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BRIEF ARTICLE

Peroxisome proliferator-activated receptor-γ 34C>G polymorphism and colorectal cancer risk: A meta-analysis

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Abstract

AIM: To investigate the association between peroxisome proliferator-activated receptor-γ (*PPAR-γ*) gene polymorphism 34 C>G and colorectal cancer (CRC), a meta-analysis review was performed in this report.

METHODS: A systematic literature search and selection of eligible relevant studies were carried out. Nine independent studies with a total number of 4533 cases and 6483 controls were included in the meta-analysis on the association between polymorphism 34 C>G and CRC.

RESULTS: There was no evidence for the association between PPAR-γ 34 C>G and CRC if all of the subjects in the nine studies were included. However, CG + GG showed a marginally significant difference from CC (OR = 0.84, 95% CI: 0.69-1.01, *P* = 0.07) in random-effect model. Stratified meta-analysis indicated that PPAR-γ 34 C>G was associated with colon cancer (OR = 0.8, 95% CI: 0.65-0.99, *P* = 0.04) in random-effect model, and the G allele decreased colon cancer risk. No significant association was observed between PPAR-γ 34 C>G and rectal cancer.

CONCLUSION: PPAR-γ 34 C>G is associated with colon cancer risk, but not associated with CRC and rectal cancer risk.

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Key words: Peroxisome proliferator-activated receptor-γ; Colorectal cancer; Polymorphism; Meta-analysis

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INTRODUCTION

Colorectal cancer (CRC) is one of the major causes of cancer death in developed countries, with over 9500 new cases in Netherlands in 2002 alone, for instance[1]. In 2003, it was estimated that about 147 500 new cancer cases and 57 100 deaths were caused by CRC in the USA[2]. With more than 71 000 new occurrences per year, the incidence and mortality rate of CRC in Germany is almost the highest all over the world[3]. Epidemiological and experimental evidences attributed CRC to both genetic and experimental factors were involved. Accumulating evidences suggested that the peroxisome

proliferator-activated receptor-γ (*PPAR-γ*) gene is related to CRC, which has been implicated in the pathogenesis of CRC in animal models and clinical studies. PPAR-γ is a member of the nuclear hormone receptor super-family, and plays a pivotal role in regulating adipocyte differentiation, glucose and lipid metabolism, insulin sensitivity, atherogenesis and immune[4]. A proline to alanine substitution has been detected in the *PPAR-γ* gene which is a common structural polymorphism (34 C>G, rs1801282) located at codon 12 (Pro12Ala) of PPAR-γ2-specific exon B. Although many studies were performed to investigate the relationship between the polymorphism 34 C>G of *PPAR-γ* gene and CRC, results were contradictory. Our study aims to confirm the former data of the association between *PPAR-γ* gene 34 C>G and CRC.

MATERIALS AND METHODS

Identification and eligibility of relevant studies

A systematic literature search in PubMed and Google was carried out in January 2010 using '*PPAR* gene', 'association' and 'CRC' with restriction to 'human' or 'homo sapiens'. Additional articles were identified through references cited in retrieved articles. Publications containing the same or overlapping data from the same authors were excluded. Studies were considered as eligible for the meta-analysis if the frequency of relevant genotypes was reported in both CRC cases and CRC-free controls, or in both colon cancer cases and CRC-free controls, as well as in both rectal cancer cases and CRC-free controls. Moreover, all of them were case-control studies or cohort studies. Nine articles reported on the analysis of the association between PPAR-γ Pro12Ala and CRC[1,2,4-10], four of which focused on the association between the polymorphism PPAR-γ Pro12Ala and colon cancer risk or rectal cancer risk[4-7].

Data extraction and statistical analysis

For each study, information was gathered about the first author, year of publication, country where the study was conducted and the distribution of each PPAR-γ 34 C>G genotype in cases and controls (Table 1). Some calculated data collected from the original data of the articles were applied in the subsequent meta-analysis.

