PPARγ polymorphisms and cancer risk: A meta-analysis involving 32,138 subjects

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Abstract. The peroxisome proliferator-activated receptor γ (PPARγ) has been suggested to act as a tumor suppressor gene. Two common variations of PPARγ, P12A (Pro12Ala, rs1801282) and C161T (His447His, rs3856806), are thought to have an effect on susceptibility to various carcinomas but the results are inconsistent. In this meta-analysis, we assessed published studies of the association between two common PPARγ polymorphisms and cancer risk from 26 studies with 27,677 subjects for PPARγ P12A, from 4 studies with 4,461 subjects for C161T. No significant associations were found in carriers of the rare Ala allele of the P12A polymorphism versus the common Pro/Pro genotype among the studies. In the subgroup analyses by cancer types, carriers of the Ala variant of P12A polymorphism were associated with protection from colorectal cancer (OR=0.84, 95% CI=0.72-0.98, $P_{heterogeneity}$ = 0.014), but the inverse association was found in gastric cancer (OR=2.31, 95% CI=1.59-3.36, $P_{heterogeneity}$ = 0.941). In the stratified analysis by ethnicity, no significant risks were found among Asians, Americans and Caucasians. For PPARγ C161T, no significant associations were found in any of the studies (OR=1.08, 95% CI=0.95-1.23, $P_{heterogeneity}$ = 0.430) or subgroups. This meta-analysis suggests that the Ala allele of the PPARγ P12A polymorphism might be a protective factor for colorectal cancer, but a risk factor for gastric cancer. The PPARγ C161T is marginally associated with cancer susceptibility.

Introduction

Over the past decade, strides have been made in treating several solid tumor malignancies resulting in measurable increases in survival, but cancer is projected to become the leading cause of death worldwide in 2010 and a great challenge remains to establish improved cancer prevention and treatment strategies for most cancers. The world urgently needs safe and effective drugs against cancer. The potential of peroxisome proliferator-activated receptor γ (PPARγ) as a useful target for the prevention and treatment of cancer has been widely studied. In addition to the known roles in regulation of metabolism and inflammation, mounting evidence shows once activated PPARγ will down-regulate carcinogenesis by preferentially binding with retinoid X receptor α (RXR), and signaling antiproliferative, antiangiogenic, and prodifferentiation pathways (1).

PPARs are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. Of the three PPAR isoforms identified to date (PPARα, PPARß, and PPARγ), PPARγ has been the most intensively studied in part because of the availability of PPARγ agonists (2). The PPARγ gene at chromosome 3p25 (OMIM *601487) in humans appears to be a suitable candidate gene for cancer susceptibility through its pleiotropic activity (3). Two PPARγ common polymorphisms, a C→G transition in exon B resulting in a proline to alanine exchange at amino acid position 12 (P12A) (OMIM *0002; rs1801282) and a C→T transition at position 161 in exon 6 (C161T) (OMIM *0009; rs3856806) have been identified and found to be associated with the risk of type 2 diabetes and cardiovascular events (4,5). In recent years evidence shows that both variations may also influence individual susceptibility to several types of cancer, such as those that occur in the central nervous system (6), lung (7,8), stomach (9-12), biliary tract (13), colorectum (14-22), bladder (23), breast (24-27), ovaries (28), endometrium (29), prostate (30-32), kidney (28) and skin (33). However, the observed results of these studies were inconsistent. We performed a meta-analysis to derive a more precise estimation of the association of PPARγ polymorphisms with cancer risk.

