Cytochrome P450 1A1 gene polymorphisms and digestive tract cancer susceptibility: a meta-analysis

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Abstract

Cytochrome P450 1A1 (CYP1A1) is a phase I enzyme that regulates the metabolism of environmental carcinogens and alter the susceptibility to various cancers. Many studies have investigated the association between the CYP1A1 MspI and Ile462Val polymorphisms and digestive tract cancer (DTC) risk in different groups of populations, but their results were inconsistent. The PubMed and Embase Database were searched for case–control studies published up to 30th September, 2015. Data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the relationship. Totally, 39 case–control studies (9094 cases and 12,487 controls) were included. The G allele in Ile/Val polymorphism was significantly associated with elevated DTC risk with per-allele OR of 1.24 (95% CI = 1.09–1.41, P = 0.001). Similar results were also detected under the other genetic models. Evidence was only found to support an association between MspI polymorphism and DTC in the subgroups of caucasian and mixed individuals, but not in the whole population (the dominant model: OR = 1.19, 95% CI = 0.94–1.91, P = 0.146). In conclusion, our results suggest that the CYP1A1 polymorphisms are potential risk factors for DTC. And large sample size and well-designed studies with detailed clinical information are needed to more precisely evaluate our founding.

Keywords: CYP1A1 • digestive tract cancer • polymorphism • meta-analysis

Introduction

Digestive tract cancers (DTCs), well known as the most common malignant tumours globally, include oesophageal, gastric and colorectal cancers [1–4]. Data from Global Cancer Statistics, 2012 [1] suggest that DTC has contributed to an enormous burden on society today. Actually, colorectal cancer is confirmed as the third most frequently diagnosed cancer in males and the second in females. Both the incidence rates of gastric cancer and oesophageal cancer keep the highest in Eastern Asia. Despite of the updating advances in surgery and chemotherapy, DTC remains the high-mortality disease, even the leading cause of cancer-related death [4]. As generally accepted, the mechanism of the digestive tract tumorigenesis is a comprehensive combination of multiple risk factors including environmental conditions, dietary habits and genetic predispositions [5–7]. Among these, metabolism-associated genetic susceptibility has become an important focus. As a member of the CYP1 family, Cytochrome P4501A1 (CYP1A1) regulates the metabolism of many endogenous and exogenous carcinogens [3, 8, 9]. CYP1A1, as its protein-coding gene, is located on Chr15q22–q14, encoding aryl hydrocarbon hydroxylase. Aryl hydrocarbon hydroxylase is active in metabolizing some pro-carcinogens, particularly the polycyclic aromatic hydrocarbons (PAHs), into intermediates. The intermediate substitues may contribute to carcinogenesis eventually if bind to DNA and form adducts [10–15].

CYP1A1 gene consists of many single nucleotide polymorphisms (SNPs). These diverse variants could break the initial physiological equilibrium between activation and detoxification of metabolic carcinogens by adjusting the quantity and function of such enzyme. The two functional polymorphisms in CYP1A1 gene, MspI (T →C, occurring in the noncoding 3'-flanking region, rs4646903) and Ile462Val (A→G, found at codon 462 in exon 7,
rs1048943), may associate with the risk of DTC by the mechanism above [9].

Many studies have been carried out to examine the association between the two polymorphisms of CYP1A1 and risk of many cancers [9]. However, because of different subject selections, the results were inconsistent. In addition, the relationship for DTC risk has been only explored in Chinese population by Liu et al. [14]. Hence, to further explore that association in the whole of humanity and clarify the former results, we conduct this meta-analysis with more eligible studies.

Materials and methods

Literature search strategy

The published case–control studies about the associations between the CYP1A1 polymorphisms and DTC were searched manually on PubMed and Embase Database up to 30th September, 2015. The search was limited to English language papers, using the key words ‘(CYP1A1 or P4501A1 or MspI or exon7 or Ile/Val or cytochrome)’ and ‘(polymorphism)’ and ‘(colorectal cancer or gastric cancer or oesophageal cancer)’. And the following criteria were established: (i) case–control studies, (ii) exploring the association between MspI or Ile/Val polymorphism and DTC, (iii) DTC confirmed histologically or pathologically, (iv) providing sufficient data to calculate the odds ratio (OR) with its 95% confidence interval (CI) and P-value. The exclusion criteria were as follows: (i) a case report or a review, (ii) no sufficient genotype frequency, (iii) a duplicated publication [10–15].

