RESEARCH ARTICLE

Meta-analysis of Association Studies of *CYP1A1* Genetic Polymorphisms with Digestive Tract Cancers Susceptibility in Chinese

Chang Liu[1], Zheng Jiang[2]*, Qian-xi Deng[2], Ya-nan Zhao[2]

Abstract

Background: A great number of studies have shown that cytochrome P450 1A1 (*CYP1A1*) genetic polymorphisms, *CYP1A1 Msp I* and *CYP1A1 Ile/Val*, might be risk factors for digestive tract cancers, including esophageal cancer (EC), gastric cancer (GC), hepatic carcinoma (HC), as well as colorectal cancer (CC), but the results are controversial. In this study, a meta-analysis of this literature aimed to clarify associations of *CYP1A1* genetic polymorphisms with digestive tract cancers susceptibility in Chinese populations. Materials and Methods: Eligible case-control studies published until December 2013 were retrieved by systematic literature searches from PubMed, Embase, CBM, CNKI and other Chinese databases by two investigators independently. The associated literature was acquired through deliberate search and selection based on established inclusion criteria. Fixed-effects or random-effects models were used to estimate odds ratios (*ORs* and *95%CIs*). The meta-analysis was conducted using Review Manager 5.2 and Stata 12.0 softwares with stability evaluated by both stratified and sensitivity analyses. Moreover, sensitivity analysis and publication bias diagnostics confirmed the reliability and stability. Results: Eighteen case-control studies with 1, 747 cases and 2, 923 controls were selected for *CYP1A1 MspI* polymorphisms, and twenty case-control studies with 3, 790 cases and 4, 907 controls for the *CYP1A1 Ile/Val* polymorphisms. Correlation associations between *CYP1A1 Ile/Val* polymorphisms and digestive tract cancers susceptibility were observed in four genetic models in the meta-analysis (GG *vs* AA:*OR*= 2.03, *95%CI* =1.52-2.72; AG *vs* AA: *OR*=1.26, *95%CI* =1.07-1.48; [GG+AG *vs* AA] :*OR* =1.42, *95%CI*=1.20-1.68, [GG *vs* AA+AG]:*OR*=1.80, *95%CI* =1.40-2.31). There was no association between *CYP1A1 Msp I* polymorphisms and digestive tract cancers risk. Subgroup analysis for tumor type showed a significant association of *CYP1A1 Ile/Val* genetic polymorphisms with EC in China. However, available data collected by the study failed to reveal remarkable associations of GC or HC with *CYP1A1 Ile/Val* genetic polymorphisms and EC, GC or CC with *CYP1A1 MspI* genetic polymorphisms. Conclusions: Our results indicated that *CYP1A1 Ile/Val* genetic polymorphisms, but not *CYP1A1 Msp I* polymorphisms, are associated with an increased digestive tract cancers risk in Chinese populations. Additional well-designed studies, with larger sample size, focusing on different ethnicities and cancer types are now warranted to validate this finding.

Keywords: *CYP1A1* - genetic - polymorphisms - digestive tract cancers - meta-analysis

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Introduction

In recent years, the incidence of digestive tract cancers throughout the world, has shown a marked increase and become a worldwide health burden, especially in developing countries like China. Nevertheless, the incidence has gradually decreased in many western countries. The survival rate of digestive tract cancers in China is far behind europe and the united states. Digestive tract cancers is a heterogeneous, multifactorial disease while its initiation or development can be attributed to the cumulative effect of genetic predispositions, environment factors, and their complex interplay. Moreover, possible risk factors for digestive tract cancers include cigarette smoking, alcohol consumption, food, low intake of vegetables, salty food, pickled vegetables, nutrient deficiency, chronic mucosal irritation and a family history of cancer. According to International Agency for Research on Cancer, China will enter a period of high incidence of cancers in the next period of time. As the current growth rate, new cancer cases of chinese populatioon will be more than five millions annual deaths by 3.86 millions in 2030 (World Health Organization, 2014). Due to a high mortality, esophageal cancer (EC) is the sixth leading

[1]*Department of Gastroenterology, The First People's Hospital of Chongqing New North Zone,* [2]*Department of Gastroenterology, University of The First Affiliated Hospital of Chongqing Medical, Chongqing, China *For correspondence: jiangz1753@163.com*

cause of cancer-related deaths in the world with a rising incidence. A growing body of epidemiological evidence has evident regional characteristics. The morbidity and mortality rates of EC in China are the highest in the world, and over 50% of patients have locally advanced or metastatic disease at presentation (Jun et al., 2013). Gastric cancer (GC) is rampant in most countries as the fourth most common cancer and the second leading cause of cancer death in the world (Gonzalez et al., 2012). In addition, hepatic carcinoma (HC) and colorectal cancer (CC) are increasing year by year.

