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BRIEF ARTICLE

CYP1A1 Ile462Val polymorphism contributes to colorectal cancer risk: A meta-analysis

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Abstract

AIM: To study the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk by meta-analysis.

METHODS: A meta-analysis was performed to investigate the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk by reviewing the related studies until September 2010. Data were extracted and analyzed. Crude odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk.

RESULTS: Thirteen published case-control studies including 5336 cases and 6226 controls were acquired. The pooled OR with 95% CI indicated that CYP1A1 Ile462Val polymorphism was significantly related with colorectal cancer risk (Val/Val *vs* Ile/Ile: OR = 1.47, 95% CI: 1.16-1.86, *P* = 0.002; dominant model: OR = 1.33, 95% CI: 1.01-1.75, *P* = 0.04; recessive model: OR = 1.49, 95% CI: 1.18-1.88, *P* = 0.0009). Subgroup ethnicity analysis showed that CYP1A1 Ile462Val polymorphism was also significantly related with colorectal cancer risk in Europeans (Ile/Val *vs* Ile/Ile: OR = 1.22, 95% CI: 1.05-1.42, *P* = 0.008; dominant model: OR = 1.24, 95% CI: 1.07-1.43, *P* = 0.004) and Asians (Val/Val *vs* Ile/Ile: OR = 1.40, 95% CI: 1.07-1.82, *P* = 0.01; recessive model: OR = 1.46, 95% CI: 1.12-1.89, *P* = 0.005).

CONCLUSION: CYP1A1 Ile462Val may be an increased risk factor for colorectal cancer.

Key words: CYP1A1; Polymorphism; Colorectal cancer; Meta-analysis

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INTRODUCTION

Colorectal cancer, one of the most prevalent cancers worldwide, ranks fourth in frequency in men and third in women[1]. In recent years, the incidence of colorectal cancer has increased in most countries but its prognosis is still poor. A number of researches have shown that colorectal cancer is possibly related with tobacco and alcohol con-

sumption as well as other environmental sources[2-4]. It has been shown that inter-individual differences including single nucleotide polymorphism (SNP) may influence human susceptibility to colorectal cancer[5,6].

Metabolic enzymes including phase I and phase II enzymes are involved in activation and detoxification of xenobiotics, which play an important role in the pathogenesis of colorectal cancer[7]. Cytochrome P450, including family 1, subfamily A, polypeptide 1 (CYP1A1), is one of the phase I enzymes, metabolizing a large number of endogenous and exogenous substances, such as polycyclic aromatic hydrocarbons, heterocyclic amines, aromatic amines, and N-nitrosamines[8,9]. Thus, CYP1A1 plays an important role in human susceptibility to colorectal cancer due to various exogenous factors.

Non-synonymous SNP (rs1048943) leads to amino acid change in exon 7 of CYP1A1 from Ile to Val (nucleotides A-G) at codon 462, which may alter the protein activity and the human susceptibility to colorectal cancer. Since the first study on the relation between colorectal cancer and CYP1A1 Ile462Val polymorphism conducted by Sivaraman *et al*[10] in 1994, a large number of epidemiological studies on the relation between colorectal cancer and CYP1A1 Ile462Val polymorphism have been conducted, but their conclusions are different or even contradictory. In this study, a meta-analysis of the published case-control studies was performed to assess the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk.

MATERIALS AND METHODS

Search strategy

Studies on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk were search from PubMed from 1994 to September 2010 using the key words "CYP1A1", "colorectal cancer", "colon cancer", "rectum cancer", and "polymorphism". Related studies were also searched from the references of original papers or reviews. All studies were selected according to the following criteria: only case-control studies on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk, sufficient published data for estimating odds ratio (OR) with 95% confidence interval (CI), and selection of the largest or most recent studies when several publications reporting the same or overlapping data[11]. Only the data published in 2007 were selected from two studies by Kiss *et al*[12,13] who reported overlapping data in Hungarians. Finally, 13 case-control studies including 5336 patients with colorectal cancer and 6226 controls were enrolled in our meta-analysis.