Data extraction

Based on the inclusion criteria listed above, two authors independently extracted data from all qualified publications. Controversies were eliminated through discussion with another investigator. Following data were collected: first author’s name, year of publication, cancer type, country and ethnicity of population, genotyping method, source of controls, number of cases and controls with different genotypes, adjusted OR and 95% CI and adjustment of variables if available and Hardy–Weinberg equilibrium (HWE) [14, 15] (See in Tables 1 and 2).

Statistical analysis

The HWE in control group was assessed by Pearson’s goodness-of-fit chi-square test and P < 0.05 was considered as significant disequilibrium. OR and 95% CI were calculated for CYP1A1 MspI/Ile462Val polymorphisms and DTC risk in each study. The pooled OR was also determined by the Z-test (if P < 0.05, then considered as significant). Stratified analyses by cancer type, source of controls, ethnicity, sample size and genotyping method were performed [9–15]. The influence of study size of each evaluated publication on the results was assessed by the weight.

Heterogeneity in our meta-analysis was assessed by the chi-square-based Q-test and /P/. A fixed-effects model (the Mantel–Haenszel method) was applied if P > 0.05, which indicated no or little heterogeneity among eligible studies. Otherwise, the random-effects model (Der Simonian and Laird method) was used. Galbraith graph was performed to explore the source of heterogeneity. Sensitivity analysis was tested to assess the stability of our results. The funnel plot was performed for potential publication bias. Funnel plot asymmetry was statistically assessed by Egger’s linear regression test (publication bias exists if P < 0.05). All statistical analyses were carried out by Stata software (version 12.0, StataCorp LP, College Station, TX, USA) [13–15].

Results

Characteristics of studies

Totally 37 publications [16–52] containing 39 studies (6 pieces not consistent with HWE were also included), which investigated the relationship between CYP1A1 (MspI rs4646903 or Ile/Val rs1048943) polymorphisms and DTC risk, were included in the present meta-analysis. The literature selection process was illustrated in Figure 1. All the eligible studies involved 9094 DTC cases and 12,487 controls. 13 studies (2 oesophageal cancer studies, 5 gastric cancer studies and 6 colorectal cancer studies) were identified for the MspI polymorphism, including a total of 1717 cases and 2046 controls. And for the Ile/Val polymorphism, 26 studies (11 oesophageal cancer studies, 5 gastric cancer studies and 10 colorectal cancer studies) were retrieved, covering a total of 7377 cases and 10,441 controls. More detailed characteristics about population source, ethnicity distribution, sample size, genotyping method and adjusted OR and 95% CI and adjustment of variables if available can be seen in Tables 1 and 2.

Association of MspI with digestive tract cancer

Overall, no sufficient evidence was found to support an association between increased susceptibility of DTC and MspI (rs4646903) polymorphism in all genetic models when all the eligible case–control studies were pooled together. Moreover, the adjusted pooled result was consistent with the crude one (data shown in Table 3 and Fig. 2A for the dominant model). In subgroup analysis by cancer type, a significant association was only found between MspI polymorphism and elevated colorectal cancer risk (the allele contrast: OR = 1.82, 95% CI = 1.16–2.86, P = 0.010). However, because of unavailable adjusted data on colorectal cancer, this positive result could not be validated (Fig. S1). Stratifying for ethnicity, an increased susceptibility was found in individuals with CC genotype among Caucasians and mixed population (the codominant model: OR = 1.39, 95% CI = 1.06–1.82, P = 0.018; OR = 5.7, 95% CI = 1.37–23.60, P = 0.016 respectively). However, no evidence was observed to prove that among Asians. In the stratified analysis by the source of controls, sample size or genotyping method, some statistical correlations were observed in the group of ‘population with sources unreported (NR)’, ‘size <300’ and ‘PCR-RFLP method’ respectively (data shown in Table S1).

