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REVIEW

Association between the *CYP1A2-164 A/C* polymorphism and colorectal cancer susceptibility: a meta-analysis

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Abstract To date, epidemiological studies have assessed the association between *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility. However, the results of these studies remained controversial. We aimed to examine the associations by conducting a meta-analysis of case–control studies. A total of 11 studies including 5,093 cases and 5,941 controls evaluated the association between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility. No significantly associations were found in all genetic models (CC vs. AA: OR = 1.14, 95 % CI = 0.93–1.40; AC vs. AA: OR = 1.05, 95 % CI = 0.91–1.20; dominant model: OR = 1.08, 95 % CI = 0.95–1.24; recessive model: OR = 1.10, 95 % CI = 0.95–1.28). In the subgroup analysis by ethnicity or source of controls, there were still no significant associations detected in all genetic models. This meta-analysis suggested the *CYP1A2*-164 A/C polymorphism was not a risk factor for increasing colorectal cancer, further large and well-designed studies are needed to confirm these conclusions.

Keywords Meta-analysis · *CYP1A2* · Polymorphism · Colorectal cancer

Introduction

Colorectal cancer is the third most commonly diagnosed human cancer in the world, with over 143,820 new cancer cases and 50,830 deaths estimated to be occurred in the US in 2013 (Siegel et al. 2013). Modifiable risk factors for colorectal cancer include smoking, physical inactivity, overweight and obesity, red and processed meat consumption, and excessive alcohol consumption (Ferrari et al. 2007). Genetic susceptibility to this disease may result from inherited mutations in genes involved in carcinogen metabolism and DNA repair (Shields and Harris 2000; Goode et al. 2002). It is now commonly accepted that the pathogenesis of colorectal cancer involves the

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multi-factorial interactions of environmental triggers and genetic susceptibility. A recent study has revealed that approximately 35 % of colorectal cancer cases can be attributed to inherited genetic susceptibility (Markowitz and Bertagnolli 2009).

In recent years, several common low-penetrant genes have been identified as potential colorectal cancer susceptibility genes. Cytochrome P450 enzymes catalyze Phase I metabolism reactions, such as C-, N- and S-oxidation and dealkylation (Sergentanis et al. 2011). Cytochrome P450 1A2 (*CYP1A2*) is a member of the CYP1 family and it is an important gene in catalyzing 2- and 4-hydroxylations of estrogens (Yamazaki et al. 1998; Nebert and Dalton 2006) and metabolism of carcinogens (Nebert et al. 2004). It is reasonable that *CYP1A2* may play an important role in the etiology of colorectal cancer. A single nucleotide polymorphism (*CYP1A2*-164 A/C or *CYP1A2**1F, rs762551) in intron 1 of the *CYP1A2* gene at position 734 downstream of the first transcribed nucleotide was identified. The A to C base substitution might influence the inducibility and activity of *CYP1A2* (Sachse et al. 1999).

To date, molecular epidemiological studies (Sachse et al. 2002; Landi et al. 2005; Saebø et al. 2008; Rudolph et al. 2011; Eichholzer et al. 2012) have investigated the relationship between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility. However, results of these studies were controversial. Therefore, we performed this meta-analysis of all eligible studies to demonstrate the effect of the *CYP1A2*-164 A/C polymorphism on colorectal cancer susceptibility.

Materials and methods

Publication search

Prospective cohort and case–control studies on *CYP1A2*-164 A/C polymorphism and the susceptibility of colorectal cancer published before Oct 13, 2013 were identified through computer-based searches of PubMed, Embase, and Web of Science electronic databases using the terms "cytochrome P-450 1A2", "*CYP1A2*", "*CYP1A2**1F", "polymorphism" and "colon", "rectum", "colorectal", "cancer", "carcinoma". All searched studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand searched to find additional eligible studies. 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 or complete study was used in this meta-analysis.

