Does CYP2E1 Rsal/PstI polymorphism confer head and neck carcinoma susceptibility?

A meta-analysis based on 43 studies

Xianlu Zhuo, MD<sup>a,b,c</sup>, Jue Song, MS<sup>b</sup>, Jian Liao, MD<sup>b</sup>, Wei Zhou, MD<sup>b</sup>, Huipeng Ye, MD<sup>b</sup>, Qi Li, MS<sup>b</sup>, Zhaolan Xiang, MS<sup>b</sup>, Xueyuan Zhang, MD<sup>a</sup>.

Abstract

Background: Previous reports showed that CYP2E1 Rsal/PstI polymorphism may be a risk factor for cancers. Published meta-analyses in 2010 and 2011, respectively, on the relationship of CYP2E1 Rsal/PstI polymorphisms with the susceptibility to head and neck carcinoma (HNC) have generated inconsistent results. Thus, this study aimed to conduct an updated meta-analysis involving published studies up to Nov 2015 to get a more confident result.

Methods: Eligible studies up to Nov 2015 were retrieved and screened. Data were extracted and a quantitative meta-analysis was conducted. Subgroup analyses on ethnicity, source of controls, sample size, genotyping method, smoking status, and drinking status were also performed.

Results: Forty-one publications including a total of 43 case-control studies were selected for analysis. The overall data under a homozygote comparison model indicated a significant association of CYP2E1 Rsal/PstI polymorphisms with HNC risk (c2c2 vs c1c1: odds ratio [OR] = 1.97; 95% confidence interval [CI] = 1.53–2.53). Similar results were observed in the Asian subgroup (c2c2 vs c1c1: OR = 1.98; 95% CI = 1.51–2.60; c2 vs c1: OR = 1.20; 95% CI = 1.03–1.39) and mixed population (c2 vs c1: OR = 1.41; 95% CI = 1.06–1.88) when the data were stratified by ethnicities. Interestingly, increased cancer risk only was shown among never-smokers (c2c2 vs c1c2 vs c1c1: OR = 1.44; 95% CI = 1.05–1.98) but not ever-smokers.

Conclusion: CYP2E1 Rsal/PstI polymorphisms may modify the susceptibility to HNC, particularly among Asians, mixed population, and never-smokers. Future large and well-designed studies are needed to verify this conclusion.

Abbreviations: CI = confidence interval, CYP = cytochrome P450, HB = hospital-based, HNC = head and neck cancer, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PB = population-based, SNP = single nucleotide polymorphism.

Keywords: CYP2E1 Rsal/PstI, head and neck cancer, meta-analysis, polymorphism, susceptibility

1. Introduction

Head and neck carcinoma (HNC) is a group of biologically similar cancers originating from the head and neck regions and has ranked the sixth most frequent malignant cancer in the world. HNC often severely affect the life qualities of patients because it impairs the body appearance, and influences speaking, swallowing, and breathing. Etiological research has been devoted to preventing this disorder.

Previous evidence indicates that external factors such as smoking, drinking, papilloma virus infection, betel quid chewing, and exposure to toxic substances might be risk factors for HNC. However, more attention has been focused on the roles of internal factors such as gene polymorphisms in the susceptibility to cancers.

Exposure to the toxic substances in the polluted air and water and even in some life styles such as smoking are established risk factors for a variety of cancers. Once absorbed, the toxic substances may be metabolized by a series of complex mechanisms. In this process, metabolizing enzymes play critical roles in the bioactivation and detoxification of xenobiotics. Polymorphisms in the genes of these enzymes, probably by changing their functions, might increase or decrease carcinogen activation/detoxification, thus indirectly enhancing or weakening the effects of the xenobiotics on the tissues and cells.