Association of Ile/Val with digestive tract cancer

The G allele was significantly associated with elevated DTCs risk with per-allele OR of 1.24 (95% CI = 1.09–1.41, P = 0.001). Similar
Table 1 Characteristics of CYP1A1 MspI polymorphism included in the meta-analysis

| Year  | Ethnicity | Source | Case Genotypes N | Control Genotypes N | Method | Sample size | P for HWE | OR 95% CI* | Adjustment of variables |
|-------|-----------|--------|------------------|---------------------|--------|-------------|-----------|------------|------------------------|
|       |           |        | TT/T/T/T/T/T/T/T | CC/T/T/T/T/T/T/T |        |             |           |            |            |                        |
| Jain et al. | 2007   | Asian | PB 171 59 83 19 | 201 79 99 23 | PCR | ≥300 | 0.629 | 1.1 (0.71–1.7) 1.1 (0.55–2.2) | Age, gender, smoking, drinking |
| Malik et al. | 2010   | Asian | PB 135 76 52 7  | 195 95 88 12 | MLPA | ≥300 | 0.361 | 0.72 (0.45–1.14) 0.70 (0.26–1.87) | Age, gender |
| Ma et al. | 2006    | Asian | PB 60 26 27 7  | 57 26 28 3 | PCR-RFLP | <300 | 0.423 | – – – | – – |
| Malik et al. | 2009 | Asian | HB 108 60 46 2 | 195 95 88 12 | PCR | ≥300 | 0.361 | 0.84 (0.52–1.37) 0.34 (0.07–1.60) | Age, gender |
| Luo et al. | 2011    | Asian | PB 123 38 61 24 | 129 47 54 28 | PCR-RFLP | <300 | 0.261 | – – – | – – |
| Ghoshal et al. | 2014 | Asian | PB 88 41 36 11 | 170 78 80 12 | PCR-RFLP | <300 | 0.370 | – – – | – – |
| Darszy et al. | 2011 | Caucasian | PB 11 9 0 2 | 56 54 1 1 | PCR-RFLP | <300 | **0.000** | 0.87 (0.5–1.5) 1.8 (0.7–4.4) | Age, gender |
| Sivasman et al. | 1994 | Mixed | PB 43 23 10 10 | 47 23 22 2 | PCR-RFLP | <300 | 0.508 | – – – | – – |
| Ye et al. | 2002     | Caucasian | NR 41 35 6 0 | 82 73 9 0 | PCR-RFLP | <300 | 0.871 | – – – | – – |
| Tabeth et al. | 2006 | Caucasian | NR 118 94 20 | 100 91 9 0 | PCR-RFLP | <300 | 0.895 | – – – | – – |
| Darszy et al. | 2011 | Caucasian | PB 46 42 2 | 56 54 1 | PCR-RFLP | <300 | **0.000** | – – – | – – |
| Saeed et al. | 2013    | Asian | HB 94 70 21 3 | 79 73 6 0 | PCR-RFLP | <300 | 0.940 | – – – | – – |
| Rudolph et al. | 2011 | German | PB 679 539 134 6 | 679 564 102 13 | KASPar assays | ≥300 | **0.007** | – – – | – – |

Significance of bold value: P < 0.05 for HWE is considered as significant disequilibrium.

*Adjusted. EC: oesophageal cancer; GC: gastric cancer; CC: colorectal cancer; HB: Hospital based; PB: Population based; NR: no record; HWE: Hardy–Weinberg equilibrium; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR–ASO: PCR–allele specific oligonucleotide.
Table 2 Characteristics of *CYP1A1* Ile462Val polymorphism included in the meta-analysis