Inclusion criteria

Inclusion criteria were defined as follows: (1) the articles evaluated the association between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility, (2) the studies designed as prospective cohorts or case–controls, (3) sufficient data available to estimate an odds ratio (OR) with its 95 % CI, and (4) studies demonstrated that the distribution of genotypes among controls were in Hardy–Weinberg equilibrium.

Data extraction

Information was extracted carefully from all eligible publications independently by two authors according to the inclusion criteria listed above, discrepancies were adjudicated by the other authors until consensus was achieved on every item. For each study, the following characteristics were collected: the first author's name, country or region, year of publication, study design, method of genotyping, total numbers of cases and controls, and numbers of cases and controls who harbored the *CYP1A2*-164 A/C polymorphism. The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Stang 2010) for quality of case control and cohort studies in this meta-analyses, a study awarded seven or more stars was considered as a high-quality study.

Statistical analysis

The strength of association between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility were assessed by OR with the corresponding 95 % CI. Although fixed-effect model and random-effects model yielded similar conclusions, we chose to use the random-effects model with Mantel–Haenszel statistics (DerSimonian and Laird 1986; Ades et al. 2005), which assumed that the true underlying effect varied among included individuals. The pooled ORs were performed for co-dominant model (CC vs. AA, AC vs. AA), dominant model (CC + AC vs. AA), and recessive model (CC vs. AA + AC) respectively. Heterogeneity assumptions among studies were checked by the Chi-square test based on Q-statistic ($p < 0.05$ indicated heterogeneity) (Cochran 1954). Furthermore, we measured the effect of heterogeneity by another measure, $I^2 = 100\ \% \times (Q - df)/Q$ (Higgins and Thompson 2002). Venice criteria (Ioannidis et al. 2008) for the I^2 test included: '$I^2 < 25$ % represents no heterogeneity, $I^2 = 25$–50 % represents moderate heterogeneity, $I^2 = 50$–75 % represents large heterogeneity, and $I^2 > 75$ % represents extreme heterogeneity'. Funnel plots were used to access publication bias by the method of Begg's test (Begg and Mazumdar 1994) and Egger's test (Egger et al. 1997) ($p \geq 0.05$ suggests no bias). Statistical analyses were performed using STATA statistical software (version 10.0). A

