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HIF1A gene Pro582Ser polymorphism and susceptibility to digestive tract cancers: a meta-analysis of case-control studies

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ABSTRACT. Many existing studies have demonstrated that common polymorphisms in the hypoxia inducible factor-1α (*HIF-1A*) may contribute to the development of digestive tract cancers, but individually published studies showed inconclusive results. This meta-analysis aimed to derive a precise estimation of the relationships between *HIF1A* Pro582Ser polymorphism and the risk of digestive tract cancers. We searched CISCOM, CINAHL, Web of Science, PubMed, Google Scholar, EBSCO, Cochrane Library, and CBM databases from inception through May 1, 2013. Meta-analysis was performed using the STATA 12.0 software. We assessed 6 case-control studies that included a total of 911 digestive tract cancer patients and 2774 healthy controls. Our meta-analysis indicated that *HIF1A* Pro582Ser polymorphism was associated with an increased risk of digestive tract cancer. Subgroup analysis by ethnicity suggested that *HIF1A* Pro582Ser polymorphism might

increase an individual's susceptibility to digestive tract cancer in Asian populations. However, similar association was not observed in Caucasian populations. In conclusion, our findings suggest that *HIF1A* Pro582Ser polymorphism may contribute to the risk of digestive tract cancers, especially in Asian populations.

Key words: Digestive tract cancer; Hypoxia inducible factor-1α; Polymorphism; Meta-analysis

INTRODUCTION

Digestive tract cancers which refers to malignant conditions of the gastrointestinal tract and comprises gastric, colorectal, and esophageal cancers, is among the leading causes of death in the world (Nikolopoulos et al., 2010). Gastric cancer causes about 800,000 deaths worldwide per year and remains the second most common cause of cancer-related death globally (Li et al., 2012). Colorectal and esophageal cancers are also deadliest cancers and have been a serious threat to human (Siegel et al., 2012). In general, digestive tract cancers develop as a result of the combination of several genetic causes and environmental factors. Although the potential risk factors related to digestive tract cancers are not well understood, smoking, alcohol and obesity have been reported to be associated with the development and progression of digestive tract cancers (Donohoe et al., 2010; Fedirko et al., 2011). Genetic factors may also play an important role in the risk of GIT cancers. Several studies have shown that *MMP-9*, *CYP1A1*, and *XRCC1* genetic variations may be intensively linked to the development of digestive tract cancers (Langers et al., 2012; Ghoshal et al., 2014). Large quantity of evidence have documented that the genetic polymorphism of hypoxia inducible factor-1*α* (*HIF-1A*) may also contribute to the susceptibility of digestive tract cancers (Rohwer et al., 2009; Takala et al., 2011).

The HIF-1, consisting of α and β protein subunits (HIF-1A/1B), is a helix-loop-helix transcription factor that regulates adaptive responses to hypoxia (Kizaka-Kondoh et al., 2003). HIF-1A is an important transcription factor which was first found as a regulator of renal production of erythropoietin (Nagy et al., 2009). Human *HIF-1A* gene is located on chromosome 14q21~q24, spanning approximately 52.9 kbps in length and consists of 14 exons and 13 introns (Yamada et al., 2005). It is well established that *HIF-1A* gene exists in malignant tumors extensively and may play a key role in promoting tumor growth and metastasis (Semenza, 2012). Generally, in normoxic condition, HIF-1A is hydroxylated at specific proline residues (Kizaka-Kondoh et al., 2003). While under hypoxic condition, HIF-1A is induced to combine with the β subunit, and then removes to the nucleus and initiates gene transcription, which shows hypoxia in the tumor microenvironment is sufficient to activate HIF-dependent gene expression (Dachs et al., 1997). As a result, HIF-1A is over-expressed in regional or distant metastases and is also highly expressed in pre-neoplastic and premalignant lesions, indicating that over-expression of HIF-1A can occur very early in carcinogenesis and thus might be utilized as a potential biomarker of predicting tumor progress and a good target for the detecting of tumor metastasis (Nagy et al., 2009; Lu and Kang, 2010). In recent studies, high expression level of HIF-1A have been found in human malignancies including colon, colorectal, gastric, and esophageal

