RESEARCH ARTICLE

Peroxisome Proliferator-Activated Receptor-Gamma Pro12Ala Polymorphism Could be a Risk Factor for Gastric Cancer

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Abstract

  <u>Background</u>: Due to the strong inhibitory effects of PPARγ gene on the growth of cancer cells, the role of Pro12Ala polymorphism in PPARγ gene has been extensively investigated in cancer recently. However, the results were inconsistent according to cancer type. The aim of this study was to comprehensively evaluate the PPARγ Pro12Ala polymorphism and gastric cancer susceptibility. <u>Materials and Methods</u>: Search strategies were conducted in Pubmed, Medline (Ovid), Chinese biomedical database (CBM), China national knowledge infrastructure (CNKI), VIP, and Wanfang database, covering all publications, with the last search up to November 01, 2014. The strength of association between PPARγ Pro12Ala polymorphism and gastric cancer risk was assessed by OR with 95%CI. <u>Results</u>: A total of 546 cases and 827 controls in 5 case-control studies were included in this meta-analysis. The results indicated that the variant G allele carriers (CG+GG) had a 2.31 times higher risk for gastric cancer when compared with the homozygote CC (odds ratio (OR)=2.31, 95% confidence interval (CI)=1.67-3.21 for CG+GG *vs.* CC). In the subgroup analysis by ethnicity, significantly elevated risks were both found in Asians (OR=2.56, 95% CI=1.42-4.64) and Caucasians (OR=2.20, 95% CI=1.48-3.25). Similarly, in the subgroup analysis by H. pylori status, a significantly increased risk was identified in *H. pylori* (+) populations (OR=3.68, 95%CI=2.07-6.52), but not in H. pylori(-) populations (OR=1.17, 95%CI=0.58-2.39). <u>Conclusions</u>: This pooled analysis suggested that the PPARγ Pro12Ala polymorphism could be an independent predictive risk factor for gastric cancer especially in *H. pylori* infected populations in Asians and Caucasians. Nevertheless, prospectively designed cohort studies are needed to further investigate gene-gene and gene-environment interactions to confirm the combined effects of PPARγ Pro12Ala polymorphisms and *H. pylori* infection on gastric cancer risk.

Keywords: Peroxisome proliferator-activated receptor γ (PPARγ) - polymorphism - gastric cancer

Introduction

  Globally, the incidence and mortality of gastric cancer have decreased dramatically over the past several decades. However, gastric cancer remains a significant public health burden both economically and socially, as the fourth most common cancer and the second leading cause of cancer related death worldwide (Siegel et al., 2014). The incidence of gastric cancer largely varies among ethnicity, which is twice higher in Asian and American compared with Caucasian and consistent with regional prevalence of Helicobacter pylori (*H. pylori*) infection (Ajani et al., 2013; Guggenheim et al., 2013). Although the treatments of gastric cancer have improved, the prognosis is still poor with 10-year survival rate ranged from 3 to 42 percent even after surgery and adjuvant chemotherapy (Chen et al., 2013; Wei et al., 2013; Xu et al., 2013; Liu et al., 2013; Bringeland et al., 2014; Liu et al., 2014; Ji et al., 2014).

  The risk factors of gastric cancer are multifactorial and complex involving genetic variations, environmental exposures or lifestyle factors, and gene-environment interactions (Guggenheim et al., 2013; Karimi et al., 2014). *H. pylori* infection, tobacco smoking, alcohol drinking, and dietary factors such as nitrites, represent exogenous risk factors for gastric cancer. World Health Organization has classified *H. pylori* as a definite carcinogen for gastric cancer especially intestinal-type (Schistosomes et al., 1994). Therefore, gastric cancer is thought to be preventable by eradicating *H. pylori* infection. However, most of *H. pylori* infected individuals remain asymptomatic and only fewer than 0.5% of infected individuals develop gastric cancer, even though expose in the same environment (Shi et al., 2014). This indicates that genetic differences, such as variants and single nucleotide polymorphisms (SNPs), may play a crucial role in gastric carcinogenesis. Therefore, there has been intense interest in searching for common genetic variants as biomarkers for gastric cancer genetic susceptibility (Milne et al., 2009;

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Yin et al., 2009; Shen et al., 2014).

Peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear hormone receptor superfamily and plays a pivotal role in regulating lipid metabolism, fatty acid uptake and storage, adipocyte differentiation and glucose homeostasis, moreover, it has also been suggested to take part in carcinogenesis, cell cycle progression, inhibition of malignant cells proliferation, induction of cell apoptosis and anti-inflammatory effect (Auwerx 2002; Michalik et al., 2004; Stamos et al., 2004). PPARγ expression was first described in hematopoietic cells (Greene et al., 1995) and later demonstrated in many tissues, including colon, stomach, small intestine, liver, pancreas, skeletal muscle and brain(Auwerx 2002; Elbrecht et al., 1996). In humans, the gene encoding for PPARγ is located on chromosome 3 at position 3p25. Several polymorphisms in PPARγ have been identified so far. A missense mutation in PPARγ gene was identified as CCA-to-GCA leading to Pro-to-Ala substitution in codon 12 (Pro12Ala) of Exon B (rs1801282) (Yen et al., 1997), which possibly resulted in a conformational change in protein structure and reduced the function of PPARγ gene. The PPARγ 12Ala allele has been reported to show decreased ability binding to the promoter element and weaker transactivation of responsive promoters *in vitro* (Deeb et al., 1998). Numerous studies have been conducted to estimate the association between the PPARγ Pro12Ala single nucleotide polymorphism and various diseases. Some studies have demonstrated Pro12Ala polymorphism confers protection against type 2 diabetes and polycystic ovary syndrome (Gouda et al., 2010; Huguenin et al., 2010; Zhang et al., 2012). With the strong effects of PPARγ gene on the growth of cancer cells, the role of Pro12Ala polymorphism has been widely studied in cancer recently (Michalik et al., 2004). Some authors reported that the PPARγ 12Ala allele decreased the risk of colorectal cancer and breast cancer (Lu et al., 2013). However, other similar observations could not draw such conclusion in prostate cancer (Paltoo et al., 2003; Zmuda et al., 2006), lung cancer (Campa et al., 2004), endometrial cancer (Paynter et al., 2004) and ovarian cancer (Pinheiro et al., 2010). On the contrary, recent studies found that Pro12Ala polymorphism increased the risk of gastric cancer (Canbay et al., 2012). Although there have been several studies investigating this Pro12Ala polymorphism with gastric cancer risk, due to the small sample size of the each study, it is not sufficient to form a reliable conclusion, so, we performed a meta-analysis to investigate these associations. This is, to our knowledge, the first meta-analysis of genetics studies on the association between PPARγ Pro12Ala polymorphism and gastric cancer susceptibility.

Materials and Methods

Search strategy

A systematic literature search in Pubmed, Medline (Ovid), Chinese biomedical database (CBM), China national knowledge infrastructure (CNKI), VIP, and Wanfang database was carried out to identify studies involving association between Pro12Ala polymorphism of PPARγ gene and GC risk (last search was updated on Nov 1, 2014). The search terms were used as follows: "stomach neoplasm or gastric cancer" and "PPARγ or PPARG or peroxisome proliferator-activated receptor gamma" in combination with "polymorphism or variant or variation or mutation". All the search terms were restricted to studies in human subjects but without restriction on languages.

Inclusion criteria

Studies included in the current meta-analysis met the following inclusion criteria: *i)* evaluation of the PPARγ Pro12Ala (rs1801282) polymorphism and gastric cancer risk, *ii)* the design has to be a case control study, *iii)* sufficient published data (genotype distributions for cases and controls) to estimate an odds ratio (OR) with its 95% confidence interval (CI), and *iv)* genotype distributions in control group should be consistent with Hardy-Weinberg equilibrium (HWE).

Exclusion criteria

Studies were excluded if one of the following existed: *i)* no controls, *ii)* data of genotype frequencies or number of each group not reported, and *iii)* case reports, reviews, editorials and repeat studies. If there were more than one study published by the same authors based on the same populations, the one providing the most comprehensive information was included.

Data extraction

Two investigators (J Zhao and Z Zhi) collected the data independently in duplicate according to the inclusion criteria listed above. In case of disagreement, a third author (GY Song) would assess these articles. The following items were extracted from each study: first author, publication date, original country, ethnicity, average age, sex, genotyping method and genotype number and total number in cases and controls.