Data extraction

Two investigators independently extracted the following data from the included publications, including name of the first author, publication data, country origin, source of control, racial descent of the study population, genotyping method, number of different genotypes, and Hardy-Weinberg equilibrium (HWE) in controls.

Statistical analysis

Crude OR with 95% CI was computed to assess the strength of relation between CYP1A1 Ile462Val polymorphisms and colorectal cancer risk. Codominant model (Val/Val *vs* Ile/Ile, Ile/Val *vs* Ile/Ile), dominant model [(Val/Val + Ile/Val) *vs* Ile/Ile] and recessive model [Val/Val *vs* (Ile/Val + Ile/Ile)] were evaluated. Subgroup statistical analysis of the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk in Asians and Europeans was performed. Heterogeneity assumption was checked by chi-square based Q-test[14]. Pooled OR estimation of each study was calculated with the random-effect model (DerSimonian and Laird method) when $P < 0.10$[15]. Otherwise, the fixed-effect model (Mantel-Haenszel method) was selected[16]. The publication bias was evaluated with the funnel plot and linear regression asymmetry test as previously described[17]. Statistical analysis was performed using the STATA version 9.2 (Stata Corporation, College Station, TX) and Review Manager (version 4.2, Oxford, England), using two-sided *P*-values.

RESULTS

Study characteristics

Thirteen published case-control studies including 5336 patients with colorectal cancer and 6226 controls met the inclusion criteria for the meta-analysis[10,13,18-27]. The distribution of studies in different populations is listed in Table 1. The minor allele frequency of Val in controls ranged from 0.030 in Europeans[22] to 0.255 in Asians[23]. Genotyping methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), allele-specific PCR, TaqMan, MassARRAY system, microarray system, and APEX. The distribution of genotypes in controls of all studies was in agreement with HWE except for two studies[19,20].

Meta-analysis

The results of meta-analysis and heterogeneity test are shown in Table 2. The colorectal cancer risk was significantly higher in individuals carrying the Val/Val genotype than in those carrying the Ile/Ile genotype (OR = 1.47, 95% CI: 1.16-1.86, $P = 0.002$, $P_{heterogeneity} = 0.44$, Figure 1A). The dominant and recessive models also showed that colorectal cancer risk was significantly related with the CYP1A1 Ile462Val polymorphism [(Val/Val + Ile/Val) *vs* Ile/Ile: OR = 1.33, 95% CI: 1.01-1.75, $P = 0.04$, $P_{heterogeneity} < 0.01$, Figure 1B; Val/Val *vs* (Ile/Val + Ile/Ile): OR = 1.49, 95% CI: 1.18-1.88, $P = 0.0009$, $P_{heterogeneity} = 0.77$, Figure 1C] in the total population. Subgroup race analysis showed that the CYP1A1 Ile462Val polymorphism was significantly related with colorectal cancer risk in Europeans [Ile/Val *vs* Ile/Ile: OR = 1.22, 95% CI: 1.05-1.42, $P = 0.008$, $P_{heterogeneity} = 0.25$; (Val/Val + Ile/Val) *vs* Ile/Ile: OR = 1.24, 95% CI: 1.07-1.43, $P = 0.004$, $P_{heterogeneity} = 0.24$] and in Asians [Val/Val *vs* Ile/Ile: OR = 1.40, 95% CI: 1.07-1.82, $P = 0.01$, $P_{heterogeneity} = 0.23$; Val/Val *vs* (Ile/Val + Ile/Ile): OR = 1.46, 95% CI: 1.12-1.89, $P = 0.005$, $P_{heterogeneity} = 0.24$].

