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LOC643714 Polymorphisms Contribute to an Elevated Susceptibility to Breast Cancer: A Meta-analysis of 231,191 Subjects

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Abstract

This is the most comprehensive meta-analysis on *LOC643714* polymorphisms and breast cancer so far, and our findings indicated that *LOC643714* rs3803662, rs8051542, rs12443621, and rs12922061 polymorphism were all significantly associated with breast cancer in certain populations.

Background: Several recent genome-wide association studies tried to explore associations between *LOC643714* polymorphisms and breast cancer (BC). However, the results of these studies were inconsistent. The purpose of this meta-analysis was to better analyze the effects of *LOC643714* polymorphisms on individual susceptibility to BC in a larger pooled population. **Materials and Methods:** PubMed, Web of Science, and Embase were searched for eligible studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of associations. **Results:** In total, 42 studies with 231,191 subjects were analyzed. Significant associations with BC were observed for rs3803662 (dominant comparison: OR, 0.89; 95% CI, 0.84-0.95; $P = .0008$; recessive comparison: OR, 1.17; 95% CI, 1.07-1.28; $P = .0004$; over-dominant comparison: OR, 1.07; 95% CI, 1.02-1.11; $P = .002$; allele comparison: OR, 0.90; 95% CI, 0.86-0.95; $P = .0002$), rs8051542 (dominant comparison: OR, 0.87; 95% CI, 0.83-0.91; $P < .0001$; recessive comparison: OR, 1.19; 95% CI, 1.11-1.28; $P < .0001$; over-dominant comparison: OR, 1.07; 95% CI, 1.02-1.11; $P = .004$; allele comparison: OR, 0.89; 95% CI, 0.86-0.91; $P < .0001$), and rs12922061 (dominant comparison: OR, 0.83; 95% CI, 0.73-0.93; $P = .002$; over-dominant comparison: OR, 1.43; 95% CI, 1.27-1.61; $P < .0001$) polymorphisms in the overall population. Further subgroup analyses yielded similar positive results for rs3803662 and rs8051542 polymorphisms in Asians, Caucasians, and Africans, for rs12443621 polymorphism in Caucasians, and for rs12922061 polymorphism in Asians. **Conclusions:** Our findings suggested that *LOC643714* rs3803662, rs8051542, rs12443621, and rs12922061 polymorphisms were all significantly associated with BC in certain populations.

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Introduction

Breast cancer (BC) is the second most common cancer all over the world, and the most frequent cancer among women.[1] Despite rapid progress in chemotherapy and minimally invasive surgery achieved in recent years, BC still ranks as the fifth most common cause of cancer-related deaths in both genders, and the primary cause of cancer-related deaths in women.[2] Despite its high prevalence, the pathogenesis of BC is still poorly understood. Although obesity, hormone replacement therapy, and radiation were identified as potential risk factors of developing BC,[3,4] the fact that the odds of developing BC in individuals exposed to above mentioned carcinogenic factors were quite different indicated that individual genetic traits were also involved in the development of BC.

Recently, a genome-wide association study (GWAS) conducted by Antoniou et al[5] found that the *LOC643714* rs3803662 C/T polymorphism was significantly associated with BC in Caucasians. Since then, numerous genetic association studies were performed in diverse populations to investigate potential associations between *LOC643714* polymorphisms (rs3803662, rs8051542, rs12443621, and rs12922061) and BC, with inconsistent

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results.[6-9] Therefore, we conducted a meta-analysis of all relevant studies to more comprehensively analyze the effects of *LOC643714* polymorphisms on individual susceptibility to BC in a larger pooled population.

Materials and Methods

Literature Search and Inclusion Criteria

The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[10] PubMed, Web of Science, and Embase were searched for potentially eligible articles using the combination of following terms: (*LOC643714* OR TOX3 OR TNRC9) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (breast OR mammary gland) AND (cancer OR tumor OR oncology OR carcinoma OR malignancy). The reference lists of retrieved articles were also screened for other potentially eligible studies.

To test the research hypothesis of this meta-analysis, included studies should meet all the following criteria: (1) case-control study about *LOC643714* polymorphisms and BC; (2) providing sufficient data for calculating odds ratios (ORs) and 95% confidence intervals (CIs); and (3) full text in English available. Studies were excluded if one of the following conditions was fulfilled: (1) not related to *LOC643714* polymorphisms and BC in human beings; (2) pedigree studies; (3) in vitro studies or animal studies; and (4) case reports or case series (no control). In the case of duplicate reports by the same authors, we only included the most complete study.

Data Extraction and Quality Assessment

We extracted the following information from eligible studies: (1) name of the first author; (2) year of publication; (3) country and ethnicity of participants; (4) sample size; and (5) genotypic distributions of *LOC643714* polymorphisms in cases and controls. The probability value (*P* value) of Hardy-Weinberg equilibrium was also calculated.

We used the Newcastle-Ottawa scale to evaluate the quality of eligible studies.[11] The Newcastle-Ottawa scale has a score range of 0 to 9, and studies with a score of more than 7 were thought to be of high quality.

Two reviewers (F.G. and R.G.) conducted data extraction and quality assessment independently. When necessary, we wrote to the corresponding authors for extra information. Any disagreement between the 2 reviewers was solved by discussion until a consensus was reached.

Statistical Analyses

In the current study, we performed statistical analyses by using Review Manager Version 5.3.3. We calculated ORs and 95% CIs to estimate potential associations between *LOC643714* polymorphisms and BC in dominant, recessive, over-dominant, and allele models, and a *P* value of .05 or less was defined as statistically significant. All investigated *LOC643714* polymorphisms contain a major allele (M) and a minor allele (m), the dominant model is defined as MM versus Mm + mm, the recessive model is defined as mm versus MM + Mm, the over-dominant model is defined as Mm versus MM + mm, and the allele model is defined as M versus m. Between-study heterogeneities were evaluated by the I^2 statistic. Random-effect models (DerSimonian-Laird method) would be used for analyses if I^2 was greater than 50%. Otherwise, analyses would be conducted with fixed-effect models (Mantel-Haenszel method). Subgroup analyses were subsequently carried out by ethnicity. Stabilities of synthetic results were tested in sensitivity analyses. Publication biases were assessed by funnel plots.

Results

Characteristics of Included Studies

The process of literature searching was shown in Figure 1. We found 373 articles by using our searching strategy. After excluding irrelevant and duplicate articles, 76 articles were retrieved for further evaluation. Another 34 articles were subsequently excluded after reading the full text. Ultimately, a total of 42 eligible studies involving 95,333 cases and 135,858 controls were enrolled for analyses (Figure 1). Characteristics of included studies are shown in Table 1.

