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META-ANALYSIS

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Effect of Proliferator-Activated Receptor-γ Pro12Ala Polymorphism on Colorectal Cancer Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Zhijiang Wei
BCDF Guoda Han
CD Xiyong Bai

1st Department of Tumor Surgery, Cangzhou Central Hospital, Cangzhou, Hebei, P.R. China

Corresponding Author: Zhijiang Wei, e-mail: weizifan3532@sina.com
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Background: The association between peroxisome proliferators-activated receptor γ (PPARγ) Pro12Ala polymorphism and colorectal cancer (CRC) risk is still controversial. A meta-analysis was performed.

Material/Methods: We conducted a literature search using PubMed, EMBASE, and Cochran databases. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated. Fixed-effects and random-effects models were used. Dominant model, recessive model, and additive model were used in this meta-analysis.

Results: Fifteen studies including 13575 cases and 17085 controls were included in our meta-analysis. Result of this meta-analysis found that PPARγ Pro12Ala polymorphism was significantly associated with a reduced risk of CRC (OR=0.90; 95% CI 0.83–0.98; *P*=0.01). No significant association was found between PPARγ Pro12Ala polymorphism and CRC risk in Asians (OR=0.80; 95% CI 0.60–1.09; *P*=0.15). However, PPARγ Pro12Ala polymorphism was significantly associated with a reduced risk of CRC in Caucasians (OR=0.91; 95% CI 0.83–0.99; *P*=0.03). When stratified analysis was performed by CRC site, no positive association was found between PPARγ Pro12Ala polymorphism and rectal cancer (OR=0.95; 95% CI 0.74–1.22; *P*=0.71). However, a reduced risk of colon cancer was observed (OR=0.85; 95% CI 0.76–0.94; *P*=0.002).

Conclusions: In summary, this study suggests that PPARγ Pro12Ala polymorphism was a protective factor of CRC.

MeSH Keywords: Colorectal Neoplasms • Genetic Association Studies • Meta-Analysis

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Background

Colorectal cancer (CRC) is a common digestive tumor; the incidence of CRC is just lower than gastric and esophageal cancer. More than one million new cases of CRC were diagnosed globally each year [1]. CRC is becoming a very urgent public health concern, especially in the developed countries. In USA, the incidence rate and mortality rate of CRC ranked third among all tumors in both men and women [2]. Body mass index, height, smoking status, and alcohol use have been reported to be associated with CRC risk [3]. However, the pathogenesis of CRC is still uncertain. Identification of related genetic variants could elucidate mechanisms underlying this disease.

Peroxisome proliferators-activated receptors (PPAR), which have PPARα, PPARβ/δ and PPARγ, are members of the nuclear receptor superfamily of ligand-activated transcription factors [4]. Due to its association with many human cancers such as colon, thyroid, breast, and prostate, PPARγ has been suggested to be an attractive target for cancer therapy [4]. Although the PPARγ nuclear receptor pathway was involved in cancer development, it might appear to have both oncogenic and tumor suppressor functions. Sarraf et al. showed that ligand activation of PPARγ in colon cancer cells could cause a considerable reduction in linear and clonogenic growth, increase expression of carcinoembryonic antigen, and the reversal of many gene expression events specifically associated with colon cancer [5]. However, Saez et al. suggested that PPARγ activation may provide a molecular link between a high-fat diet and increased risk of CRC [6].

A common polymorphism in the PPARγ, CCA→GCA, causing a Pro→Ala substitution at codon 12 (Pro12Ala), has been reported. The Pro12Ala polymorphism has been suggested to be associated with decreased receptor activity, lower body mass index, and improved insulin sensitivity [7]. The Pro→Ala change might cause a conformational change in the PPARγ protein, and thus affect its activity. Several studies have reported the association between PPARγ Pro12Ala polymorphism and CRC risk [8–22]. However, the results were still equivocal. Recently, a meta-analysis with nine studies found that this polymorphism was not associated with CRC risk [23]. However, six case-control studies were published and not all studies supported that result. Therefore, we performed a meta-analysis of all eligible studies to evaluate the association between PPARγ Pro12Ala polymorphism and CRC risk.

Material and Methods

Material

We conducted a literature search using PubMed, EMBASE, and Cochran databases. The following terms were used: "colorectal neoplasms" or "colorectal cancer") and ("PPARγ" or "peroxisome proliferators-activated receptor γ"). The last search was updated on December, 2014. All searched studies were retrieved and only published studies with full-text articles were included. In duplicate samples, only the largest study was used in this research.

Inclusion/exclusion criteria

The inclusion criteria was as follows: (1) a case-control study or a cohort study; (2) the study evaluated the association between PPARγ Pro12Ala polymorphism and CRC risk; (3) the PPARγ Pro12Ala genotypes were provided.

