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Four *CYP19A1* Polymorphisms and Breast Cancer Risk: A Meta-Analysis

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Abstract

Many molecular epidemiological studies have investigated an association between *CYP19A1* gene single-nucleotide polymorphisms (SNPs) and breast cancer risk, but results have remained controversial and inconclusive. In order to reveal the real association, we performed an updated meta-analysis including two *CYP19A1* gene polymorphisms (rs700519, rs10046). Moreover, we performed a meta-analysis of another two *CYP19A1* (rs2236722 and rs4646) gene polymorphisms for the first time to evaluate their relevance in susceptibility to breast cancer risk.

A systematic database search was conducted to retrieve eligible articles. The odds ratio (OR) with 95% confidence interval (95% CI) were used to assess the strength of the association.

A total of 38 eligible studies were included in the meta-analysis, and the results showed that three *CYP19A1* gene polymorphisms (rs700519, rs10046, and rs2236722) had no relationship with an increased/decreased breast cancer risk in overall or ethnicity-based populations (all *P* values were more than 0.05); *CYP19A1* rs4646 polymorphism was significant associated with an increased breast cancer risk in overall populations under dominant genetic model (CC+AC vs. AA, OR=1.179, 95% CI=1.056 - 1.315, *P*-value=0.003). However, we did not find an association between *CYP19A1* rs4646 polymorphism and breast cancer susceptibility among Asian populations (*P* value was more than 0.05).

The meta-analysis indicates that *CYP19A1* rs4646 polymorphism may be associated with breast cancer risk. Further epidemiological studies with larger sample sizes are needed to validate the association between *CYP19A1* rs4646 polymorphism and breast cancer risk in various populations.

Keywords

CYP19A1; Polymorphism; Breast cancer; Risk; Meta-analysis

Introduction

Breast cancer is the most common malignancy among women worldwide. Numerous studies suggest that breast carcinogenesis and progression is influenced by steroid hormones, particularly estrogens [1,2].

Some genetic variations of steroid hormone pathway genes involved in the metabolism of androgens and estrogens are associated with the risk of breast cancer [3,4]. The cytochrome P450 family 19 subfamily a member 1 (*CYP19A1*) gene is located on chromosome 15q21.2 region and encodes aromatase, which converts androstenedione and testosterone into estrone and estradiol, respectively [5]. *CYP19A1* mutations can alter aromatase activity, which affects estrogen levels indirectly, and may ultimately alter susceptibility to breast cancer [6,7].

To date, an increasing number of studies have evaluated the potential association between the *CYP19A1* polymorphisms and the risk of breast cancer in diverse populations. Four *CYP19A1* genetic polymorphisms including rs700519 (Arg264Cys) located in exon 7 codon 264, the rs10046 located in the 3' untranslated region (3'-UTR), *CYP19A1* polymorphism at codon 39 Trp/Arg (rs2236722), and the rs4646 located in the 3'-UTR have been focused on a large scale. However, the results are inconsistent and inconclusive.

One previous meta-analysis suggested no association between *CYP19A1* rs700519 polymorphism and breast cancer risk [6], and another meta-analysis indicated that rs10046 polymorphism on *CYP19A1* did not affect breast cancer risk [8]. However, limited studies were included in both meta-analyses. Recently, several more studies assessing the association between the *CYP19A1* polymorphisms (rs700519 and rs10046) and breast cancer risk have been published. We therefore conducted an updated meta-analysis to clarify the association of the *CYP19A1* polymorphisms (rs700519 and rs10046) with risk of breast cancer in different populations. In addition, we performed a meta-analysis of another two *CYP19A1* (rs2236722 and rs4646) gene polymorphisms for the first time to evaluate their relevance in susceptibility to breast cancer risk.

Materials and Methods

Literature and search strategy

PubMed, Web of Science and Embase database were searched (until April 30, 2017) for eligible articles. The search strategy used combinations of the following keywords: "*CYP19*" or "*CYP19A1*" and "polymorphism" or "variant" or "mutation" and "breast cancer".