It is suggested that Cytochrome P450 (CYP) enzymes catalyze Phase 1 metabolism reactions. Previously, we found that 2 polymorphic sites of CYP1A1, Ile462Val and MspI, may modify oral cancer susceptibility. Recently, another member of the CYP superfamily, Cytochrome P4502E1 (CYP2E1), has attracted much attention. CYP2E1 is an enzyme that metabolizes various procarcinogens present in diets and tobacco smoke, such
as nitrosamines, aniline, and benzopyrene.[11] Several single nucleotide polymorphisms in CYP2E1 gene have been identified. Important genetic variations in the 5′-flanking promoter region of CYP2E1, Rsal and PstI polymorphisms, are in complete linkage disequilibrium and have been indicated to affect the transcriptional activation of CYP2E1 gene.[12] These polymorphisms result in 3 different genotypes, namely, wild-type homozygous (c2c2), heterozygous (c1c2), and variant homozygous (c2c2) genotypes.

A number of studies have focused on the association between CYP2E1 Rsal/PstI polymorphisms with HNC risk. Nevertheless, the results were inconsistent. Previously, 2 meta-analyses concerning this issue, which were published in 2010[13] and 2011,[14] respectively, reported conflicting results. The discrepancy of these 2 meta-analyses might be owing to the limited number of the included studies. Thus, in the present study, we aimed to perform an updated meta-analysis that contained published data up to Nov 2015 to derive a more precise estimation of the relationship.

2. Materials and methods

2.1. Ethnic statement

Ethical approval is not necessary for the present meta-analysis.

2.2. Literature search strategy

Relevant publications were searched from the biomedical databases such as Medline, EMBASE, OVID, ScienceDirect, and Chinese National Knowledge Infrastructure (CNKI) without a language limitation. The following keywords were used for searching: Cytochrome P4502E1, CYP2E1, oral, mouth, larynx, pharynx, nasopharynx, head and neck, neoplasm, cancer, variation, and polymorphism. Papers published up to Nov 2015 were searched and all potential relevant studies were retrieved and the bibliographies were further checked for other possible publications.

2.3. Inclusion criteria

For the literature inclusion, we used the criteria as follows: first, the study concerned the association of CYP2E1 Rsal/PstI polymorphisms with HNC risk (including oral cancer, laryngeal cancer, hypopharyngeal, oropharyngeal, and nasopharyngeal cancer). Second, the study must be observational designed (case-control or cohort). Third, the study must provide data about the sample size, odds ratios (ORs), and their 95% confidence intervals (CIs), as well as the genetic distribution or the information that help infer the results.

2.4. Exclusion criteria

Papers that met the following criteria were excluded: first, the designs of the experiments were obviously different from those of the included papers; second, the essential information regarding sample size, description of the participants, and definition of the study types were missed; third, review articles and duplicated publications.

2.5. Data extraction

Two of the authors independently reviewed the retrieved publications and extracted information from the primary literature. If the extracted data were conflicting, a discussion was conducted to reach an agreement. If the disagreement still existed, another author was consulted and then a final decision was made on the basis of a majority of votes. When 2 of more studies shared the same population, only the study with the larger or largest sample size was selected for data extraction.

2.6. Statistical analysis

The ORs of CYP2E1 Rsal/PstI polymorphisms with HNC risk were calculated for each study. The pooled ORs were determined for an allelic contrast model (c2 allele vs c1 allele), a homozygote comparison model (c2c2 vs c1c1), and a dominant model (c2c2+c1c2 vs c1c1). To detect any possible sample size bias, the OR and its 95% CI for each study were plotted against the number of participants for each study. A chi-squared-based Q-statistic test was performed to assess between-study heterogeneity. If the P value for the Q-test was >0.05, ORs were pooled according to the fixed-effect model (Mantel-Haenszel)[13]; otherwise, the random-effect model (DerSimonian and Laird) was used to calculate the pooled OR.[16] The significance of the pooled ORs was determined by the Z-test. Separated analyses according to the confounding factors such as ethnicity, source of controls, and genotyping method were conducted as much as we could in order to diminish the effects of the factors on the overall results.