The exclusion criteria were as follows: (1) animal studies; (2) not relevant to CRC or PPARγ; (3) reviews or abstracts; (4) not offer enough data.

Data extraction

Two authors extracted the following data: first author, year, race, sample size, and genotype distribution. The disagreements were resolved by consensus.

Statistical analysis

Statistical analysis was all conducted using Stata software 11.0 (StataCorp, College Station, Texas, USA). HWE test in healthy control group was conducted using χ^2 test. Odds ratio (OR) with a 95% confidence interval (CI) was presented for dichotomous data, and significance level was 0.05. Dominant model, recessive model, and additive model were used in this meta-analysis. *Q*-statistic and I^2-statistic were used to measure statistical heterogeneity and significance level was 0.10. Effect model selection was on the basis of heterogeneity test. Fixed-effect models was selected when no significant heterogeneity, otherwise we used the random-effects model. Subgroup analyses were carried out based on race and cancer site. To evaluate the reliability of the results, one-way sensitivity analyses and cumulative meta-analysis were performed. Publication bias was investigated by the method of Egger's test. The two-sided $P<0.05$ was considered statistically significant.

Results

Eligible studies

Figure 1 shows the study selection procedure. Based on the inclusion and exclusion criteria, 15 studies including 13575 cases and 17085 controls were included in our meta-analysis. Only three studies were performed in Asian populations, while other studies were performed in Caucasian populations. The characteristics of the included studies are listed in Table 1.

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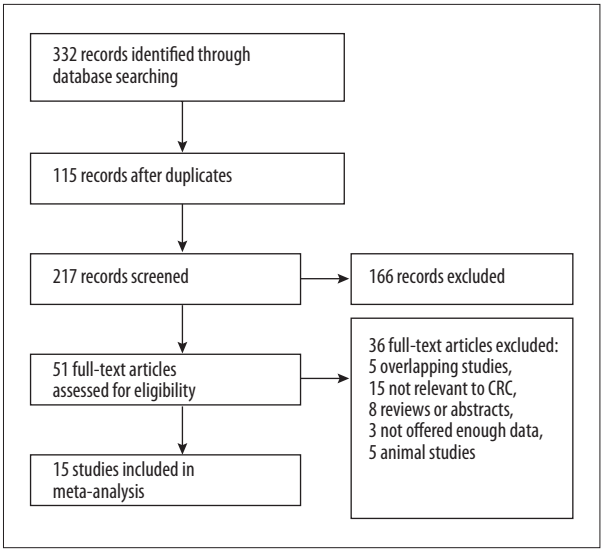

Figure 1. Flow diagram of the selection of eligible studies.

Quantitative synthesis

Result of this meta-analysis suggest that PPARγ Pro12Ala polymorphism was significantly associated with a reduced risk of CRC in dominant genetic model (OR=0.90; 95% CI 0.83–0.98; *P*=0.01; Figure 2). No significant association was found between PPARγ Pro12Ala polymorphism and CRC risk in Asians (OR=0.80; 95% CI 0.60–1.09; *P*=0.15). However, PPARγ Pro12Ala polymorphism was significantly associated with a reduced risk of CRC in Caucasians (OR=0.91; 95% CI 0.83–0.99; *P*=0.03). When stratified analysis was performed by CRC site, no positive association was found between PPARγ Pro12Ala polymorphism and rectal cancer (OR=0.95; 95% CI 0.74–1.22; *P*=0.71). However, a reduced risk of colon cancer was observed (OR=0.85; 95% CI 0.76–0.94; *P*=0.002). Results of other genetic models are listed in Table 2.

To evaluate the reliability of the results, we conducted cumulative meta-analysis by pooling the data, and each time one study was added. The results showed that the pooled ORs tended to be stable (Figure 3). We also performed the one-way sensitivity analysis by omitting studies one at a time. We found that any single study did not influence the pooled OR, suggesting that the results of this meta-analysis were robust (Figure 4). Moreover, no significant publication bias was found by funnel plot (Figure 5) and Egger's test (*P*=0.12)

Table 1. Characteristics of case-control studies included in this meta-analysis of the association between the PPARγ Pro12Ala polymorphism and CRC risk.