Inclusion and exclusion criteria

Eligible studies had to meet the following criteria: (1) studies addressed the potential association of four *CYP19A1* genetic polymorphisms [rs700519, rs10046, rs2236722, and rs4646] and breast cancer risk, (2) studies based on case–control design and (3) studies with sufficient data about genotype distribution of controls and cases. The exclusion criteria were: (1) studies with no sufficient data about genotype distribution of controls and cases, (2) duplicate publications and (3) comments, case reports, abstract and review articles (including meta-analysis).

Data extraction

The following data was extracted: (1) name of the first author, (2) year of publication, (3) country of origin, (4) ethnicity, (5) source of control groups (hospital-based or population-based controls or mixed), (6) number of genotyped cases and controls, Data was extracted from the final selected studies independently by two authors.

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Statistical analysis

The relationship between *CYP19A1* polymorphisms and breast cancer risk was assessed by a combined odds ratio (OR) with corresponding 95% confidence interval (95% CI) under co-dominant model, dominant model, and recessive model, respectively. Subgroup analyses based on ethnicity (Caucasians/Asians) was performed. The significance of the pooled OR estimate was determined by a Z test. The statistical significance was set at p value < 0.05.

Cochran's chi-square-based Q and I^2 statistics were used to evaluate heterogeneity across studies. If heterogeneity did not exist (P value > 0.1 for the Q test) among studies, the fixed effects model was used [9]; otherwise, the random effects model was applied [10]. I^2 statistic was calculated to quantify the proportion of the total heterogeneity among studies. Generally, I^2 values of 75%, 50%, and 25% indicated high, moderate, and low heterogeneity, respectively.

Sensitivity analysis was conducted to assess the influence of each study on the overall estimate by excluding studies one by one and recalculating the combined results of the remaining studies.

Publication bias of literatures was detected by funnel-plot analysis and Egger's test [11]. Data analyzes were performed with STATA version 11.0 (Stata Corporation, College Station, Texas, USA).

Results

Characteristics of the studies

We retrieved a total of 38 studies according to the inclusion/exclusion criteria, of which included a total of 13 studies containing 4,099 cases and 5,624 controls for the rs700519 polymorphism (Table 1) [12-24] , 22 studies containing 12,589 cases and 17,277 controls referring to the rs10046 polymorphism (Table 2) [7-8,23-39] , 6 studies with 957 cases and 1,368 controls involved in the rs2236722 polymorphisms (Table 3) [12,40-44] , and 4 studies with 4,970 cases and 5,925 controls involved in the rs4646 polymorphism (Table 4) [28,38,45,46] . A detailed flow chart of the exclusion and inclusion process was showed in Figure 1.

Quantitative synthesis

The summary of meta-analysis and heterogeneity test results for *CYP19A1* polymorphisms with breast cancer risk were presented in Table 5. For rs700519 polymorphism, no significant associations were found with the risk of breast cancer in overall or race-based populations in any of the genetic models tested. For *CYP19A1* rs10046 polymorphism, we found no significant association with breast cancer risk in overall population. The analysis by racial/ethnic subgroups also failed to produce significant associations in any of the genetic models tested. Furthermore, we observed no significant association for *CYP19A1* rs2236722 polymorphism with the risk of breast cancer in overall or ethnicity-based populations. I^2 > 75.0 % was observed in overall analyses. Sensitivity analysis was conducted to investigate the influence of each study on the overall pooled OR. The exclusion of Surekha et al., 2014 study made the biggest drop for heterogeneity values and still no significant association of the *CYP19A1* rs2236722 polymorphism with breast cancer risk was observed (data not shown).

For *CYP19A1* rs4646 polymorphism, the meta-analysis showed that individuals with the CC/AC genotype were significantly associated with an increased breast cancer risk as compared with AA genotype in overall or Caucasian populations (Overall: OR=1.179, 95% CI=1.056–1.315; Caucasian: OR=1.199, 95% CI=1.068-1.346). However, we found no evidence of association between *CYP19A1* rs4646 polymorphism and susceptibility to breast cancer among Asian women (Table 5, Figure 2).