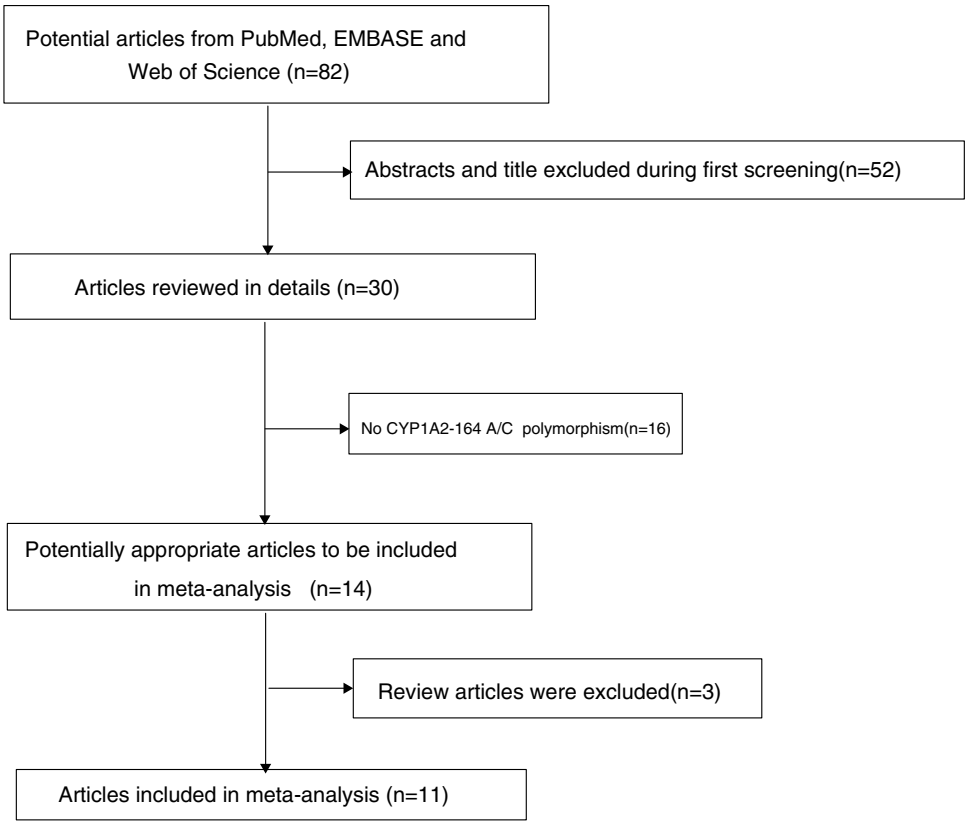

Fig. 1 Study selection process for meta-analysis

p value <0.05 was considered statistically significant, and all the p values were two sided.

Results

Characteristics of studies

The study selection process is shown in Fig. 1. A total of 11 eligible studies including 5,093 cases and 5,941 controls met the inclusion criteria (Sachse et al. 2002; Landi et al. 2005; Bae et al. 2006; Kiss et al. 2007; Küry et al. 2007; Yoshida et al. 2007; Saebø et al. 2008; Kobayashi et al. 2009; Cleary et al. 2010; Rudolph et al. 2011; Eichholzer et al. 2012). We established a database according to the extracted information from each article. The characteristics of selected studies were summarized in Table 1. There were three studies of Asians, eight studies of Caucasians. Among these studies, seven were hospital-based and four were population based. Controls were mainly healthy populations and matched for age. Genotypes distribution in the controls of each study was in agreement with Hardy–Weinberg equilibrium.

Quantitative analysis

Table 2 lists the main results of this meta-analysis. Overall, no significantly elevated colorectal cancer risk was found in all genetic models when all studies were pooled into the meta-analysis (CC vs. AA: OR = 1.14, 95 % CI = 0.93–1.40, $p = 0.06$ for heterogeneity, Fig. 2a; AC vs. AA: OR = 1.05, 95 % CI = 0.91–1.20, $p = 0.01$ for heterogeneity, Fig. 2b; dominant model: OR = 1.08, 95 % CI = 0.95–1.24, $p = 0.00$ for heterogeneity, Fig. 2c; recessive model: OR = 1.10, 95 % CI = 0.95–1.28, $p = 0.30$ for heterogeneity, Fig. 2d). In the subgroup analysis by ethnicity or source of controls, there was still no significant association detected in all genetic models.

Sensitivity analysis

Sensitivity analysis was performed according to heterogeneity. We found heterogeneity for CA vs. AA ($p = 0.01$) and the dominant model ($p = 0.00$) of *CYP1A2*-164 A/C polymorphism in overall population, in the stratified analysis by ethnicity and source of control, no heterogeneity was found in Caucasian and population-based groups (Table 2).

Publication bias

Publication bias was examined using Begg's funnel, the shape of the funnel plot seemed to be approximately symmetrical in the dominant model (Fig. 3a) and the recessive model (Fig. 3b), but there was some uncertainty because the symmetrical degrees were not content. Therefore, the

