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Original Article

Peroxisome proliferator-activated receptor gamma (PPARG) polymorphisms and breast cancer susceptibility: a meta-analysis

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Abstract: Background: Peroxisome proliferator-activated receptor gamma (PPARG), a nuclear hormone receptor, plays a critical role in the lipid and glucose homeostasis, adipocyte differentiation, as well as intracellular insulin-signaling events. Several studies have been conducted to explore the associations of *PPARG* polymorphisms with breast cancer (BC), yet the findings are inconsistent. Methods: Databases of Pubmed and Embase were searched until October 5, 2014. The association between *PPARG* polymorphisms and BC risk was determined by crude odds ratios (ORs) with their 95% confidence intervals (CIs). Results: Finally, there are nine publications involving 3,931 BC cases and 5,382 controls included in this meta-analysis. No significant association was observed between *PPARG* rs1801282 C>G variants and overall BC risk in all genetic comparison models. However, in a subgroup analysis by ethnicity, significant association was observed between *PPARG* rs1801282 C>G variants and decreased BC risk in three genetic models: GG+CG vs. CC (OR, 0.83; 95% CI, 0.71-0.96; *P* = 0.011), CG vs. CC (OR, 0.82; 95% CI, 0.71-0.96; *P* = 0.011) and G vs. C (OR, 0.85; 95% CI, 0.75-0.97; *P* = 0.016) in Caucasians and in a subgroup analysis by menopausal status, significantly decreased BC risk was also found in two genetic models: GG+CG vs. CC (OR, 0.79; 95% CI, 0.67-0.95; P = 0.011) and CG vs. CC (OR, 0.77; 95% CI, 0.64-0.92; P = 0.005) in post-menopause subgroup. For *PPARG* rs3856806 C>T, we found no significant association between *PPARG* rs3856806 C>T polymorphism and breast cancer. Conclusions: In summary, despite some limitations, the results suggest that *PPARG* rs1801282 C>G polymorphism may be a protective factor for BC in Caucasians and in post-menopause women.

Keywords: Breast cancer, polymorphism, peroxisome proliferator-activated receptor gamma, meta-analysis

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in female with an estimated 1,676,600 new BC cases and 521,900 BC related deaths in 2012 worldwide [1]. BC is a common disease that is attributed to multiple genetic and environmental risk factors. Recently, a number of candidate genes, such as *BRCA1/2*, *TP53*, *BRIP1* and *PALB2*, have been confirmed to contribute to the risk of breast cancer [2-6]. These mutations may play a critical role in the development of BC. *BRCA1/2* is a high penetrance gene [4] and 80% of individuals who carry this mutation may develop to BC. Compared to the normal population, the medium penetrance genes *PALB2, CHEK2* and *BRIP1* can increase 2.3-, 2.2-, and 2.0-fold risks of BC, respectively [2, 3]. Some low penetrance genes *FGFR2*, *ESR1*, *MAP3K1* and *TOX3* have been investigated in several genome-wide association studies (GWAS) and were confirmed as candidates of BC [7-11]. Thus, in all probability, there are a crowd of low penetrance mutations in genes contributing to the remaining unexplained susceptibility of BC, which have not yet been verified.

Accumulating epidemiological evidence highlights that impaired glucose tolerance and type

2 diabetes are associated with the risk of cancer [12-15]. Peroxisome proliferator-activated receptor gamma (PPARG), a nuclear hormone receptor, acts as a critical regulator of lipid and glucose homeostasis, adipocyte differentiation, and intracellular insulin-signaling events. A number of investigations have therefore explored the hypothesis that the mutation of *PPARG* gene influences the development and progression of malignancy [16-21]. The *PPARG* single nucleotide polymorphisms (SNPs) are deemed to alter the activity of *PPARG*. This gene is polymorphic, and a number of SNPs have been studied, such as the rs1801282, rs3856806, rs4135247, rs1175543, rs709158 and rs2938395 polymorphisms, etc. Among them, the rs1801282 C>G and rs3856806 C>T are the most widely explored for correlation with cancer susceptibility. In a previous review, *PPARG* rs1801282 C>G polymorphism were correlated with protection from colorectal cancer, but with an increased susceptibility of gastric carcinoma and rs3856806 C>T polymorphism was marginally associated with the risk of cancer [22].

Recently, more studies have focused on the association of *PPARG* SNPs with BC [23-30]. Some of them identified the potential correlation between *PPARG* SNPs with BC risk [26, 28]. A meta-analyses including three investigations confirmed that *PPARG* rs1801282 C>G was associated with the decreased risk of BC [31]; however, the other meta-analysis suggested that *PPARG* SNPs were not associated with BC [30]. At present, more studies have demonstrated that *PPARG* SNPs may clarify the causes and events correlated with BC; nevertheless, the results remain inconclusive. Therefore, in this study, we performed an updated meta-analysis to further explore the role of the *PPARG* polymorphisms in BC risk.

Materials and methods

Our study is reported on the basis of the PRISMA (Preferred Reporting Items for Meta-analyses) guideline (Table S1. PRISMA checklist) [32].

Search strategy

We searched literatures from PubMed and Embase databases (published up to October 5, 2014) using the following terms 'Peroxisome proliferator-activated receptor gamma', 'PPARG' 'PPARγ', 'polymorphism', 'mutation', 'variant', 'cancer', 'carcinoma', 'malignance' and 'breast'. In order to minimize potential publication bias, additional relevant studies in the citations were also manually scanned. Only the latest study with the largest samples was recruited in our study to avoid overlapping data.