Potential publication bias

The shape of funnel plot did not show obvious asymmetry (Figure 3). Egger's test revealed no statistical evidence for publication bias (All P>0.05).

Discussion

CYP19A1 is a key estrogen biosynthesis enzyme and play an important role in the development of breast cancer. In the current study, we have analyzed an almost 1.63 and 1.83 fold larger number of studies than Ma [6] and Pineda [8], respectively. We found no statistically significant association between breast cancer risk and *CYP19A1* polymorphisms (rs700519 and rs10046), which is consistent with the results of the previous meta-analysis for breast cancer [6,8]. Our results confirmed and established the trend of association between the *CYP19A1* polymorphisms (rs700519 and rs10046) and breast cancer risk indicated by the meta-analysis of Ma and Pineda [6,8]. To explain the result, we can speculate that the effect of *CYP19A1* rs700519 polymorphism on breast cancer risk

Table 1: Characteristics of case–control studies included in *CYP19A1* R264C polymorphism (rs700519) and breast cancer risk.

First author (Year)	Country	Ethnicity	Source	Cases					Controls				
				CC	CT	TT	CT+TT	CC+CT	CC	CT	TT	CT+TT	CC+CT
Miyoshi (2000) [12]	Japan	Asian	H	109	-	-	89	-	85	-	-	93	-
Lee (2003) [13]	Korea	Asian	H	150	134	4	138	284	176	106	6	112	282
Hefler (2004) [14]	Austria	Caucasian	P	367	22	0	22	389	1503	107	9	116	1610
Song (2006) [15]	China	Asian	P	84	22	2	24	106	87	24	1	25	111
Hu (2007) [16]	China	Asian	H	87	24	1	25	111	84	22	2	24	106
Gulyaeva (2008) [17]	Russia	Caucasian	H	100	8	0	8	108	168	10	4	14	178
Justenhoven (2008) [18]	Germany	Caucasian	P	549	49	1	50	598	561	60	1	61	621
Sangrajrang (2009) [19]	Thailand	Asian	H	331	201	31	232	532	297	167	19	186	464
Wang (2009) [20]	China	Asian	H	97	78	25	103	175	98	77	25	102	175
Khvostova (2012) [21]	Russia	Caucasian	H	283	39	1	40	322	477	57	2	59	534
Chattopadhyay (2014) [22]	India	Asian	P	226	115	19	134	341	258	91	11	102	349
Sun (2015) [23]	China	Asian	H	410	111	9	120	521	392	143	11	154	535
Pan (2016) [24]	China	Asian	H	225	87	9	96	312	289	96	5	101	385
H=hospital-based; P=population-based													

Table 2: Characteristics of case–control studies included in *CYP19A1* polymorphism (rs10046) and breast cancer risk.