Cytochrome P450 superfamily is the important phase I metabolizing enzyme. *CYP1A* subfamily includes *CYP1A1* which is widely distributed in the lung, kidney, gastrointestinal tract, skin, larynx, placenta, lymphocyte, and brain tissues outside the liver. It is mainly involved in the metabolism of polycyclic aromatic hydrocarbons. Polycyclic aromatic hydrocarbon activation, as a carcinogen, is closely related with the occurrence and development of tumor (Crewe et al., 2002). *CYP1A*l is an isozyme of cytochrome P450, located on chromosome 15, q22 qter. So far, two single nucleotide polymorphisms (SNPs) in the *CYP1A1* gene have been most frequently studied in relation to cancer risk: *MspI* and *Ile/Val* polymorphism. The former occurs in the *CYP1A1* gene 3' noncoding region of adenylate 264 bp upstream and downstream, which locates in 6235 sites. The increasing activity of the enzyme is caused by base T→C variant. *MspI* polymorphism of three genotypes: wild type (TT type); heterozygous type (type TC) and homozygous type (CC type). We can clear *MspI* polymorphic types by restriction enzyme *MspI*. The *Ile/Val* polymorphism is also known as the exon7 polymorphism. The amino acids of *CYP1A1* exon 7 A→G replacement are equivalent to codon 462 of *IIe* into *Val* isoleucine valine. The polymorphism of *Ile/Val* has three genotypes: mutation homozygous (*Val/VaI*), heterozygous (*Ile/Val*), and wild type (*Ile/Ile*) in three forms by restriction enzyme *NcoI* (Sivaraman et al., 1994; Liu et al., 2007).

In the context of the world, extensive case control studies had been conducted to investigate the potential role of the *CYP1A1* polymorphisms about digestive tract cancers in China. However, the research results were unclear, which could be due to the differences in the small sample size, insufficient statistics, effects of environmental and genetic interactions power. Meta-analysis might increase statistical power to address this problem. In this paper, the meta-analysis study was performed to explore the relationship between *MspI* and *Ile/Val* genetic polymorphisms in the *CYP1A1* gene and digestive tract cancers in Chinese populations.

Materials and Methods

Search strategy and selection criteria

Computerized literature search studies were published from building databases to December 2013 that were written in Chinese and English languages. Published literatures from PubMed, Embase, CBM, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data and other Chinese databases were retrieved by two investigators independently. We used the following keywords and their combinations: *CYP1A1*, esophageal cancer, gastric cancer, colorectal cancer, liver cancer and hepatic carcinoma, gene polymorphism and China or Chinese. Meanwhile, reference lists of the relevant articles were also collected.

The inclusion and exclusion criteria of this meta-analysis were: (1) A need for the experimental design and definition. (2) Case-control studies or nested case-control express published journals in English or Chinese. (3) In the Chinese populations. (4) Raw data not available for retrieval. (5)The articles provided raw data including odds ratio (*OR*) with 95% confidence interval (*CI*). (6) Meeting abstract, case reports, editorials, review articles and other meta-analysis for exclusion. (7) Case subjects were confirmed by endoscopy or operation pathology, histological diagnosis of digestive tract cancers. The study cases were accorded with the diagnostic standard guide. (8) In control-case, non-gastrointestinal symptoms, healthy people were adopted. (9) In the case-control group, there were the total number and genotype distribution and frequency with the Hardy-Weinberg balance ($p<0.05$ that did not conform to the Hardy-Weinberg balance).

Data extraction

Two authors extracted the following data independently using a standardized data extraction form designed by our group.The following information was collected from each the eligible reports:the first name of the author, published time, race, the types of study design, sample size, tumor type. In case-control, the genotype frequency, consistent with the Hardy-Weinberg balance. Disagreements were resolved by discussion among all the authors.