Statistical analysis

OR with 95%CI was used to assess the strength of association between PPARγ Pro12Ala polymorphism and gastric cancer risk. The pooled OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity among eligible studies was measured by χ^2-based Q-test and I^2 statistical test and $p<0.1$ was considered statistically significant. If $p<0.1$, the assumption of homogeneity was deemed invalid and the pooled OR was calculated by random-effects model after exploring the cause of heterogeneity. Otherwise, the fixed-effects model was used. Findings of our meta-analysis are shown in forest plots. The two-tailed $p<0.05$ was considered statistically significant.

To evaluate the ethnic-specific effects and gene-environment interactions, subgroup analyses was performed by ethnicity and *H. pylori* status. For the subgroup analysis by ethnicity, the study populations were stratified into two groups: Asians and Caucasians. Similarly, the subgroup analysis by *H. pylori* status was stratified into two subgroups too: *H. pylori*(+) and *H. pylori*(-). Sensitivity analysis was also performed by sequence excluding individual study to check the

robustness of the result.

Hardy-Weinberg Equilibrium (HWE) test in controls was examined by a Pearson X^2 test by SPSS 13.0. The quality assessment for the eligible studies was evaluated according to Newcastle-Ottawa-Scale (NOS). The possible publication bias and the degree of asymmetry were examined by Begg's funnel plot (Begg et al., 1994). Statistical analysis was performed using Revman 5.3 and STATA 12.0 softwares.

Results

Study characteristics and meta-analysis results

A total of 39 results were identified after an initial search from the electronic databases (Figure 1). Among these articles, six were excluded for duplicate. After reading the titles and abstracts, 25 studies were excluded for being irrelevant to PPARγ polymorphism and gastric cancer risk. After reading full texts of the rest 8 articles, 2 studies were excluded because they were studies about other PPAR subtypes. One article was excluded for repeat

Figure 1. Flow of Included Studies

studies based on the same population (Liao et al., 2007). Finally, a total of 5 case-control studies (Liao et al., 2006; Prasad et al., 2008; Tahara et al., 2008; Bazargani et al., 2010; Canbay et al., 2012) including 546 cases and 827 controls were identified for further analysis. There were 2 studies of Asians (Liao et al., 2006; Tahara et al., 2008), 3 of Caucasians (Prasad et al., 2008; Bazargani et al., 2010; Canbay et al., 2012). The main characteristics of each included study are listed in Table 1. The data of genotype and allele distributions extracted from each case-control study is presented in Table 2. The genotype distributions in the control groups in each study were in HWE with $p>0.05$ (Table 2). A quality assessment for the eligible studies according to NOS is shown in Table 3. All the included 5 eligible reports were written in English language.

Quantitative data synthesis

All studies: The heterogeneity of CG+GG *vs.* CC (Figure 2A) and G *vs.* C (Figure 2B) for all 5 studies was assessed and the value of χ^2 was 0.36, 0.43 both with 4 degrees of freedom and $p=0.99$, 0.98 in a fixed-effects model respectively. Additionally, the I^2, which is another index of the test of heterogeneity, was 0%, suggesting no heterogeneity. So, we use the fixed-effects model to synthesize the data. On the risk of gastric cancer, the OR was 2.31 (95%CI=1.67-3.21), and the test for overall effect Z value was 5.02 ($p<0.00001$) for CG+GG *vs.* CC (Figure 2A). Compare with the C allele carriers, those with the G allele also have a statistical significance, the corresponding OR was 2.36 (95%CI=1.76-3.18) and the test for overall effect Z value was 5.68 ($p<0.00001$) (Figure 2B). These results indicated that there was a significant association between PPARγ Pro12Ala polymorphism and gastric cancer risk. All comparisons data were listed in Table 2.