First author (Year)	Country	Ethnicity	Source	Cases					Controls				
				CC	CT	TT	CT+TT	CC+CT	CC	CT	TT	CT+TT	CC+CT
Kristensen (2000) [25]	Norway	Caucasian	HP	95	240	146	386	335	69	114	53	167	183
Haiman (2002) [26]	US	Caucasian	H	103	240	118	358	343	134	310	167	477	444
Dunning (2004) [7]	UK	Caucasian	H	610	1286	739	2025	1896	808	1773	1049	2822	2581
Ralph-1 (2007) [27]	US	Caucasian	H	349	830	461	1291	1179	758	1650	883	2533	2408
Ralph-2 (2007) [27]	US	Caucasian	H	129	231	142	373	360	222	503	274	777	725
Chen (2008) [28]	China	Asian	H	125	308	178	486	433	163	436	277	713	599
Zhang (2008) [29]	China	Asian	H	55	151	94	245	206	94	176	120	296	270
Iwasaki-1 (2009) [30]	Japan	Asian	H	118	188	82	270	306	125	194	69	263	319
Iwasaki-2 (2009) [30]	Japan	Asian	H	24	41	14	55	65	22	44	13	57	66
Iwasaki-3 (2009) [30]	Brasil	Caucasian	H	133	179	67	246	312	121	200	58	258	321
Yoshimoto (2011) [31]	Japan	Asian	H	239	427	160	587	666	97	120	60	180	217
Pineda (2012) [8]	Spain	Caucasian	H	135	278	109	387	413	281	629	311	940	910
Clendenen (2013) [32]	US and Sweden	Mixed	P	306	548	308	856	854	549	1032	523	1555	1581
Iwasaki (2013) [33]	Japan	Asian	H	116	253		253	-	117	252		252	-
Ghisari (2014) [34]	Denmark	Caucasian	P	23	8	0	8	31	79	29	6	35	108
Zins (2014) [35]	Austria	Caucasian	P	65	142	67	209	207	55	136	62	198	191
Sun (2015) [23]	China	Asian	H	111	264	155	419	375	126	290	130	420	416
Yang (2015) [36]	China	Asian	H	30	48	34	82	78	25	82	32	114	107
Pan (2016) [24]	China	Asian	H	49	185	100	285	234	89	192	111	303	281
Farzaneh (2016) [37]	Iran	Asian	H	23	68	33	101	91	30	55	15	70	85
Kopp (2016) [38]	Denmark	Caucasian	P	159	346	182	528	505	146	353	188	541	499
Ghisari (2017) [39]	Denmark	Caucasian	P	36	68	38	106	104	47	93	56	149	140
H=hospital-based; P=population-based; HP=hospital-based and population-based													

Table 3: Characteristics of case–control studies included in *CYP19A1* polymorphism (rs2236722) and breast cancer risk.

First author (Year)	Country	Ethnicity	Source	Cases					Controls				
				TT	CT	CC	CT+CC	TT+CT	TT	CT	CC	CT+CC	TT+CT
Miyoshi (2000) [12]	Japan	Asian	H	195	-	-	8	-	180	-	-	19	-
Hirose (2004) [40]	Japan	Asian	H	227	20	1	21	247	561	38	4	42	599
Sobczuk (2009) [41]	Poland	Caucasian	H	20	45	35	80	65	18	58	30	88	76
TÜZÜNER (2010) [42]	Turkey	Caucasian	P	3	52	0	52	55	27	64	0	64	91
Ramalhinho (2012) [43]	Portugal	Caucasian	H	40	-	-	61	-	65	-	-	56	-
Surekha (2014) [44]	India	Asian	P	227	23	0	23	250	170	78	0	78	248
H=hospital-based; P=population-based.													

Table 4: Characteristics of case–control studies included in *CYP19A1* polymorphism (rs4646) and breast cancer risk.

First author (Year)	Country	Ethnicity	Source	Cases					Controls				
				CC	AC	AA	AC+AA	CC+AC	CC	AC	AA	AC+AA	CC+AC
Chen (2008) [28]	China	Asian	H	298	260	53	313	558	441	358	77	435	799
Boone (2014) [45]	US	Caucasian	P	-	-	540	-	2984	-	-	756	-	3452
Alanazi (2015) [46]	Kingdom of Saudi Arabia	Asian	P	94	46	8	54	140	99	47	8	55	146
Kopp (2016) [38]	Denmark	Caucasian	P	372	265	50	315	637	371	262	54	316	633
H=hospital-based; P=population-based.													

is limited. *CYP19A1* rs700519 polymorphism is not the only factor that influences aromatase activity for estrogens biosynthesis. In fact, R264C and R264H polymorphisms differentially influenced human aromatase activity and function [47].

The present meta-analysis is the first to evaluate the association between *CYP19A1* polymorphisms (rs2236722 and rs4646) and breast cancer risk. Pooled analysis found no evidence of association between *CYP19A1* polymorphism (rs2236722) and susceptibility to breast cancer. In addition, the sensitivity analysis results showed that Surekha et al., 2014 study was the source of heterogeneity [44]. The conclusion remained unchanged even after the fore-mentioned study was excluded. Overall, the *CYP19A1* rs2236722 is a rare polymorphism, the result should be interpreted cautiously owing to the relatively small sample size within these two ethnic populations for *CYP19A1* rs2236722 polymorphism. Relationship between *CYP19A1* rs2236722 polymorphism and *CYP19A1* enzyme activity are also needed for confirmation in the future studies.