Table 1 Characteristics of case-control studies included in meta-analysis

Author	Country /region	Racial descent	Source of controls	Case (*n*)	Control (*n*)	Genotype distribution						Genotying type	HWE
						Case (*n*)			Control (*n*)				
						Ile/Ile	Ile/Val	Val/Val	Ile/Ile	Ile/Val	Val/Val		
Sivaraman *et al*[10], 1994	USA	Mixed	Population control	43	47	32	9	2	33	14	0	Allele-specific PCR	0.230
Ishibe *et al*[18], 2000	USA	European	Population control	212	221	176	31	5	186	31	4	PCR-RFLP	0.057
Sachse *et al*[19], 2002	UK	European	Population control	490	592	415	68	7	539	48	5	TaqMan	< 0.01
Slattery *et al*[20], 2004	USA	European	Population control	997	1170	910	82	5	1077	86	7	Allele-specific PCR	< 0.01
Slattery *et al*[20], 2004	USA	European	Population control	794	1010	722	66	6	920	85	5	Allele-specific PCR	0.052
Landi *et al*[21], 2005	Italy	European	Hospital control	362	323	333	28	1	298	25	0	Microarray and APEX	0.469
Little *et al*[22], 2006	UK	European	Population control	251	396	235	16	0	372	24	0	PCR-RFLP	0.534
Kiss *et al*[13], 2007	Hungary	European	Hospital control	500	500	386	110	4	415	83	2	Allele-specific PCR	0.315
Yeh *et al*[23], 2007	China	Asian	Hospital control	717	729	400	228	89	410	266	53	PCR-RFLP	0.280
Yoshida *et al*[24], 2007	Japan	Asian	Not report	66	121	34	27	5	79	37	5	PCR-RFLP	0.800
Pereira Serafim *et al*[25], 2008	Brazil	Mixed	Population control	114	114	14	97	3	81	33	0	PCR-RFLP	0.071
Kobayashi *et al*[26], 2009	Japan	Asian	Hospital control	105	225	65	32	8	125	87	13	MassARRAY system	0.674
Nisa *et al*[27], 2010	Japan	Asian	Population control	685	778	418	231	36	461	276	41	PCR-RFLP	0.970

HWE: Hardy-Weinberg equilibrium in control; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; APEX: Arrayed primer extension.

Table 2 Odds ratio and 95% confidence interval of CYP1A1 Ile462Val polymorphism and colorectal cancer risk

Contrast	Racial descent	OR	95% CI	P_h
Val/Val *vs* Ile/Ile	Total	1.47	1.16-1.86	0.44
	European	1.43	0.83-2.48	0.93
	Asian	1.40	1.07-1.82	0.23
Ile/Val *vs* Ile/Ile	Total	1.28	0.96-1.72	< 0.01[1]
	European	1.22	1.05-1.42	0.25
	Asian	0.91	0.79-1.05	0.19
(Val/Val + Ile/Val)	Total	1.33	1.01-1.75	< 0.01[1]
vs Ile/Ile	European	1.24	1.07-1.43	0.24
	Asian	0.98	0.96-1.13	0.17
Val/Val *vs* (Ile/Val	Total	1.49	1.18-1.88	0.77
+ Ile/Ile)	European	1.39	0.80-2.41	0.94
	Asian	1.46	1.12-1.89	0.24

[1]Estimates for random effects. P_h: Test for heterogeneity; CYP1A1: Cytochrome P450, including family 1, subfamily A, polypeptide 1; OR: Odds ratio; CI: Confidence interval.

Publication bias

Funnel plot and Egger's test were used to estimate the publication bias of studies. The funnel plots seemed symmetrical in all models (Val/Val *vs* Ile/Ile: $P = 0.17$, (Val/Val + Ile/Val) *vs* Ile/Ile: $P = 0.17$, Val/Val *vs* (Ile/Val + Ile/Ile): $P = 0.39$, Figure 2). No publication bias concerning the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk was detected.

DISCUSSION

CYP1A1, a phase I enzyme encoded by the CYP1A1 gene, has been mapped to chromosome 15q24.1. The CYP group of enzymes is involved in metabolic activation and detoxification of tobacco-derived carcinogen and other xenobiotics. It has been shown that alcohol intake and cigarette smoking are two important risk factors for colorectal cancer[20,25,27]. Reactive intermediates can bind to DNA when they are activated, resulting in adducts that cause mutations if not repaired, thereby initiating carcinogenesis[28]. Meanwhile, valine for isoleucine transition at codon 462 can lead to genetic disequilibrium from adenine to guanine mutation. It has been shown that CYP1A1 Ile462Val polymorphism can increase the activity of enzymes and activation of carcinogens may increases the risk of colorectal cancer[29,30]. At the same time, CYP1A1 Ile462Val polymorphisms in genotypes show considerable variations in their activities in different diseases and ethnics, as the variant Val, exhibiting an elevated breast caner risk in Caucasian[31], is a risk factor for esophageal cancer in Asians but not in Caucasians[32]. However, Ile/Val polymorphism is not related with the increased risk of prostate cancer[33].