| Study        | Year | Ethnicity | Source | N   | Genotypes | Method | Sample size | OR 95% CI* | Adjustment of variables |
|--------------|------|-----------|--------|-----|-----------|--------|-------------|------------|-------------------------|
|              |      |           |        |     | AA AG GG  |        |             |            |                          |
|              |      |           |        |     | GA/AA GG/AA |       |             |            |                          |
| Morita et al. | 1997 | Asian     | HB     | 53  | 32 20 1  | PCR    | <300        | 0.355      | – – –                   |
| Nimura et al. | 1997 | Asian     | HB     | 89  | 50 26 13 | PTC-150 | <300        | 0.518      | – – –                   |
| Hori et al.   | 1997 | Asian     | NR     | 101 | 62 37 2  | non-Ri-SSCP | >300    | 0.752      | – – –                   |
| Lieshout et al. | 1999 | Caucasian | NR     | 34  | 26 8 0   | PCR-RFLP | >300        | 0.665      | – – –                   |
| Wang et al.   | 2002 | Asian     | HB     | 127 | 25 58 44 | PCR    | <300        | 0.915      | – – –                   |
| Wu et al.     | 2002 | Asian     | HB     | 146 | 68 62 16 | PCR-RFLP | >300        | 0.762      | 1.34 (0.86-2.07) 2.48 (1.15-5.34) Age, education, ethnicity, smoking, drinking, and areca consumption |
| Wang et al.   | 2003 | Asian     | PB     | 62  | 30 28 4  | PCR-RFLP | >300        | 0.870      | – – –                   |
| Wang et al.   | 2004 | Asian     | HB     | 127 | 21 56 50 | PCR    | <300        | 0.915      | 1.7 (0.83-3.58) 3.3 (1.49-7.61) Tobacco smoking, alcohol drinking, FHEC |
| Abbas et al.  | 2004 | Caucasian | PB     | 79  | 61 9 9   | PCR-RFLP | >300        | 0.000      | 2.63 (0.84-8.28) – Age, sex |
| Wang et al.   | 2012 | Asian     | PB     | 565 | 304 225 36 | PCR | >300        | 0.981      | – – –                   |
| Yun et al.    | 2013 | Asian     | PB     | 157 | 73 72 12 | PCR-RFLP | >300        | 0.348      | 2.05 (1.19-3.54) 1.12 (0.41-3.04) Age, gender, smoking, drinking and FHC |
| Suzuki et al. | 2004 | Asian     | HB     | 144 | 84 51 9  | PCR    | >300        | 0.865      | – – –                   |
| Li et al.     | 2005 | Asian     | HB     | 102 | 53 27 22 | PCR    | >300        | 0.910      | 0.59 (0.26-1.34) 5.91 (1.28-27.24) Age, sex, education, job, drinking, smoking |
| Study          | Year | Ethnicity | Source | Case | Genotypes | Control | Genotypes | Method | Sample size | P for HWE | OR 95% CI* | Adjustment of variables |
|---------------|------|-----------|--------|------|-----------|---------|-----------|--------|-------------|-----------|------------|-------------------------|
| Shen et al.   | 2005 | Asian     | PB     | 112  | 70 36 6  | 676     | 412 226 38 | PCR-RFLP | ≥300 | 0.639 | 0.9 (0.5–1.4) | 0.7 (0.2–1.8) | Age, gender, living areas, FHC, drinking |
| Agudo et al.  | 2006 | Caucasian | PB     | 243  | 229 13 1  | 906     | 874 62 0   | SNP500cd | ≥300 | 0.578 | 0.90 (0.48–1.68) | – | Age, sex, centre, and date of blood extraction |
| Kobayashi et al. | 2009 | Asian     | HB     | 141  | 91 44 6  | 286     | 162 109 15 | MassARRAY system | ≥300 | 0.832 | 0.79 (0.40–1.57) | 2.01 (0.45–9.48) | H. p status, smoking, drink, FHGC, BMI, total food intake, JA membership |

**CC**

| Sivanam et al. | 1994 | Mixed     | PB     | 43   | 32 9 2  | 47      | 33 14 0     | PCR-RFLP | ≥300 | 0.487 | – | – | – |
| Kiss et al.    | 2000 | Mixed     | PB     | 163  | 119 41 3 | 163     | 132 31 0    | PCR-ASO | ≥300 | 0.407 | – | – | – |
| Slattery et al.| 2004 | Mixed     | HB     | 1791 | 1632 148 11 | 2180 | 1997 171 12 | PCR | ≥300 | **0.001** | 1.0 (0.7, 1.4) | 1.5 (0.5, 4.9) | Age, sex |
| Little et al.  | 2006 | Caucasian | PB     | 251  | 235 16 0  | 396     | 372 24 0    | PCR | ≥300 | 0.824 | 1.31 (0.59–2.91) | – | Age, sex, FHCC, aspirin use, use of other NSAIDs and physical activity |
| Yeh et al.     | 2007 | Asian     | HB     | 717  | 400 228 89 | 729     | 410 265 53  | PCR-RFLP | ≥300 | 0.558 | – | – | – |
| Yoshida et al. | 2007 | Asian     | NR     | 66   | 34 27 5  | 121     | 79 37 5     | PCR-RFLP | ≥300 | 0.968 | 1.54 (0.78–3.04) | 1.99 (0.41–9.63) | Age, gender, smoking habit |
| Pereira Serafin et al. | 2008 | Mixed | PB     | 114  | 14 97 3  | 114     | 81 33 0     | PCR-RFLP | ≥300 | 0.196 | – | – | – |
results were also detected under other genetic models and in our adjusted pooled result (data shown in Table 3 and Fig. 2B, the dominant model). In the further subgroup analysis based on tumour type, the statistics strongly supported the significant relationship between Ile/Val and the chance of suffering oesophageal and colorectal cancer (the allele contrast: OR = 1.36, 95% CI = 1.19–1.56, P = 0.000, OR = 1.27, 95% CI = 1.01–1.61, P = 0.043 respectively). But the positive result was only observed in oesophagus cancer from the adjusted result partially together (Fig. S2). A significant association was also observed in Asians (the codominant model: OR = 1.62, 95% CI = 1.26–2.09, P = 0.000), but not in caucasians or mixed individuals. Stratified by the source of controls, significant association was observed both in HB and NR group. Stratified by sample size and genotyping method, associations were found in most groups. Detailed analyses of the genetic variant are provided in Table S2.

