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Association between rs11200014, rs2981579, and rs1219648 polymorphism and breast cancer susceptibility

A meta-analysis

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Abstract

Background: Research on the polymorphism of breast cancer (BC) helps to search the BC susceptibility gene for mass screening, early diagnosis, and gene therapy, which has become a hotspot in BC research field. Previous studies have suggested associations between rs11200014, rs2981579, and rs1219648 polymorphisms and cancer risk. The aim of this study was to evaluate the relationship between rs11200014, rs2981579, and rs1219648 polymorphism and BC risk.

Methods: PubMed, Web of science, and the Cochrane Library databases were searched before October 11, 2015, to identify relevant studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of associations. Sensitivity and subgroup analyses were conducted. All included cases should have been diagnosed by a pathological examination.

Results: Twenty-six studies published from 2007 to 2015 were included in this meta-analysis. The pooled results showed that there was a significant association between all the 3 variants and BC risk in any genetic model. When stratified by Source of controls, the results showed the same association between rs2981579 polymorphism and BC susceptibility in hospital-based (HB) group, although there was not any genetic model attained statistical correlation in population-based (PB) group. Subgroup analysis was performed on rs1219648 by ethnicity and Source of controls, and the effects remained in Asians, Caucasians, HB, and PB groups.

Conclusion: This meta-analysis of case–control studies provides strong evidence that fibroblast growth factor 2 (FGFR2; rs11200014, rs2981579, and rs1219648) polymorphisms are significantly associated with the BC risk. For rs2981579, the association remained in hospital populations, while not in general populations. For rs1219648, the association remained in Asians, Caucasians, hospital populations, and general populations. However, further large-scale multicenter epidemiological studies are warranted to confirm this finding and the molecular mechanism for the associations need to be elucidated in future studies.

Abbreviations: BC = breast cancer, CIs = confidence intervals, FGFR2 = fibroblast growth factor 2, GWAS = genome-wide association study, HB = hospital-based, ORs = odds ratios, PB = population-based.

Keywords: breast cancer, polymorphism, rs11200014, rs1219648, rs2981579

1. Introduction

Breast cancer (BC) has become one of the most common malignant tumors in women, whose incidence accounts for about 23% of all female malignant tumors, and more than 400,000 people worldwide die from BC each year.[1] The rising morbidity and mortality should not be ignored.[2] Exploring the BC susceptible factors, etiology, and pathogenesis, establishing the model of BC risk, so as to guide clinical prevention and treatment better, is still a very challenging subject.

Currently, study on the interaction between BC gene and environment has gradually attracted the attention of researchers. The main methods of this study include candidate gene and genome-wide association study (GWAS).[3] GWAS has made some achievements in the association between the polymorphism of fibroblast growth factor 2 (FGFR2), TNRC9, MAP3K1, H19, and LSP1 and the significant increase of BC risk.[4] Research on the polymorphism helps to search the BC susceptibility gene for mass screening, early diagnosis, and gene therapy, which has become a hotspot in BC research field.

Recently, researches have paid more attention to the human FGFR2, whose several SNPs, rs11200014 (G > A), rs2981579 (C > T), rs1219648 (A > G), may associated with BC susceptibility in different crowds and different regions.[5–30] However, conclusions of related reports are still inconclusive between susceptible[5,9–13] and protective.[6–8] These different conclusions may due to differences in ethnic and regional and other factors.

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Therefore, a systematic analysis with large samples should be applied to assess the association. To clarify the role of FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism in BC susceptibility, 5 meta-analyses[31–35] on the correlation between FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and BC susceptibility had been implemented. However, the results remain inconclusive and number of their studies included for each SNP is small, and some just no subgroup. Therefore, we carried out this meta-analysis on all the included case–control studies to make a more accurate assessment of the relationship.

2. Methods

2.1. Literature searching strategy

We searched PubMed, Web of science, and the Cochrane Library for relevant studies published before October 11, 2015. The following keywords were used: (FGFR2) and (variant* or genotype or polymorphism or SNP) and (breast) and (cancer or carcinom* or neoplasm* or tumor), and the combined phrases for all genetic studies on the association between the FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and BC risk. The reference lists of all articles were also manually screened for potential studies. Abstracts and citations were screened independently by 2 researchers independently. All the eligible articles need a second screening for full-text. The searching was done without language limitations.

2.2. Selection and exclusion criteria

Inclusion criteria included that a study was included in this meta-analysis if it meets the following criteria: independent case–control studies for humans; the study evaluating the association between FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and BC risk; the study presenting available genotype frequencies in cancer cases and control subjects for risk estimate; and cases should have been diagnosed by a pathological examination. We excluded comments, editorials, systematic reviews, and studies lacking sufficient data or studies with male cases. If the researches were duplicated or shared in more than one study, the most recent publications were included.

2.3. Data extraction and synthesis

We used endnote bibliographic software to construct an electronic library of citations identified in the literature search. All the PubMed, Web of science, and the Cochrane Library searches were performed using Endnote. Duplicates were found automatically by endnote and deleted manually. All data extraction was checked and calculated twice according to the inclusion criteria listed above by 2 independent investigators. Data extracted from the included studies were as follows: First author, year of publication, country, ethnicity, source of controls, genotyping method, number of cases and controls, and evidence of HWE in controls. A third reviewer would participate if some