Overall and Subgroup Analyses

In total, 231,191 subjects were analyzed. Significant associations with BC were observed for rs3803662 (dominant comparison: OR, 0.89; 95% CI, 0.84-0.95; $P = .0008$; recessive comparison: OR, 1.17; 95% CI, 1.07-1.28; $P = .0004$; over-dominant comparison: OR, 1.07; 95% CI, 1.02-1.11; $P = .002$; allele comparison: OR, 0.90; 95% CI, 0.86-0.95; $P = .0002$), rs8051542 (dominant comparison: OR, 0.87; 95% CI, 0.83-0.91; $P < .0001$; recessive comparison: OR, 1.19; 95% CI, 1.11-1.28; $P < .0001$; over-dominant comparison: OR, 1.07; 95% CI, 1.02-1.11; $P = .004$; allele comparison: OR, 0.89; 95% CI, 0.86-0.91; $P < .0001$) and rs12922061 (dominant comparison: OR, 0.83; 95% CI, 0.73-0.93; $P = .002$; over-dominant comparison: OR, 1.43; 95% CI, 1.27-1.61; $P < .0001$) polymorphisms in the overall population. Further subgroup analyses yielded similar positive results for rs3803662 and rs8051542 polymorphisms in Asians, Caucasians, and Africans, for rs12443621 polymorphism in Caucasians, and for rs12922061 polymorphism in Asians (Table 2).

Sensitivity Analyses

We conducted sensitivity analyses to test the effects of individual study on pooled results. The significant associations detected in pooled analyses remained unchanged in all comparisons, which suggested that our findings were statistically robust.

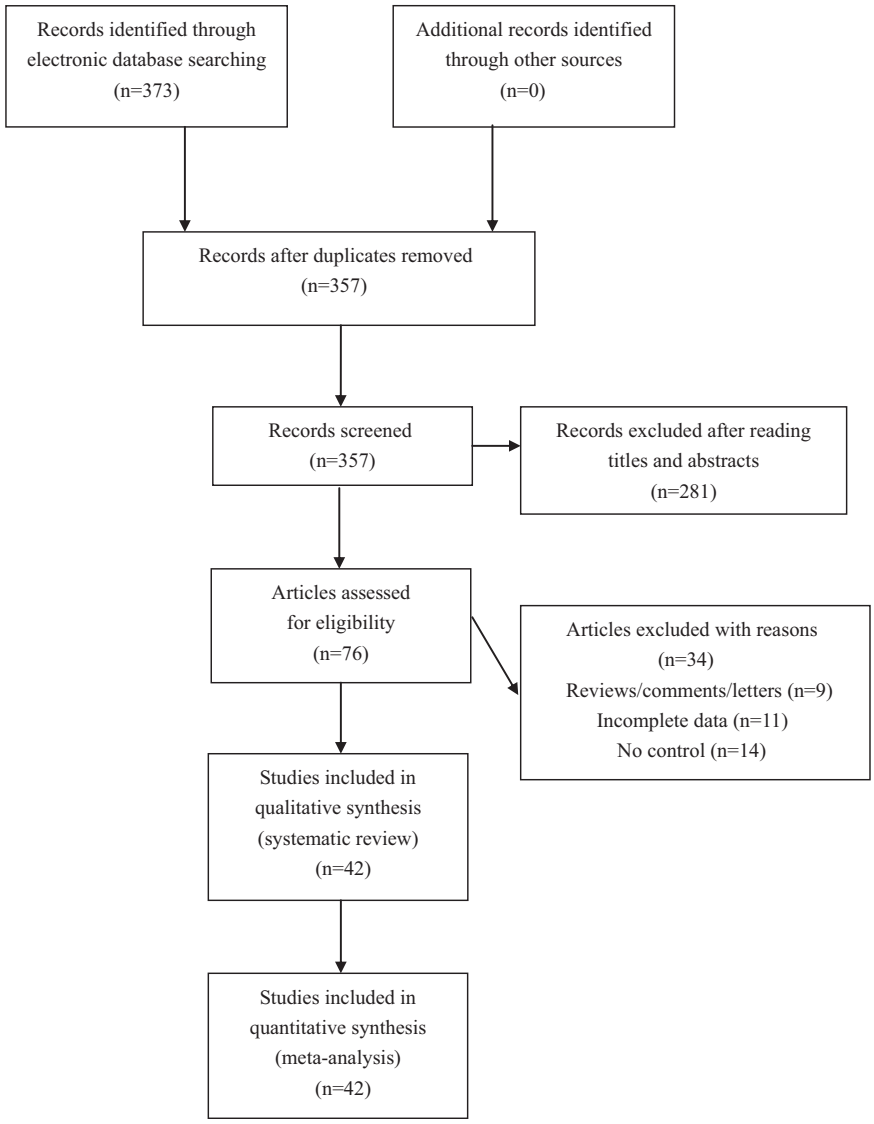
Publication Biases

We used funnel plots to evaluate potential publication biases. The shape of funnel plots was symmetrical for every comparison, which indicated that severe publication biases were unlikely (see Supplemental Figure 1 in the online version).

Discussion

As far as we know, this is so far the most comprehensive meta-analysis about *LOC643714* polymorphisms and BC. The pooled analyses revealed that the *LOC643714* rs3803662, rs8051542, rs12443621, and rs12922061 polymorphisms were all significantly associated with BC in certain populations. The stabilities of synthetic results were evaluated by sensitivity analyses, and no alterations of results were observed in any comparisons, which suggested that our findings were statistically stable. As for evaluation of heterogeneities, significant heterogeneities were detected for rs3803662

Figure 1 Flowchart of Study Selection for the Present Study



polymorphism in every comparison of overall analyses, and thus all analyses were performed with random-effect models. But in further subgroup analyses, a reduction tendency of heterogeneity was found for Caucasians, which suggested that differences in ethnicity could partially explain observed heterogeneities between studies.

There are several points that worth noting about this meta-analysis. First, the functional significances of investigated polymorphisms were still largely unclear, and thus future studies are still warranted to explore the underlying molecular mechanisms of our positive findings. Second, it is notable that the trends of associations in different ethnicities for rs3803662 and rs12443621 polymorphisms were not consistent, and this may be attributed to ethnic differences in genotypic distributions of investigated polymorphisms. However, it is also possible that this phenomenon may be resulted from a complex interaction of genetic and environmental factors. Third, the genetic traits of BC are extremely complex, so to better elucidate potential roles of genetic polymorphisms in BC, we strongly recommend future studies to conduct haplotype analyses and investigate potential gene-gene interactions.[12,13]

Some limitations of this meta-analysis should also be noted when interpreting our findings. First, owing to the lack of raw data, our pooled analyses were based on unadjusted estimations, and we have to admit that failure to perform further adjusted analyses may impact the reliability of our findings.[14] Second, heterogeneities between studies remained significant in certain subgroup comparisons for rs3803662 and rs12443621 polymorphisms, which suggested that the inconsistent results of included studies could not be fully attributed to ethnicity, and differences in other unmeasured characteristics of participants may also contribute to

