16	198	82	77	82	15	236	112	P = 0.438 with OR (95% CI) = 1.10 (0.51–2.41)for TT
Hemminki				1896	934				2708	952	P<0.001 with OR (95% CI) = 1.33 (1.19–1.46)for at-risk allele
Slattery	778	755	204	2311	1163	978	862	202	2818	1266	P value was NA; OR (95 % CI)=1.54 (1.14-2.08)for TT
Teraoka	306	309	88	921	485	640	606	143	1886	892	P=0.06with OR (95% CI) =1.16 (0.99-1.36)for at-risk allele
Butt	353	278	64	984	406	780	512	95	2072	702	P value was NA; OR (95 % CI) =1.21 (1.05-1.40)for at-risk allele
Ottini	143	195	74	481	343	352	323	70	1027	463	P=0.0001with OR (95% CI) =1.65 (1.35–2.01)for TT
Li	118	141	32	377	205	123	128	40	374	208	P=0.854with OR (95% CI)=0.978 (0.769–1.243)for T allele
Long				4061	8629				2656	4934	P<0.001with OR (95% CI) =1.12 (1.05-1.19)for at-risk allele
Liang	126	413	486	665	1385	127	464	455	718	1374	P = 0.122 with OR (95% CI) = 1.08 (0.82–1.42)for TT
Seuta				560	834				1310	1478	P<0.001with OR (95% CI) =1.32 (1.15–1.52)for at-risk allele
Han	369	1435	1481	2173	4397	516	1617	1361	2649	4339	P<0.001with OR (95% CI) =1.27 (1.15–1.41)for Dominant model
Kim				1408	3106				1477	2627	P<0.001 with OR (95% CI) = 1.24 (1.14-1.36)for at-risk allele
Barnholtz-Sloan	166	378	196	710	770	142	333	182	617	697	P value was NA; OR (95 % CI) = 0.95 (0.81–1.11)for at-risk allele
Garcia-Closas	7759	7132	1848	22650	10828	13295	9705	2026	36295	13757	P = 0.015 with OR (95% CI) = 1.14 (1.09–1.21)for per allele by ER-negative cases
Antoniou	2422	2173	497	7017	3167	2244	1831	382	6319	2595	P<0.001 with HR (95% CI) = 1.13 (1.06–1.20)for per allele
Campa	3706	3528	1071	10940	5670	5721	4724	1150	16166	7024	P<0.001 with HR (95% CI) =1.16 (1.11-1.21)for per allele
Muligan	3109	2652	585	8870	3822	2899	2197	426	7995	3049	P = 0.21 with HR (95 % CI) =1.05 (0.97-1.13)in BRCA1 cohort
Harlid	1794	1420	330	5008	2080	2768	1898	352	7434	2602	P<0.001with OR (95% CI) =1.18 (1.11–1.27)for at-risk allele
Rinella				219	187				326	200	P<0.001 with OR (95% CI) = 1.80 (1.38-2.35)for at-risk allele