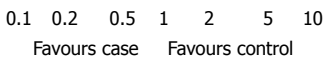
The first study, published in 1994[10], did not reveal the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer. To date, no consensus conclusion is

A

Review: CYP1A1 Ile462Val polymorphisms and colorectal cancer
Comparison: Val/Val *vs* Ile/Ile
Outcome: Total

Study or sub-category	Case *n/N*	Control *n/N*	Odds ratio (fixed) 95% CI	Weight (%)	Odds ratio (fixed) 95% CI
Sivaraman *et al*[10], 1994	2/34	0/33		0.42	5.15 (0.24-111.52)
Ishibe *et al*[18], 2000	5/181	4/190		3.36	1.32 (0.35-5.00)
Sachse *et al*[19], 2002	7/422	5/544		3.80	1.82 (0.57-5.77)
Slattery *et al*[20], 2004	5/915	7/1084		5.64	0.85 (0.27-2.67)
Slattery *et al*[20], 2004	6/728	5/925		3.86	1.53 (0.46-5.03)
Landi *et al*[21], 2005	1/334	0/298		0.47	2.69 (0.11-66.17)
Little *et al*[22], 2006	0/235	0/372			Not estimable
Kiss *et al*[13], 2007	4/390	2/417		1.69	2.15 (0.39-11.81)
Yeh *et al*[23], 2007	89/489	53/463		39.40	1.72 (1.19-2.48)
Yoshida *et al*[24], 2007	5/39	5/84		2.45	2.32 (0.63-8.55)
Pereira Serafim *et al*[25], 2008	3/17	0/81		0.13	39.34 (1.93-802.51)
Kobayashi *et al*[26], 2009	8/73	13/138		7.08	1.18 (0.47-3.00)
Nisa *et al*[27], 2010	36/454	41/502		31.71	0.97 (0.61-1.54)
Total (95% CI)	4311	5131		100.00	1.47 (1.16-1.86)
Total events	171	135			

Test for heterogeneity: χ^2 = 11.04, *df* = 11 (*P* = 0.44), I^2 = 0.3%
Test for overall effect: *Z* = 3.17 (*P* = 0.002)

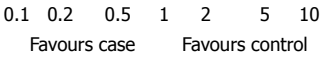


B

Review: CYP1A1 Ile462Val polymorphisms and colorectal cancer
Comparison: (Val/Val + Ile/Val) *vs* Ile/Ile
Outcome: Total

Study or sub-category	Case *n/N*	Control *n/N*	Odds ratio (random) 95% CI	Weight (%)	Odds ratio (random) 95% CI
Sivaraman *et al*[10], 1994	11/43	14/47		4.68	0.81 (0.32-2.05)
Ishibe *et al*[18], 2000	36/212	35/221		7.45	1.09 (0.65-1.81)
Sachse *et al*[19], 2002	75/490	53/592		8.43	1.84 (1.26-2.67)
Slattery *et al*[20], 2004	87/997	93/1170		8.90	1.11 (0.82-1.50)
Slattery *et al*[20], 2004	72/794	90/1010		8.77	1.02 (0.74-1.41)
Landi *et al*[21], 2005	29/362	25/323		7.09	1.04 (0.59-1.81)
Little *et al*[22], 2006	16/251	24/396		6.39	1.06 (0.55-2.03)
Kiss *et al*[13], 2007	114/500	85/500		8.85	1.44 (1.05-1.97)
Yeh *et al*[23], 2007	317/717	319/729		9.46	1.02 (0.83-1.25)
Yoshida *et al*[24], 2007	32/66	42/121		6.70	1.77 (0.96-3.26)
Pereira Serafim *et al*[25], 2008	100/114	33/114		6.13	17.53 (8.79-34.97)
Kobayashi *et al*[26], 2009	40/105	100/225		7.71	0.77 (0.48-1.24)
Nisa *et al*[27], 2010	267/685	317/778		9.44	0.93 (0.75-1.15)
Total (95% CI)	5336	6226		100.00	1.33 (1.01-1.75)
Total events	1196	1230			