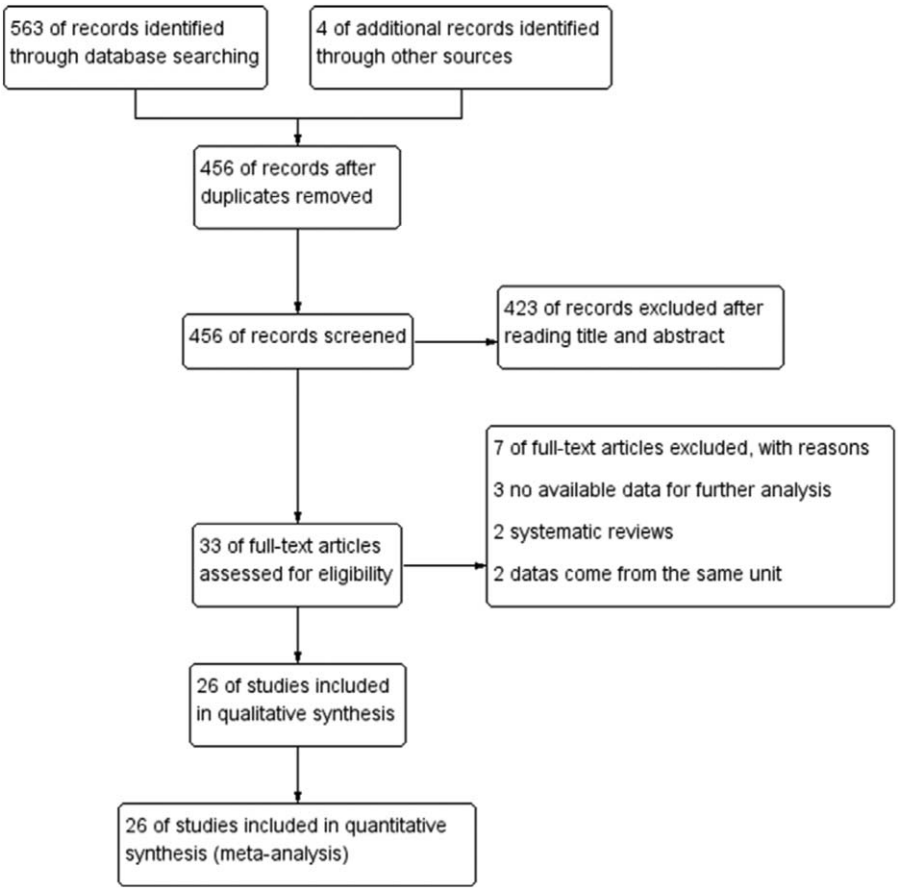

Figure 1. Flow chart of studies selection in this meta-analysis.

Table 1

Characteristics of the studies included in the meta-analysis.

Ref.	Year	Country	Ethnicity	Source of controls	Genotyping method	Number (case/control)	HWE
rs11200014 (G > A)							
Raskin et al[23]	2008	USA	Caucasian	PB	TaqMan	1481/1477	0.20404
Kawase et al[17]	2009	Japan	Asian	HB	TaqMan	453/912	0.643882
Ma et al[29]	2011	China	Asian	PB	AS-PCR	200/200	0.919583
Fu et al[15]	2012	Chinese	Asian	HB	iPLEX	118/104	0.766128
Chan et al[12]	2012	China	Asian	HB	Taqman	1173/1464	0.045705
rs2981579 (C > T)>(G > A)							
Raskin et al[23]	2008	USA	Caucasian	PB	TaqMan	1480/1471	0.372365
Kawase et al[17]	2009	Japan	Asian	HB	TaqMan	456/912	0.156544
Liu et al[21]	2009	China	Asian	PB	PCR–RFLP	106/116	0.719587
Zhou et al[26]	2010	China	Asian	HB	PCR-LDR	304/308	0.481568
Hu et al[27]	2011	China	Asian	PB	PCR–RFLP	203/200	0.199691
Li et al[28]	2011	China	Asian	HB	MassArray	403/461	0.728638
Zhao et al[30]	2012	China	Asian	PB	DHPLC	120/120	0.30919
Fu et al[15]	2012	China	Asian	HB	iPLEX	118/104	0.541378
Xia et al[10]	2015	China	Asian	HB	MassARRAY	181/196	0.403599
Chan et al[12]	2012	China	Asian	HB	Taqman	1174/1477	0.202667
Liang et al[6]	2015	China	Asian	HB	MassARRAY	608/876	0.207053
Liu et al[19]	2013	China	Asian	HB	PCR-RFLP	203/200	0.199691
rs1219648 (A > G)							
Raskin et al[23]	2008	USA	Caucasian	PB	TaqMan	1487/1477	0.267724
Kawase et al[17]	2009	Japan	Asian	HB	TaqMan	456/912	0.551982
Hu et al[27]	2011	China	Asian	PB	PCR–RFLP	203/200	0.740568
Li et al[28]	2011	China	Asian	HB	MassArray	403/443	0.516038
Shan et al[24]	2012	Tunisian	African	PB	TaqMan	596/360	0.058241
Ma et al[20]	2012	British	Caucasian	HB	KASPar	232/461	0.121646
Fu et al[15]	2012	Chinese	Asian	HB	iPLEX	117/104	0.597686
Slattery et al[25]	2011	American	Caucasian	PB	Taqman	1737/2042	0.963729
Chen et al[13]	2011	Chinese	Asian	PB	Taqman	447/406	0.800884
Liang et al[18]	2008	Chinese	Asian	HB	Taqman	1028/1062	0.269848
Hunter et al[16]	2007	USA	Caucasian	PB	Array, Taqman	2921/3213	0.585653
Liu et al[22]	2010	China	Asian	PB	PCR–RFLP	106/116	0.747684
Andersen et al[11]	2013	USA	Caucasian	PB	Taqman	869/808	0.143531
Chan et al[12]	2012	China	Asian	HB	Taqman	1174/1469	0.066628
Cherdyntseva et al[14]	2012	Russian	Caucasian	PB	PCR	344/228	0.010879
Jara et al[5]	2013	Chile	Caucasian	PB	TaqMan	351/802	0.124152
Liu et al[19]	2013	China	Asian	HB	PCR-RFLP	203/200	0.740568
Ozgoz et al[7]	2013	Turkey	Caucasian	PB	PCR-RFLP	31/30	0.070383
Saadatian et al[8]	2014	Iran	Asian	PB	PCR-RFLP	100/100	0.666743
Siddiqui et al[9]	2014	India	Asian	HB	PCR-RFLP	368/484	0.569268

HB = hospital-based, HWE = Hardy–Weinberg equilibrium, PB = population based.

disagreements were emerged, and a final decision was made by the majority of the votes.

2.4. Statistical analysis

All statistical analyses were performed using STATA version 11.0 software (StataCorp LP, College Station, TX) and Review Manage version 5.2.0 (The Cochrane Collaboration, 2012). Hardy–Weinberg equilibrium (HWE) was assessed by χ^2 test in the control group of each study.[36] The strength of associations between the FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and BC risk was measured by odds ratios (ORs) with 95% confidence interval (95% CIs). Z test was used to assess the significance of the ORs, and I^2 and Q statistics was used to determine the statistical heterogeneity among studies. A random-effect model was used if the P value of heterogeneity tests was no more than .1 ($P \leq 0.1$), and otherwise, a fixed-effect model was selected.[36,37] Sensitivity analyses were performed to assess the stability of the results. We used Begg funnel plot and Egger test to evaluate the publication bias.[38,39] The strength of the association was estimated in the allele model, the dominant model, the recessive model, the homozygous genetic model, and the heterozygous genetic model, respectively. $P < .05$ was considered statistically significant. We performed subgroup according to ethnicity and source of controls.