Inclusion and exclusion criteria

In our meta-analysis, all studies included had to meet all the following criteria: (a) case-control or cohort studies which assessed the association of *PPARG* SNPs with BC risk; (b) the available frequencies of genotypes or alleles must be provided and the genotype distribution among controls complied with the Hardy-Weinberg equilibrium (HWE). The major reasons for exclusion of studies were: (a) incomplete data; (b) duplicated studies or overlapping data; (c) only relevant to BC treatment; (d) meta-analysis, review, editorial, comment or letter.

Data extraction

In a standardized form, three reviewers (W. Tang, Y. Chen and Y. Wang) independently checked and extracted the data from all included publications. The following characteristic terms were extracted: the surname of first author, the year of publication, the country of origin, the ethnicity of participants, the allele and genotype frequencies, the genotyping method, the sample size, and the evidence of HWE in controls. If different results generated, disputes were settled by consulting the third reviewer (H. Gu).

Methodological quality assessment

The quality assessment was carefully performed by three authors (W. Tang, Y. Chen and Y. Wang) according to the 'methodological quality assessment scale' described previously [33, 34]. Scores range from 0 to 10, and if the quality scores were ≥ 6, publications were defined as 'high quality'; otherwise, they were classified as 'low quality'.

Statistical analysis

In our study, the pooled odds ratios (ORs) with 95% confidence intervals (CIs) were assessed

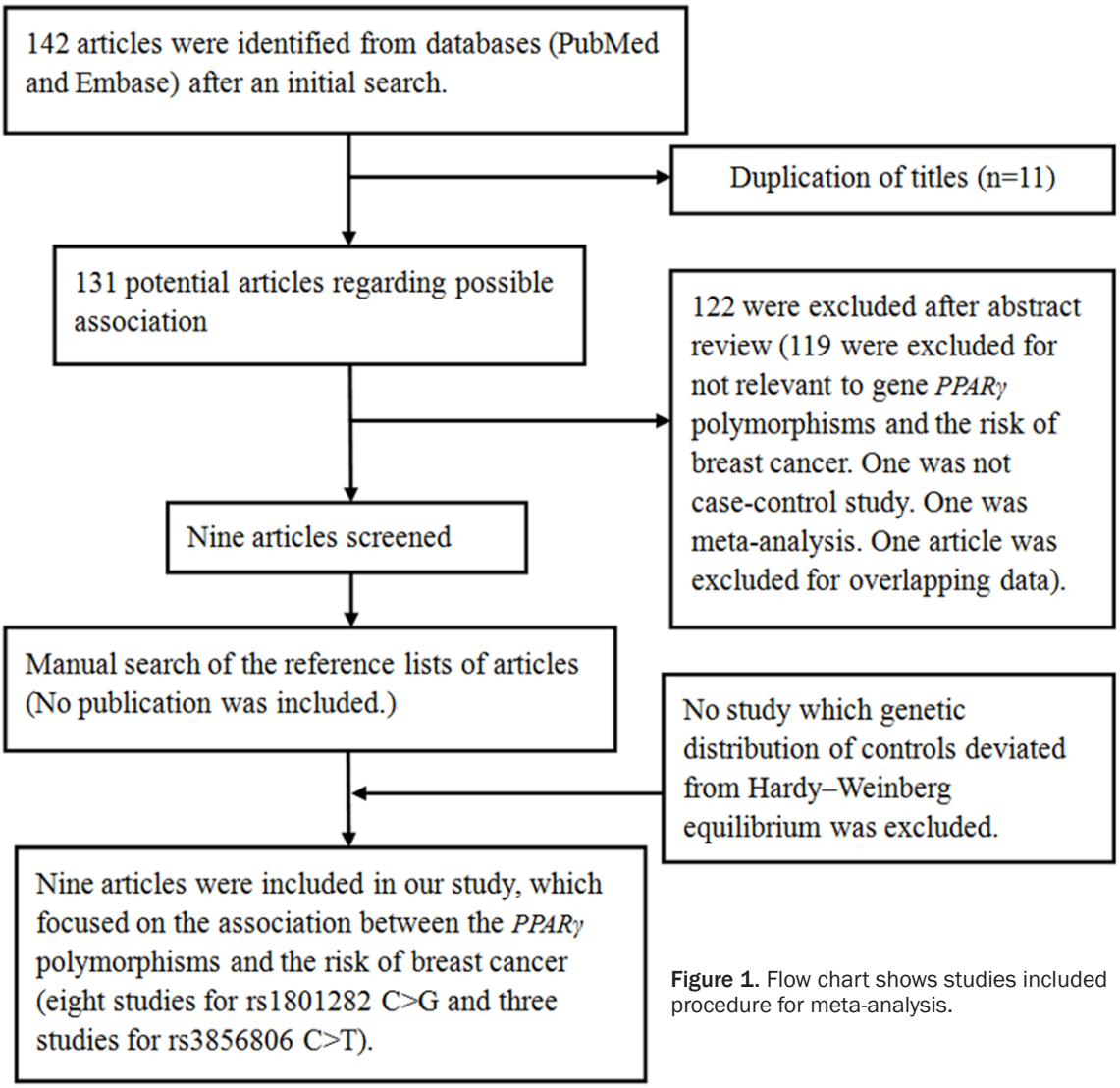

Figure 1. Flow chart shows studies included procedure for meta-analysis.