Materials and methods

Publication search and inclusion criteria. The electronic databases, PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) were searched for studies to include in the present meta-analysis, using the terms: 'peroxisome proliferator-activated receptor/PPAR', 'gene

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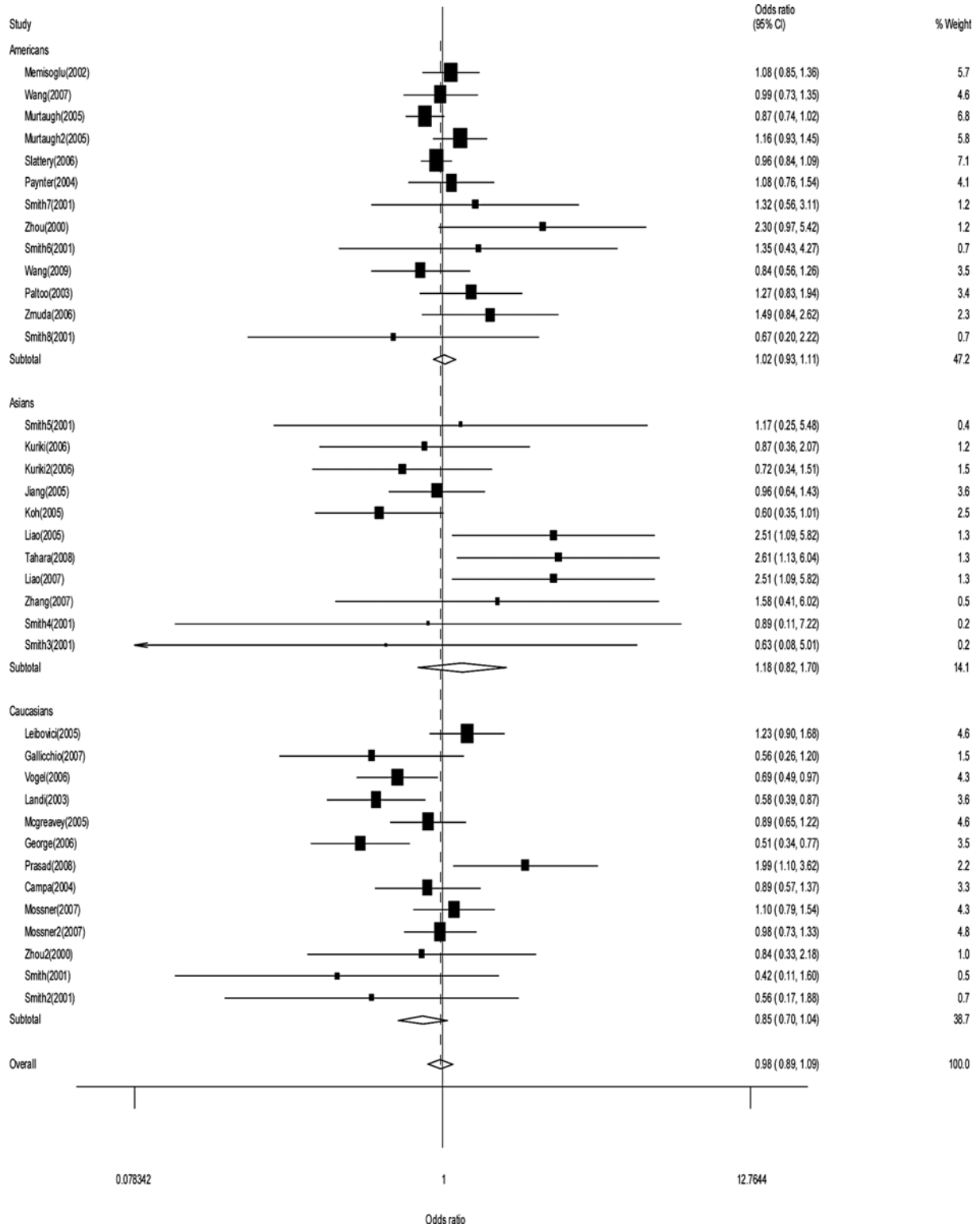

Figure 1. Forest plot of cancer risk associated with the PPARγ P12A polymorphism (CG+GG vs. CC) by ethnicity. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

polymorphism' and 'carcinoma' (last search was updated on January 1, 2010). The search was done without restriction on the language but was focused on the studies that had been conducted on human subjects. We also reviewed the Cochrane Library for relevant articles. The reference lists of reviews and retrieved articles were hand searched simultaneously. Only published studies with full text articles were included. When more than one of the same patient population was included in several publications, only the most recent study was used in this meta-analysis.