2.5. Ethical approval

The ethical approval was not necessary for the reason that our study was a meta-analysis belonging to secondary analysis.

3. Results

3.1. Characteristics of included papers

The specific search process is shown in Fig. 1. A total of 563 references were preliminarily identified at first based on our selection strategy. We also identified 4 papers through other sources. Four hundred fifty-six records were left after removing

Table 2

Polymorphisms genotype distribution and allele frequency in cases and controls.

Ref.	Genotype (N)								Allele frequency (N)			
	Case				Control				Case		Control	
rs11200014 (G > A)	Total	AA	AG	GG	Total	AA	AG	GG	A	G	A	G
Raskin et al[23]	1481	366	698	417	1477	288	701	488	1430	1532	1277	1677
Kawase et al[17]	453	45	191	217	912	79	369	464	281	625	527	1297
Ma et al[29]	200	12	177	11	200	18	85	97	201	199	121	279
Fu et al[15]	118	17	47	54	104	5	38	61	81	155	48	160
Chan et al[12]	1173	109	481	583	1464	118	541	805	699	1647	777	2151
rs2981579 (C > T)	Total	TT	TC	CC	Total	TT	TC	CC	T	C	T	C
Raskin et al[23]	1480	381	722	377	1471	301	710	460	1484	1476	1312	1630
Kawase et al[17]	456	91	233	132	912	141	461	310	415	497	743	1081
Liu et al[21]	106	26	48	32	116	28	56	32	100	112	112	120
Zhou et al[26]	304	68	149	87	308	69	147	92	285	323	285	331
Hu et al[27]	203	52	97	54	200	43	109	48	201	205	195	205
Li et al[28]	403	102	201	100	461	93	224	144	405	401	410	512
Zhao et al[30]	120	32	61	27	120	43	62	15	125	115	148	92
Fu et al[15]	118	30	59	29	104	21	48	35	119	117	90	118
Xia et al[10]	181	55	96	30	196	56	92	48	206	156	204	188
Chan et al[12]	1174	294	565	315	1477	303	705	469	1153	1195	1311	1643
Liang et al[6]	608	158	297	153	876	186	415	275	613	603	787	965
Liu et al[19]	203	52	97	54	200	43	109	48	201	205	195	205
rs1219648 (A > G)	Total	GG	GA	AA	Total	GG	GA	AA	G	A	G	A
Raskin et al[23]	1487	350	717	420	1477	277	701	499	1417	1557	1255	1699
Kawase et al[17]	456	60	227	169	912	100	416	396	347	565	616	1208
Hu et al[27]	203	53	81	69	200	36	95	69	187	219	167	233
Li et al[28]	403	75	195	133	443	72	205	166	345	461	349	537
Shan et al[24]	596	127	296	173	360	61	153	146	550	642	275	445
Ma et al[20]	232	49	113	70	461	48	224	189	211	253	320	602
Fu et al[15]	117	25	54	38	104	9	47	48	104	130	65	143
Slattery et al[25]	1737	328	879	530	2042	333	982	727	1535	1939	1648	2436
Chen et al[13]	447	97	211	139	406	72	195	139	405	489	339	473
Liang et al[18]	1028	184	517	327	1062	149	520	393	885	1171	818	1306
Hunter et al[16]	2921	616	1410	895	3213	495	1551	1167	2642	3200	2541	3885
Liu et al[22]	106	53	27	26	116	34	56	26	133	79	124	108
Andersen et al[11]	869	142	464	263	808	111	403	294	748	990	625	991
Chan et al[12]	1174	217	576	381	1469	232	661	576	1010	1338	1125	1813
Cherdyntseva et al[14]	344	63	193	88	228	22	124	82	319	369	168	288
Jara et al[5]	351	80	181	90	802	148	368	286	341	361	664	940
Liu et al[19]	203	53	81	69	200	36	95	69	187	219	167	233
Ozgoz et al[7]	31	9	18	4	30	11	10	9	36	26	32	28
Saadatian et al[8]	100	17	49	34	100	9	39	52	83	117	57	143
Siddiqui et al[9]	368	66	192	110	484	67	234	183	324	412	368	600

repeated studies. We refer to titles or abstracts of all the included literatures, and then removed obviously irrelevant papers. In the end, the whole of the rest of the papers were checked based on the inclusion and exclusion criteria. Finally, 26 studies on FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and the occurrence of BC were eventually included in our study. Characteristics of eligible analysis are summarized in Table 1. The 26 case–control papers were published between 2007 and 2015; among them, 1 study was performed in African, 17 in Asians, and 8 in Caucasians. All studies were case-controlled and all included cases had been diagnosed by a pathological examination.

3.2. Meta-analysis results

Table 2 summarizes the FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphisms genotype distribution and allele frequencies in case groups and control groups. Main results of our study are summarized in Table 3. There were 26 studies with 3425 cases and 4157 controls for FGFR2 rs11200014 variants. As shown in Table 3 and Fig. 2, the pooled results indicated that the correlation between FGFR2 rs11200014 polymorphism and the occurrence of BC was significant in any genetic model: Allele model (OR: 1.37; 95% CI: 1.14–1.66; $P=.001$), Dominant model (OR: 1.88; 95% CI: 1.23–2.85; $P=.003$), Recessive model (OR: 1.28; 95% CI: 1.12–1.46; $P=.0003$), Homozygous genetic model (OR: 1.66; 95% CI: 1.18–2.33; $P=.003$), Heterozygote comparison (OR: 1.85; 95% CI: 1.16–2.93; $P=.009$).

For rs2981579, 12 studies with 5356 cases and 6441 controls were included to assess the association. As shown in Table 3 and Fig. 3, the pooled ORs suggested that rs2981579 was significantly associated with BC susceptibility in all the 5 genetic models: Allele model 1.19 (95% CI: 1.13–1.25; $P<.00001$), Dominant model 1.25 (95% CI: 1.15–1.35; $P<.00001$), Recessive model 1.26 (95% CI: 1.16–1.38; $P<.00001$), Homozygous genetic model 1.40 (95% CI: 1.27–1.56; $P<.00001$), Heterozygote comparison 1.18 (95% CI:

Table 3

Meta-analysis results.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate	*P*	Heterogeneity	
						I^2	*P*
Allele model							
rs11200014 (G > A)	5	15,164	OR (M-H, Random, 95% CI)	1.37 [1.14–1.66]	.001	83%	.0001
rs2981579 (C > T)	12	23,594	OR (M-H, Fixed, 95% CI)	1.19 [1.13–1.25]	<.00001	34%	.12
HB	8	15,962	OR (M-H, Fixed, 95% CI)	1.20 [1.13–1.28]	<.00001	0%	.79
PB	4	7632	OR (M-H, Random, 95% CI)	0.99 [0.76–1.29]	.94	76%	.007
rs1219648 (A > G)	20	56,180	OR (M-H, Fixed, 95% CI)	1.25 [1.20–1.29]	<.00001	0%	.48
Asian	11	20,202	OR (M-H, Fixed, 95% CI)	1.23 [1.16–1.30]	<.00001	0%	.59
Caucasian	8	34,066	OR (M-H, Fixed, 95% CI)	1.25 [1.20–1.30]	<.00001	20%	.27
HB	8	18,232	OR (M-H, Fixed, 95% CI)	1.24 [1.17–1.32]	<.00001	16%	.3
PB	12	37,948	OR (M-H, Fixed, 95% CI)	1.25 [1.20–1.30]	<.00001	0%	.5
Dominant model							
rs11200014 (G > A)	5	7582	OR (M-H, Random, 95% CI)	1.88 [1.23–2.85]	.003	93%	< .00001
rs2981579 (C > T)	12	11,797	OR (M-H, Fixed, 95% CI)	1.25 [1.15–1.35]	<.00001	36%	.1
HB	8	7981	OR (M-H, Fixed, 95% CI)	1.27 [1.15–1.41]	<.00001	0%	.57
PB	4	3816	OR (M-H, Random, 95% CI)	0.91 [0.60–1.38]	.66	73%	.01
rs1219648 (A > G)	20	28,090	OR (M-H, Fixed, 95% CI)	1.32 [1.26–1.39]	<.00001	2%	.43
Asian	11	10,101	OR (M-H, Fixed, 95% CI)	1.28 [1.18–1.39]	<.00001	0%	.49
Caucasian	8	17,033	OR (M-H, Fixed, 95% CI)	1.33 [1.24–1.42]	<.00001	0%	.47
HB	8	9116	OR (M-H, Fixed, 95% CI)	1.32 [1.21–1.44]	<.00001	0%	.68
PB	12	18,974	OR (M-H, Fixed, 95% CI)	1.32 [1.24–1.40]	<.00001	24%	.21
Recessive model							
rs11200014 (G > A)	5	7582	OR (M-H, Fixed, 95% CI)	1.28 [1.12–1.46]	.0003	47%	.11
rs2981579 (C > T)	12	11,797	OR (M-H, Fixed, 95% CI)	1.26 [1.16–1.38]	<.00001	0%	.62
HB	8	7981	OR (M-H, Fixed, 95% CI)	1.27 [1.14–1.41]	<.0001	0%	.93
PB	4	3816	OR (M-H, Random, 95% CI)	1.10 [0.81–1.50]	.53	54%	.09
rs1219648 (A > G)	20	28,090	OR (M-H, Fixed, 95% CI)	1.36 [1.28–1.45]	<.00001	26%	.14
Asian	11	10,101	OR (M-H, Fixed, 95% CI)	1.35 [1.22–1.50]	<.00001	14%	.31
Caucasian	8	17,033	OR (M-H, Random, 95% CI)	1.39 [1.22–1.58]	<.00001	50%	.05
HB	8	9116	OR (M-H, Fixed, 95% CI)	1.35 [1.21–1.51]	<.00001	40%	.11
PB	12	18,974	OR (M-H, Fixed, 95% CI)	1.37 [1.27–1.47]	<.00001	22%	.23
Homozygous genetic model							
rs11200014 (G > A)	5	4254	OR (M-H, Random, 95% CI)	1.66 [1.18–2.33]	.003	69%	.01
rs2981579 (C > T)	12	6034	OR (M-H, Fixed, 95% CI)	1.40 [1.27–1.56]	<.00001	33%	.13
HB	8	4083	OR (M-H, Fixed, 95% CI)	1.44 [1.27–1.63]	<.00001	0%	.8
PB	4	1951	OR (M-H, Random, 95% CI)	0.97 [0.57–1.65]	.92	75%	.007
rs1219648 (A > G)	20	14,530	OR (M-H, Fixed, 95% CI)	1.54 [1.44–1.66]	<.00001	5%	.39
Asian	11	5328	OR (M-H, Fixed, 95% CI)	1.48 [1.32–1.67]	<.00001	0%	.73
Caucasian	8	8695	OR (M-H, Fixed, 95% CI)	1.57 [1.44–1.72]	<.00001	42%	.1
HB	8	4759	OR (M-H, Fixed, 95% CI)	1.54 [1.35–1.74]	<.00001	34%	.15
PB	12	9771	OR (M-H, Fixed, 95% CI)	1.55 [1.42–1.68]	<.00001	0%	.59
Heterozygote comparison							
rs11200014 (G > A)	5	6525	OR (M-H, Random, 95% CI)	1.85 [1.16–2.93]	.009	94%	<.00001
rs2981579 (C > T)	12	9129	OR (M-H, Fixed, 95% CI)	1.18 [1.08–1.28]	.0002	23%	.22
HB	8	6219	OR (M-H, Fixed, 95% CI)	1.21 [1.09–1.34]	.0005	0%	.57
PB	4	2910	OR (M-H, Random, 95% CI)	0.90 [0.62–1.31]	.59	62%	.05
rs1219648 (A > G)	20	23,104	OR (M-H, Fixed, 95% CI)	1.24 [1.18–1.31]	<.00001	28%	.12
Asian	11	8385	OR (M-H, Fixed, 95% CI)	1.21 [1.11–1.32]	<.0001	38%	.1
Caucasian	8	13,951	OR (M-H, Fixed, 95% CI)	1.25 [1.16–1.34]	<.00001	0%	.45
HB	8	7674	OR (M-H, Fixed, 95% CI)	1.26 [1.14–1.38]	<.00001	0%	.74
PB	12	15,430	OR (M-H, Random, 95% CI)	1.26 [1.13–1.41]	<.0001	50%	.02

CI = confidence interval.

1.08–1.28; $P = .0002$). When stratified by Source of controls, the results showed the same association between FGFR2 rs2981579 polymorphism and BC susceptibility in HB (Allele model: OR = 1.20, 95% CI = 1.13–1.28, $P < .00001$; Dominant model: OR = 1.27, 95% CI = 1.15–1.41, $P < .00001$; Recessive model: OR = 1.27, 95% CI = 1.14–1.41, $P < .0001$; Homozygous genetic model: OR = 1.44, 95% CI = 1.27–1.63, $P < .00001$; Heterozygote comparison: OR = 1.21, 95% CI = 1.09–1.34, $P = .0005$), although there not any genetic models attained statistical correlation in PB.