for dominant model, recessive model, heterozygote comparison, homozygote comparison and allelic comparison. Stratified analyses were conducted by ethnicity, menopausal status, source of controls and sample sizes. Heterogeneity among the studies was assessed by using a χ^2-test-based Q statistic test. The value of $P < 0.1$ showed substantial heterogeneity across the publications, then the data were pooled by using the random-effects model (DerSimonian and Laird) [35]; otherwise, the fixed-effects model was used (Mantel-Haenszel) [36]. Both one-way sensitivity analysis and "trim-and-fill" method were conducted to evaluate the stability of this meta-analysis. Potential publication bias across the studies was assessed by a funnel plots and Egger's linear regression test. The distribution of the genotypes in control subjects was checked for HWE using a web-based χ^2 test program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). All data analysis was conducted with STATA 12.0 software package (Stata Corp LP, College Station, Texas).

Results

Study characteristics

As shown in **Figure 1**, a total of 142 potentially relevant publications were obtained based on the search terms from PubMed and Embase databases. Finally, there were nine publications involving 3,931 BC cases and 5,382 controls included in this meta-analysis. All subjects were female. For *PPARG* rs1801282 C>G poly-

Table 1. Characteristics of the included studies and the results of the methodological quality assessment scale

Study	Publication year	Ethnicity	Country	Source of controls	Menopausal status	Sample size (case/control)	*PPARG* polymorphisms	Genotype method
Park et al.	2014	Asians	Korea	HB	Mixed status	456/461	rs1801282 and rs3856806	MALDI-TOF MS
Martinez-Nava et al.	2013	Mixed populations	Mexico	PB	Mixed status	208/220	rs1801282	RT-PCR
Wei	2013	Asians	China	HB	Mixed status	216/216	rs3856806	MALDI-TOF MS
Petersen et al.	2012	Caucasians	Denmark	PB	Post-menopaused	798/798	rs1801282	TaqMan
Wu et al.	2011	Asians	China	HB	Mixed status	291/589	rs1801282 and rs3856806	RT-PCR
Justenhoven et al.	2008	Caucasians	German	PB	Mixed status	688/724	rs1801282	MALDI-TOF MS
Gallicchio et al.	2007	Caucasians	USA	PB	Post-menopaused	61/933	rs1801282	TaqMan
Wang et al.	2007	Caucasians	USA	PB	Post-menopaused	488/488	rs1801282	TaqMan
Memisoglu et al.	2002	Mixed populations	USA	PB	Mixed status	725/953	rs1801282	PCR-RFLP

RT-PCR: real-time PCR; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry.

Table 2. Distribution of *PPARG* polymorphisms genotype and allele

PPARG polymorphisms	Study	Case genotype			Control genotype			Case allele		Control allele		HWE	Quality scores
rs1801282 C>G		CC	CG	GG	CC	CG	GG	G	C	G	C		
	Martinez-Nava et al.	165	43	0	169	49	2	43	373	53	387	0.448105	8.0
	Park et al.	413	40	2	412	42	1	44	866	44	866	0.948224	6.5
	Wu et al.	260	29	0	546	40	0	29	549	40	1132	0.392337	7.0
	Gallicchio et al.	48	7	1	689	188	18	9	103	224	1566	0.223793	8.5
	Wang et al.	376	87	15	375	98	5	117	839	108	848	0.615475	6.5
	Memisoglu et al.	563	148	14	752	190	11	176	1274	212	1694	0.795703	7.0
	Petersen et al.	616	167	15	569	209	20	197	1399	249	1347	0.876910	7.5
	Justenhoven et al.	452	135	6	462	145	15	147	1039	175	1069	0.372101	7.5
rs3856806 C>T		CC	CT	TT	CC	CT	TT	C	T	C	T		
	Park et al.	320	128	8	311	117	15	768	144	739	147	0.335483	6.5
	Wei	115	69	15	122	69	9	299	99	313	87	0.848027	6.5
	Wu et al.	162	110	19	328	219	40	434	148	875	299	0.675591	7.0

HWE: Hardy-Weinberg equilibrium.

Table 3. Meta-Analysis of *PPARG* rs1801282 C>G polymorphism with the breast cancer risk