First author	Year	Ethnicity	No. of eligible subjects		Case		Control	
			Case	Control	Ala/Ala+ Pro/Ala	Pro/Pro	Ala/Ala+ Pro/Ala	Pro/Pro
Landi	2003	Caucasian	360	309	49	311	66	243
Jiang	2005	Asian	303	293	63	240	63	230
McGreavey	2005	Caucasian	455	513	89	366	110	403
Murtaugh	2005	Caucasian	2371	2972	531	1840	689	2283
Koh	2006	Asian	362	1164	17	345	89	1075
Kuriki	2006	Asian	127	238	7	120	17	221
Slattery	2006	Caucasian	2371	2972	531	1840	689	2283
Theodoropoulos	2006	Caucasian	222	200	58	164	82	118
Vogel	2007	Caucasian	355	753	103	252	203	550
Küry	2008	Caucasian	811	811	168	633	178	643
Slattery	2009	Caucasian	1577	1971	343	1234	478	1493
Hawken	2010	Caucasian	1133	1125	239	886	290	843
Abulí	2011	Caucasian	515	502	89	426	83	419
Crous-Bou	2012	Caucasian	812	1479	102	710	172	1307
Sainz	2012	Caucasian	1801	1783	447	1354	449	1334

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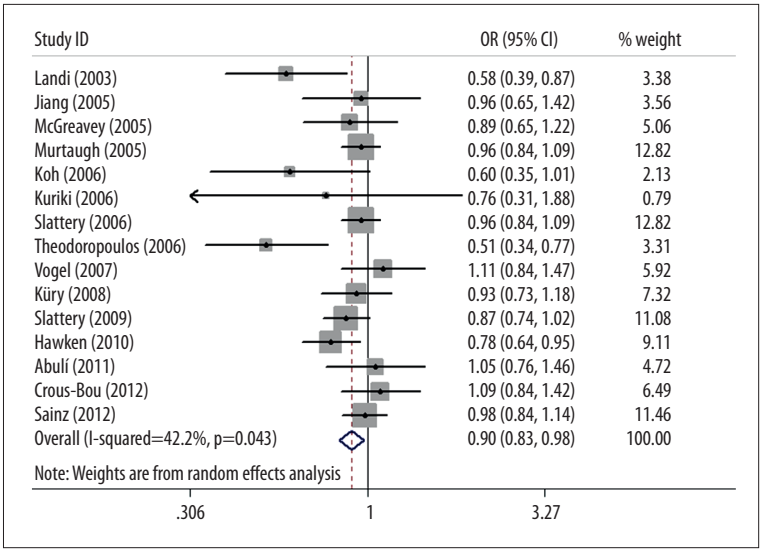

Figure 2. Forest plot of the overall risk of CRC associated with the PPARγ Pro12Ala polymorphism.

Table 2. Meta-analysis of association between the PPARγ Pro12Ala polymorphism and CRC risk.

	Pooled OR (95% CI)		P_{OR}	I^2	P_Q
Dominant model					
All	0.90	(0.83–0.98)	0.01	42%	0.04
Asian	0.80	(0.60–1.09)	0.15	1%	0.37
Caucasian	0.91	(0.83–0.99)	0.03	49%	0.03
Rectal	0.95	(0.74–1.22)	0.71	56%	0.06
Colon	0.85	(0.76–0.94)	0.002	0%	0.45
Recessive model					
All	0.87	(0.79–0.94)	0.001	32%	0.35
Asian	0.94	(0.73–1.21)	0.64	11%	0.34
Caucasian	0.87	(0.78–0.97)	0.02	0%	0.74
Rectal	0.87	(0.76–1.02)	0.07	61%	0.01
Colon	0.86	(0.74–0.99)	0.04	39%	0.37
Additive model					
All	0.84	(0.72–0.97)	0.03	50%	0.03
Asian	0.82	(0.62–1.12)	0.34	21%	0.22
Caucasian	0.89	(0.80–0.96)	0.01	34%	0.33
Rectal	0.93	(0.72–1.20)	0.65	43%	0.08
Colon	0.83	(0.74–0.92)	0.001	14%	0.56

P_{OR} and P_Q refer to the significance levels of the odds ratio and Q-test of heterogeneity, respectively.

Discussion

PPARγ Pro12Ala polymorphism has been reported to be associated with breast cancer, gastric cancer, and inflammatory bowel disease [24–26]. Lu et al. suggested that PPARγ Pro12Ala polymorphism was not associated with CRC risk [23]. However, a previous meta-analysis found that PPARγ Pro12Ala polymorphism might be a protective factor for CRC [26]. Thus, we did

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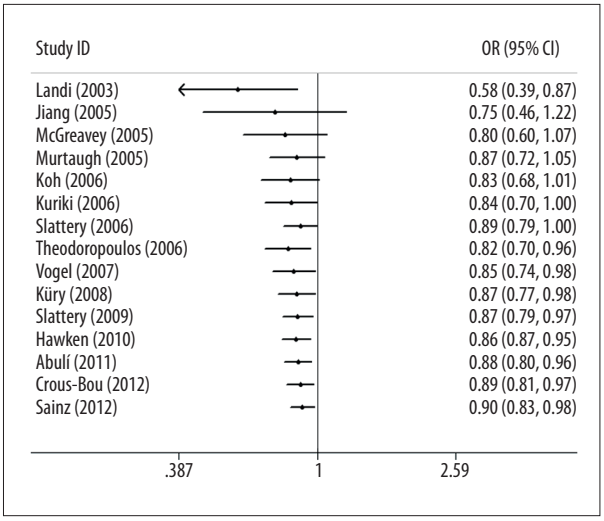

Figure 3. Cumulative meta-analysis for the risk of CRC associated with the PPARγ Pro12Ala polymorphism.