Twenty papers with 13,173 cases and 14,917 controls were adopted to evaluate the association between the rs1219648 polymorphism and the BC risk. As shown in Table 3, Figs. 4 and 5, the association between rs1219648 variant and BC susceptibility was significant in any genetic model (Allele model: OR = 1.25, 95% CI = 1.20–1.29, $P < .00001$; Dominant

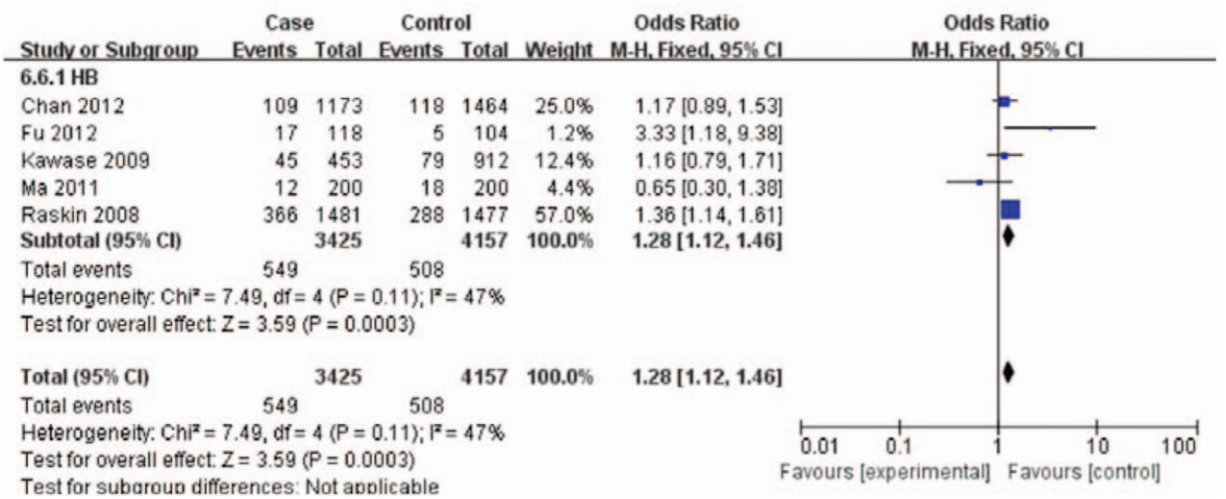

Figure 2. Forest plots of rs11200014 (G > A) polymorphism and breast cancer risk (Recessive model AA vs GG + AG).

model: OR = 1.32, 95% CI = 1.26–1.39, $P < .00001$; Recessive model: OR = 1.36, 95% CI = 1.28–1.45, $P < .00001$; Homozygous genetic model: OR = 1.54, 95% CI = 1.44–1.66, $P < .00001$; Heterozygote comparison: OR = 1.24, 95%CI = 1.18–1.31, $P < .00001$). The subgroup study stratified by Ethnicity showed an increased BC risk both in Asians (Allele model: OR = 1.23, 95% CI = 1.16–1.30, $P < .00001$; Dominant model: OR = 1.28, 95% CI = 1.18–1.39, $P < .00001$; Recessive model: OR = 1.35, 95% CI = 1.22–1.50, $P < .00001$; Homozygous genetic model: OR = 1.48, 95% CI = 1.32–1.67, $P < .00001$; Heterozygote comparison: OR = 1.21, 95% CI = 1.11–1.32, $P < .0001$) and Caucasians (Allele model: OR = 1.25, 95% CI = 1.20–1.30, $P < .00001$; Dominant model: OR = 1.33, 95% CI = 1.24–1.42, $P < .00001$; Recessive model: OR = 1.39, 95% CI = 1.22–1.58, $P < .00001$; Homozygous genetic model: OR = 1.57, 95% CI = 1.44–1.72, $P < .00001$; Heterozygote comparison: OR = 1.25, 95% CI = 1.16–1.34, $P < .00001$).We did not discuss the African subgroup for just 1 study from Africa. When stratified by Source of controls, the results showed the same association between FGFR2 rs1219648 polymorphism and BC susceptibility in HB (Allele model: OR = 1.24, 95% CI = 1.17–1.32, $P < .00001$; Dominant model: OR = 1.32, 95% CI = 1.21–1.44, $P < .00001$; Recessive model: OR = 1.35, 95% CI = 1.21–1.51, $P < .00001$; Homozygous genetic model: OR = 1.54, 95% CI = 1.35–1.74, $P < .00001$; Heterozygote comparison: OR = 1.26, 95% CI = 1.14–1.38, $P < .00001$) and PB (Allele model: OR = 1.25, 95% CI = 1.20–1.30, $P < .00001$; Dominant model: OR = 1.32, 95% CI = 1.24–1.40, $P < .00001$; Recessive model: OR = 1.37, 95% CI = 1.27–1.47, $P < .00001$; Homozygous genetic model: OR = 1.55, 95% CI = 1.42–1.68, $P < .00001$; Heterozygote comparison: OR = 1.26, 95% CI = 1.13–1.41, $P < .0001$).

3.3. Sensitivity analyses

As summarized in Table 1, all the studies conformed to the balance of HWE in controls except the studies by Chan et al[12] in rs11200014 group and Cherdyntseva et al[14] in rs1219648 group; however, after performing the sensitivity analyses, the overall outcomes were no statistically significant change when removing any of the articles, indicating that our study has good stability and reliability.

3.4. Detection for heterogeneity

Heterogeneity among studies was obtained by Q statistic. Random-effect models were applied if P value of heterogeneity tests was less than 0.1 ($P \leq .1$); otherwise, fixed-effect models were selected (Table 3).

3.5. Publication bias

As Fig. 6 indicated, the symmetrical funnel plot indicated that there is no significant publication bias in the total population. We used Begg funnel plot and Egger test to evaluate the published bias, and no significant publication bias was found in the Begg test and Egger test ($P > .05$).