	No. of study	G vs. C			GG vs. CC			GG+CG vs. CC			GG vs. CG+CC			CG vs. CC		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	8	0.95 (0.81-1.11)	0.503	0.065	1.02 (0.54-1.93)	0.963	0.062	0.92 (0.82-1.03)	0.132	0.119	1.05 (0.56-1.96)	0.884	0.071	0.91 (0.81-1.02)	0.107	0.178
Ethnicity																
Asians	2	1.19 (0.86-1.64)	0.302	0.225	2.00 (0.18-22.09)	0.573	NA	1.18 (0.85-1.65)	0.327	0.192	2.00 (0.18-22.18)	0.571	NA	1.17 (0.83-1.64)	0.363	0.171
Caucasians	4	0.85 (0.75-0.97)	0.016	0.158	0.90 (0.37-2.16)	0.809	0.038	0.83 (0.71-0.96)	0.011	0.287	0.94 (0.39-2.25)	0.890	0.038	0.82 (0.71-0.96)	0.011	0.353
Mixed populations	2	1.05 (0.86-1.26)	0.647	0.265	1.39 (0.66-2.92)	0.389	0.184	1.03 (0.83-1.27)	0.792	0.402	1.38 (0.66-2.90)	0.394	0.190	1.01 (0.81-1.25)	0.939	0.582
Menopausal status																
Post-menopaused	3	0.85 (0.63-1.15)	0.298	0.075	1.21 (0.41-3.57)	0.723	0.062	0.79 (0.67-0.95)	0.011	0.202	1.29 (0.46-3.64)	0.631	0.074	0.77 (0.64-0.92)	0.005	0.442
Mixed status	5	1.00 (0.88-1.15)	0.958	0.237	0.85 (0.30-2.38)	0.750	0.093	1.01 (0.87-1.01)	0.865	0.395	0.85 (0.31-2.35)	0.754	0.099	1.02 (0.88-1.18)	0.801	0.537
Source of controls																
PB	6	0.91 (0.77-1.06)	0.234	0.093	0.97 (0.49-1.93)	0.930	0.039	0.89 (0.79-1.00)	0.051	0.203	1.00 (0.51-1.98)	0.991	0.045	0.88 (0.78-0.99)	0.041	0.322
HB	2	1.19 (0.86-1.64)	0.302	0.225	2.00 (0.18-22.09)	0.573	NA	1.18 (0.85-1.65)	0.327	0.192	2.00 (0.18-22.09)	0.571	NA	1.17 (0.83-1.64)	0.363	0.171
Sample sizes																
< 1000	5	1.02 (0.85-1.22)	0.829	0.242	1.78 (0.85-3.73)	0.125	0.316	0.98 (0.81-1.19)	0.837	0.252	1.86 (0.89-3.89)	0.102	0.332	0.94 (0.77-1.15)	0.563	0.231
≥ 1000	3	0.90 (0.72-1.12)	0.341	0.043	0.80 (0.37-1.73)	0.578	0.064	0.89 (0.71-1.12)	0.318	0.069	0.83 (0.39-1.74)	0.619	0.075	0.89 (0.77-1.03)	0.118	0.115

PB: Population-based; HB: Hospital-based.

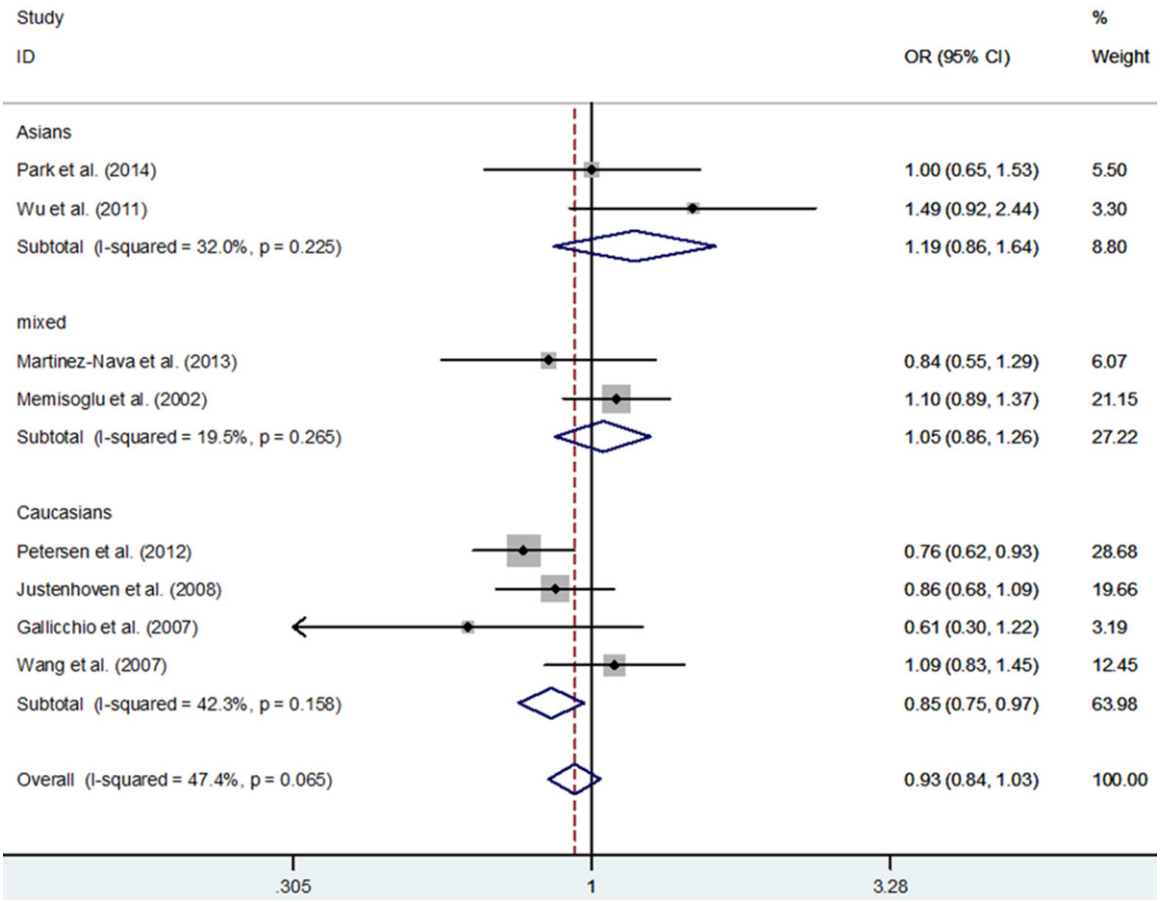

Figure 2. Forest plot of breast cancer risk associated with *PPARG* rs1801282 C>G polymorphism for the G vs. C (fixed effects model).