Table 1 Main characteristics of all studies included in the meta-analysis

Study	Year	Country	Gene test	Source	Case/control	Case			Control			HWE	NOS
						AA	AC	CC	AA	AC	CC		
Eichholzer M	2012	Switzerland	The MassArray system	PB	424/821	207	171	46	403	348	70	0.674	8
Rudolph A	2011	USA	KASPar assays	PB	678/680	354	261	63	353	280	47	0.395	8
Cleary SP	2010	Canada	TaqMan assays	PB	1,165/1,290	598	461	106	648	517	125	0.143	7
Kobayashi M	2009	Japan	MassARRAY system	HB	104/225	53	40	11	96	94	35	0.141	8
Saebø M	2008	Norway	PCR–RFLP	HB	183/189	87	96		106	83			7
Yoshida K	2007	Japan	PCR–RFLP	HB	64/111	26	32	6	42	52	17	0.891	9
Küry S	2007	France	Applied Biosystems ABI 7900HT sequence detection system	PB	1,013/1,118	514	420	79	553	480	85	0.169	8
Kiss I	2007	Hungary	PCR–RFLP	HB	500/500	219	212	69	228	207	65	0.100	8
Bae SY	2006	Korea	PCR–RFLP	HB	111/93	24	71	16	44	37	12	0.347	8
Landi S	2005	Italy	Genorama image analysis software	HB	361/321	141	172	48	158	137	26	0.625	7
Sachse C	2002	UK	PCR–RFLP	HB	490/593	264	193	33	325	233	35	0.424	8

HB hospital based, *PB* population based, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism, *HWE* Hardy–Weinberg equilibrium, *NOS* Newcastle-Ottawa Scale

Egger's test based on linear regression of the standard normal deviate against its precision was used to test the funnel plot symmetry. The Egger's test suggested that publication biases may not have a significant influence on the results of the *CYP1A2*-164 A/C polymorphism in the dominant model ($p = 0.12$), the recessive model ($p = 0.79$) and other models (data was not shown).

Discussion

The association between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility had been studied extensively, but the results were inconsistent. A potential rationale behind these gene–cancer risk associations was that these genetic variants might result in alterations in phenotypes. This meta-analysis suggested that *CYP1A2*-164 A/C polymorphism was not associated with colorectal cancer susceptibility when all studies were pooled together. In the subgroup analysis by ethnicity or source of controls, there was still no significant association detected in all genetic models.

It was reported that C allele causing decreased activity of the encoded enzyme may lead to decreased metabolism of estradiol. Therefore, C allele carriers might potentially increase the colorectal cancer risk (Sachse et al. 2003). Actually, it might be not uncommon that the epidemiology results were not coincident with the results of functional study. Cancer development was a complicated process involving many genes, different genetic backgrounds might contribute to the discrepancy. The influence of the C allele might be decreased by the presence of other unidentified causal genes involved in colorectal cancer susceptibility.

There was a moderate heterogeneity of studies for CA vs. AA and the dominant model of the *CYP1A2*-164 A/C polymorphism in the overall population, but when we analysed by ethnicity and source of control, the heterogeneity disappeared in Caucasian and population-based groups. These results suggested that the heterogeneity might be partly due to ethnicity and lacking of sufficient data, large studies should be needed and subgroup should be performed such as according to smoking and other factors.

Some limitations of this meta-analysis should be acknowledged. First, a common limitation of meta-analysis was heterogeneity, heterogeneity was often caused by variation in the environmental and genetic background of study participants, which was unavoidable when combing many studies, and we found evidence of study heterogeneity in our study, presumably due to ethnicity and the small number of included studies. Second, in the subgroup analysis, the number of each subgroup was relatively small, not having enough statistical power to explore the real association. Third, only published articles were included in the meta-analysis, we cannot exclude the possibility of publication

Table 2 Summary odds ratios relations between the *CYP1A2-164 A/C* polymorphism and colorectal cancer susceptibility