Statistical analysis

The STATA 12.0 and RevMan 5.2 statistical packages was used for the meta-analysis. The associations were estimated by calculating pooled *OR* with *95%CI*. There were four kinds of different models calculated for each genotype, (homozygous and wild-type), (heterozygous and wild-type), dominant genetic model: (homozygote and heterozygote combinations), recessive model, namely (purezygote and "wild type and heterozygous carriers" grouped together). The heterogeneity among studies was evaluated by the Q-statistic and I^2-statistic. The test level was for alpha =0.10. If the research results were ($p>0.1$), there was no heterogeneity and fixed effect model was accepted to merge.If the results were heterogeneous ($p\leq0.1$), the random effects model were combined. The significance of the pooled *ORs* was determined by Z-test ($p<0.05$ was considered statistically significant). Provided that the *95%CI* did not contain 1, it was equivalent to $p\leq0.05$, the results made sense, Conversely no significance. Subgroup analyses were used according to the type of tumor. Sensitivity analysis was also tested by removing one study at a time to calculate the overall homogeneity and effect size. Publication bias was assessed using Begg 's funnel plot and Egger 's regression, putting the research into the general reanalysis, and finding the sources of heterogeneity ($p<0.05$ suggested the presence of publication bias).

Results

Literature search

According to the search strategy and complement, we identified 483 relevant articles, including 82 relevant Chinese articles, and 401 relevant English articles. After preliminary screening and full text reading, on the basis of the inclusive and exclusive criteria, six articles were excluded for lack of original data (Nimura, 1997; Shao et al., 2000; Nan et al., 2005; Wideroff et al., 2007; Zhang et al., 2011; Saeed et al., 2013) and two articles were excluded without case-control group (Yin et al., 2004;Yuan et al., 2008), then two articles for repetitive publication, were chosen which one (Wang et al., 2004). Twenty Chinese articles and ten English articles were included in the final analysis (Yu et al., 1999; Zhang et al., 2000; Zhu et al., 2001; Shen et al., 2002; Wu et al., 2002; Wang et al., 2003; Zhou et al., 2003; Wang et al., 2004; Yang et al., 2004; Chen et al., 2005; Han et al., 2005; Li et al., 2005; Shen et al., 2005; Yin et al., 2005; Fan et al., 2006; Lu et al., 2006; Ma et al., 2006; Wu et al., 2007; Yeh et al., 2007; Zhou et al., 2007; Deng et al., 2008; Li et al., 2009; Zheng et al., 2009; Ji et al., 2010; Yin et al., 2010; Luo et al., 2011; Gao et al., 2012; Huang et al., 2012; Wang et al., 2012; Yun et al., 2013) (Figure 1). The characteristics of the studies including eighteen case-control studies of *CYP1A1 MspI* polymorphisms (1, 747 cases and 2, 923 controls), twenty case-control studies of *CYP1A1 Ile/Val* polymorphisms (3, 790 cases and 4, 907 controls), and three Chinese articles, four articles in English of both *CYP1A1 MspI* and *CYP1A1 Ile/Val* polymorphisms, then another one article in the *Ile/Val* gene about two cases, were shown in Tables 1 and 2.

Meta-analysis databases

The relationship between *CYP1A1* gene *MspI* polymorphism and digestive tract cancers: meta-analysis in Chinese populations.

As shown in Table 3, we had no discovered to find significant association between *CYP1A1 MspI* polymorphism and digestive tract cancers susceptibility in the overall analysis under all genetic models We analyzed the heterogeneity for all studies and the test value of χ^2 about $p \leq 0.1$ in a random-effect model or $p > 0.1$ in a fixed-effect model [(For CC *vs* TT: there was statistical heterogeneity in studies (p=0.02; I^2=44%); *OR*=1.11, *95%CI*=0.85-1.46, test for overall effect: Z=0.77 (p_z=0.44); For CT *vs* TT: no statistical heterogeneity existed in the studies (p=0.11; I^2=30%; *OR*=1.04, *95%CI* =0.88-1.22, test for overall effect: Z=0.43 (p_z=0.67); For CC+CT *vs* TT: there was statistical heterogeneity in studies (p=0.02; I^2=46%); *OR*=1.05, *95%CI*=0.88-1.26, test for overall effect: Z=0.55 (p_z=0.58); For CC *vs* TT+CT: no statistical heterogeneity existed in the studies (p=0.12; I^2=29%); *OR*=1.07, *95%CI* =0.86-1.33), test for overall effect: Z=0.58 (p_z=0.56)].