Table 1 The Characteristics of Included Studies

First Author, Year	Country	Ethnicity	Sample Size	Genotype Distribution		*P* Value for HWE	NOS Score
				Cases	Controls		
rs3803662 C/T				CC/CT/TT			
Antoniou 2008	UK	Caucasian	5092/4457	2422/2173/497	2244/1831/382	.756	8
Barnholtz-Sloan 2010	USA	Caucasian	1230/1118	585/512/133	589/440/89	.591	8
Barnholtz-Sloan 2010	USA	African	740/657	196/378/166	182/333/142	.654	8
Barzan 2013	Germany	Caucasian	311/960	135/140/36	526/369/65	.979	7
Barzan 2013	Germany	Asian	984/2176	482/413/89	961/990/225	.200	7
Butt 2012	Sweden	Caucasian	694/1387	353/278/64	780/512/95	.380	8
Campa 2011	Germany	Mixed	8305/11,595	3706/3528/1071	5721/4724/1150	<.001	8
Campa 2015	Germany	Mixed	1202/12,098	572/514/116	6132/4896/1070	.038	7
Chen 2014	China	Asian	388/482	159/178/51	217/227/38	.042	8
Chen 2015	China	Asian	253/343	109/114/30	167/155/21	.055	8
Chen 2016	China	Asian	105/382	76/21/8	250/96/36	<.001	8
Elematore 2014	Chile	Mixed	347/801	100/185/62	330/371/100	.786	8
Garcia-closas 2008	USA	Mixed	16,739/25,026	7759/7132/1848	13,295/9705/2026	<.001	8
Gorodnova 2010	Russia	Caucasian	140/174	74/50/16	77/82/15	.294	8
Han 2011	Korea	Asian	3285/3494	1481/1435/369	1361/1617/516	.317	8
Harlid 2012	Sweden	Caucasian	3544/5018	1794/1420/330	2768/1898/352	.280	8
He 2014	China	Asian	623/620	271/280/72	270/278/72	.973	8
He 2016	China	Asian	254/339	109/115/30	164/154/21	.053	8
Huo 2012	USA	African	1509/1383	393/754/362	368/691/324	.991	7
Jiang 2011	China	Asian	493/510	233/212/48	232/224/54	.995	7
Kim 2012	Korea	Asian	4325/4221	1887/1939/499	1677/1967/577	.996	7
Latif 2010	UK	Caucasian	901/373	422/395/84	217/137/19	.660	8
Li 2009	China	Asian	291/291	118/141/32	123/128/40	.470	8
Liang 2010	China	Asian	1025/1046	486/413/126	455/464/127	.603	8
Liao 2018	China	Asian	104/112	48/44/12	37/60/15	.226	8
Long 2010	USA	Caucasian	2760/2609	1330/1172/258	1391/1028/190	.997	7
Long 2010	USA	Asian	6345/3795	2934/2761/650	1603/1727/465	.996	7
Low 2013	Japan	Asian	5522/5489	1801/2705/1016	1496/2739/1254	.996	7
Mazhar 2016	Pakistan	Mixed	96/90	50/46/0	64/25/1	.397	8
Mizoo 2013	Japan	Asian	464/460	160/230/74	142/227/91	.987	8
Mulligan 2011	UK	Mixed	6346/5522	3109/2652/585	2899/2197/426	.730	8
O'Brien 2014	USA	Caucasian	1247/1105	NA	NA	NA	7
O'Brien 2014	USA	African	766/681	NA	NA	NA	7
Orr 2012	UK	Mixed	1259/3265	529/576/154	1797/1227/241	.116	8
Ottini 2013	Italy	Caucasian	412/745	143/195/74	352/323/70	.741	8
Rinella 2013	USA	Caucasian	680/787	214/335/131	315/366/106	.984	7
Ruiz-Narváez 2010	USA	African	753/825	188/376/189	214/412/199	.980	7
Shan 2012	Qatar	Caucasian	640/369	200/293/147	126/165/78	.083	8
Slattery 2011	USA	Caucasian	1737/2042	755/778/204	978/862/202	.550	8
Stacey 2007	Iceland	Caucasian	4554/17,577	2100/1985/469	9392/6913/1272	.999	7
Stacey 2007	Iceland	Asian	552/557	155/275/122	147/278/132	.980	7
Stacey 2007	Iceland	African	422/447	95/211/116	130/222/95	.990	7
Stacey 2007	Iceland	Mixed	562/713	183/275/104	259/340/114	.891	7
Tajbakhsh 2018	Iran	Mixed	430/513	160/211/59	240/225/48	.649	7

Table 1 Continued

First Author, Year	Country	Ethnicity	Sample Size	Genotype Distribution		*P* Value for HWE	NOS Score
				Cases	Controls		
Tamimi 2010	USA	Caucasian	687/783	333/300/54	415/273/50	.576	8
Tapper 2008	UK	Caucasian	899/2980	452/371/76	1647/1137/196	.990	7
Thanh 2018	Vietnam	Asian	100/100	38/47/15	23/55/22	.317	8
Udler 2010	UK	Caucasian	2177/2259	1041/942/194	1273/829/157	.255	8
Zheng 2009	USA	Asian	3039/3082	1401/1325/313	1286/1410/386	.987	7
rs8051542 C/T				CC/CT/TT			
Barnholtz-Sloan 2010	USA	Caucasian	1230/1118	386/587/257	358/559/201	.501	8
Barnholtz-Sloan 2010	USA	African	742/658	313/342/87	295/304/59	.121	8
Barzan 2013	Germany	Asian	984/2206	614/327/43	1483/651/72	0.957	7
Barzan 2013	Germany	Caucasian	311/960	75/155/81	301/473/186	0.994	7
Butt 2012	Sweden	Caucasian	679/1352	192/338/149	443/637/272	0.119	8
He 2014	China	Asian	623/620	399/199/25	427/175/18	0.989	8
Li 2009	China	Asian	295/308	198/82/15	209/90/9	0.854	8
Liang 2010	China	Asian	1032/1064	670/314/48	708/309/47	0.078	8
Long 2010	USA	Asian	6158/3658	3941/1971/246	2460/1080/118	0.968	7
Long 2010	USA	Caucasian	1587/1439	463/788/336	451/709/279	0.991	7
Mazhar 2016	Pakistan	Mixed	96/90	45/37/14	35/38/17	0.253	8
O'Brien 2014	USA	Caucasian	1247/1105	NA	NA	NA	7
O'Brien 2014	USA	African	766/681	NA	NA	NA	7
Shan 2012	Qatar	Caucasian	635/368	208/289/138	146/176/46	0.529	8
Tamimi 2010	USA	Caucasian	685/735	194/359/132	220/380/135	0.193	8
Udler 2010	UK	Caucasian	2155/2228	611/1089/455	736/1067/425	0.274	8
Zheng 2009	USA	Asian	810/1784	381/349/80	852/762/170	0.984	7
rs12443621 A/G				AA/AG/GG			
Barnholtz-Sloan 2010	USA	Caucasian	1230/1118	313/580/337	302/574/242	0.319	8
Barnholtz-Sloan 2010	USA	African	742/658	208/370/164	164/329/165	0.999	8
Butt 2012	Sweden	Caucasian	698/1383	195/338/165	451/657/275	0.202	8
Chen 2016	China	Asian	105/382	71/24/10	209/94/79	<0.001	8
He 2014	China	Asian	623/620	209/304/110	201/304/115	0.998	8
Jiang 2011	China	Asian	493/510	170/239/84	162/251/97	0.990	7
Li 2009	China	Asian	298/293	106/138/54	97/141/55	0.766	8
Liang 2010	China	Asian	1040/1061	347/507/186	338/519/204	0.850	8
Long 2010	USA	Asian	2954/2997	960/1448/546	974/1469/554	0.998	7
Long 2010	USA	Caucasian	1145/1142	286/573/286	297/571/274	0.989	7
Shan 2012	Qatar	Caucasian	638/363	190/301/147	98/180/85	0.894	8
Tamimi 2010	USA	Caucasian	681/737	193/337/151	241/366/130	0.659	8
Udler 2010	UK	Caucasian	2184/2277	546/1111/527	681/1099/497	0.176	8
Zheng 2009	USA	Asian	810/1784	216/405/189	470/891/423	0.986	7
rs12922061 C/T				CC/CT/TT			
Liao 2018	China	Asian	104/112	49/44/11	69/40/3	0.318	8
Low 2013	Japan	Asian	5522/5489	NA	NA	NA	7
Udler 2010	UK	Caucasian	2087/2273	1176/881/130	1375/767/131	0.082	8