Subgroup analyses: Subgroup analyses by ethnicity and *H. pylori* status for CG+GG *vs.* CC contrast were performed. The subgroup analysis by ethnicity was stratified into two subgroups: Asians and Caucasians. Significantly increased risks of gastric cancer were both
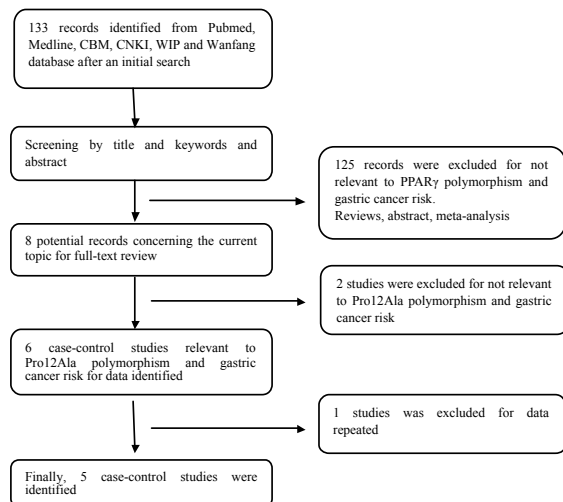
Table 1. Characteristics of Studies Included in this Meta-analysis

First author	Year	Country	Ethnicity	Case age (year)	Sex Male	Sex Female	Case/Control	Genotyping method	Study design
Canbay E.	2012	Turkey	Caucasians	58.6±8.6	59	27	86/129	PCR-RFLP	Case-control
Bazargani A.	2010	Iran	Caucasians	53.2	42	37	79/152	PCR-RFLP	Case-control
Prasad.K.N.	2008	India	Caucasians	56.60±15.42	47	15	62/241	PCR-RFLP	Case-control
Tahara T.	2008	Japan	Asians	64.7(29-93)	153	62	215/201	PCR-RFLP	Case-control
Liao SY.	2006	China	Asians	59.3±10.6	63	41	104/104	PCR-RFLP	Case-control

*PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism

Table 2. Distribution of PPARγ Pro12Ala Genotype and Allele among Gastric Cancers and Controls

First author	Case CC	Case CG	Case GG	Control CC	Control CG	Control GG	Case C	Case G	Control C	Control G	Case HP+ CC	Case HP+ CG+GG	Case HP- CC	Case HP- CG+GG	Control HP+ CC	Control HP+ CG+GG	Control HP- CC	Control HP- CG+GG	HWE for control X²/P
Canbay E.	68	14	4	116	12	1	150	22	244	14	NM	NM	NM	NM	NM	NM	NM	NM	1.132/0.287
Bazargani A.	60	18	1	134	17	1	138	20	285	19	53	18	7	1	58	6	76	12	0.316/0.574
Prasad.K.N.	39	18	5	186	52	3	96	28	424	58	21	14	18	9	112	21	74	34	0.089/0.766
Tahara T.	194	21	0	193	8	0	409	21	394	8	NM	NM	NM	NM	NM	NM	NM	NM	0.083/0.773
Liao SY.	84	17	3	95	9	0	185	23	199	9	69	16	15	4	59	3	36	6	0.213/0.645

*HWE, Hardy-Weinberg equilibrium; NM, not mentioned; HP (+), H. pylori infection (positive); HP (-), H. pylori infection (negative)
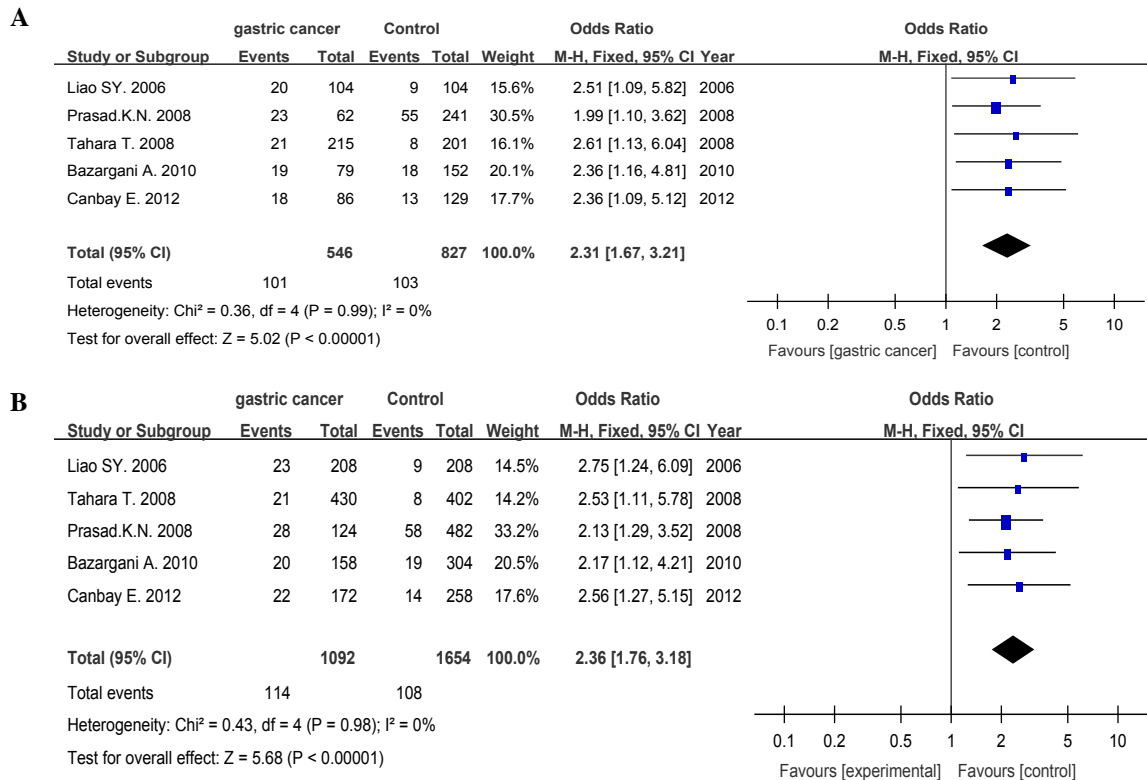
A