Heterogeneity analyses

For MspI polymorphism, moderate heterogeneity was detected (e.g. the dominant model: \( I^2 = 47.1\% \), \( P_h = 0.030 \)). As shown in Tables S3 and S4, subgroup analyses stratified by cancer type, ethnicity, source of controls, sample size and genotyping method could not explain the source of heterogeneity at length. Hence, to further explore the heterogeneity source, we performed Galbraith graph. The study conducted by Saeed et al. [24] may be the main source of heterogeneity (data shown in Fig. 3A). Removing this study, the result of the meta-analysis did not change essentially (e.g. the dominant mode: OR = 1.10, 95% CI = 0.90–1.35, \( P = 0.336 \)), but its heterogeneity decreased significantly (the dominant model: \( I^2 = 28.6\% \), \( P_h = 0.046 \) (Fig. S3)). Similar results were observed in other genetic models. In the same way, we found the source of heterogeneity in Figure 3B for Ile/Val polymorphism. When we removed the study conducted by Pereira Serafim et al. [47], the heterogeneity decreased sharply, while the results remained qualitatively (the dominant mode: OR = 1.14, 95% CI = 1.03–1.27, \( P = 0.016 \); \( I^2 = 34.8\% \), \( P_h = 0.046 \) (Fig. S4)).

Sensitivity analyses

The corresponding pooled ORs were not qualitatively influenced when any particular study had been removed from the meta-analysis (including the studies not conforming to HWE) for the two polymorphisms respectively (see in Fig. 4A and B). It confirmed that the results of the present meta-analysis are reliable and stable.

Publication Bias

Begg’s funnel plot and Egger’s test were performed to diagnose the publication bias of papers. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models for MspI (e.g. the dominant model in Fig. 5A). Statistically the results
of both tests showed no publication bias (Begg’s test \( P = 0.127 \), Egger’s test \( P = 0.136 \), \( t = 1.61 \), 95% CI = −0.46 to 2.97). Regarding \( \text{Ile/Val} \), no publication bias was detected as well in the dominant model (Begg’s test \( P = 0.071 \), Egger’s test \( P = 0.085 \), \( t = 1.80 \), 95% CI = −0.23 to 3.30) (Fig. 5B).

**Discussion**

CYP1A, the subfamily of Cytochrome P450, is an important phase I metabolic enzyme. As a key subtype of CYP1A, CYP1A1 is distributed widely in the kidney, lung, stomach, colon, larynx, placenta, skin, and digestive tract. Understanding the genetic polymorphisms of CYP1A1 is essential for its functional study.