Percentage of GG genotype in controls of each study was calculated, followed by Hardy-Weinberg Equilibrium (HWE) test in controls to determine the reliability of data, using a Chi-squared Goodness-of-fit Test by SPSS 13.0. Analysis was also conducted on inter-ethnicity difference in minor allele frequency. One-way ANOVA was used to compare more than two independent groups, while two-tailed *t* test was used to compare two independent groups by SPSS 13.0 software.

To investigate the effect of each allele, the ORs of G allele were calculated, referenced by C. Subsequently, pairwised combinations of genotypes were used to determine the hereditary models, including GG *vs* CC, CG *vs* CC, and GG *vs* CG, CG *vs* CC + GG, GG *vs* CC + CG and CG *vs* GG + GC, and the later genotype was used as a reference in each pair.

We also conducted meta-analyses for a combination of CG and GG genotypes *vs* CC genotype in each subgroups (European and USA population). In addition, stratified analyses were performed based on the case collection, including meta-analyses on the association between PPAR-γ 34 C>G and colon cancer risk and rectal cancer risk.

Heterogeneity among studies was tested to estimate which effect model, the fixed-effect one or the random-effect one, should be used. With a $P > 0.05$, the included studies were considered homogeneous and the fixed-effect model should be selected, otherwise, random-effect model should be used.

All of the meta-analyses above were conducted using Review Manager 4.2 software. The two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Nine studies published from 2003-2007 were about the analysis on the relationship between PPAR-γ 34 C>G polymorphism and CRC risk, with a total number of 4533 cases and 6483 controls (Table 1). Seven studies (3870 cases/5028 controls) were conducted in Western countries, including 4 in Europe[1,5,9,10] and 3 in the USA[2,6,8]. Another two studies were performed in Asian countries[4,7]. There were four studies concerning colon cancer or rectal cancer with a total number of 2073 cases/3735 controls and 1321 cases/2765 controls, respectively[4-7].

The genotype distribution in the control groups in each study did not depart from the HWE with $P > 0.05$, except for two studies, in which HWE test could not be performed because of the incomplete data (Table 1).

The G allele frequency of PPAR-γ 34 C>G was 0.13 in the control group (626 cases/4694 controls) and 0.12 in the case group (424 cases/3600 controls), respectively. No statistical significance was found between case group and control group ($P = 0.381$). The G allele frequency of PPAR-γ 34 C>G in the Western controls (seven studies) was 0.14, the same as in the European controls (four studies). And in USA controls of three studies, G allele frequency of PPAR-γ 34 C>G was 0.13. In conclusion, there is no inter-ethnicity difference in minor allele frequency ($P = 0.968$).

Overall and subgroup-specific summary ORs and 95% CIs for the relationship between PPAR-γ 34 C>G and CRC risk are summarized in Table 2. For G *vs* C allele, GG *vs* CC, CG *vs* CC, GG *vs* CG, CG *vs* CC + GG, GG *vs* CC + CG and CG + GG *vs* CC genotypes of the overall study population, the fixed-effect and the random-effect ORs (95% CIs) were listed, respectively. Test for heterogeneity indicated that studies in the analyses for G *vs* C allele, CG *vs* CC, CG *vs* CC + GG, CG + GG *vs* CC genotypes, respectively were heterogeneous with $P < 0.05$. Hence, random-effect models were selected. And