Table 1. Case-control Studies about *CYP1A1 MspI* Polymorphisms and Digestive Tract Cancers

First author	Publication year	Area	Genotype Case (T T/T C/C C)	Distribution Control (T T/T C/C C)	Tumor type
H Lu	2006	Xinjiang	64 (23/28/13)	116 (44/56/16)	EC
HX Shen	2005	Liaoning	60 (26/27/7)	57 (26/28/3)	GC
LH Ying	2005	Jiangsu	106 (42/54/10)	106 (41/49/16)	EC
Q Zhou	2003	Henan	19 (9/9/1)	72 (24/38/10)	EC
CH Fan	2006	Zhejiang	139 (65/60/14)	340 (122/165/53)	CC
P Gao	2012	Ningxia	40 (15/17/8)	80 (28/41/11)	EC
YX Yun	2013	Henan	157 (47/98/12)	157 (62/77/18)	EC
X Huang	2012	Guangxi	98 (38/41/19)	100 (40/43/17)	EC
LJ Zheng	2009	Shānxī	79 (35/33/11)	110 (57/41/12)	CC
D Ying	2010	Xinjiang	96 (35/45/16)	174 (69/88/17)	EC
R Ji	2010	Gansu	189 (49/95/45)	216 (70/98/48)	EC
MT Wu	2002	Taiwan	146 (60/65/21)	324 (136/146/42)	EC
LD Wang	2003	Henan	62 (33/25/4)	38 (12/22/4)	EC
YB Han	2005	Shānxī	89 (25/39/25)	98 (47/38/13)	EC
K Chen	2005	Zhejiang	139 (65/60/14)	340 (122/165/53)	CC
JX Ma	2006	Liaoning	60 (26/27/7)	57 (26/28/3)	GC
MW Yu	1999	Taiwan	81 (25/42/14)	409 (152/193/64)	HC
YP Luo	2011	Hunan	123 (38/61/24)	129 (47/54/28)	GC

The relationship between *CYP1A1 Ile/Val* substitution gene polymorphisms and digestive tract cancers; meta-analysis in Chinese populations:

As shown in Table 4, we fould a significant association between *CYP1A1 Ile/Val* polymorphism susceptibility in the overall analysis under all genetic models [(For GG *vs* AA: there was statistical heterogeneity in studies (p=0.0004; I^2=59%); *OR*= 2.03, *95%CI*=1.52-2.72, test for overall effect: Z=4.79 (p_z<0.00001). For AG *vs* AA: there was statistical heterogeneity in studies (p=0.002; I^2 =55%); *OR*=1.26, *95%CI*=1.07-1.48, test for overall effect: Z=2.79 (p_z=0.005). For GG+AG *vs* AA: there was statistical heterogeneity in studies (p<0.0001; I^2=64%); *OR* =1.42, *95%CI*=1.20-1.68, test for overall effect: Z=4.02 (p_z<0.0001). For GG *vs* AA+AG: there was statistical heterogeneity in studies (p=0.005; I^2=51%); *OR*=1.80, *95%CI* =1.40-2.31, test for overall effect: Z=4.63 (p_z<0.00001)]. The *95%CI* did not contain 1, it was equivalent to $p_z \leq 0.05$, the results found a significant association .

In the further subgroup analyses based on tumor type,

Table 2. Case-control Studies about *CYP1A1 Ile-Val* Substitution Polymorphisms and Digestive Tract Cancers