cancer, and is considered to increase cancer cell survival (Li et al., 2009; Knechtel et al., 2010; Ranasinghe et al., 2013). Therefore, genetic polymorphisms of HIF-1A have been postulated to be responsible for cancer metastasis. Large quantity of evidence indicates that several single-nucleotide polymorphisms (SNPs) in the *HIF-1A* gene may play a critical role in mediating genetic predisposition to digestive tract cancers (Ling et al., 2005; Chai et al., 2010). More specifically, *HIF-1A* Pro582Ser polymorphism (rs11549465 C>T) was thought as a common SNP which have shown significantly association with the development and progression of digestive tract cancers (Kuwai et al., 2004; Knechtel et al., 2010). However, some other studies have failed to identify any associations between HIF-1A Pro582Ser polymorphism and the risk of digestive tract cancers (Ling et al., 2005; Kang et al., 2011). In view of the controversial results, we performed this meta-analysis to provide a comprehensive and reliable conclusion on the relationships of *HIF-1A* Pro582Ser polymorphism with susceptibility to digestive tract cancers, and to understand the biological processes associated with the formation and progression of digestive tract cancers, which subsequently may be further utilized as a diagnostic tool for digestive tract cancers.

MATERIAL AND METHODS

Literature search

We searched CISCOM, CINAHL, Web of Science, PubMed, Google Scholar, EBSCO, Cochrane Library, and CBM databases from inception through May 1, 2013 without language restrictions. The following keywords and MeSH terms were used: ("SNP" or "mutation" or "polymorphism" or "variation" or "variants") and ("digestive tract neoplasms" or "gastrointestinal tract neoplasms" or "cancer of digestive tract" or "cancer of gastrointestinal tract" or " digestive tract cancer" or "gastrointestinal tract cancer") and ("hypoxia inducible factor-1α" or "HIF-1A" or "HIF-1α"). We also performed a manual search to find other potential articles.

Selection criteria and data extraction

In our meta-analysis, included studies had to meet all the following criteria: (a) the study design must be a clinical cohort or case-control study; (b) the study must be related to the relationships between *HIF-1A* Pro582Ser polymorphism and the risk of digestive tract cancers; (c) all patients diagnosed with digestive tract cancers must be confirmed by histopathologic examination; (d) the study must provide sufficient information about genotype frequencies; and (e) the genotype distribution of the controls should conform to Hardy-Weinberg equilibrium (HWE). If the study could not meet the inclusion criteria, it would be excluded. The most recent or the largest sample size publication was included when the authors published several studies using the same subjects.

Using to a standardized form, relevant data were systematically extracted from all included studies by two research. The standardized form included the following items: language of publication, publication year of article, the first author's surname, geographical location, design of study, sample size, the source of the subjects, allele and genotype frequencies, genotyping method of SNP, evidence of HWE in controls, etc.

Quality assessment

We evaluated the methodological quality of the studies included according to the Newcastle-Ottawa Scale (NOS) criteria (Stang, 2010). The NOS criteria included three aspects: (1) subject selection: 0-4 scores; (2) comparability of subject: 0-2 scores; (3) clinical outcome: 0-3 scores. NOS score ranged from 0 to 9; and score ≥ 7 indicate a good quality.

Statistical analysis

We performed the meta-analysis by using the STATA 12.0 software (Stata Corp, College Station, TX, USA). The risk ratios (RRs) and their 95% confidence intervals (CIs) were estimated under 5 genetic models: allele model (C allele versus T allele), dominant model (CC + CT versus TT), recessive model (CC versus CT + TT), homozygous model (CC versus TT), and heterozygous model (CC versus CT). The Z test was used to estimate the statistical significance of RRs. Genotype frequencies of controls were tested for HWE using the χ^2 test for each study included in the meta-analysis. Power calculations were done by PS Power and Sample Size Calculations (Dupont and Plummer, 1998). The Cochran's Q-statistic and I^2 test were used to evaluate the potential heterogeneity between studies (Jackson et al., 2012). If Q-test shows a $P < 0.05$ or I^2 test exhibits > 50% which indicates significant heterogeneity, the random-effect model was conducted, or the fixed-effects model was used (Zintzaras and Ioannidis, 2005). We also performed subgroup analysis to explore potential sources of heterogeneity. Begger's funnel plots and Egger's linear regression test were conducted to investigate publication bias (Peters et al., 2006). All tests were 2-sided and $P < 0.05$ was considered to represent a statistically significant difference.