Abbreviations: HWE = Hardy-Weinberg equilibrium; NA = not available; NOS = Newcastle-Ottawa scale.

Table 2 Results of Overall and Subgroup Analyses

Polymorphisms	Population	Sample Size	Dominant Comparison		Recessive Comparison		Over-dominant Comparison		Allele Comparison	
			P Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
rs3803662 C/T	Overall	95,333/135,858	**.0008**	**0.89 (0.84-0.95)**	**.0004**	**1.17 (1.07-1.28)**	**.002**	**1.07 (1.02-1.11)**	**.0002**	**0.90 (0.86-0.95)**
	Asian	28,152/27,499	**<.0001**	**1.15 (1.09-1.23)**	**.009**	**0.88 (0.80-0.97)**	**<.0001**	**0.93 (0.90-0.96)**	**.0001**	**1.11 (1.05-1.16)**
	African	4190/3993	.14	0.92 (0.83-1.03)	.16	1.08 (0.97-1.21)	.97	1.00 (0.91-1.10)	**.04**	**0.94 (0.88-1.00)**
	Caucasian	27,705/44,743	**<.0001**	**0.79 (0.74-0.83)**	**<.0001**	**1.35 (1.28-1.43)**	**<.0001**	**1.15 (1.11-1.19)**	**<.0001**	**0.81 (0.77-0.85)**
rs8051542 C/T	Overall	20,035/20,374	**<.0001**	**0.87 (0.83-0.91)**	**<.0001**	**1.19 (1.11-1.28)**	**.004**	**1.07 (1.02-1.11)**	**<.0001**	**0.89 (0.86-0.91)**
	Asian	9902/9640	**<.0001**	**0.88 (0.82-0.93)**	**.01**	**1.20 (1.04-1.38)**	**.001**	**1.11 (1.04-1.18)**	**<.0001**	**0.89 (0.84-0.94)**
	African	1508/1339	.32	0.90 (0.73-1.11)	.09	1.35 (0.95-1.91)	.97	1.00 (0.81-1.23)	**.002**	**0.84 (0.75-0.94)**
	Caucasian	8529/9305	**<.0001**	**0.85 (0.79-0.91)**	**<.0001**	**1.19 (1.09-1.29)**	.34	1.03 (0.97-1.10)	**<.0001**	**0.89 (0.85-0.93)**
rs12443621 A/G	Overall	13,641/15,325	.77	0.99 (0.91-1.07)	.45	1.04 (0.94-1.14)	.91	1.00 (0.95-1.05)	.76	0.99 (0.93-1.06)
	Asian	6323/7647	.20	1.05 (0.97-1.13)	.24	0.95 (0.87-1.03)	.80	0.99 (0.93-1.06)	.13	1.04 (0.99-1.09)
	Caucasian	6576/7020	**<.0001**	**0.86 (0.80-0.93)**	**<.0001**	**1.18 (1.09-1.28)**	.92	1.00 (0.94-1.07)	**<.0001**	**0.89 (0.85-0.93)**
rs12922061 C/T	Overall	7713/7874	**.002**	**0.83 (0.73-0.93)**	.36	1.85 (0.50-6.89)	**<.0001**	**1.43 (1.27-1.61)**	.32	0.90 (0.73-1.11)
	Asian	5626/5601	**.03**	**0.56 (0.32-0.95)**	.03	4.30 (1.16-15.87)	.32	1.32 (0.76-2.28)	**<.0001**	**0.81 (0.76-0.86)**

The values in bold represent there is statistically significant differences between cases and controls.
All investigated *LOC643714* polymorphisms contain a major allele (M) and a minor allele (m), the dominant model is defined as MM versus Mm + mm, the recessive model is defined as mm versus MM + Mm, the over-dominant model is defined as Mm versus MM + mm, and the allele model is defined as M versus m.
Abbreviations: CI = confidence interval; NA = not available; OR = odds ratio.

heterogeneities.[15] Third, associations between *LOC643714* polymorphisms and BC may also be modified by gene-environmental interactions. However, most studies did not evaluate the effects of these potential interactions, which impeded us from conduct relevant analyses.[16] Considering the above mentioned limitations, our findings should be interpreted with caution.

Conclusion

In summary, our meta-analysis suggested that *LOC643714* rs3803662, rs8051542, rs12443621, and rs12922061 polymorphisms may serve as potential genetic biomarkers of BC in certain populations. Further well-designed experimental studies should try to elucidate the underlying molecular mechanisms of our positive findings.

Clinical Practice Points

- Several recent genome-wide association studies tried to explore associations between *LOC643714* polymorphisms and BC. However, the results of these studies were inconsistent.
- The purpose of this meta-analysis was to better analyze the effects of *LOC643714* polymorphisms on individual susceptibility to BC in a larger pooled population. As far as we know, this is so far the most comprehensive meta-analysis about *LOC643714* polymorphisms and BC.
- The pooled analyses revealed that the *LOC643714* rs3803662, rs8051542, rs12443621, and rs12922061 polymorphisms were all significantly associated with BC in certain populations, suggesting that these polymorphisms may be used as genetic biomarkers of BC.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.04.016.