First author	Publication year	Area	Genotype Case (AA/AG/GG)	Distribution Control (AA/AG/GG)	Tumor type
T Zhou	2007	Shandong	102 (53/27/22)	62 (35/24/3)	GC
XH Wu	2007	Shānxī	63 (24/29/10)	86 (53/27/6)	HC
J Yang	2004	Shandong	67 (32/26/9)	63 (15/27/21)	EC
WC Zhu	2001	Guangdong	52 (20/24/8)	100 (62/32/6)	HC
AH Wang	2002	Shānxī	127 (21/56/50)	101 (31/48/22)	EC
J Shen	2005	Jiangsu	112 (70/36/6)	676 (412/226/38)	GC
J Deng	2008	Hebei	87 (24/37/26)	162 (60/81/21)	EC
H Li	2005	Shandong	102 (53/27/22)	62 (35/24/3)	GC
YX Yun	2013	Henan	157 (73/72/12)	157 (95/50/12)	EC
LD Wang	2003	Henan	62 (30/28/4)	38 (20/16/2)	EC
MT Wu	2002	Taiwan	146 (68/62/16)	324 (179/127/18)	EC
YB Han	2005	Shānxī	89 (21/54/14)	98 (31/54/13)	EC
HY Zhang	2000	Shānxī	111 (31/41/39)	70 (34/28/8)	EC
MW Yu	1999	Taiwan	81 (46/29/6)	409 (239/150/20)	HC
DL Wang	2012	Guangdong	253 (116/120/17)	254 (155/90/9)	EC
DL Wang	2012	Taihang	312 (188/105/19)	214 (140/64/10)	EC
CC Yeh	2007	Taiwan	717 (400/228/89)	729 (410/266/53)	CC
LJ Zheng	2009	Shānxī	79 (23/31/25)	110 (58/37/15)	CC
D Ying	2010	Xinjiang	101 (47/48/6)	192 (117/66/9)	EC
R Li	2009	Huadong	970 (560/349/61)	1000 (598/357/45)	HC

Table 3. Summary of Pooled *ORs* and *95%CI* for *CYP1A1 MspI* Genetic Polymorphism

	(CC *vs* TT)		(CT *vs* TT)		(CC+CT *vs* TT)		(CC *vs* TT+CT)	
	OR (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)
Total	1.11 (0.85, 1.46)	*p*=0.02; I^2=44%	1.04 (0.88, 1.22)	*p*=0.11; I^2 =30%	1.05 (0.88, 1.26)	*p*=0.02; I^2=46%	1.07 (0.86, 1.33)	*p*=0.12;I^2=29%
EC	1.23 (0.89, 1.70)	*p*=0.12; I^2=34%	1.10 (0.88, 1.36)	*p*=0.19; I^2 =27	1.12 (0.90, 1.40)	*p*=0.09; I^2=39%	1.16 (0.88, 1.54)	*p*=0.18;I^2=28%
GC	1.37 (0.78, 2.42)	*p*=0.46; I^2=0%	1.15 (0.78, 1.69)	*p*=0.65; I^2 =0%	1.18 (0.82, 1.71)	*p*=0.92; I^2=0%	1.17 (0.70, 1.95)	*p*=0.24;I^2=29%
CC	0.61 (0.41, 0.92)	*p*=0.11; I^2=54%	0.77 (0.59, 1.01)	*p*=0.18; I^2 =42%	0.78 (0.51, 1.19)	*p*=0.07; I^2= 62%	0.70 (0.48, 1.04)	*p*=0.30;I^2=18%

Table 4. Summary of Pooled *ORs* and *95%CI* for *CYP1A1 Ile/Val* Genetic Polymorphism

	(GG *vs* AA)		(AG *vs*AA)		(GG+AG *vs* AA)		(GG *vs* AA+AG)	
	OR (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)	*OR* (*95%CI*)	*p* (I^2)
Total	2.03 (1.52, 2.72)	*p*=0.0004; I^2=59%	1.26 (1.07, 1.48)	*p*=0.002; I^2=55%	1.42 (1.20, 1.68)	*p*<0.0001; I^2= 64%	1.80 (1.40, 2.31)	*p*=0.005; I^2=51%
EC	1.81 (1.12, 2.91)	*p*=0.0006; I^2=68%	1.42 (1.18, 1.71)	*p*=0.21; I^2=24%	1.50 (1.18, 1.89)	*p*=0.01; I^2= 55%	1.58 (1.06, 2.35)	*p*=0.004; I^2=62%
GC	2.59 (0.78, 8.55)	*p*=0.04; I^2=69%	0.85 (0.61, 1.17)	*p*=0.79; I^2=0%	1.05 (0.77, 1.42)	*p*=0.73; I^2=0%	2.83 (0.80, 10.00)	*p*=0.02; I^2=74%
HC	2.01 (1.19, 3.38)	*p*=0.20; I^2=36%	1.40 (0.92, 2.13)	*p*=0.03; I^2=66%	1.54 (0.98, 2.42)	*p*=0.001; I^2=74%	1.61 (1.16, 2.25)	*p*=0.56; I^2=0%