It is particularly worth noting that the association of *CYP19A1* rs4646 polymorphism with breast cancer risk was observed in overall and Caucasian populations, but not in Asian populations. One possibility is that the sample size for rs4646 among Asian populations is too small to show significant evidence. It is also possible that the

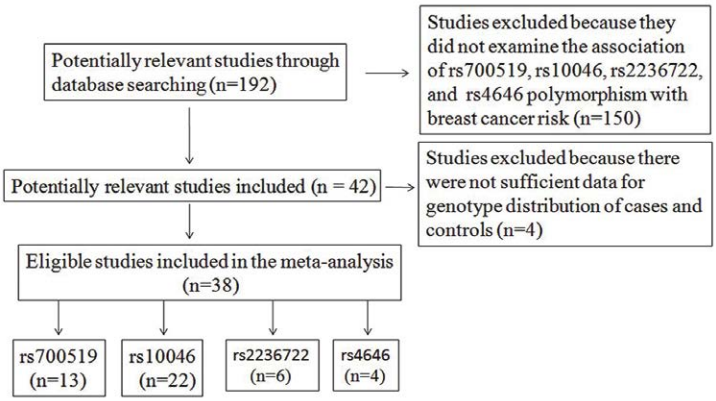

Figure 1: Flow chart of meta-analysis for exclusion/inclusion of studies. Thirty-eight eligible studies were included.

Table 5: Meta-analysis of *CYP19A1* genes polymorphisms and breast cancer risk.

Polymorphisms	Comparisons	No. of studies	Sample size		OR[95% CI]	P value	I^2(P)	Model
			Cases	Controls				
CYP19A1 R264C								
Overall	TT *vs.* CC	12	3011	4486	1.178 [0.877, 1.583]	p=0.277	0.0% (p=0.638)	F
	TC *vs.* CC	12	3799	5350	1.062 [0.951, 1.185]	p=0.286	33.1% (p=0.125)	F
	TT+TC *vs.* CC	13	4099	5624	1.034 [0.894, 1.196]	p=0.653	43.9% (p=0.045)	R
	TT *vs.* TC+CC	12	3901	5446	1.141 [0.853, 1.526]	p=0.374	0.0% (p=0.696)	F
Caucasian	TT *vs.* CC	4	1301	2725	0.387 [0.107, 1.398]	p=0.148	0.0% (p=0.735)	F
	TC *vs.* CC	4	1417	2943	0.950 [0.747, 1.207]	p=0.672	0.0% (p=0.586)	F
	TT+TC *vs.* CC	4	1419	2959	0.909 [0.718, 1.152]	p=0.431	0.0% (p=0.634)	F
	TT *vs.* TC+CC	4	1419	2959	0.386 [0.107, 1.394]	p=0.146	0.0% (p=0.733)	F
Asian	TT *vs.* CC	8	1710	1761	1.283 [0.942, 1.747]	p=0.114	0.0% (p=0.588)	F
	TC *vs.* CC	8	2382	2407	1.102 [0.920, 1.322]	p=0.292	48.2% (p=0.061)	R
	TT+TC *vs.* CC	9	2680	2665	1.073 [0.895, 1.287]	p=0.447	55.9% (p=0.020)	R
	TT *vs.* TC+CC	8	2482	2487	1.236 [0.913, 1.674]	p=0.171	0.0% (p=0.650)	F
rs10046								
Overall	TT *vs.* CC	21	6144	8497	1.058 [0.951, 1.177]	p=0.297	46.8% (p=0.010)	R
	TC *vs.* CC	21	8993	12451	1.020 [0.932, 1.117]	p=0.668	45.2% (p=0.013)	R
	TT+TC *vs.* CC	22	12589	17277	1.030 [0.946, 1.121]	p=0.498	46.9% (p=0.008)	R
	TT *vs.* TC+CC	21	12220	16908	1.022 [0.969, 1.079]	p=0.423	25.6% (p=0.139)	F
Caucasian	TT *vs.* CC	11	4735	6710	0.979 [0.855, 1.120]	p=0.755	47.6% (p=0.039)	R
	TC *vs.* CC	11	5685	8510	0.975 [0.907, 1.050]	p=0.506	16.4% (p=0.288)	F
	TT+TC *vs.* CC	11	7754	11617	0.969 [0.876, 1.071]	p=0.533	38.4% (p=0.093)	R
	TT *vs.* TC+CC	11	7754	11617	0.993 [0.930, 1.061]	p=0.838	22.3% (p=0.231)	F
Asian	TT *vs.* CC	9	1624	1598	1.219 [0.997, 1.490]	p=0.053	41.4% (p=0.091)	R
	TC *vs.* CC	9	2454	2360	1.139 [0.924, 1.404]	p=0.224	59.4% (p=0.011)	R
	TT+TC *vs.* CC	10	3673	3556	1.145 [0.971, 1.352]	p=0.108	50.3% (p=0.034)	R
	TT *vs.* TC+CC	9	3303	3187	1.081 [0.964, 1.212]	p=0.184	32.4% (p=0.158)	F
rs2236722								
Overall	CC *vs.* TT	2	283	613	0.979 [0.464, 2.066]	p=0.956	0.0% (p=0.656)	F
	CT *vs.* TT	4	617	1014	1.007 [0.295, 3.436]	p=0.991	92.1% (p=0.000)	R
	CC+CT *vs.* TT	6	957	1368	0.955 [0.404, 2.258]	p=0.916	90.1% (p=0.000)	R
	CC+CT *vs.* TT[a]	5	707	1120	1.272 [0.644, 2.513]	p=0.489	77.8% (p=0.001)	R
	CC *vs.* CT+TT	2	348	709	1.281 [0.729, 2.251]	p=0.389	0.0% (p=0.484)	F