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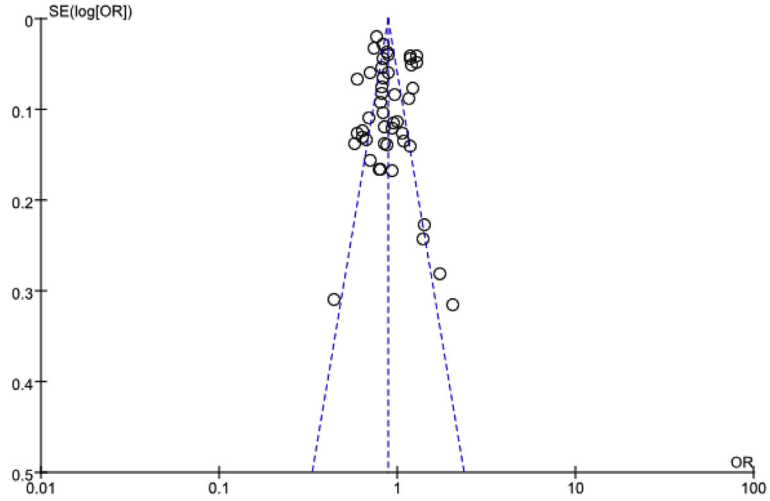
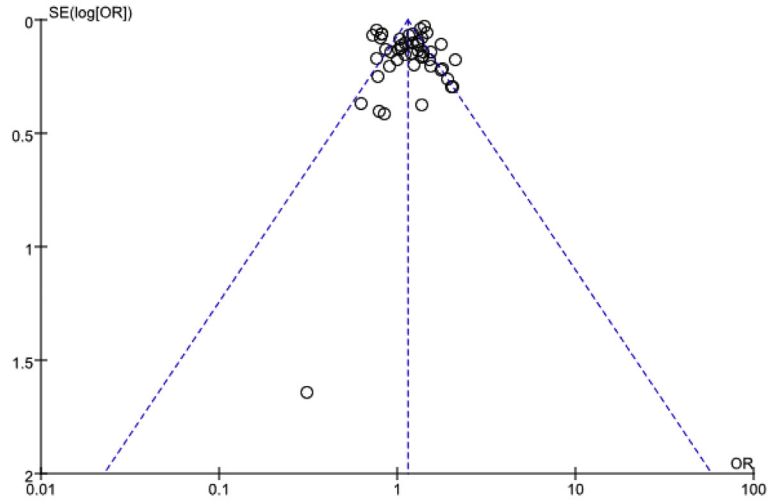
Supplemental Figure 1 **Funnel Plots. A, Funnel Plot of rs3803662 Polymorphism and Breast Cancer Under Dominant Comparison; B, Funnel Plot of rs3803662 Polymorphism and Breast Cancer Under Recessive Comparison; C, Funnel Plot of rs3803662 Polymorphism and Breast Cancer Under Over-dominant Comparison; D, Funnel Plot of rs3803662 Polymorphism and Breast Cancer Under Allele Comparison; E, Funnel Plot of rs8051542 Polymorphism and Breast Cancer Under Dominant Comparison; F, Funnel Plot of rs8051542 Polymorphism and Breast Cancer Under Recessive Comparison; G, Funnel Plot of rs8051542 Polymorphism and Breast Cancer Under Over-dominant Comparison; H, Funnel Plot of rs8051542 Polymorphism and Breast Cancer Under Allele Comparison; I, Funnel Plot of rs12443621 Polymorphism and Breast Cancer Under Dominant Comparison; J, Funnel Plot of rs12443621 Polymorphism and Breast Cancer Under Recessive Comparison; K, Funnel Plot of rs12443621 Polymorphism and Breast Cancer Under Over-dominant Comparison; L, Funnel Plot of rs12443621 Polymorphism and Breast Cancer Under Allele Comparison; M, Funnel Plot of rs12922061 Polymorphism and Breast Cancer Under Dominant Comparison; N, Funnel Plot of rs12922061 Polymorphism and Breast Cancer Under Recessive Comparison; O, Funnel Plot of rs12922061 Polymorphism and Breast Cancer Under Over-dominant Comparison; P, Funnel Plot of rs12922061 Polymorphism and Breast Cancer Under Allele comparison**



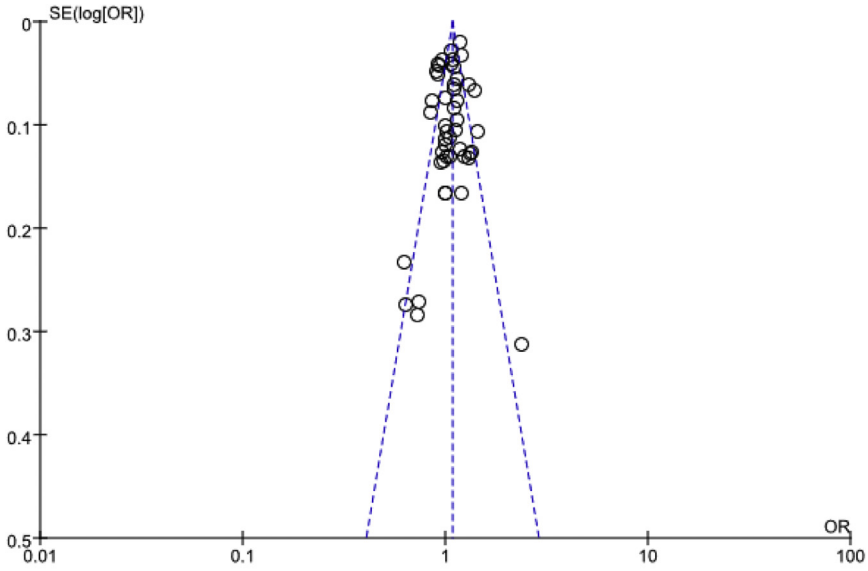
Funnel plot of rs3803662 polymorphism and breast cancer under dominant comparison



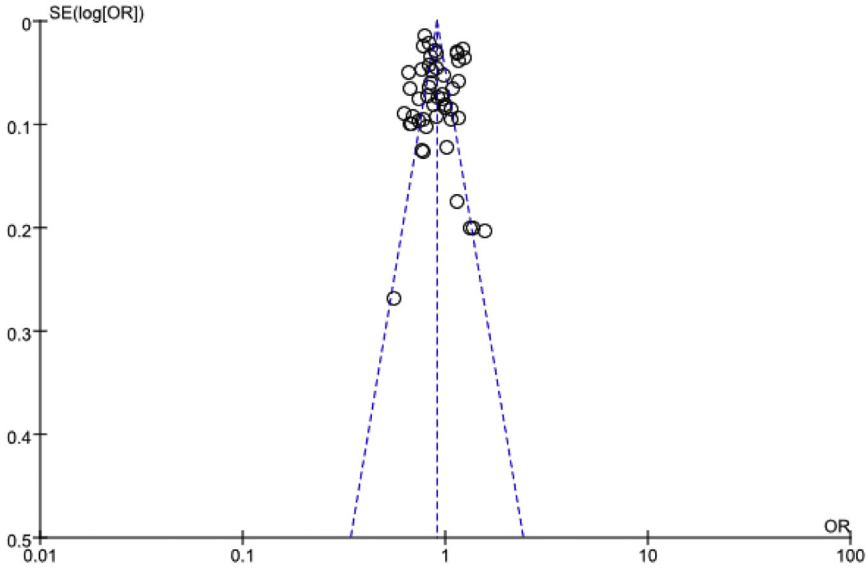
Funnel plot of rs3803662 polymorphism and breast cancer under recessive comparison

Abbreviations: OR = odds ratio; SE = standard error.