Table 1 Study characteristics

No.	Ref.	Yr	Country	Number of cases					Number of controls					34G allele frequency in control	P^1
				CC	CG	GG	Total	CG + GG	CC	CG	GG	Total	CG + GG		
1	Landi *et al*[5]	2003	Spain (W, E)	311	46	3	360	49	243	61	5	309	66	0.11	0.773
2	Gong *et al*[2]	2005	USA (W)	129	30	4	163	34	153	52	7	212	59	0.16	0.743
3	Murtaugh *et al*[6]	2005	USA (W)	1840	-	-	2371	531	2283	-	-	2972	689	-	-
4	Jiang *et al*[4]	2005	India (A)	240	57	4	301	61	230	57	4	291	61	0.11	1.000
5	Siezen *et al*[1]	2006	Netherlands (W, E)	160	40	1	201	41	325	71	2	398	73	0.09	0.783
6	Koh *et al*[7]	2006	Singapore (A)	345	-	-	362	17	1075	-	-	1164	89	-	-
7	Gunter *et al*[8]	2006	USA (W)	153	41	4	198	45	146	37	1	184	38	0.11	0.838
8	Theodoropoulos *et al*[9]	2006	Greek (W, E)	164	48	10	222	58	118	70	12	200	82	0.24	0.950
9	Vogel *et al*[10]	2007	Denmark (W, E)	252	96	7	355	103	550	190	13	753	203	0.14	0.816

[1]*P* value for Hardy-Weinberg equilibrium (HWE) for peroxisome proliferator-activated receptor-γ (PPAR-γ) 34C>G polymorphism among controls. W: Western country; E: European country; A: Asian country; -: No data was shown in reference.

Table 2 Overall and group-specific summary statistics for PPAR-γ 34 C>G and colorectal, colon and rectal cancers

	No. of studies	Polymorphisms	P^1	Fixed-effect OR (95% CI), P^2	Random-effect OR (95% CI), P^3
Colorectal cancer					
Total	7	G *vs* C	0.010	0.88 (0.77, 1.00), 0.060	0.86 (0.69, 1.08), 0.210
	7	GG *vs* CC	0.720	0.85 (0.53, 1.35), 0.480	0.83 (0.52, 1.33), 0.440
	7	CG *vs* CC	0.020	0.86 (0.74, 1.00), 0.050	0.83 (0.65, 1.07), 0.160
	7	GG *vs* CG	0.990	1.10 (0.68, 1.79), 0.690	1.09 (0.67, 1.78), 0.720
	7	CG *vs* CC + GG	0.020	0.86 (0.74, 1.00), 0.060	0.84 (0.66, 1.07), 0.150
	7	GG *vs* CC + CG	0.830	0.91 (0.57, 1.44), 0.680	0.89 (0.56, 1.43), 0.630
	9	CG + GG *vs* CC	0.009	0.90 (0.82, 0.99), 0.030	0.84 (0.69, 1.01), 0.070
Western	6	G *vs* C	0.006	0.87 (0.75, 1.00), 0.050	0.85 (0.65, 1.11), 0.230
	6	GG *vs* CC	0.600	0.83 (0.51, 1.36), 0.470	0.81 (0.49, 1.34), 0.420
	6	CG *vs* CC	0.009	0.84 (0.72, 1.00), 0.040	0.81 (0.60, 1.09), 0.170
	6	GG *vs* CG	0.970	1.12 (0.67, 1.87), 0.670	1.11 (0.66, 1.86), 0.700
	6	CG *vs* CC + GG	0.010	0.85 (0.72, 1.00), 0.050	0.82 (0.61, 1.09), 0.160
	6	GG *vs* CC + CG	0.730	0.90 (0.55, 1.47), 0.680	0.88 (0.54, 1.45), 0.630
	7	CG + GG *vs* CC	0.006	0.91 (0.82, 1.01), 0.070	0.85 (0.68, 1.06), 0.140
USA	3	CG + GG *vs* CC	0.320	0.95 (0.84, 1.07), 0.360	0.94 (0.80, 1.11), 0.450
Europe	4	CG + GG *vs* CC	0.002	0.84 (0.70, 1.00), 0.060	0.79 (0.52, 1.19), 0.260
Colon cancer	4	CG + GG *vs* CC	0.030	0.83 (0.72, 0.96), 0.010	0.80 (0.65, 0.99), 0.040
Rectal cancer	4	CG + GG *vs* CC	0.050	0.98 (0.82, 1.18), 0.860	0.84 (0.58, 1.22), 0.370

[1]*P* value for test for heterogeneity; [2]*P* value for fixed-effect model; [3]*P* value for random-effect mode.

for the rest ones with $P > 0.05$, fixed-effect model was used. As a result, no statistical significance was observed among the above analyses. However, the data of CG + GG *vs* CC genotypes was marginally significant with OR = 0.84 (95% CI: 0.69-1.01, $P = 0.07$).