Test for heterogeneity: χ^2 = 79.39, *df* = 12 (*P* < 0.00001), I^2 = 84.9%
Test for overall effect: *Z* = 2.03 (*P* = 0.04)



C

Review: CYP1A1 Ile462Val polymorphisms and colorectal cancer
Comparison: Val/Val *vs* (Ile/Val + Ile/Ile)
Outcome: Total

Study or sub-category	Case *n/N*	Control *n/N*	Odds ratio (fixed) 95% CI	Weight (%)	Odds ratio (fixed) 95% CI
Sivaraman *et al*[10], 1994	2/34	0/47		0.39	5.72 (0.27-122.64)
Ishibe *et al*[18], 2000	5/212	4/221		3.30	1.31 (0.35-4.95)
Sachse *et al*[19], 2002	7/490	5/592		3.85	1.70 (0.54-5.39)
Slattery *et al*[20], 2004	5/997	7/1170		5.53	0.84 (0.26-2.65)
Slattery *et al*[20], 2004	6/794	5/1010		3.77	1.53 (0.47-5.03)
Landi *et al*[21], 2005	1/362	0/323		0.45	2.68 (0.11-66.13)
Little *et al*[22], 2006	0/251	0/396			Not estimable
Kiss *et al*[13], 2007	4/500	2/500		1.71	2.01 (0.37-11.01)
Yeh *et al*[23], 2007	89/717	53/729		39.75	1.81 (1.26-2.58)
Yoshida *et al*[24], 2007	5/66	5/121		2.82	1.90 (0.53-6.82)
Pereira Serafim *et al*[25], 2008	3/114	0/114		0.42	7.19 (0.37-140.77)
Kobayashi *et al*[26], 2009	8/105	13/225		6.60	1.34 (0.54-3.35)
Nisa *et al*[27], 2010	36/685	41/778		31.41	1.00 (0.63-1.58)
Total (95% CI)	5336	6226		100.00	1.49 (1.18-1.88)
Total events	171	135			

Test for heterogeneity: χ^2 = 7.35, *df* = 11 (*P* = 0.77), I^2 = 0%
Test for overall effect: *Z* = 3.32 (*P* = 0.0009)

0.1 0.2 0.5 1 2 5 10
Favours case Favours control

Figure 1 Odds ratio of colorectal cancer associated with CYP1A1 Ile462Val for Val/Val *vs* Ile/Ile genotypes (A), Val/Val + Ile/Val *vs* Ile/Ile genotypes (B), and Val/Val *vs* Ile/Val + Ile/Ile genotypes (C).

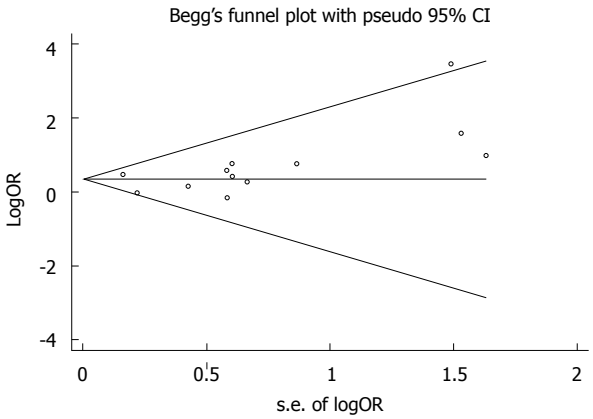


Figure 2 Funnel plot analysis showing publication bias for Val/Val *vs* Ile/Ile genotypes. Each point represents a separate study for the indicated association.