RESULTS

Characteristics of included studies

A total of 74 articles relevant to the searched key words were initially identified. Of these articles, 25 were excluded after a review of their titles and abstracts; then, full texts and data integrity were reviewed, and another 43 papers were excluded. Finally, 6 case-control studies met our inclusion criteria for this meta-analysis (Kuwai et al., 2004; Ling et al., 2005; Fransen et al., 2006; Li et al., 2009; Knechtel et al., 2010; Kang et al., 2011). The publication year of studies involved ranged from 2004 to 2011. The flow chart of the study selection process is shown in Figure 1. The distribution of the number of topic-related literatures in the electronic database during the last decade was shown in Figure 2. A total of 3685 subjects were involved in this meta-analysis, including 911 digestive tract cancer patients and 2774 healthy controls. All the power for the sample size of included studies were higher than 0.70. There were 4 studies conducted in Asian populations and 2 in Caucasian populations. All of the studies used population-based cases except 1 study of Austrian populations that used hospital-based controls. Of the 6 studies, 3 used blood samples for genotyping and the other 3 used tissue samples. A classical polymerase chain reaction-restriction fragment length polymorphism (PCR-RELP) method was performed in 4 of 6 studies. For the other 2 studies, one used a TaqMan assay and

the other used a MicroArray method. No study cohort deviated from the HWE (all P > 0.05). NOS scores of all included studies were higher than 6 (moderate-high quality). Characteristics and methodological quality of the included studies are summarized in Table 1.

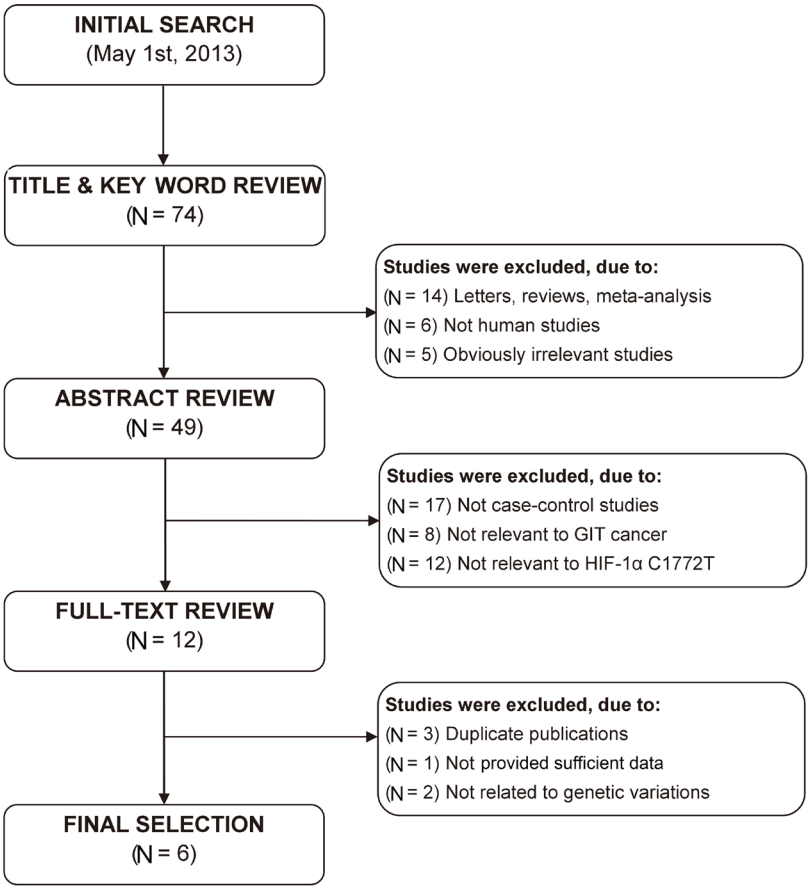

Figure 1. Flow chart of literature search and study selection. Six studies were included in this meta-analysis.