Limited results in studies from Western countries, the fixed-effect and random-effect ORs (95% CIs) for G *vs* C allele, GG *vs* CC, CG *vs* CC, GG *vs* CG, CG *vs* CC + GG, GG *vs* CC + CG and CG + GG *vs* CC genotypes are listed in Table 2, respectively. Same to the former analyses of the total study population, there was no evidence for the association between PPAR-γ 34 C>G and CRC risk.

Further subgroup-specific analyses were performed in the European and USA studies. In studies from European countries, summary ORs (95% CIs) for CG + GG *vs* CC genotypes in fixed-effect model and random-effect model were 0.84 (0.70, 1.00) and 0.94 (0.80, 1.11), respectively. In studies from the USA, the corresponding ORs (95% CIs) were 0.79 (0.52, 1.19) and 0.95 (0.84, 1.07), respectively. No evidence was found for the association between PPAR-γ 34 C>G and CRC risk in each of the two study populations.

However, when stratified analyses were performed, the results were different. As shown in Table 2, four studies were involved in the meta-analyses for the association of PPAR-γ 34 C>G with colon cancer risk and rectal cancer risk. In the four studies, only the data for CG + GG *vs* CC genotypes was sufficient enough for the analyses. As *P* values of the heterogeneity test in the two meta-analyses were less than 0.05, random-effect model was used. Summary ORs (95% CIs) for CG + GG *vs* CC genotypes in colon cancer studies and rectal cancer studies were 0.80 (0.65, 0.99) and 0.84 (0.58, 1.22),