### Table 3 The overall results for MspI and Ile462Val polymorphisms in CYP1A1 and digestive tract cancer risk

|             | OR  | 95% CI | \( P^* \) | \( I^2 \) (%) | \( Ph^* \) | OR*  | 95% CI* | \( P^* \) | \( I^2 \) (%) | \( Ph^* \) |
|-------------|-----|--------|-----------|--------------|------------|-----|---------|-----------|--------------|------------|
| **MspI**    |     |        |           |              |            |     |         |           |              |            |
| Allele      |     |        |           |              |            |     |         |           |              |            |
| C/T         | 1.24| 0.99–1.54| 0.058     | 59.60%       | 0.003      | –   | –       | –         |              | –          |
| Dominant    | CC+CT/TT | 1.19| 0.94–1.91| 0.146     | 47.10%     | 0.030| –       | –         |              | –          |
| Resessive   | CC/CT+TT | 1.32| 0.80–2.17| 0.283     | 49.50%     | 0.026| –       | –         |              | –          |
| Codominant  | CT/TT  | 1.12| 0.88–1.42| 0.341     | 42.00%     | 0.055| 0.88    | 0.69–1.12 | 0.296       | 0.0%       | 0.624   |
|             | CC/TT  | 1.30| 0.80–1.21| 0.296     | 43.50%     | 0.053| 1.01    | 0.64–1.62 | 0.937       | 24.4%      | 0.265   |
| **Ile462Val** |     |        |           |              |            |     |         |           |              |            |
| Allele      |     |        |           |              |            |     |         |           |              |            |
| G/A         | 1.24| 1.09–1.41| \( \textbf{0.001} \) | 69.40%   | 0.000      | –   | –       | –         |              | –          |
| Dominant    | GA+GG/AA | 1.27| 1.07–1.50| \( \textbf{0.006} \) | 74.40%   | 0.000| –       | –         |              | –          |
| Resessive   | GG/AA+GA | 1.49| 1.21–1.82| \( \textbf{0.000} \) | 22.30%   | 0.157| –       | –         |              | –          |
| Codominant  | GA/AA  | 1.21| 1.02–1.45| \( \textbf{0.032} \) | 74.20%   | 0.000| 1.03    | 0.92–1.67 | 0.593       | 37.9%      | 0.074   |
|             | GG/AA  | 1.58| 1.24–2.00| \( \textbf{0.000} \) | 35.40%   | 0.042| 1.49    | 1.23–1.96 | \( \textbf{0.005} \) | 30.1%      | 0.160   |

Significance of bold value: \( P < 0.05 \) means a significant relationship between the polymorphism and digestive tract cancer risk.

*Adjusted. \( Ph \): \( P \)-value of Q-test for heterogeneity identification; \( I^2 \) index: a quantitative measurement which indicates the proportion of total variation in study estimates that is due to between-study heterogeneity.
lymphocyte, brain and other tissues [14]. What’s more, recent studies have demonstrated that it involves the metabolism of some exogenous carcinogens such as PAHs. CYP1A1 gene can promote the carcinogenic process by converting PAHs into their ultimate DNA-binding forms [11].

MspI and Ile/Val, the main gene polymorphisms of CYP1A1, have been both verified associated with many kinds of cancers by large number of meta-analyses [9]. However, inconsistent results have been reported. To clarify this inconsistency, this meta-analysis was established. To our best knowledge, it is the first one to explore the association of CYP1A1 polymorphisms and DTC risk in the whole population. Correlation association between CYP1A1 Ile/Val polymorphism and DTC susceptibility were detected in our meta-analysis. While no evidence showed the association between CYP1A1 MspI polymorphism and DTC risk. The overall result is consistent with that of the meta-analysis performed by Liu et al. [14] which was designed only in Chinese population.

Stratified by cancer type, the MspI CC genotype carriers were confirmed with an increased susceptibility to colorectal cancer but not to esophageal or gastric cancer. While an A to G mutation in Ile/Val polymorphism increased the cancer risk in EC and CC groups. The results were partially inconsistent with Wu et al. [9]. In fact, the studies we included in the present meta-analysis were updated compared with Wu et al. And unhealthy eating habits could contribute to the digestive tract damage, such as excessive drinking. That is why different primary cancers of digestive tract may be caused by similar risk factors [13]. On the other hand, DTC includes so many kinds of malignant tumours that heterogeneities among

Fig. 2 (A) Forest plot of digestive cancer risk associated with MspI polymorphism (the dominant model CC + CT versus TT). (B) Forest plot of digestive cancer risk associated with Ile/Val polymorphism (the dominant model GA+GG versus AA).