Meta-analysis results

The random effects model was used to pool the results due to significant heterogeneity that existed between studies. Our meta-analysis results revealed that *HIF1A* Pro582Ser polymorphism was associated with an increased risk of digestive tract cancer (C allele *vs* T allele: RR = 1.06, 95%CI = 1.02-1.09, P = 0.001; CC *vs* CT+TT: RR = 1.13, 95%CI = 1.01-1.25, P = 0.026). Subgroup analysis by ethnicity suggested that *HIF1A* Pro582Ser polymorphism might increase an individual's susceptibility to digestive tract cancer in Asian populations (C allele versus T allele: RR = 1.09, 95%CI = 1.05-1.12, P < 0.001; CC versus CT+TT: RR = 1.21, 95%CI = 1.13-1.28, P < 0.001). However, similar association was not observed in Caucasian populations (all P > 0.05) (Figure 3). Further subgroup analysis of cancer type showed that

HIF1A Pro582Ser polymorphism had significant associations with increased risk of gastric and colorectal cancers under the allele model (gastric cancer: RR = 1.10, 95%CI = 1.04-1.16, P = 0.001; colorectal cancer: RR = 1.05, 95%CI = 1.00-1.10, P = 0.041). Nevertheless, we found no associations in esophageal cancer (all P > 0.05). In the stratification analysis by NOS score, sample size, sample type and detection method, significant associations of *HIF1A* Pro582Ser polymorphism with increased risks of digestive tract cancers were also found in the majority subgroups. We found no evidence of obvious asymmetry in the Begger's funnel plots (Figure 4). Egger's test also did not display strong statistical evidence for publication bias (allele model: t = 0.73, P = 0.508; dominant model: t = -6.24, P = 0.003).

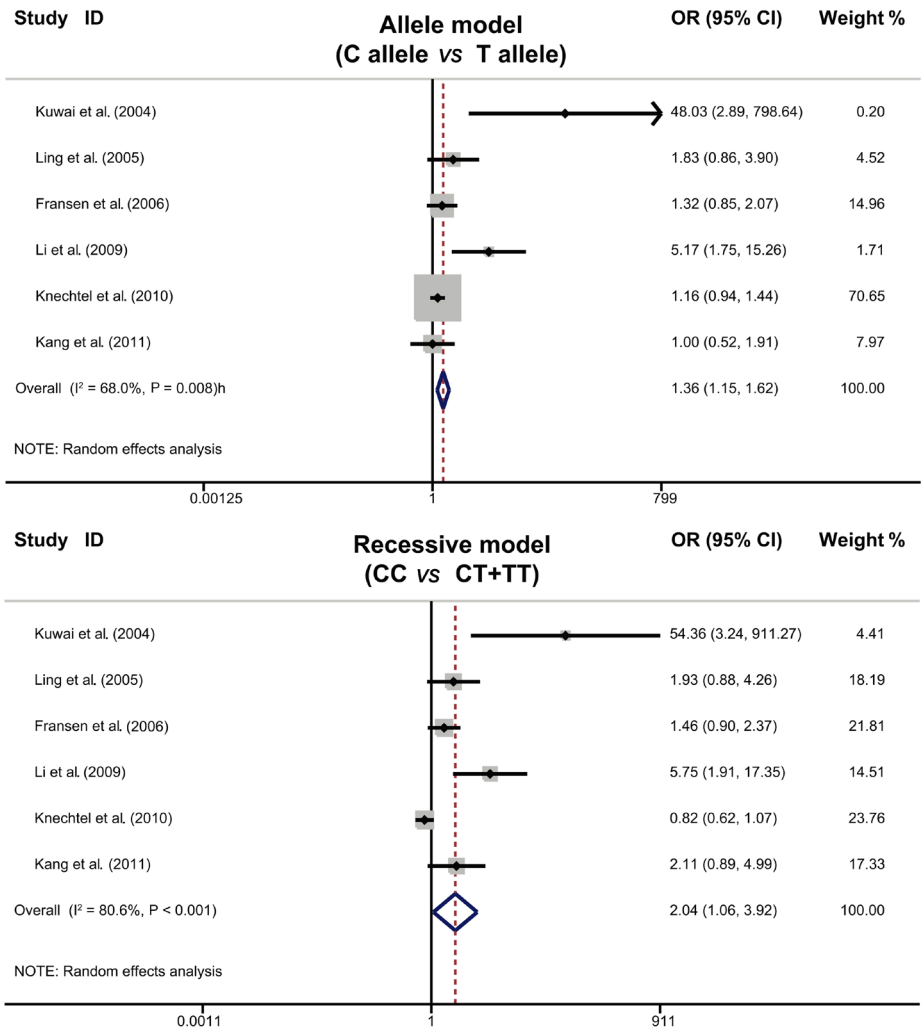

Figure 2. Forest plots for the associations between HIF-1α C1772T polymorphism and gastrointestinal tract cancer risk under the allele and recessive models.