Supplemental Figure 1 Continued

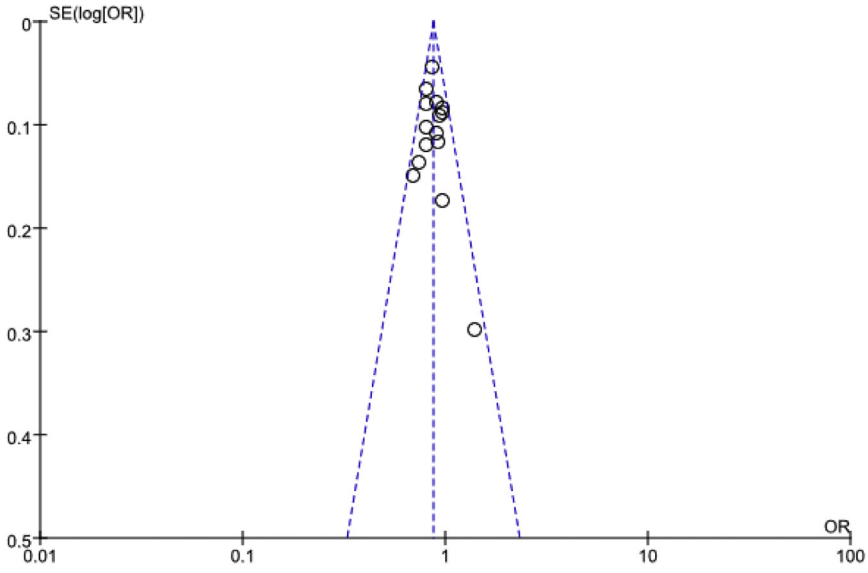


Funnel plot of rs3803662 polymorphism and breast cancer under over-dominant comparison

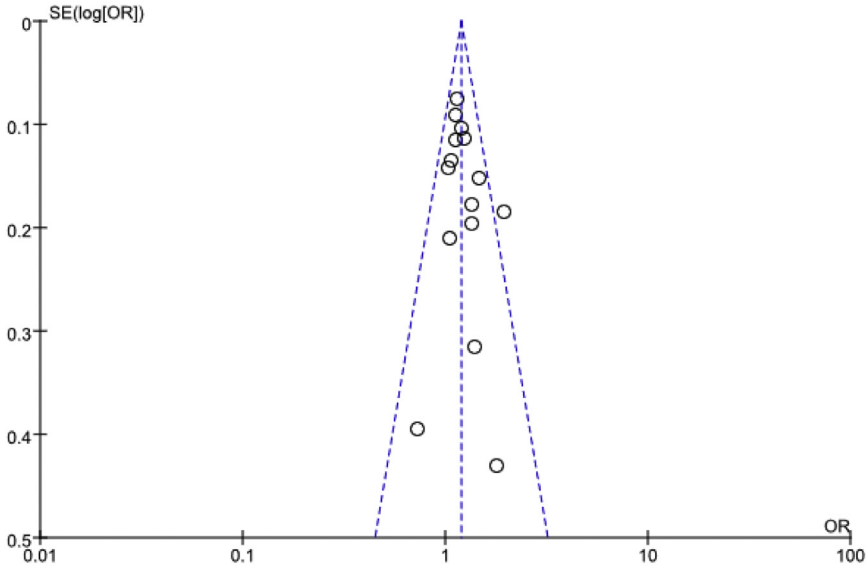


Funnel plot of rs3803662 polymorphism and breast cancer under allele comparison

Supplemental Figure 1 Continued

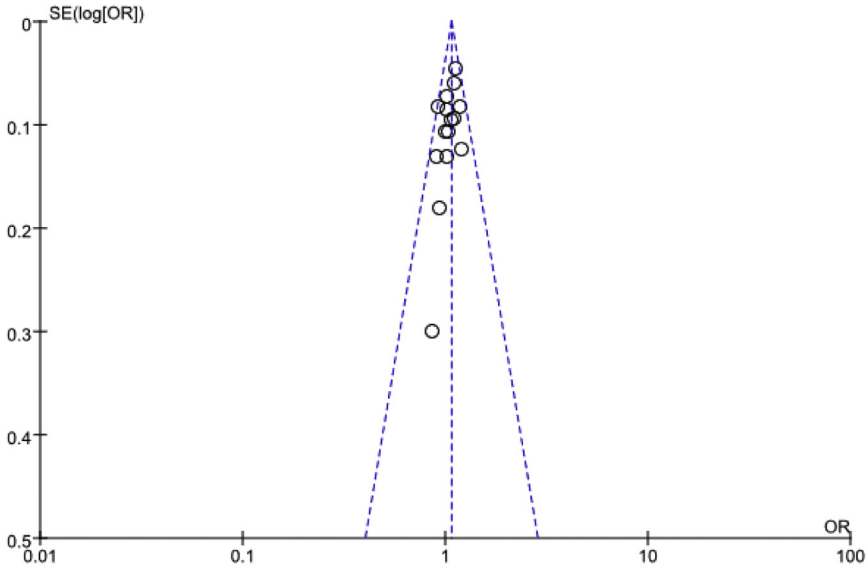


Funnel plot of rs8051542 polymorphism and breast cancer under dominant comparison

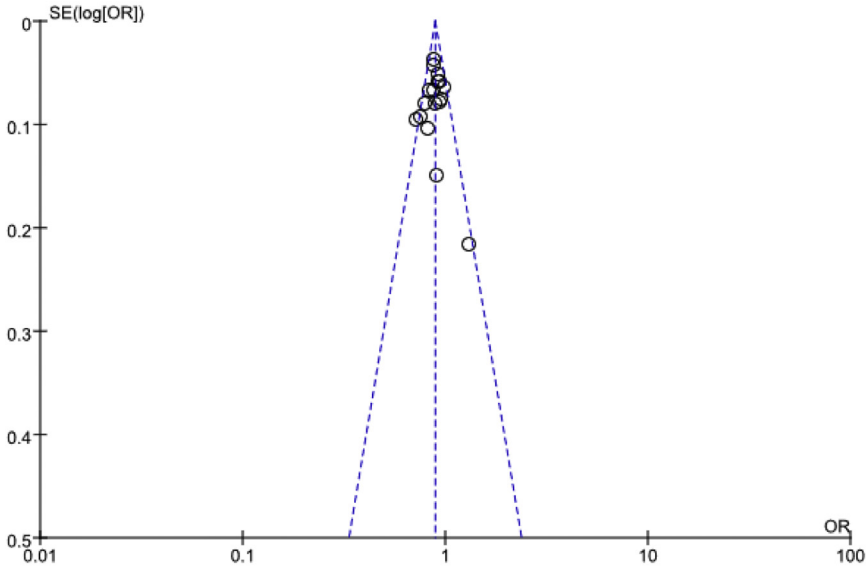


Funnel plot of rs8051542 polymorphism and breast cancer under recessive comparison