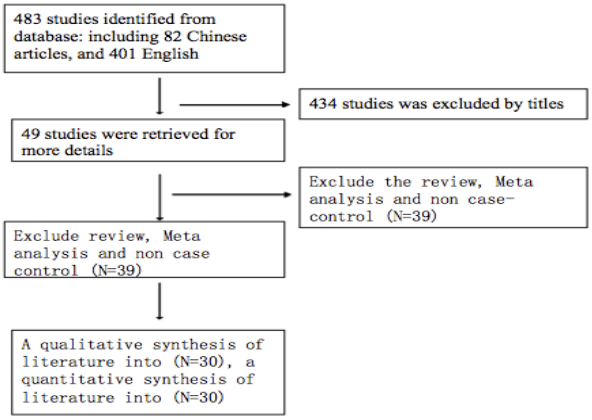

Figure 1. Literature Search Flow Diagram

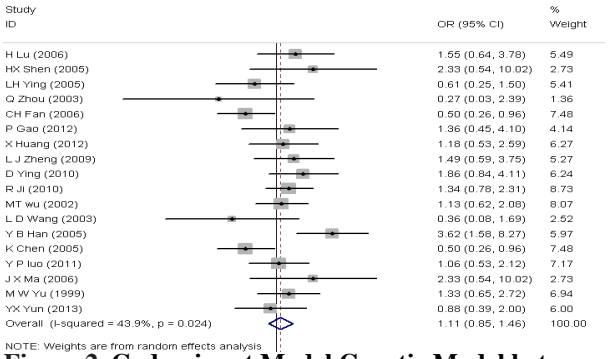

Figure 2. Codominant Model Genetic Model between CC *vs* TT and *CYP1A1 MspI* Genentic Polymorphism

there was little association between *CYP1A1* gene *MspI* polymorphism and digestive tract cancers risk including EC, GC, CC, and HC. However, there was association between *CYP1A1 Ile/Val* substitution gene polymorphisms and digestive tract cancers risk in EC group [(GG *vs* AA):*OR*:1.81, *95%CI*: (1.12, 2.91), test for overall effect:*Z*=2.44 (p_z=0.01); (AG *vs* AA): *OR*:1.42, *95%CI*: (1.18, 1.71), test for overall effect: *Z*=3.70 (p_z=0.0002); (GG+AG *vs* AA): *OR*: 1.50, *95%CI* : (1.18, 1.89), test for overall effect: *Z*=3.39 (p_z=0.0007); (GG *vs* AA+AG) :*OR*:1.58, *95%CI*: (1.06, 2.35) test for overall effect: *Z*=2.22 (p_z=0.03)]. Other subgroup analyses by ethnicity of controls did not reveal significant associations with GC or HC in *CYP1A1 Ile/Val* polymorphisms and EC, GC and CC in *CYP1A1 Msp I* polymorphisms.The Partial forest plots were shown in Figures 2- 3.

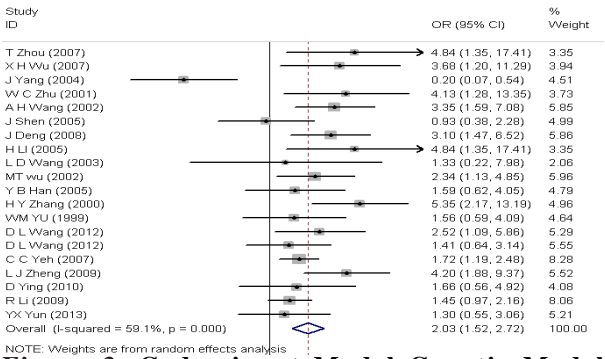

Figure 3. Codominant Model Genetic Model between (AG *vs* AA) and *CYP1A1 Ile/Val* Genentic Polymorphism

Sensitivity analyses

When we investigated *CYP1A1* two genetic polymorphisms, a single study method was deleted each time to reflect the influence of the individual data-set to the pooled *ORs*. The corresponding pooled *ORs* were not markedly altered under all models in both the overall analyses and the subgroup analyses, with more than two studies. It indicated that our results were statistically robust. Looking for heterogeneity: all studies were eliminated one by one in the genetic model, these analyses, however, the results did not altered substantially under any genetic models.