Table 1. Characteristics and methodological quality of the studies included in this meta-analysis.

First author	Year	Country	Ethnicity	Number		Gender (M/F)		Age (years)		Source		Cancer type	Sample	Genotype method	Gene	SNP ID	Alias name	STREGE score
				Case	Control	Case	Control	Case	Control	Case	Control							
Kuwai et al.	2004	Japan	Asian	100	100	61/39	57/43	59.1 ± 8.67	56.0 ± 17.2	HB	PB	Colorectal cancer	Blood	PCR-RFLP	HIF-1α	rs11549465 (C/T)	C1772T	15/22
Ling et al.	2005	China	Asian	95	104	70/25	-	-	-	HB	PB	Esophageal cancer	Blood	PCR-RFLP	HIF-1α	rs11549465 (C/T)	C1772T	14/22
Fransen et al.	2006	Sweden	Caucasian	198	258	93/99	-	73 (25-93)	-	HB	PB	Colorectal cancer	Tissue	PCR-RFLP	HIF-1α	rs11549465 (C/T)	C1772T	16/22
Li et al.	2009	China	Asian	87	106	61/26	74/32	51.8 ± 12.3	52.3 ± 12.5	HB	PB	Gastric cancer	Blood	MicroArray	HIF-1α	rs11549465 (C/T)	C1772T	18/22
Knechtel et al.	2010	Austria	Caucasian	381	2156	223/158	947/1209	-	58.2 ± 17.6	HB	HB	Colorectal cancer	Tissue	TaqMan	HIF-1α	rs11549465 (C/T)	C1772T	17/22
Kang et al.	2011	Korea	Asian	50	50	27/23	27/23	68.0 ± 12.0	68.0 ± 11.0	HB	PB	Colorectal cancer	Tissue	PCR-RFLP	HIF-1α	rs11549465 (C/T)	C1772T	20/22

M = male; F = female; PB = population-based; HB = hospital-based; SNP = single nucleotide polymorphism; GIT = gastrointestinal tract; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