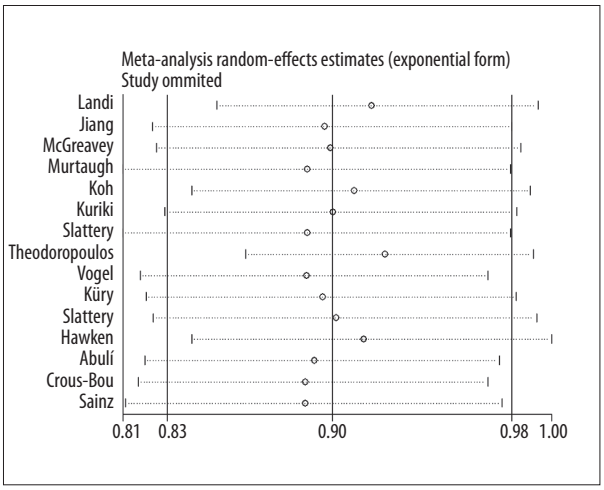

Figure 4. Sensitivity analysis for the risk of CRC associated with the PPARγ Pro12Ala polymorphism.

this update meta-analysis to find the association between PPARγ Pro12Ala polymorphism and CRC risk. We found that PPARγ Pro12Ala polymorphism was significant associated with CRC risk, suggesting that PPARγ Ala allele carriers had reduced CRC risk compared to PPARγ Pro allele carriers. Furthermore, we found that this effect was only existed in Caucasians but not in Asians, suggesting a possible influence among different genetic backgrounds and environmental exposures, but these were only studies with Asians. More studies with Asians are needed to further investigate the association between PPARγ Pro12Ala polymorphism and CRC risk. Results from this meta-analysis found that PPARγ Pro12Ala polymorphism was only associated with colon cancer. No significant association was found between PPARγ Pro12Ala polymorphism and rectal

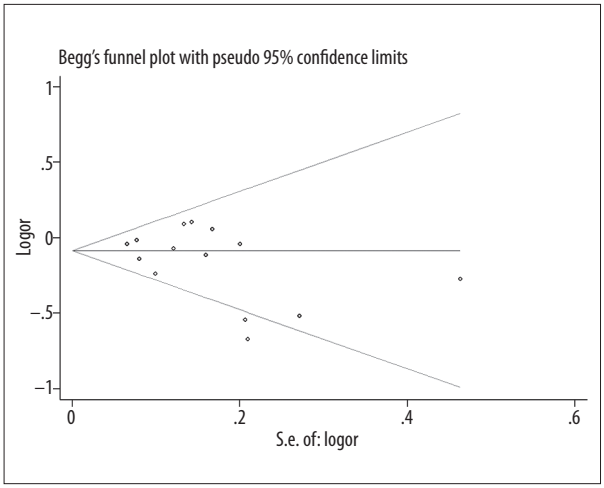

Figure 5. Funnel plots of the overall risk of CRC associated with the PPARγ Pro12Ala polymorphism.

cancer. It has been suggested that PPARγ activity was higher in the distal colon [27]; it is possible that the Ala/Ala+Pro/Ala genotypes had the greatest effect in the segment of the colon with the least PPARγ activity [28].

Ligands for the PPARγ have proven to be effective in preclinical models of CRC. Tanaka and coworkers indicated that administration of the PPARγ ligand troglitazone significantly reduces the number of aberrant crypt foci (ACF) lesions [29]. Aires et al. found that the combination of resveratrol with a PPARγ agonist could be a promising pharmacological approach for treatment of CRC [30]. Thus, PPARγ agonists combined with other chemotherapy drugs or other targeted therapies are worth pursuing in the treatment of CRC [31–36].

There were some limitations in this meta-analysis. First, the number of included studies was moderate. Therefore, the results could be influenced by random error. Second, CRC is a multifactorial disease, but the interactions among gene-environment and gene-gene were not considered in this meta-analysis. Third, other factors such as gender or diet habit may participate in the progression of CRC. However, we did not conduct subgroup analysis by these factors due to limited data.

Conclusions

In summary, this study suggested that PPARγ Pro12Ala polymorphism was a protective factor of CRC.

Disclosure of conflict of interest

None.

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