B

Figure 2. Forest Plot of the Association between Gastric Cancer Risk and the PPARγ Pro12Ala Polymorphism with Fixed-Effects Model. A, (CG+GG *vs*. CC); B, (G *vs*. C)
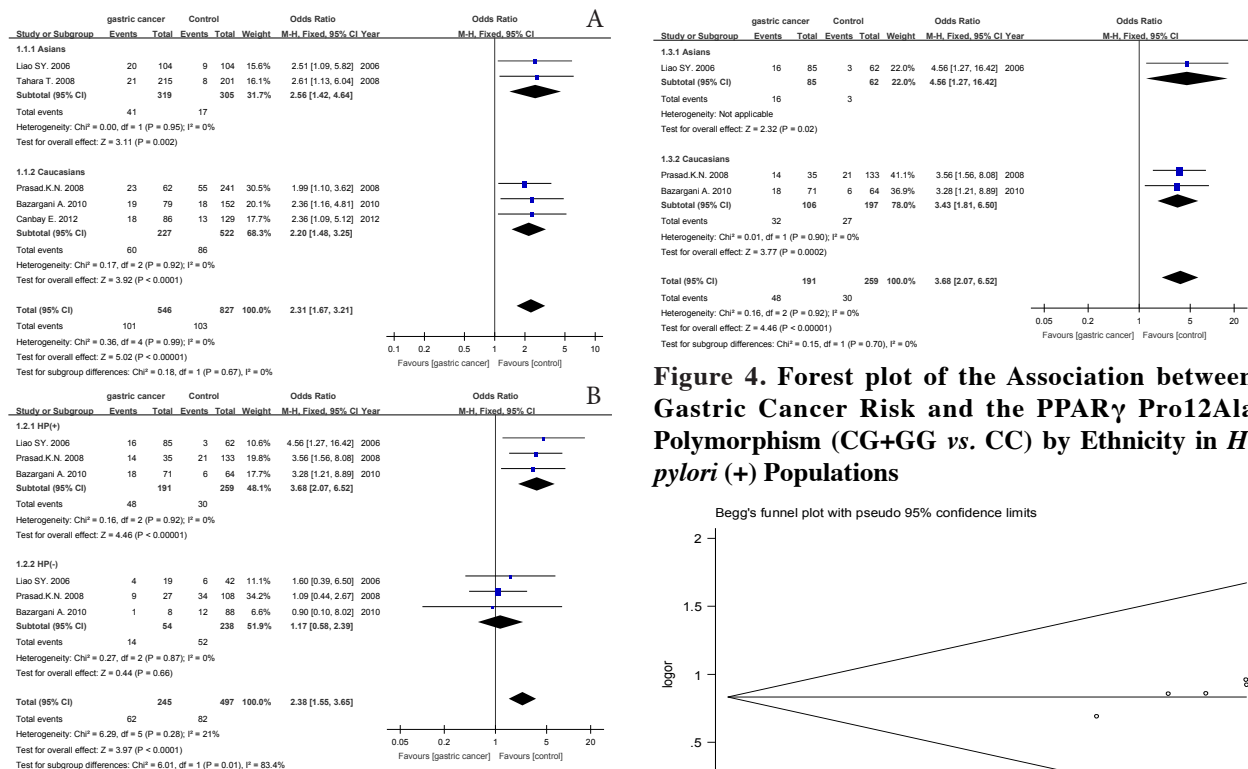