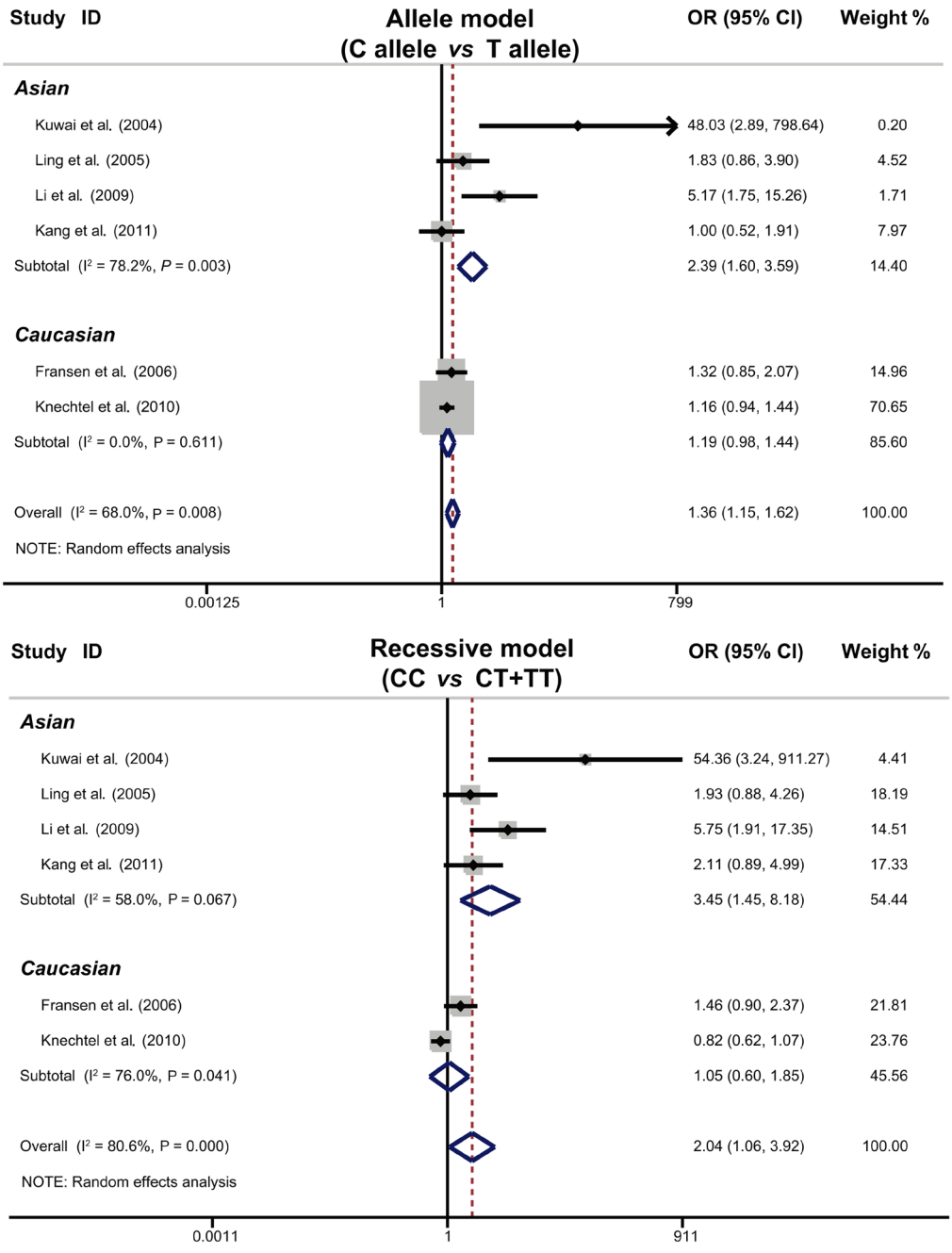

Figure 3. Subgroup analysis by ethnicity of odds ratio for the associations between HIF-1α C1772T polymorphism and gastrointestinal tract cancer risk under the allele and recessive models.