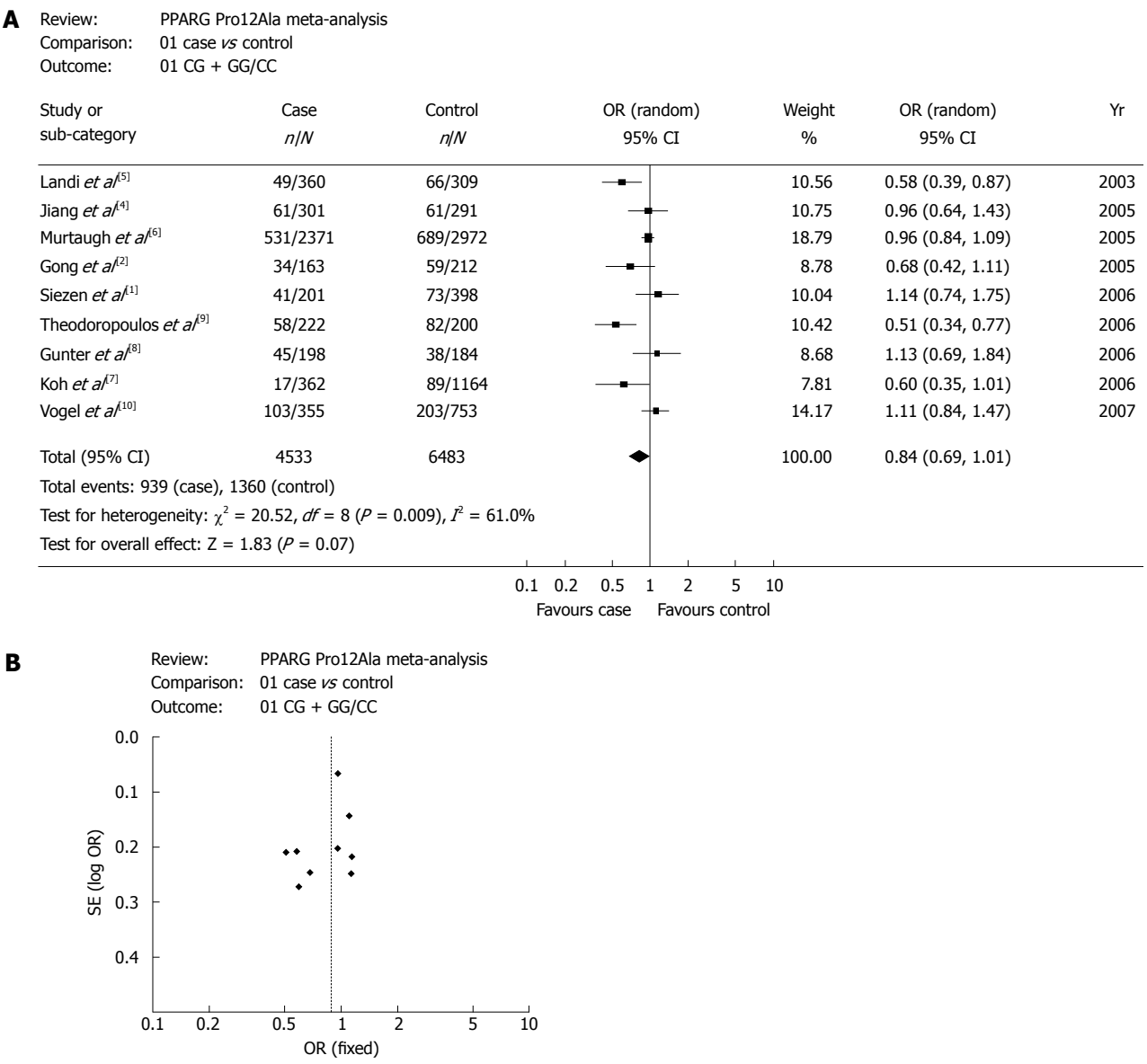

Figure 1 Association between peroxisome proliferator-activated receptor-γ (PPAR-γ) 34 C>G and colorectal cancer risk (CG + GG *vs* CC). A: Forest plot-studies are sorted in order of publication year; B: Funnel plots for the associations.

respectively. Statistical significance was observed in the association meta-analysis between PPAR-γ 34 C>G and colon cancer risk (P = 0.04), indicating that PPAR-γ 34 C>G was associated with colon cancer risk, and G allele decreased the colon cancer risk. However, there was no evidence for the association between PPAR-γ 34 C>G and rectal cancer risk (P = 0.37).

Figure 1A shows the forest plots of meta-analysis for CG + GG *vs* CC genotypes to confirm the association between PPAR-γ 34 C>G and CRC risk in the overall study population. The association between PPAR-γ 34 C>G and CRC risk had a marginally statistical significance. Figure 1B is the funnel plot, suggesting that there was no publication bias in the studies.

Figure 2A displays the forest plots of the study on the association between PPAR-γ 34 C>G and colon cancer risk. Obviously, there was a significant association of PPAR-γ 34 C>G with colon cancer risk. Publication bias was not found in this study as shown in Figure 2B. Other forest plots and funnel plots of meta-analyses on the association between PPAR-γ 34 C>G and CRC risk, colon cancer risk and rectal cancer risk were not shown. However, the results are presented in Table 2.