4. Discussion

Human *FGFR2* gene is located in 10q26, containing 22 exons and including 2 subtypes (FGFR2b and FGFR2c). FGFR2b is mainly expressed in epithelial cells, while FGF2c is mostly expressed in stromal cells.[40] Studies indicated that FGFR2 may inhibit the occurrence and development of cancer. In a variety of epithelial tumor cell lines and tumor tissues, the expression of FGFR2b was significantly lower than that of normal epithelial cells, speculating that it might be related to the carcinostasis.[41] But the mutations in *FGFR2* gene can induce tumor occurrence, and the missense mutations in *FGFR2* gene exist in the BC, gastric cancer, lung cancer, ovarian cancer, and endometrial cancer.[42–46] As early as 1992, it was found that the expression of FGFR2 in human was significantly higher in ER-positive BC.[47] Subsequently, a large number of studies on the relationship between the polymorphism of *FGFR2* gene and BC have been implemented in different countries and regions around the world.[33]

Recently, researches have paid more attention to the human FGFR2, whose several SNPs, rs11200014 (G > A), rs2981579 (C > T), rs1219648 (A > G), may be associated with BC susceptibility in different crowds and different regions.[5–30] The 3 SNPs are located in intron 2 of FGFR2, encoded by *FGFR2* gene. Through interacting with the mitogenic ligand fibroblast growth factors (FGFs), a cascade of downstream signals will be activated, thus influencing on angiogenesis, wound healing, cell

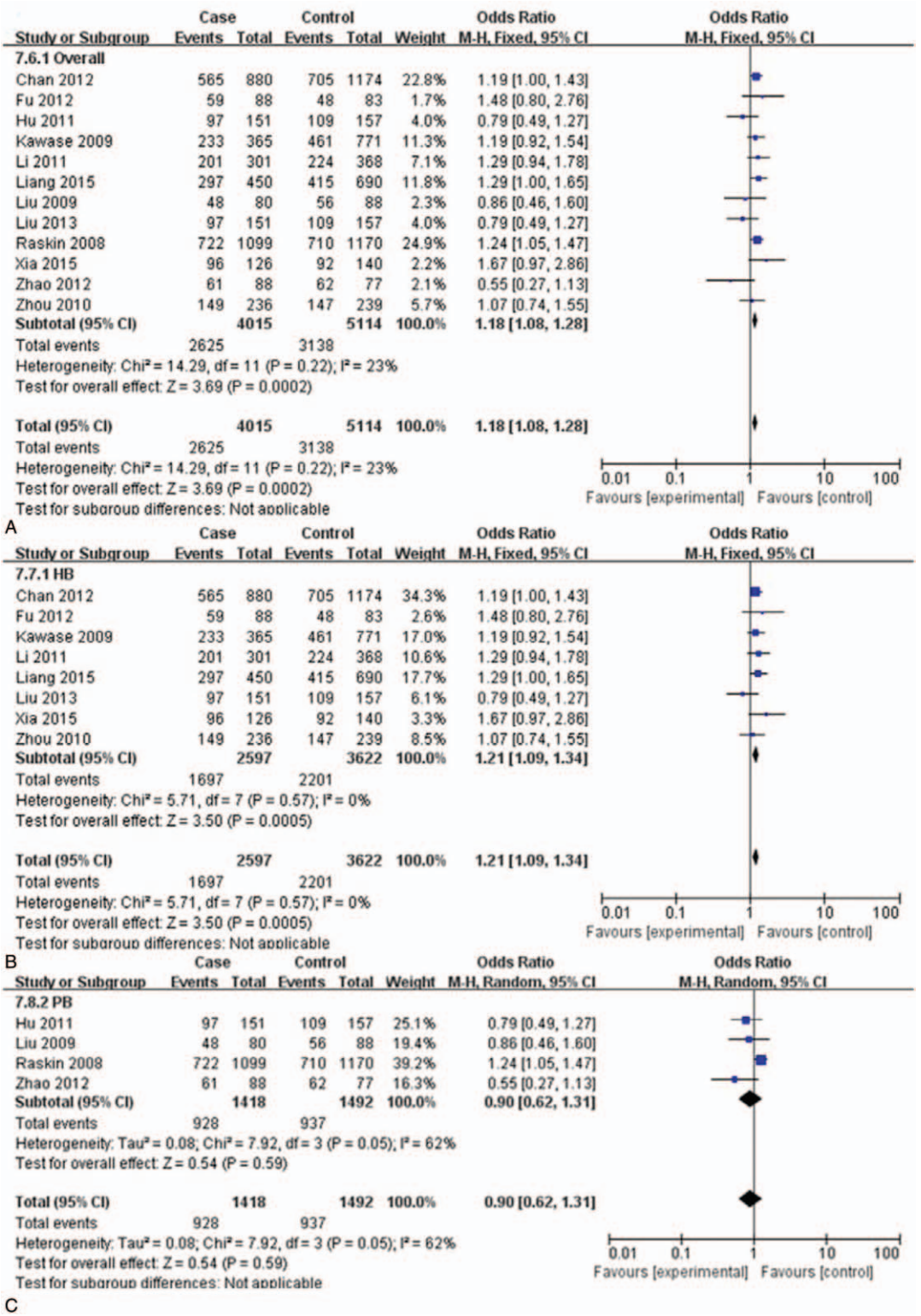

Figure 3. Forest plots of rs2981579 (C > T) polymorphism and breast cancer risk (Heterozygote comparison TC vs CC). (A) Overall. (B) HB. (C) PB.

migration neural outgrowth, and embryonic development.[41] However, the association between rs11200014, rs2981579, and rs1219648 polymorphism and BC susceptibility in related reports is still inconclusive between susceptible[5,9–13] and protective.[6–8] Thus, we conducted the meta-analysis to evaluate the relationship between FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphism and BC risk.

Main results of our study are summarized in Table 3. There were 26 studies with 3425 cases and 4157 controls for rs11200014 variants. In the total population, the pooled results