Bias diagnostics

Using Egger's test, no publication bias could be detected for studies published on *MspI* polymorphism (TC+CC *vs* TT, P_E=0.992; CC *vs* TC+TT, P_E=0.667; CC *vs* TT, P_E=0.908;TC *vs* TT, P_E=0.708) and *Ile/Val* polymorphism (AG+GG *vs* AA, P_E=0.047; GG *vs* AG+AA, P_E=0.735; GG *vs* AA, P_E=0.401; AG *vs* AA, P_E=0.117).

Using Begg's test, no publication bias could be dominant model detected for studies published on *MspI* polymorphism (TC+CC *vs* TT, p_b=0.363; CC *vs* TC+TT, p_b=0.306; CC *vs* TT, p_b=0.596;TC *vs* TT, p_b=0.112) and *Ile/Val* polymorphism (AG+GG *vs* AA, p_b=;0.436 GG *vs* AG+AA, p_b=0.697; GG vs.AA, p_b=0.399; AG *vs* AA, p_b=0.795) ($P_{E/b}$<0.05 suggested the presence of publication bias). the publication biases were not evident because the funnel plots appeared to be approximately symmetrical. Moreover, Egger's test and Begg's test was

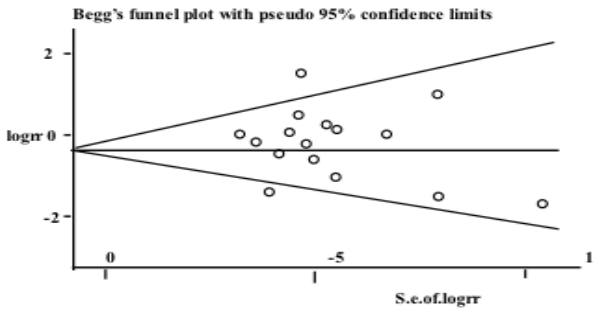

Figure 4. Begg's Funnel Plot of Codominant Model Genetic Model (CC *vs* TT) in *CYP1A1* (*MspI* Genentic Polymorphism Group

for the quantitative evaluation of the symmetry of the meta-analysis funnel plot and its results were listed in Figure 4.

Discussion

CYP1A1 is an important aspect that plays an essential role in the metabolic activation of major classes of procarcinogens, thus affecting the metabolism of the environmental carcinogens and altering susceptibility to digestive tract cancers.Enzyme gene in the phase of metabolism is more than 95% *CYP* and these variant enzymes could enhance toxicity of the extraneous stimulating factors that directly influence tissues.In a word, the *CYP1A1* gene is considered to be an vital indicator of carcinogens. At present, a series of studies about humans not animals or cellulars have indicated that *CYP1A1* polymorphisms may contribute to the risk of digestive tract cancers, then the rate varies significantly among different races and ethnicities.

In the past 10 years, there had been a lot of studies on the *CYP1A1* polymorphism and EC, GC, CC, HC susceptibility in China and abroad, but these claims were inconsistent as the current research results. The reason might be that there was an obvious contrast between east and west and this difference in populations implied that mutations in genotype frequencies result in various degrees of cancers susceptibility. Some researches had contributed enormously to the understanding of digestive tract cancers. One meta-analyses published in 2012 with the association between *CYP1A1 MspI/Ile462Val* polymorphisms and cancers risk among asians failed to cover all conclusive articles published in Chinese databases, and was short of match properly for the Chinese population, not for digestive tract cancers with unclear case and control numbers (Wu et al., 2012). To our knowledge, our study was the first investigation of the worldwide evidence about the Chinese population on the association of *CYP1A1* genetic polymorphisms with digestive tract cancers. Other studies, Fujun Han (Han et al., 2012) conducted a meta-analysis about the association of two cytochrome *CYP1A1* polymorphisms with gastric cancer risk that also failed to show that the *CYP1A1 MspI* genetic polymorphism conferred no significant risk for GC. However, studies were necessary to provide more on the number for the evaluation.One meta-analysis study (Wang et al., 2012) demonstrated there was no association between endometrial cancer risk and the *CYP1A1 Ile462Val* polymorphism.But their studies had only seven researches, merely for *CYP1A1 Ile462Val* and EC.A recently published article (Yun et al., 2013)was included in our meta-analysis. At the moment, for the most part, these studies aimed at the all races rather than individual race. Further, we devoted to the individual race, it could get less heterogeneities and more reliable results.