DISCUSSION

CRC is one of the leading causes of cancer death in the developed countries[11,12]. Both sporadic and hereditary CRC is caused by a set of molecular events[13]. Accumulated evidences indicate that lipid metabolism, especially the one involved in the arachidonic acid (AA)-pathway, appears to play a critical role in the development of colorectal tumor[14]. *PPARγ* gene, one of the most important components of the AA-pathway, has been veri-

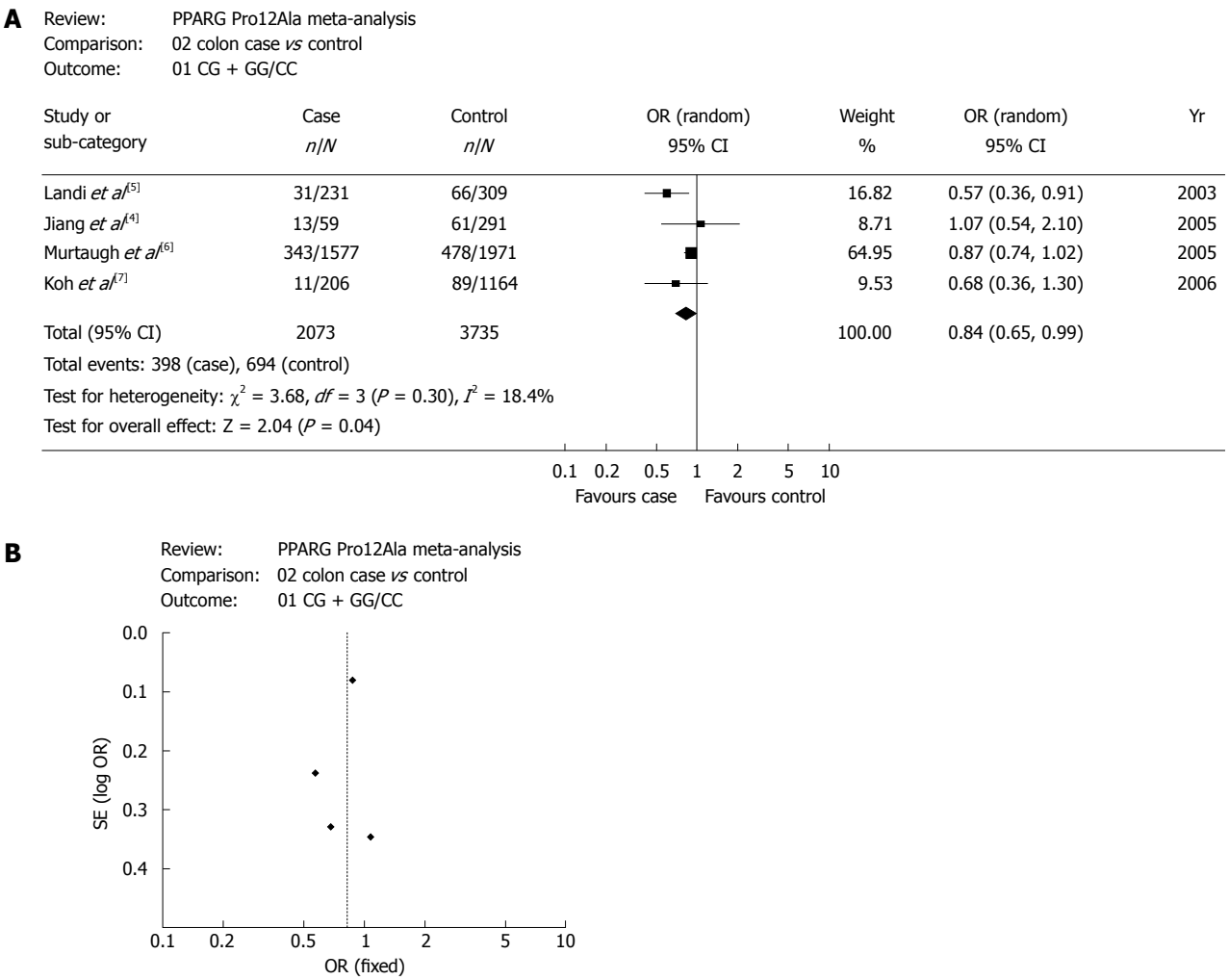

Figure 2 Association between PPAR-γ 34 C>G and colon cancer risk (CG + GG *vs* CC). A: Forest plot-studies are sorted in order of publication year; B: Funnel plots for the associations.

fied to express in a variety of tumor cells. And it will lead to either inhibition of cell proliferation or induction of apoptosis after bonding with ligands[15,16]. Many studies reported that PPAR-γ was also expressed in colon tumors, normal colon mucosa and colon cancer cell lines[17-19]. Genomics research showed that there was a polymorphism in the coding region 34 C>G in PPAR-γ which resulted in the amino acid change of Pro12 Ala[20]. So far, many studies have been performed on the association between PPAR-γ 34 C>G polymorphism and CRC risk, but produced controversial results.