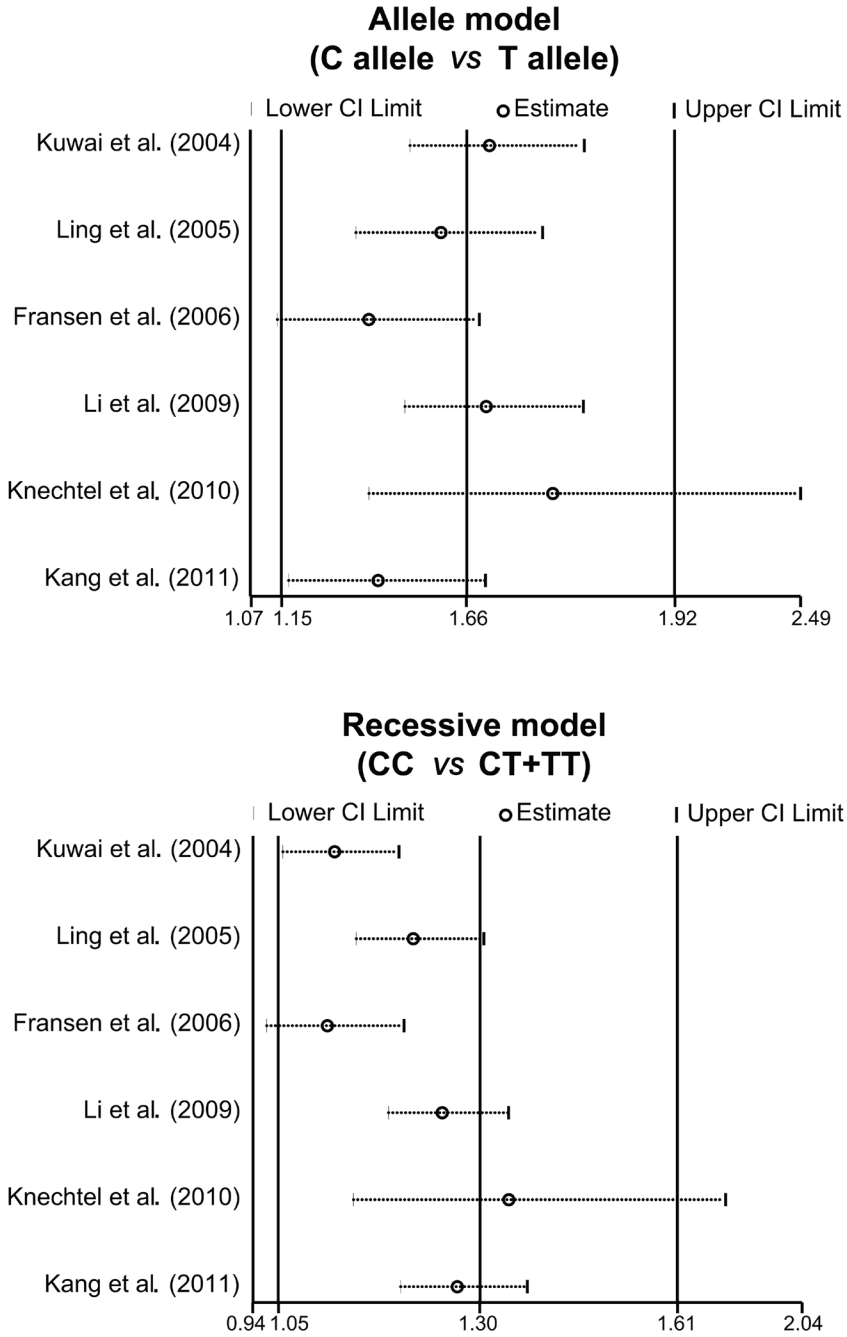

Figure 4. Sensitivity analysis of odds ratio for the associations between HIF-1α C1772T polymorphism and gastrointestinal tract cancer risk under the allele and recessive models. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95%CI.

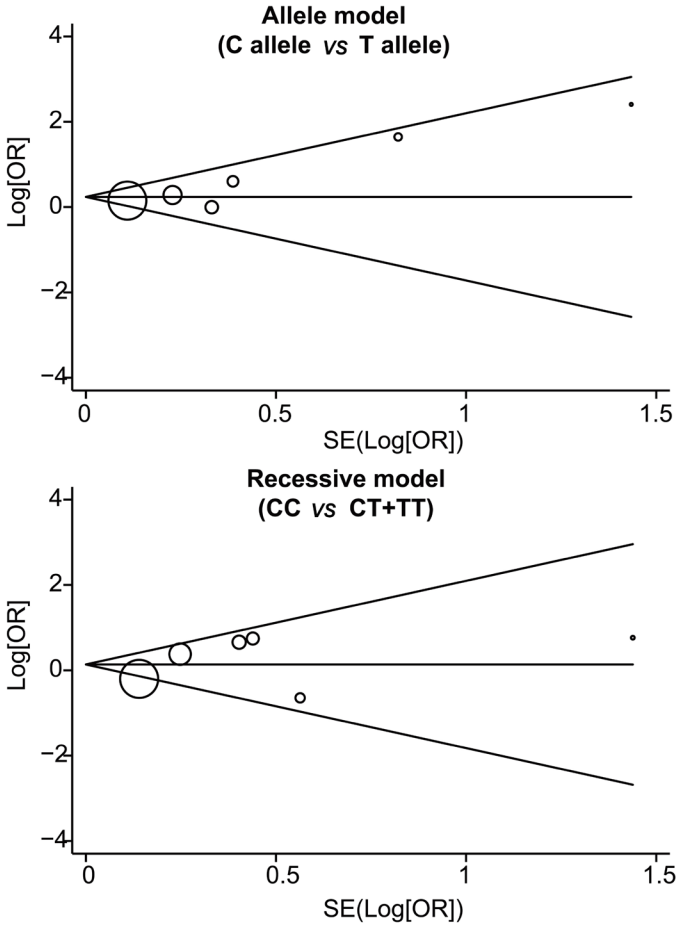

Figure 5. Begger's funnel plot of the meta-analysis of HIF-1α C1772T polymorphism and gastrointestinal tract cancer risk under the allele and recessive models. Each point represents a separate study for the indicated association. Log[OR], natural logarithm of odds ratio. Horizontal line, mean magnitude of the effect.