Supplemental Figure 1 Continued

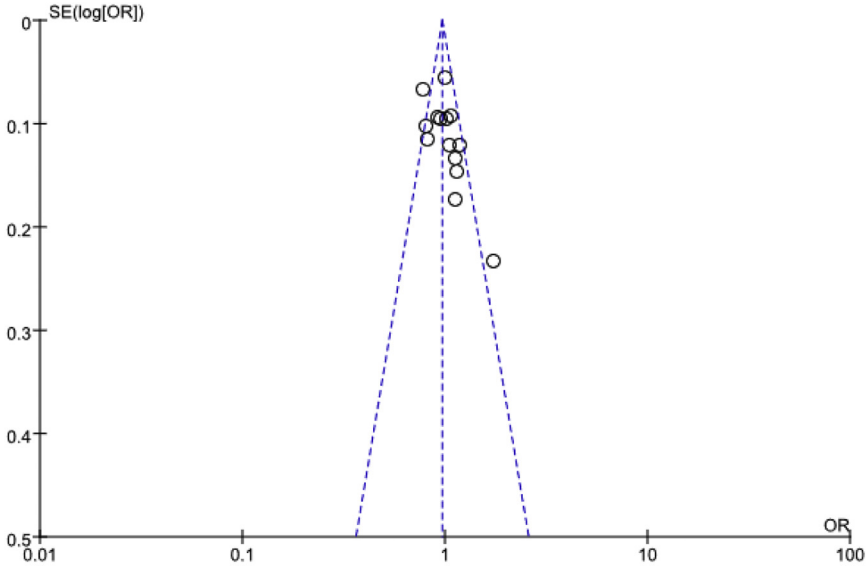


Funnel plot of rs8051542 polymorphism and breast cancer under over-dominant comparison

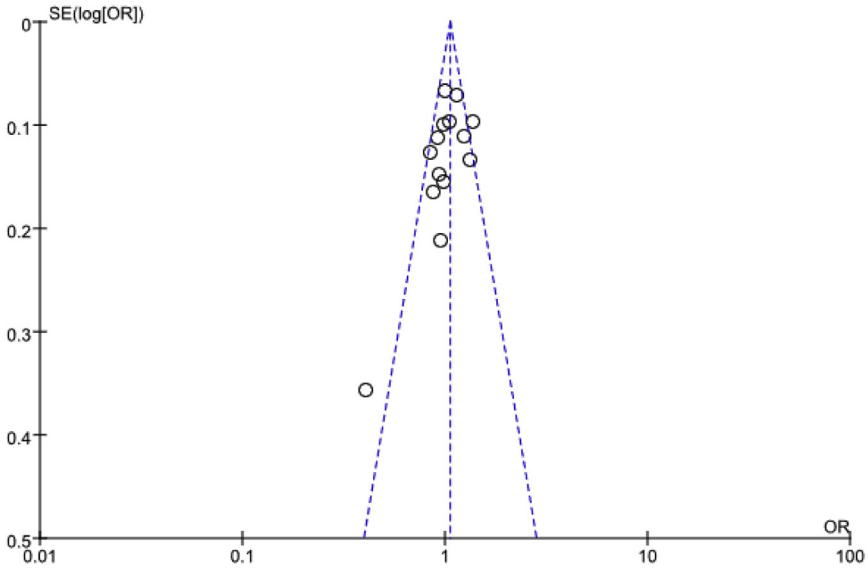


Funnel plot of rs8051542 polymorphism and breast cancer under allele comparison

Supplemental Figure 1 Continued

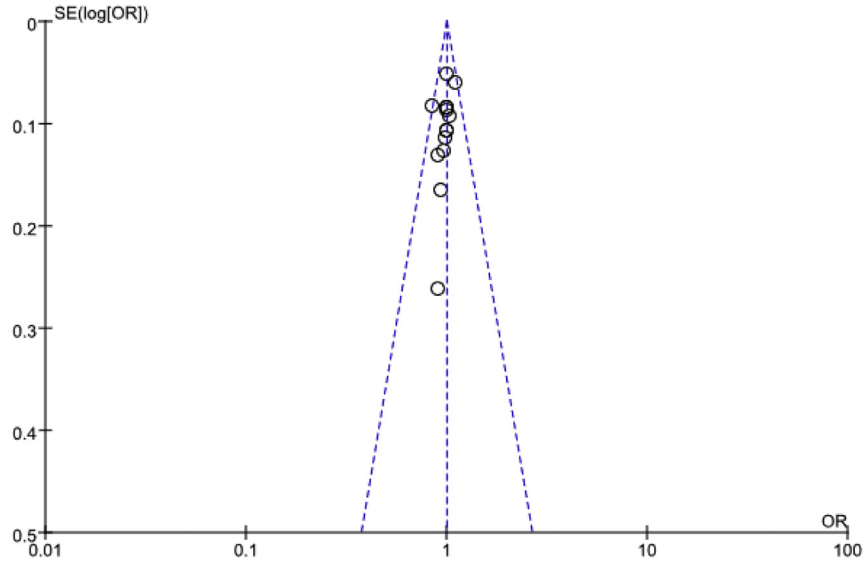


Funnel plot of rs12443621 polymorphism and breast cancer under dominant comparison

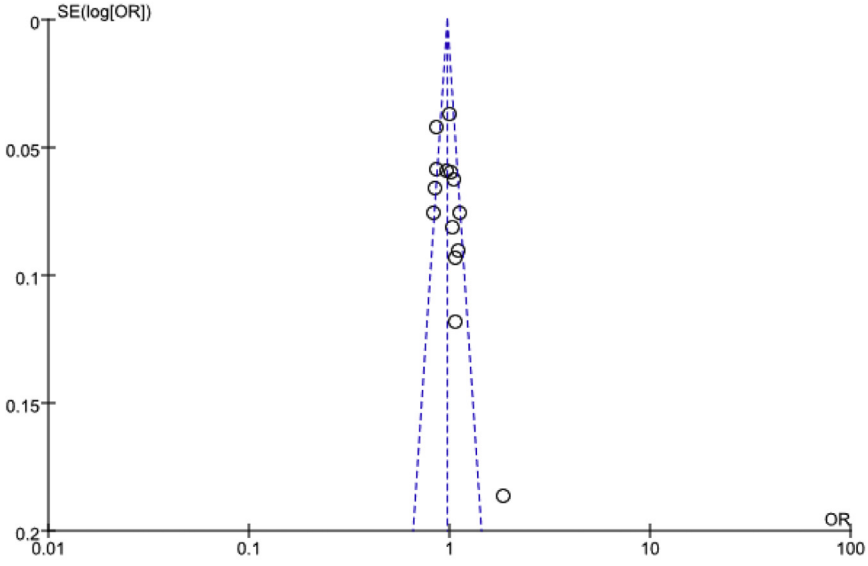


Funnel plot of rs12443621 polymorphism and breast cancer under recessive comparison