About races, location and environment, the morbidity of a vast country of digestive tract cancers like China could be higher, accompany with different countries. Therefore, our leverage lied in the parallel comparison of the accuracy in Chinese people instead of the world. Studies on the specific crowd might reduce the regional and ethnic influence, thus increase the reliability of the results. So further epidemiological and molecular biological studies were necessary to clarify the role of *CYP1A1* genetic polymorphisms in digestive tract cancers and other countries.Genetic polymorphism referd to one or more allelic mutation genetic variation and the occurrence of multi-peak curve discontinuities in the crowd.For the moment, *CYP1A1* genetic polymorphism was one of the most common kinds, which we had discussed in the study group. To evaluate the association of *CYP1A1* genetic polymorphism and susceptibility to digestive tract cancers in the Chinese population, we performed an updated systematic meta-analysis. In *CYP1A1* genetic *MspI* polymorphism group, thirteen of eighteen studies showed no correlation between *CYP1A1 MspI* genetic polymorphism and digestive tract cancers. Subgroup analysis based on ethnicity of controls and tumor type did not discover correlation between *CYP1A1 MspI* polymorphisms and digestive tract cancers risk. Particularly nine studies of EC were applied for evaluation for the *CYP1A1 MspI* genetic support our result while only two cases were in contrast to it. In GC groups, three studies with cases (less than 1000) might denote no relationship between *CYP1A1 MspI* genetic polymorphism and digestive tract cancers. Random effects model of meta-analysis with 3,790 cases and 4,907 controls showd significant associations of polymorphisms of *CYP1A1 Ile-Val* genetic in the overall analysis under all genetic models, respectively, with digestive tract cancers risk in Chinese populations. Subgroup analyses on *CYP1A1 Ile-Val* substitution gene in EC group indicated that tumor type of controls were significantly associated with digestive tract cancers risk.Moreover, limited investigative numbers of the case-control followed up ethnicity studies from Chinese region might result in difficulty for getting stable risk estimation. *CYP1A1 Ile-Val* substitution in exon 7 results in a two-fold increased in microsomal enzyme activity and therefore the *Val* allele would be expected to increase the susceptibility to EC. However, subgroup analyses, GC group and HC group had not found any correlation between them. Two previous meta-analyses (Yang et al., 2005; Zhuo et al., 2009) was consistent with our results. Individuals with the *Ile-Val* substitution in *CYP1A1* exon 7 had increased esophageal cancer risk, with *ORs* (*95%CI*) compared with *Ile/Ile* of 1.37 (1.09-1.71), 2.52 (1.62-3.91) and 1.44 (1.17-1.78) for *Ile-Val*, *Val/Val* genotype and the combined group.No significant

association was found between esophageal cancer risk and *CYP1A1 MspI* genetic parameters. It was regrettable that these were not especially for the Chinese populations.

Tumor has a multi-factor, multi-step of development. It may be involved in gene-gene and gene-environment interactions. some studies without clear explanation for the pathologic diagnostic results of some subjects and each study has its own inclusive criteria.Therefore, some selection bias might be unavoidable. Heterogeneity is an important factor to affect the results of the study. The part of the presence of heterogeneity in all genetic models might be through sensitivity analysis and subgroup, eliminating any document for the reason of the heterogeneity.Finally, significance of these results was the same that did not vary with the above statement .We used the Begg's funnel plot and Egger's test, respectively, the qualitative and quantitative assessment of publication bias tips in this paper.Publication bias might not exist together with heterogeneity across studies, which increase the statistical power.

As was known with meta-analyses, there were several limitations to the present study. Possible sources of heterogeneity, such as the number of existing clinical trials, level, method, language and the search range limitation might be considered.Then, the consolidation results were from unadjusted estimates and therefore potential covariates. At last, despite gene-gene and gene-environment interactions could be involved in the pathogenesis of digestive tract cancers. The results of our meta-analysis should be interpreted with caution because the sample size was relatively small for the subgroups and the lack of representation of population.

In conclusion, our meta-analysis strongly suggested that a meaningful association existed between *CYP1A1 Ile/Val* polymorphisms and risk of digestive tract cancers and EC in Chinese population. Peoples with null genotypes of *CYP1A1 Ile/Val* were more susceptible to developing digestive tract cancers. Further studies based on large-scale populations and gene-environment interactions are needed to determine, such as community or hospital source populations and selected population with various environmental background.

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