morphism, eight publications focusing on the association of this SNP with BC risk remained in the pooled analysis [23-29]. As for subjects in these studies, four were Caucasians [25, 26, 28, 29]; two were mixed populations [23, 27] and two were Asians [24, 30]. As for menopausal status, three studies investigated postmenopause women [25, 26, 28], while five studies investigated overall adult women [23, 24, 27, 29, 30]. For *PPARG* rs3856806 C>T polymorphism, three studies were included [24, 30, 37]. Among them, all were Asians and investigated overall adult women. The detailed characteristics of the eligible studies and distribution of the *PPARG* polymorphisms as well as alleles are summarized in **Tables 1** and **2**, respectively.

Association of PPARG rs1801282 C>G polymorphism with BC risk

In total, 3,715 BC cases and 5,166 controls from eight eligible studies were relevant to the association between *PPARG* rs1801282 C>G polymorphism and BC. In overall meta-analysis, we found no association between *PPARG* rs1801282 C>G polymorphism and BC risk: GG+CG vs. CC (OR, 0.92; 95% CI, 0.82-1.03; *P* = 0.132), GG vs. CG+CC (OR, 1.05; 95% CI, 0.56-1.96; *P* = 0.884), GG vs. CC (OR, 1.02; 95% CI, 0.54-1.93; *P* = 0.963), CG vs. CC (OR, 0.91; 95% CI, 0.81-1.02; *P* = 0.107) and G vs. C (OR, 0.95; 95% CI, 0.81-1.11; *P* = 0.503) (**Table 3**). In a subgroup analysis by ethnicity, significantly decreased BC risk was confirmed in three genetic models: GG+CG vs. CC (OR, 0.83; 95% CI, 0.71-0.96; *P* = 0.011), CG vs. CC (OR, 0.82; 95% CI, 0.71-0.96; *P* = 0.011) and G vs. C (OR, 0.85; 95% CI, 0.75-0.97; *P* = 0.016) in Caucasians, but not in non-Caucasians (**Table 3**; **Figure 2**). In a subgroup analysis by menopausal status, significant decreased BC risk was also found in two genetic models: GG+CG vs. CC (OR, 0.79; 95% CI, 0.67-0.95; *P* = 0.011) and CG vs. CC (OR, 0.77; 95% CI, 0.64-0.92; *P*

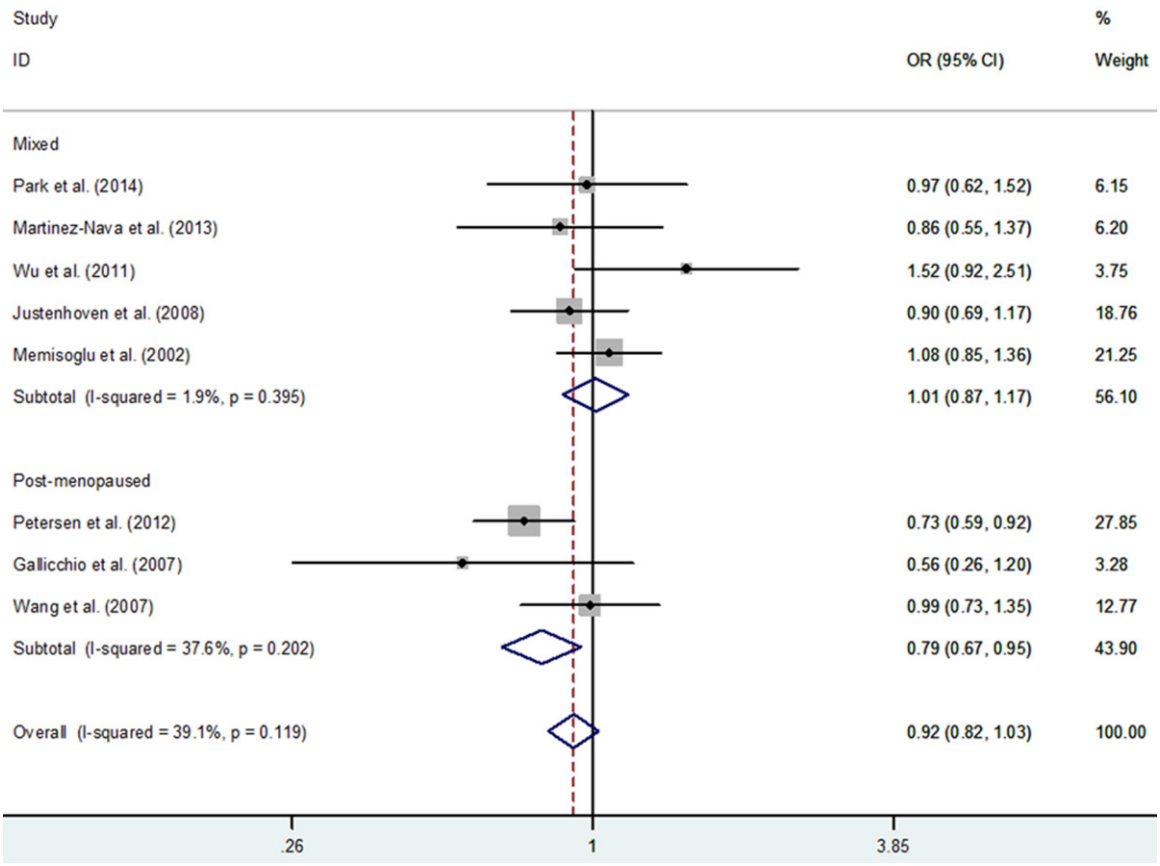

Figure 3. Forest plot of breast cancer risk associated with *PPARG* rs1801282 C>G polymorphism for the GG+CG vs. CC (fixed effects model).