Caucasian	CC *vs.* TT	1	228	565	1.050 [0.471, 2.342]	p=0.905	NA	R
	CT *vs.* TT	2	120	167	2.143 [0.205, 22.448]	p=0.525	90.4% (p=0.001)	R
	CC+CT *vs.* TT	3	256	318	1.931 [0.728, 5.125]	p=0.186	78.9% (p=0.000)	R
	CC *vs.* CT+TT	1	100	106	1.364 [0.757, 2.459]	p=0.302	NA	R
Asian	CC *vs.* TT	1	55	48	0.618 [0.069, 5.558]	p=0.667	NA	R
	CT *vs.* TT	2	497	847	0.534 [0.094, 3.043]	p=0.479	95.3% (p=0.000)	R
	CC+CT *vs.* TT	3	701	1050	0.475 [0.151, 1.494]	p=0.203	90.4% (p=0.000)	R
	CC+CT *vs.* TT[a]	2	451	802	0.727 [0.234, 2.254]	p=0.581	80.2% (p=0.025)	R
	CC *vs.* CT+TT	1	248	603	0.606 [0.067, 5.452]	p=0.655	NA	R
rs4646								
Overall	CC *vs.* AA	3	875	1050	1.022 [0.781, 1.337]	p=0.877	0.0% (p=0.933)	F
	AC *vs.* AA	3	682	806	1.065 [0.810, 1.402]	p=0.651	0.0% (p=0.980)	F
	CC+AC *vs.* AA	4	4970	5925	1.179 [1.056, 1.315]	p=0.003	0.0% (p=0.766)	F
	CC *vs.* AC+AA	3	1446	1717	0.971 [0.843, 1.118]	p=0.680	0.0% (p=0.902)	F
Caucasian	CC *vs.* AA	1	422	425	1.083 [0.718, 1.633]	p=0.704	NA	R
	AC *vs.* AA	1	315	316	1.092 [0.717, 1.664]	p=0.681	NA	R
	CC+AC *vs.* AA	2	4211	4895	1.199 [1.068, 1.346]	p=0.002	0.0% (p=0.614)	F
	CC *vs.* AC+AA	1	687	687	1.006 [0.814, 1.244]	p=0.957	NA	R
Asian	CC *vs.* AA	2	453	625	0.978 [0.685, 1.395]	p=0.901	0.0% (p=0.952)	F
	AC *vs.* AA	2	367	490	1.046 [0.729, 1.501]	p=0.807	0.0% (p=0.896)	F
	CC+AC *vs.* AA	2	759	1030	1.008 [0.715, 1.422]	p=0.964	0.0% (p=0.918)	F
	CC *vs.* AC+AA	2	759	1030	0.944 [0.781, 1.140]	p=0.547	0.0% (p=0.911)	F