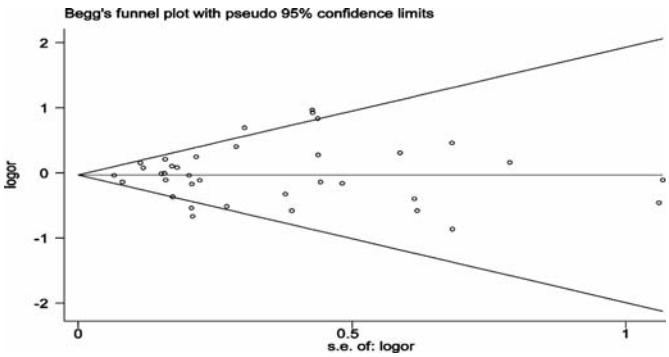

Figure 2. Funnel plot of the Egger's test of PPARγ P12A polymorphism for publication bias.

Studies included in the current meta-analysis had to meet all the following criteria: a) evaluation of the PPARγ polymorphisms and cancer risk, b) malignant tumors were histologically confirmed and c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction. Data were independently abstracted in duplicate by two investigators using a standard protocol and data-collection form according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. Characteristics abstracted from the studies included the first author's surname, publication date, country origin, ethnicity, tumor type, characteristics of controls, genotyping methods, total number of cases and controls, and numbers of genotypes, respectively. Different racial descents were categorized as Asians, Caucasians and Americans. When studies included subjects of more than one ethnicity and they could be separated, data were extracted separately for each ethnic group.

Statistical methods. OR corresponding to 95% CI was used to assess the strength of association between PPARγ polymorphism and cancer. For PPARγ P12A, the meta-analysis examined the association between the carriers of the rare Ala allele and cancer risk compared with that for Pro/Pro genetype (CG+GG vs. CC). For the C161T, the association between carriers of T variant and CC genetype (CT+TT vs. CC) with cancer risk was also examined. Subgroup analyses were done by ethnicity and tumor type. Heterogeneity assumption was checked by the Chi-square-based Q-test (34). P>0.10 for the Q-test indicates a lack of heterogeneity among the studies, then the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method) (35). Otherwise, the random-effects model (the DerSimonian and Laird method) (36) was used. Hardy-Weinberg equilibrium (HWE) was assessed via Fisher's exact test and P<0.05 was considered significant. An estimate of potential publication bias was carried out by the funnel plot and an asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test. The significance of the intercept was determined by the t-test suggested by Egger *et al* (P<0.05 was considered representative of statistically significant publication bias) (37). The statistical analyses were performed with STATA 8.0. (StataCorp, College Station, TX), using two-sided P-values.

Results

Study characteristics and meta-analysis results. There were 32 eligible studies as a result of the search and screening. Of these studies, four (38-41) were excluded because they did not provide allele frequencies needed for OR calculation or they were studies about benign adenoma or other PPAR subtypes. One study (22) was also excluded because the same data were available in another study. Thus, a total of 26 studies (6-12,14-21,23-33) involving 11,627 cases and 16,050 controls were ultimately analyzed for P12A, five studies (13-16,33) involving 1,819 cases and 2,642 controls for C161T. Five studies (6,15,17,28,33) sorted the data in different race or different tumor types, therefore, each group in these studies was considered separately for pooling subgroup analyses. Table I presents the main characteristics of these studies. Among 26 publications, 24 were published in English, and two (8,12) were in Chinese. There were 11 Asians groups (8,10-12,14-16,19,28,33), 13 Caucasian groups (6,7,9,13, 18,21,23,24,27,28,33), and 13 American groups (6,17,20,25, 26,28,29,30-32). HWE had been tested in most controls, and most of the controls were in HWE, there were five studies (17,19,23,29,32) without genotype distribution in detail.