Figure 3. Forest Plot of the Association between Gastric Cancer Risk and the PPARγ Pro12Ala Polymorphism (CG+GG vs. CC). A) subgroup analysis by ethnicity; **B)** subgroup analysis by *H. pylori* status

found among Asians (OR=2.56, 95%CI=1.42-4.64, and *p*=0.002) and Caucasians (OR=2.20, 95%CI=1.48-3.25, and *p*<0.0001) (Figure 3A). Similarly, the subgroup analysis by *H. pylori* status was stratified into two subgroups too:
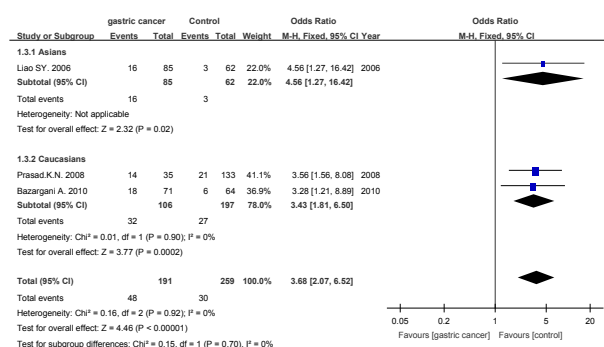
Figure 4. Forest plot of the Association between Gastric Cancer Risk and the PPARγ Pro12Ala Polymorphism (CG+GG *vs*. CC) by Ethnicity in *H. pylori* (+) Populations
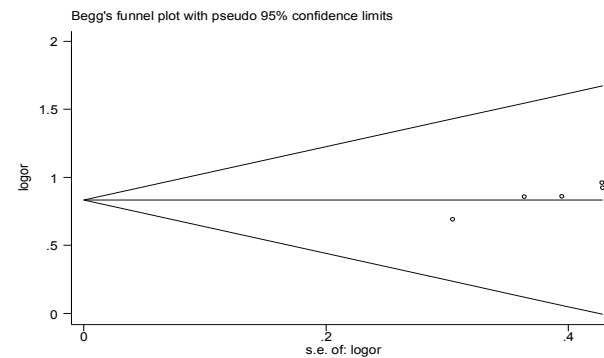

Figure 5. Begg's Funnel Plot for Publication Bias on Gastric Cancer Risk and PPARγ Pro12Ala Polymorphism (CG+GG *vs* CC)

H. pylori(+) and *H. pylori*(-). A significantly increased risk was identified among *H. pylori* (+) populations (OR=3.68, 95%CI=2.07-6.52, and *p*<0.00001), but not in *H. pylori*(-)

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Table 3. Quality Assessment for the Eligible Studies According to NOS

First author	Year	Selection (score)	Comparability (score)	Exposure (score)	Total Score
Canbay E.	2012	4	2	2	8
Bazargani A.	2010	4	2	2	8
Prasad.K.N.	2008	3	1	2	6
Tahara T.	2008	3	1	2	6
Liao SY.	2006	4	2	2	8

(OR=1.17, 95%CI=0.58-2.39, and *p*=0.66) (Figure 3B).

H. pylori status (+) patients: A total of three studies analyzed the correlation between *H. pylori* infection and Pro12Ala polymorphism in this meta-analysis. Two studies were performed among Caucasians, and the other among Asians. Subgroup analysis by ethnicity in *H. pylori* (+) patients revealed significant increased risks of gastric cancer both among Asians (OR=4.56, 95%CI=1.27-16.42, *p*=0.02) and Caucasians (OR=3.43, 95%CI=1.81-6.5, *p*=0.0002) with G carrier (CG+GG) (Figure 4).

Heterogeneity analysis

Heterogeneity was determined using the χ^2-based Q-test, and no heterogeneity was found in each pooling model (*p*>0.1), so the fixed model was utilized to generate a larger pool of studies with 95%CIs.