Supplemental Figure 1 Continued

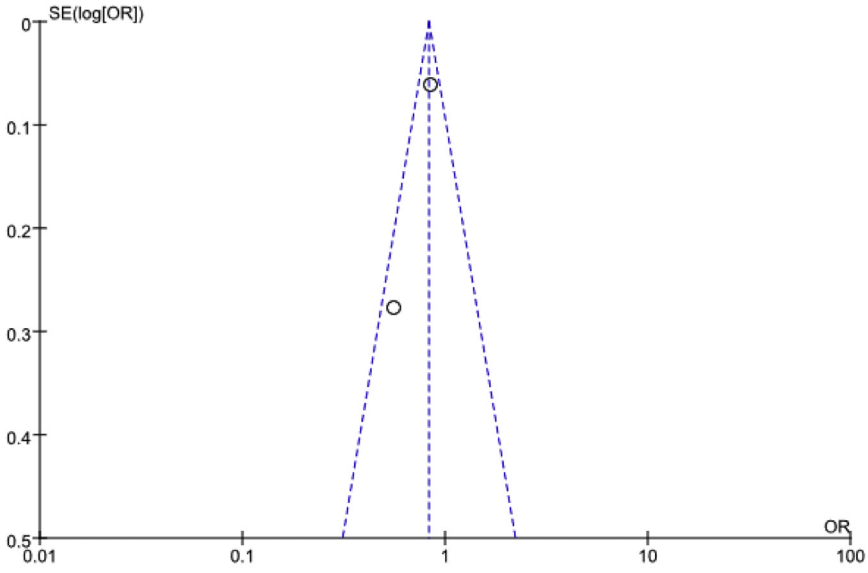


Funnel plot of rs12443621 polymorphism and breast cancer under over-dominant comparison

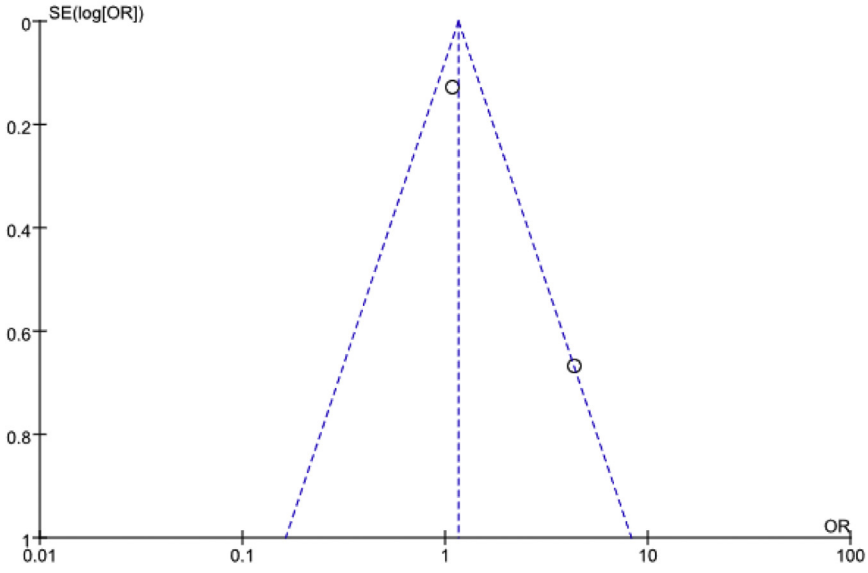


Funnel plot of rs12443621 polymorphism and breast cancer under allele comparison

Supplemental Figure 1 Continued

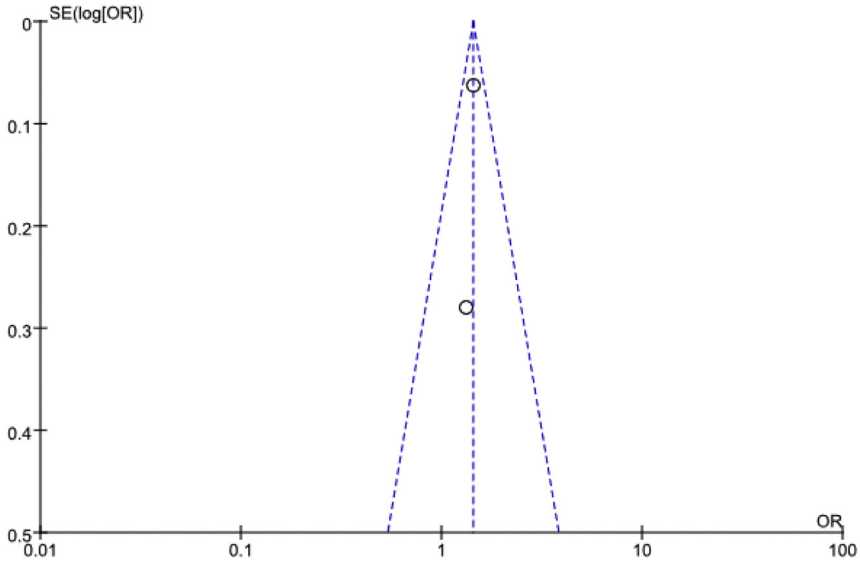


Funnel plot of rs12922061 polymorphism and breast cancer under dominant comparison

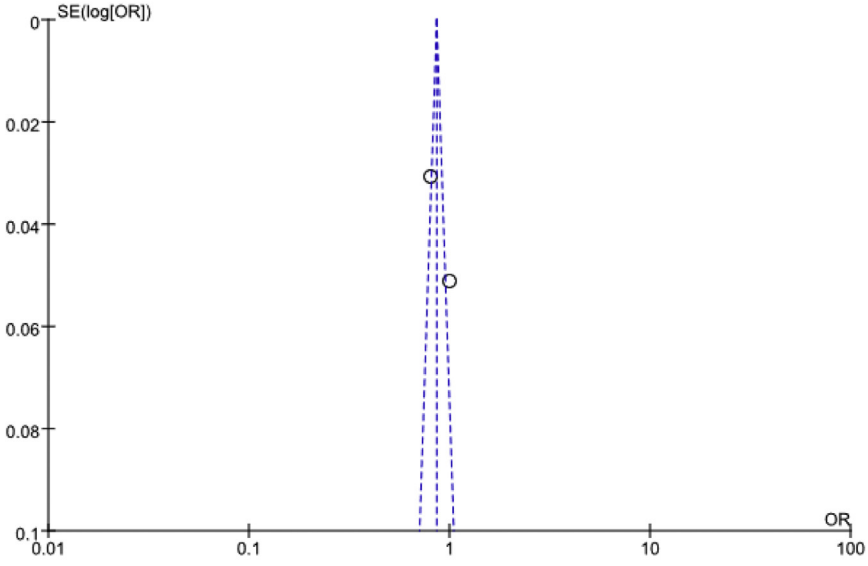


Funnel plot of rs12922061 polymorphism and breast cancer under recessive comparison

Supplemental Figure 1 Continued



Funnel plot of rs12922061 polymorphism and breast cancer under over-dominant comparison



Funnel plot of rs12922061 polymorphism and breast cancer under allele comparison