Table 4. Meta-Analysis of *PPARG* rs3856806 C>T polymorphism with the breast cancer risk

Genetic comparison	OR (95% CI)	*P*	Test of heterogeneity	
			p-Value	Model
TT+CT vs. CC	1.03 (0.86-1.23)	0.737	0.853	F
TT vs. CT+CC	0.95 (0.63-1.43)	0.806	0.143	F
TT vs. CC	0.96 (0.63-1.45)	0.843	0.147	F
CT vs. CC	1.04 (0.87-1.26)	0.652	0.975	F
T vs. C	1.01 (0.87-1.18)	0.849	0.531	F

= 0.005) in post-menopause subgroup, but not mixed status (**Table 3**; **Figure 3**).

Association of PPARG rs3856806 C>T polymorphism with BC risk

A total of 963 BC cases and 1,266 controls from three publications focused on the association of *PPARG* rs3856806 C>T with BC were enrolled for the current study. In pooled analysis, we found no significant association between them: TT+CT vs. CC (OR, 1.03; 95% CI, 0.86-1.23; *P* = 0.737), TT vs. CT+CC (OR, 0.95; 95% CI, 0.63-1.43; *P* = 0.806), TT vs. CC (OR, 0.96; 95% CI, 0.63-1.45; *P* = 0.843), CT vs. CC (OR, 1.04; 95% CI, 0.87-1.26; *P* = 0.652) and T vs. C (OR, 1.01; 95% CI, 0.87-1.18; *P* = 0.849) (**Table 4**).

Publication bias for PPARG rs1801282 C>G polymorphism

Funnel plots and the Egger's linear regression test were conducted to check potential publication bias across literatures. The shape of the funnel plot appeared to be symmetrical in all comparison models supported by Egger's test (G vs. C: Begg's test *P* = 0.711, Egger's test *P* = 0.780; GG vs. CC: Begg's test *P* = 1.000, Egger's test *P* = 0.929; GG+CG vs. CC: Begg's test *P* = 1.000, Egger's test *P* = 0.826; GG vs. CG+CC: Begg's test *P* = 1.000, Egger's test *P* =

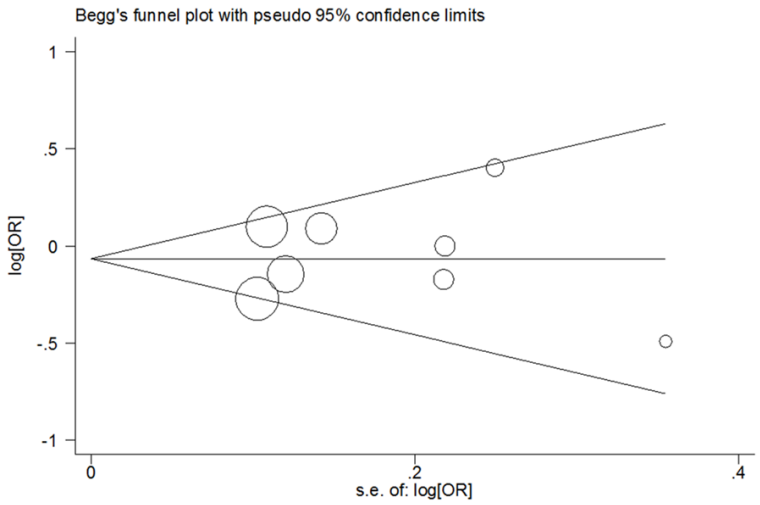

Figure 4. Begg's funnel plot analysis of *PPARG* rs1801282 C>G polymorphism with breast cancer risk for the G vs. C (random-effects model).

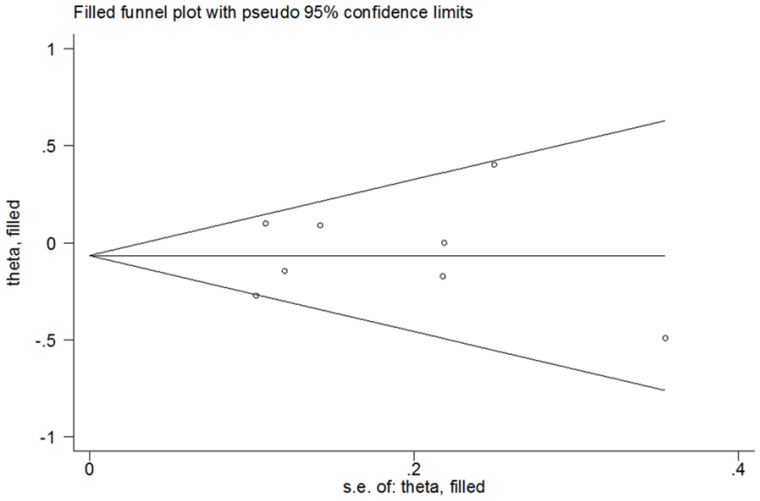

Figure 5. Filled funnel plot of *PPARG* rs1801282 C>G polymorphism with breast cancer risk for the G vs. C (random-effects model).