[a] The results of when the study of Surekha (2014) et al. was excluded.
F=fixed effects model; R=random effects model.

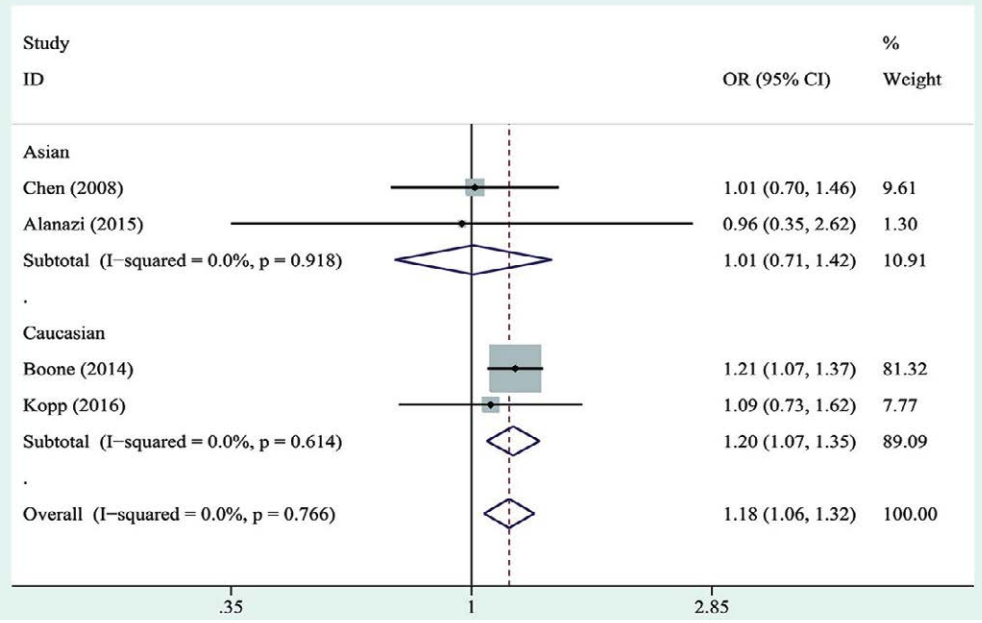

Figure 2: Meta-analysis of OR for rs4646 polymorphism associated with breast cancer (CC+AC *vs.* AA).

effect strength of genetic alterations predisposing to human diseases is different in different racial populations [48].

Conclusion

The present meta-analysis suggests that three variants (rs700519, rs10046, and rs2236722) in the *CYP19A1* gene are not significantly associated with breast cancer risk. One SNP (rs4646) may contribute to increasing susceptibility to breast cancer. More well-designed association studies with larger sample size of different ethnic populations will be needed to confirm the risk identified in the current meta-analysis.