According to our search of references, no systematic review has been published on the analysis of the association between PPAR-γ 34 C>G and CRC. In order to confirm the data on the associations between *PPAR-γ* gene polymorphism and CRC, we did a meta-analysis based on nine studies from Europe, Asia and the USA.

Our results showed that there was no evidence for the association between PPAR-γ 34C>G and CRC if all of the subjects in the nine studies were included. Subgroup-specific meta-analyses also indicated that there was no association between PPAR-γ 34C>G and CRC in European, Asian and the USA studies. As shown in our analysis, G allele might decrease CRC risk, although statistical difference was not significant in these meta-analyses.

Many studies have indicated that both genetic and environmental factors are involved in the development of colorectal tumor[21]. Environmental factors include ethnicity, gender, diet, age, NSAIDS use, BMI, smoking, drinking, family history of disease and so on. It was inferred that there must be interaction between the environmental factors and *PPAR-γ* gene, which had been proved in many researches, including the nine studies. Therefore, interaction is one of the factors of the meta-analyses. Further analysis should be conducted to confirm the influence of PPAR-γ 34 C>G on CRC risk.

Stratified meta-analysis indicated that PPAR-γ 34 C>G was associated with colon cancer, and the G allele decreased the colon cancer risk. No evidence was observed for the association between PPAR-γ 34 C>G and rectal cancer.

In conclusion, no evidence was observed for the association between PPAR-γ 34 C>G and CRC risk and rectal cancer risk. However, PPAR-γ 34 C>G is associated with colon cancer risk, which is meaningful to early

diagnosis, prevention and individual-based treatment of colon cancer. Furthermore, 34 C>G of *PPAR-γ* gene might be a potential therapeutic target for colon cancer.

COMMENTS

Background

Colorectal cancer (CRC) is one of the major causes of cancer death in the developed countries. Accumulated evidences suggest that the peroxisome proliferator-activated receptor-γ (*PPAR-γ*) gene is related to CRC.

Research frontiers

Accumulated evidences indicate that lipid metabolism, especially the one in the arachidonic acid (AA)-pathway, appears to play a critical role in the development of CRC. *PPAR-γ* gene, one of the most important components of the AA-pathway, has been verified to express in a variety of tumor cells. A proline to alanine substitution in the *PPAR-γ* gene was detected, which might be associated with CRC.

Innovations and breakthroughs

Many studies have been performed about the association between the polymorphism 34 C>G of *PPAR-γ* gene and CRC, but got conflicting results. In order to confirm the data, meta-analyses, as a better statistical analysis technique, were performed in this report.

Applications

In this report, the association between *PPAR-γ* gene polymorphism 34 C>G and colon cancer risk was observed, and the G allele decreased the colon cancer risk, which is meaningful to early diagnosis, prevention and individual-based treatment of colon cancer. Furthermore, 34 C>G of *PPAR-γ* gene might be a potential therapeutic target for colon cancer.

Terminology

Susceptibility to colon cancer differs according to genotype of PPAR-γ 34 C>G, and people with G allele might have a lower colon cancer risk.

Peer review

This is an interesting meta-analysis on the association between PPAR-γ 34C>G polymorphism and CRC risk. The main finding of the paper was that PPAR-γ 34 C>G was weakly associated with colon cancer risk, but was not associated with CRC and rectal cancer risk. The methods are properly used; authors report a high quality meta-analysis.

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