0.925; CG vs. CC: Begg's test P = 1.000, Egger's test P = 0.865; **Figure 4**).

Sensitivity analyses for PPARG rs1801282 C>G polymorphism

Both one-way sensitivity analysis and "trim-and-fill" method were carried out to verify the stability of this meta-analysis. The adjusted ORs and CIs of nonparametric "trim-and-fill" method were not substantially altered (G vs. C: adjusted pooled OR = 0.95, 95% CI: 0.81-1.11, P = 0.503; GG vs. CC: adjusted pooled OR = 1.02, 95% CI: 0.54-1.93, P = 0.963; GG+CG vs. CC: adjusted pooled OR = 0.92, 95% CI: 0.82-1.03, P = 0.148; GG vs. CG+CC: adjusted pooled OR = 1.05, 95% CI: 0.56-1.96, P = 0.884; CG vs. CC: adjusted pooled OR = 0.91, 95% CI: 0.81-1.03, P = 0.122; **Figure 5**), verifying the stability of our findings. Results of one-way sensitivity analysis were not significantly changed when any study was removed in turn, attesting the robustness of our findings (**Figure 6**).

Tests for heterogeneity for PPARG rs1801282 C>G polymorphism

Heterogeneity between studies was summarized in **Table 3**. Results of subgroup analysis indicated that the investigations conducted in Caucasians, post-menopause, population-based and large sample sizes (≥ 1000) subgroups might contribute to the major heterogeneity.

Results of quality assessment

According to the 'methodological quality assessment scale' [33, 34], quality assessment was performed in all included publications. The results indicated that all studies were "high quality" (quality scores ≥ 6; **Table 2**), suggesting the reliability of our findings.

Discussion

PPARG, a member of the nuclear hormone receptor superfamily, could recognize and bind to PPARG response elements, subsequently regulate and potentially affect the transcription of target genes in the promoter region. Given the PPARG has shown pro-apoptotic, pro-differentiation and anti-proliferative properties after activation, it is deemed to have overall anti-carcinogenic effects in a number of cell types [38]. In view of these findings, the *PPARG* SNPs have been intensively studied for the association with BC recently. Results of one pooled

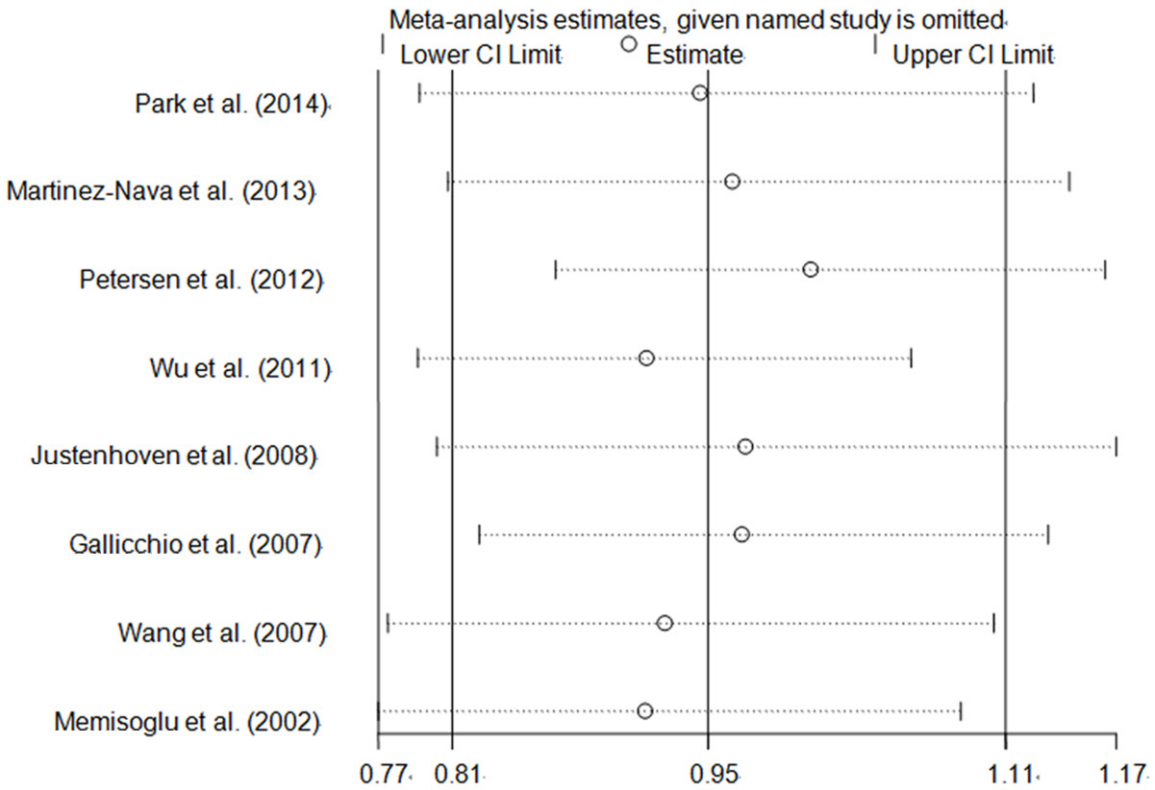

Figure 6. One-way sensitivity analysis of *PPARG* rs1801282 C>G polymorphism with breast cancer risk for the G vs. C (random-effects model).