Table II listed the main results of this meta-analysis. For PPARγ P12A, the contrast of CG+GG vs. CC did not produce significant association among 26 studies with relatively large heterogeneity (OR=0.98, 95% CI=0.89-1.09, $P_{\text{heterogeneity}}$ = 0.003). Through stratified analyses, the heterogeneity of the subgroup significantly reduced. In the stratified analysis by ethnicity (Fig. 1), no significant risks were found among Asians, Americans and Caucasians. In the subgroup analyses by cancer types, carriers of the Ala variant of P12A polymorphism were associated with protection from colorectal cancer (OR=0.84, 95% CI=0.72-0.98, $P_{\text{heterogeneity}}$ = 0.014), but with an increased risk of gastric cancer (OR=2.31, 95% CI=1.59-3.36, $P_{\text{heterogeneity}}$ = 0.941). No significant associations were found in breast cancer, prostate carcinoma, oophoroma, bladder cancer, endometrial carcinoma, lung cancer and others in the pooling analyses. For C161T, no significant risks were found in any of the studies (OR=1.08, 95% CI=0.95-1.23, $P_{\text{heterogeneity}}$ = 0.430) or subgroups.

Bias diagnostics. Begg's funnel plot and Egger's test were performed to access the publication bias of the literatures. The funnel plots for publication bias showed some asymmetry (Fig.2), but Egger's test suggested that there was no publication bias in the current meta-analysis (for P12A, P=0.493 and for C161T, P=0.742).

Discussion

PPARγ is manifested in a variety of cancer cells. Upon ligand binding, the PPAR/RXR heterodimer associates with coactivator complexes, binds peroxisome proliferator response elements (PPREs), and activates the transcription of PPAR-responsive genes (42), which generally reduces the survival

Table I. Characteristics of the studies investigated for association between PPAR polymorphisms.