available on the relation of CYP1A1 Ile462Val polymorphism and colorectal cancer. Pereira Serafim *et al*[25] demonstrated that the risk of colorectal cancer is 5-fold higher in Brazilians with the Val genotype (OR = 5.14, 95% CI: 3.15-10.80). Sachse *et al*[19] reported that the risk of colorectal cancer is about 2-fold higher in Europeans with the homozygous Val allele (OR = 2.15, 95% CI: 1.36-3.41). Kiss *et al*[13] and Yeh *et al*[23] also reported that the risk of colorectal cancer is similar to those reported by Pereira Serafim *et al*[25] and Sachse *et al*[19] in Hungarians and Asians with the Val genotype. However, other studies from USA and Europe showed that colorectal cancer risk is not significantly related with CYP1A1 Ile462Val polymorphism[10,18,20-22,24,26,27], but positively related with Val allele and smoking (OR = 2.5, 95% CI: 1.3-4.8) in Europeans[20]. The present meta-analysis of 13 eligible case-control studies including 5336 cases and 6226 controls showed that CYP1A1 Ile462Val polymorphism could contribute to colorectal cancer risk. The stratified analysis according to the ethnicity revealed that CYP1A1 Ile462Val polymorphism was positively related with colorectal cancer risk both in Asians and in Europeans. However, no report is available on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk in Africans. On the other hand, gender factor may change the risk of colorectal cancer sometimes. It was reported that the colorectal cancer risk is 3.1-fold higher in Chinese women with CYP1A1 Val/Val and XRCC3 Thr/Thr genotypes than in those with CYP1A1 Ile and XRCC3 Met alleles[23], suggesting that CYP1A1 Ile462Val polymorphism may be an important risk factor for colorectal cancer.

Heterogeneity is another problem found in our meta-analysis. A significant heterogeneity was observed in Ile/Val *vs* Ile/Ile and (Val/Val + Ile/Val) *vs* Ile/Ile. However, subgroup ethnicity analysis showed that the heterogeneity was removed apparently, indicating that the genetic background and environment are different in different ethnicities.

Several limitations in our meta-analysis need to be addressed. First, the results were obtained based on the unadjusted estimates and lacked of original data about the eligible studies, thus limiting the evaluation of effects of gene-gene and gene-environment interactions on the pathogenesis of colorectal cancer. Second, other single nucleotide polymorphisms of CYP1A1 were identified, but no linkage disequilibrium and haplotype analysis of these polymorphisms was performed. Third, the real relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk might have been influenced since the sample size was relatively small in this analysis, thus a further analysis of the relation between CYP1A1 polymorphism and colorectal cancer should be performed.

In conclusion, CYP1A1 Ile462Val polymorphism may contribute to colorectal cancer risk. Further study is needed with a large-scale case-control sample to validate the identified risk in our current meta-analysis, and potential gene-gene and gene-environment interactions should be taken into account when the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk is further studied.

COMMENTS

Background

Colorectal cancer is one of the most prevalent malignances worldwide. CYP1A1 is one of the phase I enzymes. Ile to Val transition has been supposed as a risk factor for colorectal cancer. A large number of studies on the association between CYP1A1 and colorectal cancer risk have been conducted, but their conclusions are different or even contradictory.

Research frontiers

Many studies indicate that CYP1A1 Ile462Val polymorphism plays an important role in pathogenesis of esophageal cancer in Asians and breast caner in Caucasians. However, the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk remains controversial and no meta-analysis has been conducted.

Innovations and breakthroughs

This meta-analysis systemically assessed the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk, showing that the Val allele may be a risk factor for colorectal cancer in both Europeans and Asians.

Applications

The results of meta-analysis in this study show that the CYP1A1 Ile462Val polymorphism contributes the human susceptibility to colorectal cancer in both Europeans and Asians, which may help us to make early prevention and treatment of colorectal cancer.

Peer review

This is an interesting meta-analysis of the association between CYP1A1 Ile462Val polymorphism and colorectal cancer risk. The authors carefully reviewed the literature and collected the original data. The methods they used in meta-analysis are proper.

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