Publication bias

The publication bias was assessed by Begg's funnel plot (Figure 5). No publication bias was identified (*p*=0.221), though the funnel plot appeared to be asymmetrical.

Discussion

PPARγ is a ligand-dependent transcription factor belonging to the family of nuclear receptors. When activated by specific ligand, PPARγ forms heterodimer with retinoid X receptor (RXR), the PPARγ/RXR heterodimer binds to specific DNA response elements called peroxisome proliferator response elements (PPREs), then regulates the transcription of PPAR-responsive genes(Konturek et al., 2003; Nolte et al., 1998) including lipid metabolism, inflammation, insulin sensitization, cell proliferation and carcinogenesis. It was reported that activation of PPARγ inhibits the proliferation of gastric cancer cells through induction of cell cycle arrest and apoptosis (Sato et al., 2000; Grommes et al., 2004; Leung et al., 2004; Theocharis et al., 2004). Treatment with the PPARγ ligand troglitazone was found to significantly reduce the incidence of gastric cancer in PPARγ wild-type (+/+) mice induced by carcinogens but not in PPARγ heterozygous-deficient (+/-) mice(Lu et al., 2005). These studies reveal that PPARγ activation had an inhibitory effect on the proliferation of gastric cancer *in vitro* and *in vivo* (Sato et al., 2000; Leung et al., 2004) and synthetic ligands for PPARγ may became a novel anticancer therapy agent (Cheon et al., 2009).

In addition, one of the crucial functions of PPARγ is its anti-inflammatory effect which participates in modulating the inflammatory response of the gastric epithelial cells

with chronic *H. pylori* infection. It was shown that the anti-inflammatory effect of PPARγ activation was exerted through inhibiting the nuclear factor (NF)-κB and STAT3 inflammation pathways (Chinetti et al., 2000; Gupta et al., 2001; Nakajima et al., 2001). Moreover, PPARγ has also been shown to reduce proinflammatory cytokines such as COX-2, TNF-a, IL-1 and IL-6 which are closely related to carcinogenesis (Lee et al., 2012; Pereira et al., 2013; Zhao et al., 2014). *H. pylori* infection is the main pathogen in gastric inflammation which is the strongest risk factor in the gastric carcinogenesis (Polk et al., 2010). Activation of the PPARγ pathway attenuates the ability of *H. pylori* to induce NF-κB-mediated apoptosis in gastric epithelial cells (Gupta et al., 2001). Increased expression of PPARγ may have anti-inflammatory and cytoprotective effects in gastric mucosa infected by *H. pylori*, and PPARγ activation may benefit and provide therapeutic target for *H. pylori*-associated gastric inflammation. Contrarily, the PPARγ gene mutation which reduces the transcription of PPARγ may lower its anti-inflammatory and antitumorigenic abilities.

Genomics research showed that a common PPARγ polymorphism, identified as CCA-to-GCA leading to proline-to-alanine substitution in codon 12 of Exon B (Pro12Ala), reduced the function of PPARγ gene through decreased binding to response element and reduced ability to activate target genes (Deeb et al., 1998). Therefore, Pro12Ala polymorphism may influence both the anti-tumor and anti-inflammatory effects of PPARγ and thus may modify the risk of developing cancer.

So far, many studies have been performed on the association between PPARγ Pro12Ala polymorphism and cancer risk, but the results are controversial and differ according to cancer type. Some studies have reported Pro12Ala polymorphism leads to lower risk of colorectal cancer and type 2 diabetes. On the contrary, the current meta-analysis demonstrates that the Pro12Ala polymorphism increased the risk of gastric cancer. These discrepancy results may be partly explained by the convincing evidence that obesity and type 2 diabetes increase colorectal cancer risk, which is related to hyperinsulinemia and hyperglycemia (Lu et al., 2010). However, a similar association between diabetes and gastric cancer is lacking. It indicates that gastric cancer may have different genetic background or different carcinogenic mechanisms to colorectal cancer. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) usage was considered likely to reduce the increased cancer risk caused by PPARγ Pro12Ala polymorphism. However, a recent meta-analysis did not indicate a significant association between Pro12Ala polymorphism with NSAID intake on cancer risk, but suggest that the association on cancer risk may differ by cancer type. Moreover, It is noteworthy that gastric cancer was not involved in that study (Nagao et al., 2014).