Author (year) (ref.)	Tumor site	Ethnicity (country of origin)	Genotyping	Study design	Matching criteria	PPARγ variants	Sample size (case/control)
Mossner (2007) (33)	Melanoma	Caucasians (Germany)	PCR-RFLP	Case-control	NA	P12A, C161T	334/351
Mossner (2007) (33)	Melanoma	Caucasians (Germany)	PCR-RFLP	Case-control	NA	P12A, C161T	494/432
Zhou (2000) (6)	Glioblastoma	Americans (USA)	PCR	Case-control	Ethnicity	P12A	52/80
Zhou (2000) (6)	Glioblastoma	Caucasians (Germany)	PCR	Case-control	Ethnicity	P12A	44/60
Leibovici (2005) (23)	Bladder	Caucasians (USA)	Taqman	Case-control	Age,sex, ethnicity	P12A	434/449
Paynter (2004) (29)	Endometrial	Americans (USA)	Taqman	Case-control	Age, menopausal status	P12A	217/657
Gallicchio (2007) (24)	Breast	Caucasians (USA)	Taqman	Cohort study	NA	P12A	56/895
Memisoglu (2002) (26)	Breast	Americans (USA)	PCR-RFLP	Nested case-control	Age, menopausal status	P12A	725/953
Wang (2007) (25)	Breast	Americans (USA)	Taqman	Cohort study	Age, ethnicity	P12A	478/478
Vogel (2006) (27)	Breast	Caucasians (Denmark)	PCR	Case-control	Age, menopausal status	P12A	361/361
Campa (2004) (7)	Lung	Caucasians (Norwegian)	Taqman	Case-control	Age, sex, ethnicity	P12A	246/212
Zhang (2007) (8)	Lung	Asians (China)	PCR	Case-control	Age, sex, ethnicity, BMI	P12A	45/45
Prasad (2008) (9)	Gastric	Caucasians (India)	PCR-RFLP	Case-control	NA	P12A	62/241
Liao (2005) (10]	Gastric	Asians (China)	PCR-RFLP	Case-control	Age, sex	P12A	104/104
Tahara (2008) (11)	Gastric	Asians (Japan)	PCR	Case-control	NA	P12A	215/201
Liao (2007) (12)	Gastric	Asians (China)	PCR-RFLP	Case-control	Age, sex	P12A	104/104
Landi (2003) (13)	Colorectal	Caucasians (Spain)	Taqman	Case-control	Age, sex	P12A, C161T	360/309
Kuriki (2006) (14)	Colorectal	Asians (Japan)	PCR-CTPP	Case-control	Age, sex	P12A, C161T	128/238
Jiang (2005) (16)	Colorectal	Asians (Japan)	PCR	Case-control	Age, sex	P12A, C161T	301/291
Maureen (2005) (17)	Colon	Americans (USA)	Taqman	Case-control	Age, sex	P12A	1577/1971
Maureen (2005) (17)	Rectal	Americans (USA)	Taqman	Case-control	Age, sex	P12A	794/1001
Mcgreavey (2005) (18)	Colorectal	Caucasians (UK)	PCR	Case-control	Age, sex	P12A	455/513
Koh (2005) (19)	Colorectal	Asians (Singapore)	PCR	Case-control	NA	P12A,	362/1164
Slattery (2006) (20)	Colorectal	Americans (USA)	Taqman	Case-control	Age, sex	P12A	2371/2972
George (2006) (21)	Colorectal	Caucasians (Greek)	PCR-CTPP	Case-control	Age, sex	P12A	222/200
Wang (2009) (30)	Prostate	Americans (USA)	Taqman	Case-control	Age, ethnicity	P12A	255/254
Paltoo (2003) (31)	Prostate	Americans (USA)	MALDI-TOF	Nested case-control	Age	P12A	193/188
Zmuda (2006) (32)	Prostate	Americans (USA)	Taqman	Case-control	Age, BMI	P12A	91/237
Smith (2001) (28)	Mix	Mix (UK, Japan,USA)	PCR	Case-control	Ethnicity	P12A	299/357
Chang (2008) (33)	Biliary tract	Asians (China)	Taqman	Case-control	Age	C161T	733/782

NA, not applicable.

Table II. The main results of ORs (95% CI) in the meta-analysis.

Subgroup	No.	No. of cases/controls	OR (95% CI)	P for heterogeneity
PPARγ P12A			CG+GG vs. CC	
Total	37	11627/16050	0.98 (0.89, 1.09)	0.003
Racial descent				
Asian	11	1586/3524	1.18 (0.82, 1.69)	0.192
Caucasian	13	3129/4147	0.85 (0.69, 1.04)	0.01
American	13	6886/9031	1.02 (0.93, 1.11)	0.278
Tumor site				
Colorectal	10	6878/9391	0.84 (0.72, 0.98)	0.014
Breast	4	1620/2687	0.88 (0.68, 1.13)	0.096
Gastric	4	485/650	2.31 (1.59, 3.36)	0.941
Prostate	4	577/759	1.09 (0.80, 1.47)	0.272
Ovarian	3	85/357	0.85 (0.39, 1.83)	0.559
Bladder	2	465/664	1.23 (0.91, 1.67)	0.943
Endometrial	2	286/737	1.11 (0.80, 1.54)	0.68
Lung	2	291/257	0.94 (0.62, 1.42)	0.424
Others	6	974/1200	1.05 (0.83, 1.33)	0.358
PPARγ C161			CT+TT vs. CC	
Total	8	1819/2642	1.08 (0.95, 1.23)	0.43
Racial descent				
Asian	6	987/1854	1.11 (0.96, 1.29)	0.706
Caucasian	2	232/788	1.04 (0.63, 1.60)	0.058
Tumor site				
Colorectal	3	486/941	1.11 (0.89, 1.39)	0.337
Biliary tract	3	410/782	1.12 (0.90, 1.39)	0.675
Others	2	832/788	1.04 (0.68, 1.60)	0.058

N, number of studies involved.

rate of cancer cells through induction of cell cycle arrest and apoptosis. Synthetic ligands for PPARγ are currently being studied as a possible novel therapeutic modality for certain types of cancer (43).