Fig. 3 (A) Galbraith graph for MspI polymorphism (the dominant model CC + CT versus TT): the study conducted by Saeed et al. may be the main source of heterogeneity. (B) Galbraith graph for Ile/Val polymorphism (the dominant model GA+GG versus AA): the study conducted by Pereira Serafim et al. may be the main source of heterogeneity.
them will be found. One reason for the issue may be that the gene–
gene and gene–environment interactions mechanisms differ in
diverse digestive tract parts. To our common knowledge, some of
the digestive tract tumours have their specific risk factors. For
instance eating spicy and hot food can evaluate the risk of oesopha-
geval cancer, whereas diet with high fat and low fibre may enhance
the incidence of colorectal cancer. In addition, researchers have ver-
ified that *Helicobacter pylori* infection significantly increased suscep-
tibility to gastric cancer [5, 6, 13, 18]. In a word, the aetiological
factors sensitive to various types of DTCs are not all the same. In
the subgroup analysis by ethnicity, significant difference was
detected in caucasian and mixed group for *MspI* polymorphism. Interestingly, high corelarity was otherwise observed in Asian

Fig. 4 (A) Influence analysis of the summary odds ratio coefficients on the association between *MspI* polymorphism with digestive tract cancers risk (the dominant model CC + CT versus TT). Results were computed by omitting each study (left column) in turn. Bars, 95% CI. (B) Influence analysis of the summary odds ratio coefficients on the association between Ile/Val polymorphism with digestive tract cancers risk (the dominant model GA + GG versus AA). Results were computed by omitting each study (left column) in turn. Bars, 95% CI.

This think-provoking phenomenon may excellently reveal that genetic diversity exactly exists among various ethnicities across countrywide. Individuals, disturbing in different places of the world, will experience different environments, including climate, temperature and radiation [7] and will form diverse lifestyles especially a variety of eating habits. Both of the above will contribute to the genetic background discrepancy among ethnicities. In addition, we conduct two subgroup analyses for adjusted status (Yes or no) and adjusted status especially for smoking history (Yes or no) for Ile/Val polymorphism. The result in every subgroup is corresponding (Table S5), which verified the reliability of our results again. As the number of studies with adjusted data for *MspI* polymorphism is only 4, and moreover, only one study

Fig. 5 (A) Begg’s funnel plot for publication bias test for *MspI* polymorphism (the dominant model CC + CT versus TT). Each point represents a separate study for the indicated association. (B) Begg’s funnel plot for publication bias test Ile/Val polymorphism (the dominant model GA+GG versus AA). Each point represents a separate study for the indicated association.
provided adjusted data for smoking, we did not carry out the analyses for MspI polymorphism.

Some limitations and potential bias cannot be ignored in our meta-analysis. First, we centre on the heterogeneity. Moderate and high heterogeneity were detected among the studies for MspI and Ile/Val respectively. Through Galbraith graph, we found the study conducted by Saeed et al. [24] count for the main source of heterogeneity for MspI. For Ile/Val, the heterogeneity mainly came from study conducted by Pereira Serafim et al. [47]. Through reviewing the two papers, we found some reasons to explain that. In the former study, the population was from Saudi Arabia and the number of case and control group is 94/79. While in the later, the population was from Brazil and the number of case and control group is 114/114. In our point, both Saudi Arabia and Brazil have vast territories and long histories. Hence, maybe the ethnic origins are complex. And the lifestyles and customs may vary significantly across the two countries, respectively, which would contribute to great heterogeneity. What is more, the sample sizes of both studies are relatively smaller. Concluding from the results of subgroup analyses, the sample size, the source of controls and the genotyping method also influence the heterogeneity in a certain degree. Thus, more studies with large enough sample sizes and more detailed criteria are warranted. Lastly, published studies were included in our studies, whereas many other unpublished data were ignored. Therefore, potentially publication bias will exist in our study.

In summary, our meta-analysis revealed the significant association between the CYP1A1 Ile462Val polymorphism and increased digestive tract cancers risk. While no sufficient evidence was found to support the association between the CYP1A1 MspI polymorphism and DTC. In the subgroup analyses, the positive results were found in CC group, Caucasians and mixed individuals for MspI polymorphism. Our results suggest that the CYP1A1 polymorphisms are potential risk factors for DTC. Large sample size and well-designed studies with more clinical information like age, gender, smoking and drinking are needed to clarify our finding.

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Conflict of interest

The authors declare no competing financial interest.

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