analysis highlighted that the *PPARG* rs1801282 G allele modestly modified the susceptibility of breast cancer [31]. In contrast, the other previous meta-analysis indicated that both *PPARG* rs1801282 G allele and rs3856806 T allele did not affect the BC risk [30]. These seemingly conflicting findings have inspired more studies on correlation of *PPARG* SNPs with BC risk. In the light of these results, we summarized data for 3,931 BC cases and 5,382 controls from nine recruited publications and attempted to evaluate the risk of *PPARG* SNPs to BC by a comprehensive meta-analysis. Our results indicated that *PPARG* rs1801282 G allele might modify the susceptibility of breast cancer in Caucasians and in post-menopause women [31].

PPARG is an important transcription factor which acts as a controller in inflammatory cytokine production, insulin sensitization, lipogenesis, glucose homeostasis and cell differentiation [39]. The *PPARG* rs1801282 C>G polymorphism, a most common SNP in exon B of *PPARG*, encodes a Pro→Ala substitution at amino acid residue 12 (Pro 12 Ala) [40]. As a previous study has shown this missense substitution of rs1801282 C>G could cause less transcriptional activation of target genes in vitro [41], it may presumably affect cell differentiation and then alters the risk of BC. In combination with our results, these findings suggested that the *PPARG* rs1801282 C>G variants might be a protective factor for BC, probably through increasing binding capacity for certain PPARG response elements and promoting the ability of pro-apoptotic, pro-differentiation and anti-proliferative properties.

PPARG rs3856806 C>T polymorphism, another important SNP, has been suggested to have inverse associations with body weight compared to *PPARG* rs1801282 C>G polymorphism and relate to inflammation response [42]. It has been reported that *PPARG* rs3856806 C>T polymorphism is correlated with several cancer risk including colorectal cancer [43-45], follicular lymphoma [46] and ovarian carcinoma [47]. This pooled study is to explore possible association of this functional mutation (rs3856806

C>T) in the *PPARG* gene with BC risk. Our results indicated that *PPARG* rs3856806 C>T polymorphism was not associated with the risk of BC, which was consistent with the previous study [30]. This conclusion, however, should be elucidated with caution as only three moderate sample sizes studies were included, which may have insufficient power to detect a reliable correlation. In the future, more studies with large sample sizes are warranted to verify our findings.

There are some merits in our study. First of all, the sample sizes were larger as compared with previous studies. Secondly, we confirmed for the first time *PPARG* rs1801282 G allele was correlated with the susceptibility of breast cancer in Caucasians and in post-menopause women. Finally, the quality scores of all recruited studies were ≥ 6.5 ('high quality', **Table 2**), suggesting the reliability of our results. However, certain potential limitations that may lead to bias are also acknowledged and addressed. This meta-analysis only used published studies; certain publication bias may inevitably exist. Moreover, the included publications were performed mainly in Caucasians, only two Asians and two mixed populations were recruited, which restricted the power to detect a real influence. Hence, more large-scale studies in more diverse populations are needed. Furthermore, due to lack of genotype frequency information, we did not conduct further evaluation of potential interactions, such as age, family history, hormone replacement therapy use, oral contraceptives use, body mass index, other environmental factors and lifestyle. In consideration of the complexity of cancer etiology, these gene-environment interactions should not be ignored. Finally, the association between other important polymorphisms (e.g., *PPARG* rs4135247, rs1175543, rs709158 and rs2938395) and BC was seldom explored, these polymorphisms were not considered in our study.

In summary, this updated meta-analysis suggests that *PPARG* rs1801282 C>G variants are associated with a significantly decreased risk of BC in Caucasians and in post-menopause women. As only nine publications were included in our analysis and the evidence was relatively limited, more large and well-designed epidemiological studies with the consideration of gene-gene and gene-environment interactions are definitely demanded.

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Disclosure of conflict of interest

None.

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Table S1. PRISMA checklist, Checklist of items to include when reporting a systematic review or meta-analysis (diagnostic review consisting of cohort studies)

Section/tocpic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction section
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction section
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Materials and Methods section, Inclusion and Exclusion Criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Materials and Methods section, Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Materials and Methods section, Search Strategy
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Materials and Methods section, Data Extraction
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Materials and Methods section, Data Extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Materials and Methods section, Data Extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Materials and Methods section, Statistical Analysis
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Materials and Methods section, Statistical Analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Materials and Methods section, Statistical Analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Materials and Methods section, Statistical Analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Materials and Methods section, Statistical Analysis

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results section, Tests for Publication Bias, Sensitivity Analyses, and Heterogeneity; **Figure 4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Figures 2** and **3**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results section, Quantitative Synthesis; **Table 3** and **Table 4**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results section, Tests for Publication Bias; **Figure 4**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results section, Tests for Sensitivity Analyses, and Heterogeneity; **Figure 6**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion section, 1th paragraph
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion section, 4th paragraph
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion section, 5th paragraph
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A