Study group	Homozygous		Heterozygous		Dominant model		Recessive model	
	CC vs. AA		CA vs. AA		(CC + CA vs. AA)		(CC vs. AA + CA)	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Total (*n*)	1.14 (0.93–1.40)	0.06	1.05 (0.91–1.20)	0.01	1.08 (0.95–1.24)	0.00	1.10 (0.95–1.28)	0.30
Ethnicity								
Asian (3)	0.93 (0.36–2.42)	0.03	1.38 (0.55–3.44)	0.00	1.26 (0.50–3.16)	0.00	0.76 (0.48–1.22)	0.48
Caucasian (8)	1.16 (0.97–1.39)	0.19	1.00 (0.92–1.08)	0.45	1.05 (0.95–1.16)	0.17	1.14 (0.98–1.32)	0.35
Source								
Population-based (4)	1.07 (0.90–1.28)	0.37	0.95 (0.86–1.05)	0.99	0.97 (0.88–1.06)	0.97	1.10 (0.92–1.32)	0.31
Hospital-based (7)	1.18 (0.79–1.77)	0.03	1.21 (0.90–1.62)	0.00	1.22 (0.94–1.59)	0.00	1.09 (0.82–1.448)	0.22

P value of *Q* test for heterogeneity

OR odds ratio, *CI* confidence interval

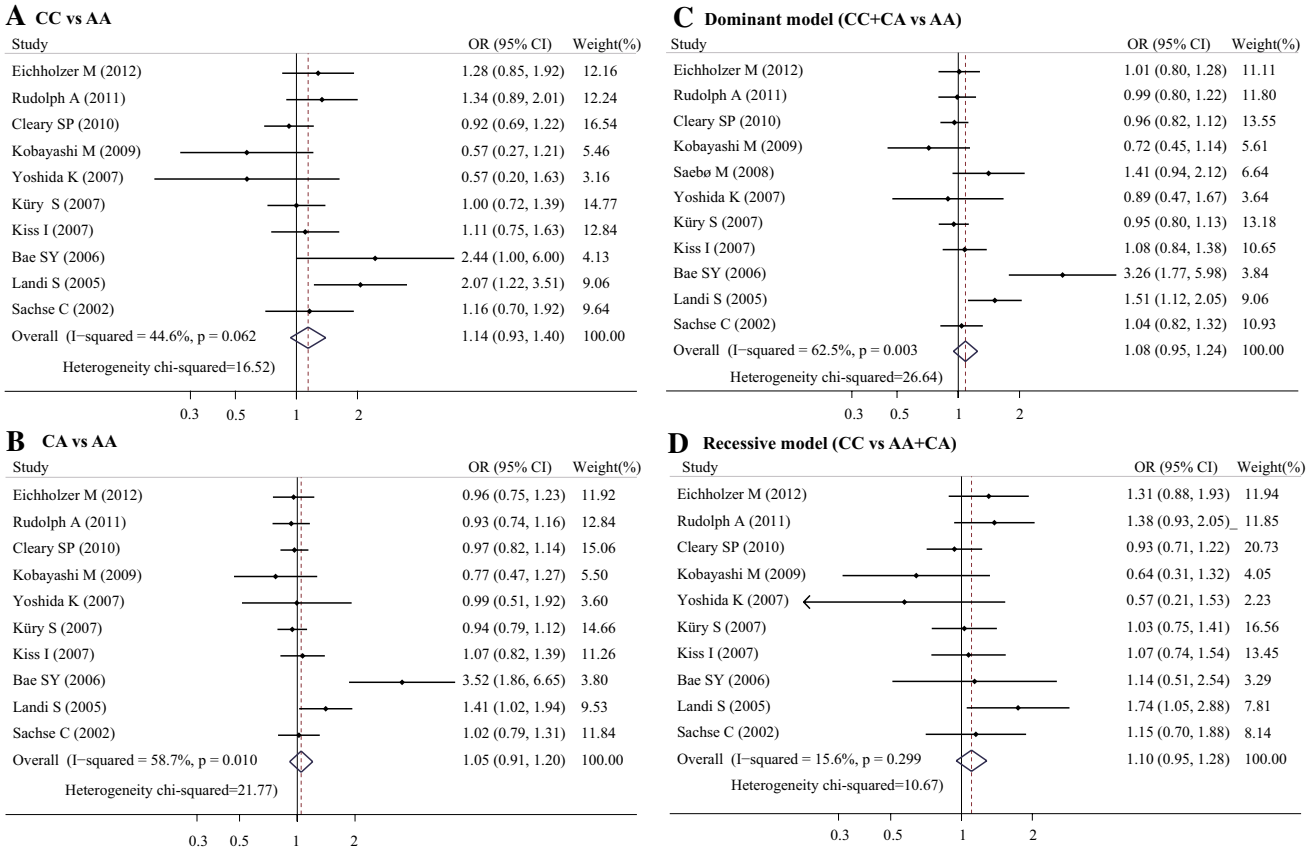

Fig. 2 Odds ratios (ORs) for associations between the *CYP1A2-164 A/C* polymorphism and colorectal cancer susceptibility

bias influencing the results of this meta-analysis, even though statistical analysis indicated no publication bias. Further, the results were based on unadjusted estimates, there would be a more precise