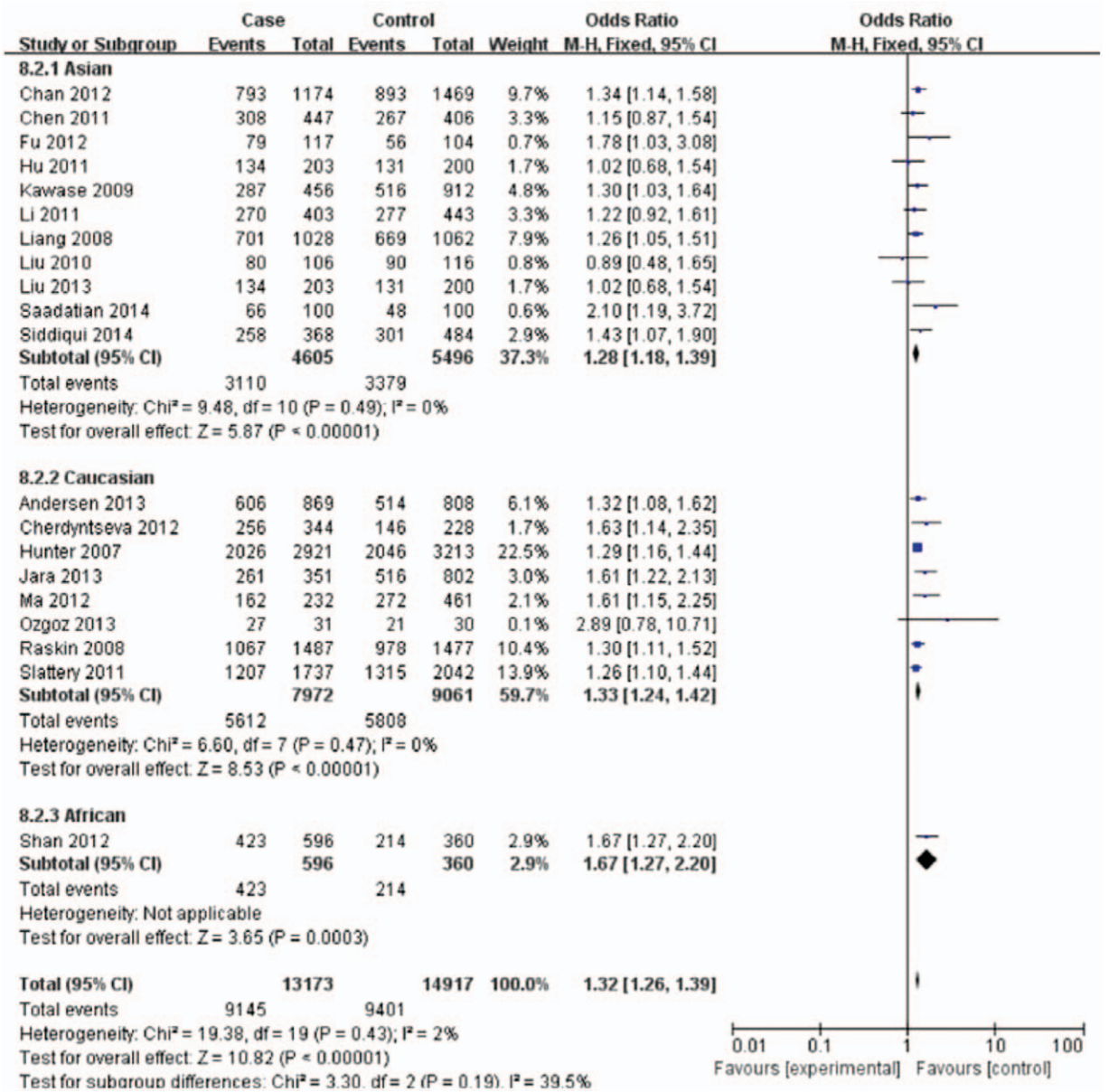

Figure 4. Forest plots of rs1219648 (A > G) polymorphism and breast cancer risk stratified by ethnicity (Dominant model GA + GG vs AA).

indicated that the correlation between rs11200014 polymorphism and the occurrence of BC was significant in any genetic model. The meta-analysis by Zhou et al[31] indicated the same remarkable associations in Caucasians, but not in Asians and Africans. However, in Asian and African subgroups, there are only a few literatures and cases, and even only 1 paper in African subgroups. Such meta-analysis may not be particularly appropriate. For rs2981579, 12 studies with 5356 cases and 6441 controls were included to assess the association. Overall, the pooled ORs suggested that rs2981579 was significantly associated with BC susceptibility in all the 5 genetic models. The results were consistent with studies by Zhou et al[31] and Peng et al[34] studies, but they did not carry out further subgroup analysis. When stratified by source of controls, the results showed the same association between rs2981579 polymorphism and BC susceptibility in hospital populations, while there was not any genetic models attained statistical correlation in general populations, indicating that there was a difference in the association between rs2981579 polymorphism and BC risk among different groups. For the first time, this study conducted a subgroup analysis for rs2981579 stratified by source of controls, and for the first time came to this conclusion. However, further large-scale, multicenter, epidemiological studies are warranted to confirm this finding. Twenty papers with 13,173 cases and 14,917 controls were adopted to evaluate the association between the rs1219648 polymorphism and the BC risk. In the total population, the association between rs1219648 variant and BC risk was significant in any genetic model. The results were consistent with the studies by Zhang et al[32] and Jia et al.[35] The subgroup study stratified by Ethnicity showed an increased BC risk both in Asians and Caucasians. We did not discuss the African subgroup for just 1 study from African meet our inclusion criteria. In the study by Zhang et al,[32] significantly increased risks were also found among Asian and Caucasian populations in