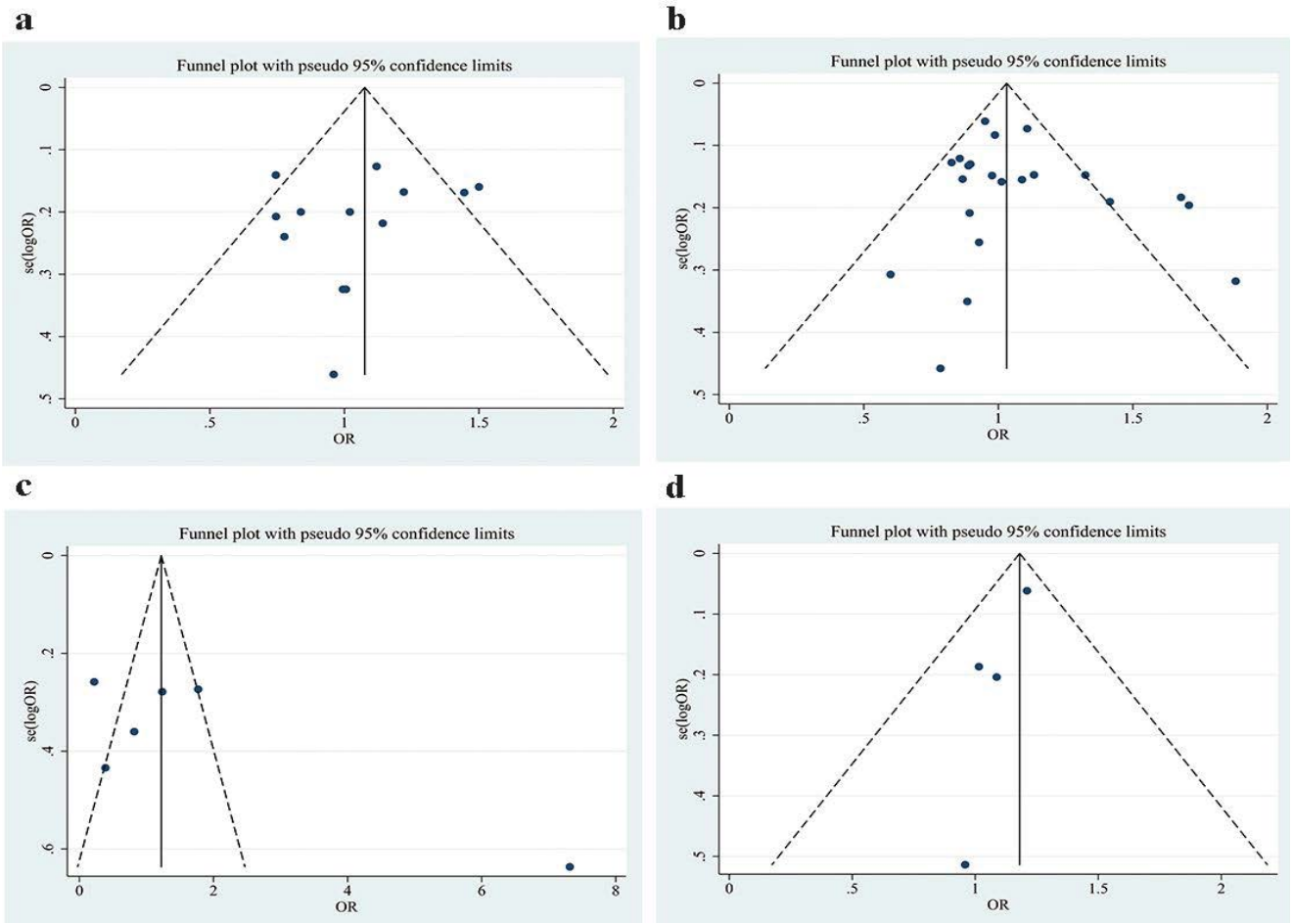

Figure 3: Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. OR, odds ratio Log (OR), natural logarithm of OR. OR is plotted on the horizontal axis and the standard error of log (OR) on the vertical axis. (**a**) Funnel plot for the association between R264C polymorphism and breast cancer risk under dominant model; (**b**) Funnel plot for the association between rs10046 polymorphism and breast cancer risk under dominant model; (**c**) Funnel plot for the association between rs2236722 polymorphism and breast cancer risk under dominant model; (**d**) Funnel plot for the association between rs4646 polymorphism and breast cancer risk under dominant model.

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Conflict of interest

Yougen Wu and Xiaofeng Qu have contributed equally to the work

The authors declare no conflict of interest.

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