estimation on the associations of *CYP1A2*-164 A/C polymorphism with colorectal cancer susceptibility if the ORs were adjusted for age, diet, tobacco, alcoholism, and other environmental factors, more studies with adjusted ORs are needed to further provide a more precise estimation.

In conclusion, this meta-analysis suggested that the *CYP1A2*-164 A/C polymorphism was not a risk factor for colorectal cancer susceptibility. Besides, large and adjusted estimates studies are warranted to validate the conclusion from this meta-analysis, furthermore, gene–gene and

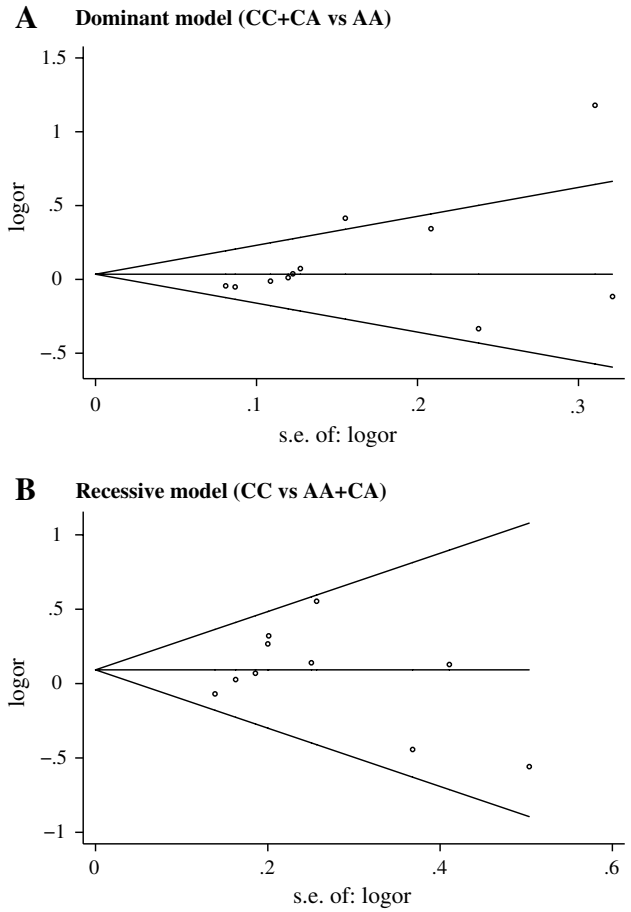

Fig. 3 Begg's funnel plot of the *CYP1A2-164 A/C* polymorphism and colorectal cancer susceptibility, a funnel plot with pseudo-95 % confidence limits (*dashed lines*) was used

gene–environment interactions should also be considered, which may eventually lead to comprehensive understanding of the association between the *CYP1A2*-164 A/C polymorphism and colorectal cancer susceptibility.

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Conflict of interest The authors declare that they have no conflict of interest.

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