The most prevalent human PPARγ gene mutation, Pro12Ala polymorphism, has been extensive investigated. In 1998, Deeb *et al* reported that a Pro12Ala substitution in PPARγ associated with reduced transactivation activity (44). Activation of PPARγ can affect tumors by inhibiting the expression of key prostanoid and integrin receptors, by reducing the expression of fibronectin, a matrix glycoprotein that stimulates tumor cell proliferation, and by inhibiting the production of angiogenic and inflammatory signals. In addition, PPARγ ligands can increase the expression and/or activity of tumor suppressors such as PTEN and p21 (45). Treatment with troglitazone was found to reduce gastric cancer formation in mice induced by carcinogens, and the chemopreventive effect of troglitazone was absent in PPARγ heterozygous-deficient mice (46). In the current meta-analysis, we found that patients with G carriers had 2.31-fold (95% CI = 1.59-3.36, $P_{heterogeneity}$ = 0.941) increased risk of gastric cancer, suggesting the presence of the Ala12 polymorphism, which is associated with reduced PPARγ activity, might increase the susceptibility of gastric cancer.

According to different cancer types, the inverse association was found in colorectal cancer. The apparent discrepancy results may be partly explained by the complex aetiological link between type 2 diabetes and colorectal cancer. There is convincing evidence across diverse populations that obesity and type 2 diabetes elevate the risk of colorectal cancer, which is related to chronic hyperinsulinaemia and hyperglycaemia (47). In particular, hyperinsulinemic state exhibits procarcinogenic effects in animal models and is believed to be the mechanism that underlies the association between diabetes and colorectal carcinogenesis. The Ala12 was recognized to be associated with increased tissue sensitivity to insulin, a decrease in insulin plasma level, reduced release of free fatty acids by adipocytes (44), which may indirectly explain the lower risk of colorectal cancer in subjects with this polymorphism. On the contrary, a similar association between

insulin sensitivity or diabetes and gastric cancer is lacking. This also shows different carcinogenic mechanisms of different cancers.

There are only 4 studies involving 1,819 cases and 2,642 controls for C161T polymorphism in the PPARγ gene and cancer susceptibility. Although a C to T substitution at nucleotide 1431 in exon 6 is a synonymous polymorphism that encodes histidine with either allele, biological relevance is suggested by the results of epidemiological studies showing an association of this polymorphism with metabolic diseases such as type 2 diabetes and atherosclerosis (48). It is proposed that this substitution may modulate expression of PPARγ by altering mRNA processing or translation, however, no significant associations were found for this polymorphism with cancer risk in this meta-analysis. Due to limited statistical power, further evaluations are warranted to confirm these results.

Caution must be taken in the interpretation of the results because of the relatively large heterogeneity in all studies. In the subgroup analyses stratified by tumor site and racial descent respectively, it can be found that the heterogeneity of the subgroup reduced significantly. Therefore, it can be presumed that the relatively large heterogeneity mainly results from differences of ethnicity and tumor types. Simultaneously, the heterogeneity may also have been caused by the differences in the selection of controls, age distribution and lifestyle factors. Publication bias may exist, because only published studies were included in this meta-analysis, and non-significant or negative findings may remain unpublished. Finally, current results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available.

In conclusion, this meta-analysis suggests that the PPARγ P12A polymorphism most likely contributes to decreased susceptibility to colorectal cancer, but Ala12 allele may be a risk factor for gastric cancer. PPARγ C161T polymorphism is marginally associated with cancer susceptibility. Due to the limitations of the current meta-analysis, larger association studies or multicentric studies and studies assessing gene-environment and gene-gene interaction are warranted to confirm these findings.

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