In the current meta-analysis, a total of 546 cases and 827 controls from 5 eligible individual studies were included in order to investigate the association between the PPARγ Pro12Ala (rs1801282) polymorphism and the risk of gastric cancer. According to the results, we found statistically significant correlation between

PPARγ Pro12Ala polymorphism and gastric cancer risk, The G carrier patients (CG+GG genotype) had 2.31-fold (95%CI=1.67-3.21, *p*<0.00001) increased risk of gastric cancer, suggesting the presence of Pro12Ala polymorphism may reduce PPARγ activity, resulting in increased susceptibility of gastric cancer. After subgroup analyses according to ethnicity, we found that the variant G allele carriers (CG+GG) had 2.56-fold and 2.20-fold increased risk of gastric cancer in Asians and Caucasians respectively. When stratified according to *H. pylori* status, a significant association was revealed between Pro12Ala polymorphism and gastric cancer risk in *H. pylori* (+) populations, but not in *H. pylori* (-) populations. Subgroup analysis by ethnicity was also performed among *H. pylori* (+) populations, and significant increased risk of gastric cancer was found both among Asians and Caucasians. It revealed that presence of G carrier (CG+GG) combined with *H. pylori* infection further increased the risk of gastric cancer. These results indicated gene-environment interactions in gastric cancer pathogenesis. Conclusions in this meta-analysis are consistent with those studies *in vitro* and *in vivo*, that are PPARγ activation inhibits the growth of gastric cancer, and Pro12Ala polymorphism in PPARγ gene increases the risk of gastric cancer.

To date, a number of genome-wide association studies (GWAS) on diffuse-type gastric cancer were conducted by using SNP, and identified PSCA gene and MUC1 gene as risk genotypes for diffuse-type gastric cancer (Saeki et al., 2013). However, intestinal-type gastric cancer mainly caused by *H. pylori* infection was more common in the prevalence region such as Asia. Furthermore, those GWAS on gastric cancer was initiated almost 10 years ago. So, other novel susceptibility genes and their interactions with non-genetic risk factors for gastric cancer should be explored by conducting a more comprehensive GWAS with the latest efficient SNP typing platforms. So far, there were no independent reports related to meta-analyses of the PPARγ Pro12Ala gene polymorphism with gastric cancer risk. Only one previous meta-analysis (Xu et al., 2010) covered this research question, but it did not study the relationship between PPARγ Pro12Ala polymorphism and *H. pylori* infection, which was classified as a definite carcinogen for gastric cancer. This is the first paper to study Pro12Ala polymorphism with gastric cancer risk and the *H. pylori* infection effect on PPARγ Pro12Ala polymorphism. Furthermore, the quality of the eligible studies was satisfactory with a high quality score according to the NOS. All the study populations were also meet H-W equilibrium.

Several limitation of the present meta-analysis should be considered. Publication bias may exist, because all eligible studies were published reports, it is possible that non-significant or negative findings unpublished may be missed. Moreover, this meta-analysis included data from Asia and Europe, no data from Africa, therefore, our study may be applicable to only these ethnic groups. Furthermore, data analyses were not stratified by other factors such as age, gender, BMI, lifestyle, drinking and smoking status because of insufficient information from the primary publication.

In conclusion, this systematic analysis assessed the relationship between Pro12Ala polymorphism in PPARγ gene and gastric cancer risk. Our results indicate that the Pro12Ala polymorphism may play a crucial role in the development of gastric cancer especially in *H. pylori* infected populations for Asians and Caucasians, which is meaningful to early diagnosis, prevention and individual-based treatment of gastric cancer. Furthermore, Pro12Ala of PPARγ gene might be a potential therapeutic target for gastric cancer. In the future, the therapy targeting PPARγ Pro12Ala polymorphism combined with anti-*H. pylori* infection probably play a significant role in the individualized treatment and prevention for gastric cancer.

Due to the limitations of this analysis, it is important to perform prospectively designed studies with large sample sizes to investigate gene-gene and gene-environment interactions to confirm the association between the PPARγ Pro12Ala polymorphisms and gastric cancer risk.

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100.0

6.3

75.0

56.3

50.0

25.0

31.3

0

Newly diagnosed without treatment

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