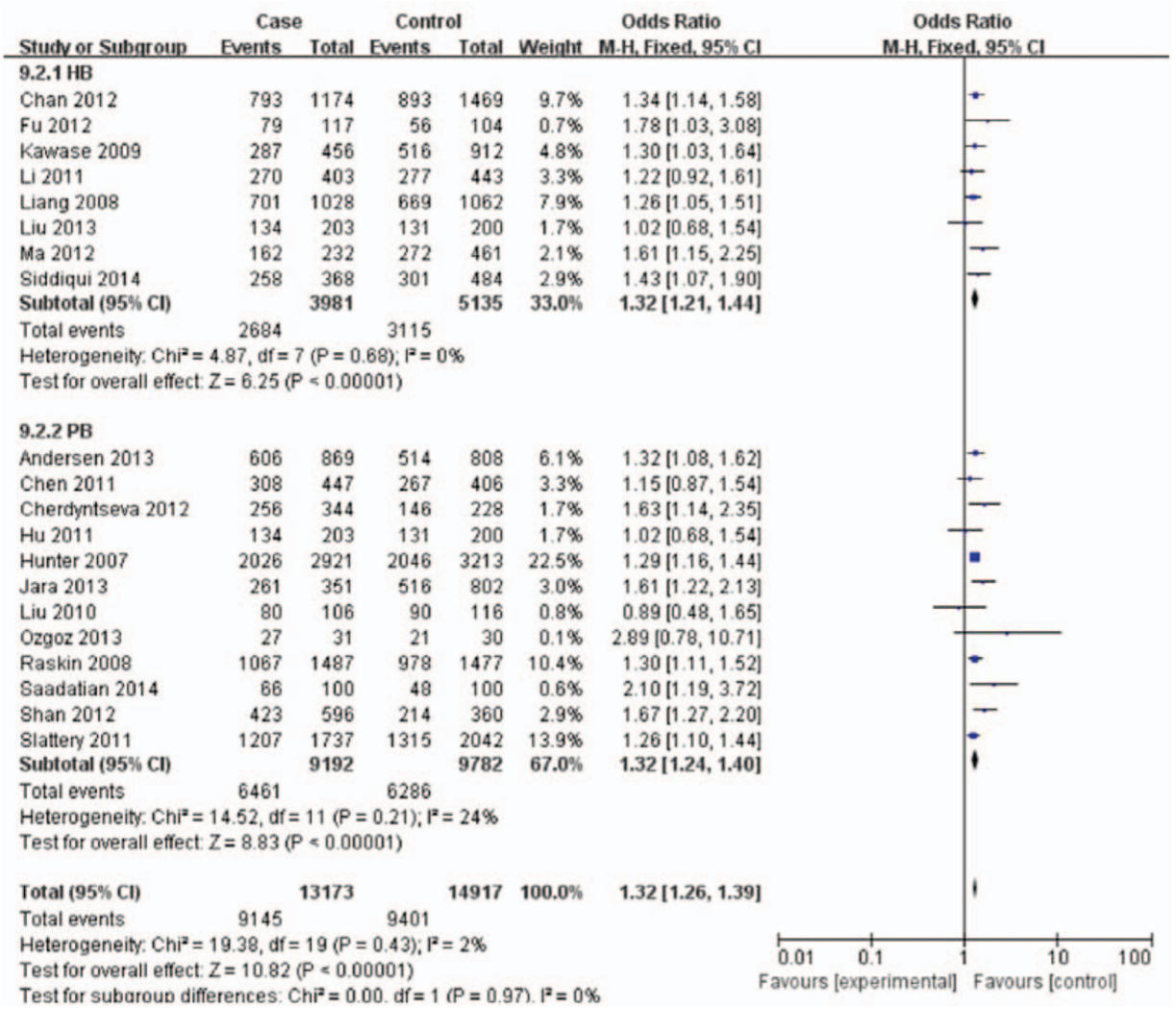

Figure 5. Forest plots of rs1219648 (A > G) polymorphism and breast cancer risk stratified by Source of controls (Dominant model GA + GG vs AA).

all genetic models. However, these similar significant associations were not observed for African population, indicating that these associations vary in different ethnic populations. When stratified by Source of controls, the results showed the same association between rs1219648 polymorphism and BC susceptibility in HB and PB.

Overall, all the results for the 3 variants (rs11200014, rs2981579, and rs1219648) were partially consistent with the consequences of previous 5 meta-analyses,[31–35] while they did not conduct analysis in different source of controls. And our sample size was several times than theirs, making our results more convincing. Furthermore, they did not use all the 5 genetic models (allele model, dominant model, recessive model, homozygous model, and heterozygous model) to assess the strength of association.

Our meta-analysis has several limitations. First, only published papers were included in our meta-analysis, and there may still be some unpublished studies in line with the conditions. Therefore, publication bias may exist; even no statistical evidence suggest publication bias in the meta-analysis. Second, for rs11200014 and rs2981579 variants, almost all of the included studies are from Asia. Therefore, we could not assess the association stratified by Ethnicity. Moreover, our study is a summary of the data. For lack of all individual raw data, we could not assess the cancer risk stratified by other covariates, including age, sex, environment, hormone level, menopause age, and other risk factors. We also need verify it from the level of molecular mechanism. Data from large-scale, multicenter, epidemiological studies are still needed to confirm the relationship between FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphisms and BC risk, and the molecular mechanism for the associations need to be elucidated in future studies.

5. Conclusion

Our meta-analysis of case–control studies provides strong evidence that FGFR2 (rs11200014, rs2981579, and rs1219648) polymorphisms are significantly associated with the BC risk. For rs2981579, the association remained in hospital populations, while not in general populations. For rs1219648, the association remained in Asians, Caucasians, hospital populations, and general populations. However, further large-scale, multicenter, epidemiological studies are warranted to

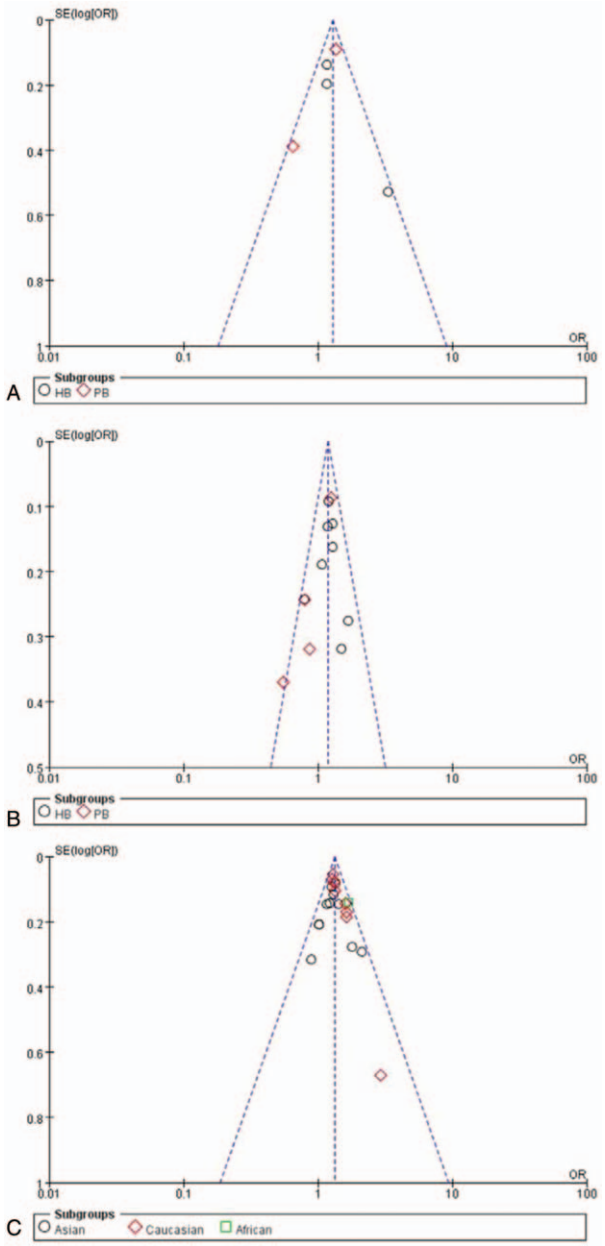

Figure 6. Funnel plot assessing evidence of publication bias. A. rs11200014 (G > A) (Recessive model AA vs GG + AG). B. rs2981579 (C > T) (Heterozygote comparison TC vs CC). C. rs1219648 (A > G) (Dominant model GA + GG vs AA). OR = odds ratio, SE = standard error.

confirm this finding, and the molecular mechanism for the associations need to be elucidated in future studies.

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