DISCUSSION

HIF-1, a hetero-dimeric protein, plays an essential role in modulating the regulation of hundreds of genes according to the cellular O_2 concentration. Additionally, HIF-1A has been demonstrated to involve in mediating transcription of the gene for vascular endothelial growth factor (VEGF) (Wang and Si, 2013). As one of the subunit of HIF-1, HIF-1A is ubiquitinated and degraded in normoxia, but stabilized in hypoxia (Marxsen et al., 2004). It has been evidenced that HIF-1A functions as a physiologic mediator of cellular responses to hypoxia in both normal and malignant tissues (Hu et al., 2006; Ahn et al., 2013). Semenza et al. (2013) have confirmed that if the function of HIF-1A is changed by mutations, the tissue became vulnerable to hypoxia which may correlate with tumor invasion and metastasis, and

thereby the genetic polymorphisms of *HIF-1A* may have an impact on the incidence of cancers. Several subsequent studies have indicated that common genetic polymorphisms in *HIF-1A* gene is involved in pre-malignant phases and developmental steps of breast cancer, renal cell carcinoma, prostate cancer, and cervical cancer (Ling et al., 2005; Konac et al., 2007; Kim et al., 2008; Foley et al., 2009). Recently, a growing number of evidences have shown that *HIF-1A* gene mutations might play important roles in the development of digestive tract cancers (Cummins et al., 2008). Fransen et al. (2006) found that *HIF1A* Pro582Ser polymorphism might regulate the invasiveness of colon cancer cells by altering the expression of genes encoding intermediate filaments, extracellular matrix components, and proteases. Wang et al. (2011) showed that human esophageal cancer expresses a dominant-negative mutant *HIF-1A*. Therefore, it is biologically plausible that genetic variations of the *HIF-1A* gene may modulate digestive tract carcinogenesis risk.

In the present meta-analysis, we evaluated the relationships between *HIF1A* Pro582Ser polymorphism and the risk of digestive tract cancers. Finally, 6 independent case-control studies were included. Our meta-analysis results suggested that *HIF1A* Pro582Ser polymorphism was associated with an increased risk of digestive tract cancer, suggesting that *HIF1A* gene polymorphism (Pro582Ser) may be a risk factor for digestive tract cancers. Although the exact function of *HIF-1A* in the development of digestive tract cancers is not clear yet, a potential explanation might be that *HIF-1A* gene mutations changed its expression level and functions as a physiologic mediator of cellular responses to hypoxia in malignant tissues (Ahn et al., 2013). Since heterogeneity obviously existed, we performed stratified analyses based on ethnicity, cancer type, NOS score, sample size, sample type and detection method. Subgroup analysis by ethnicity revealed that *HIF1A* Pro582Ser polymorphism might increase the risk of digestive tract cancers in Asian populations, while no associations were found in Caucasian populations. One possible reason for ethnic differences might be that *HIF-1A* genetic variations could be related to the changes in the adaptation of tumor cells to hypoxia, and thereby may possibly explain the interindividual differences in the susceptibility to digestive tract cancer (Zhou et al., 2006). Although the exact mechanism of ethnic differences is not fully understood, another reason might be that ethnicity is an important demographic variable contributing to the development and progression of digestive tract cancers. We also observed that *HIF1A* Pro582Ser polymorphism had positive associations with an increased risk of gastric and colorectal cancers, but not in and esophageal cancer. These controversial results may be due to relatively small sample size. All in all, our findings were consistent with previous studies that *HIF1A* Pro582Ser polymorphism may alter the risk of developing digestive tract cancers, suggesting that this polymorphisms may be useful as a biomarker for early diagnosis of digestive tract cancers.

Nevertheless, this meta-analysis also had some limitations. Firstly, our results may not provide sufficient statistical power to estimate the correlation between the *HIF1A* genetic polymorphisms and the risk of digestive tract cancers due to relatively small sample size. Secondly, meta-analysis is a retrospective study that may lead to subject selection bias, and thereby affecting the reliability of our results. Thirdly, our meta-analysis failed to obtain original data from the included studies, which may limit further evaluation of potential roles of *HIF1A* genetic polymorphisms in digestive tract cancers. Importantly, the inclusion criteria of cases and controls were not well defined in all included studies, which might also influence our results.

In conclusion, our findings suggest that *HIF1A* Pro582Ser polymorphism may contribute to the risk of digestive tract cancers, especially in Asian populations. Thus, *HIF1A* Pro582Ser polymorphism may be used as a biomarker for early diagnosis of digestive tract cancers. However, due to the limitations mentioned above, further detailed studies are still required to confirm our findings.

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