The Hardy–Weinberg equilibrium (HWE) of the controls for each study was assessed by Fisher’s exact test. Funnel plots were created to evaluate the publication bias and an asymmetric plot indicated evident publication bias.[17] To minimize the subjective influence of the visual inspection assessment, the symmetry of the funnel plot was further evaluated by Egger’s linear regression test.[18] All statistical analysis in the present study was performed using the program Microsoft Excel 2003 and STATA 11.0 software (Stata Corporation, TX).

Figure 1. The flow diagram of included/excluded studies.
| First author                  | Publication year | Number of cases (male/female) | Number of controls (male/female) | Type of controls | Median (or mean) age, (range) year (cases/controls) | Racial decent | Type | Country     |
|------------------------------|------------------|-------------------------------|---------------------------------|-----------------|-----------------------------------------------------|---------------|------|-------------|
| Lucas                        | 1996             | 104 (NA/NA)                  | 260 (NA/NA)                    | Healthy controls (PB) | NA/NA                                               | Caucasian     | Combined | France      |
| Hildesheim                   | 1997             | 364 (254/110)                | 320 (222/98)                   | Healthy controls (PB) | 45.5 (15–74/46.0 (19–74)                            | Asian         | Nasopharynx | China       |
| Hung                         | 1997             | 41 (NA/NA)                   | 122 (NA/NA)                    | Healthy controls (age, ethnicity-matched; PB) | 54.1 (NA/51.7 (NA)                                      | Asian         | Mouth     | China       |
| Gonzalez                     | 1998             | 75 (75/0)                    | 200 (150/50)                   | Healthy controls (PB) | 58.7 (35–81/45.0 (25–75)                            | Caucasian     | Combined | Spain       |
| Matthias                     | 1998             | 398 (324/74)                 | 219 (175/44)                   | Noncancer controls (PB) | 61 (NA/54.1 (NA)                                      | Caucasian     | Combined | Germany     |
| He                           | 1999             | 105 (77/28)                  | 93 (64/29)                     | Healthy controls (age, sex-matched; PB) | 47.7 (23–73/40.8 (22–65)                                | Asian         | Nasopharynx | China       |
| Katch                        | 1999             | 92 (60/32)                   | 147 (91/56)                    | Noncancer controls (PB) | 62.4 (30–88/69.9 (34–91)                              | Asian         | Mouth     | Japan        |
| Monta                        | 1999             | 145 (126/19)                 | 164 (102/62)                   | Healthy controls (PB) | 59.0 (NA/49.8 (NA)                                      | Asian         | Combined | Japan        |
| Bouchardy                    | 2000             | 250 (240/10)                 | 172 (163/9)                    | Noncancer controls (PB) | 54.4 (NA/54.9 (NA)                                      | Caucasian     | Combined | France       |
| Kongruttanachok (Chinese)    | 2001             | 56 (NA/NA)                   | 98 (NA/NA)                     | Healthy controls (PB) | NA/NA                                               | Asian         | Nasopharynx | Thailand    |
| Kongruttanachok (Thai)       | 2001             | 132 (NA/NA)                  | 99 (NA/NA)                     | Noncancer controls (age, sex-matched; PB) | 62.0 (26–91/59.9 (25–91)                                | Asian         | Nasopharynx | Thailand    |
| Liu (Caucasian)              | 2001             | 113 (60/33)                  | 236 (146/80)                   | Noncancer controls (age, sex, hospital-matched; PB) | 58.6 (39–84/59.6 (34–88)                                 | Caucasian     | Mouth     | USA          |
| Liu (African-American)       | 2001             | 58 (42/16)                   | 173 (107/66)                   | Noncancer controls (age, sex, hospital-matched; PB) | 61.6 (23–84/53.1 (50–66)                                | African-American | Mouth | USA          |
| Zervas                       | 2002             | 93 (NA/NA)                   | 99 (NA/NA)                     | Noncancer controls (age, gender-matched; HB) | NA/NA                                               | Caucasian     | Mouth     | Greece       |
| Matthias                     | 2003             | 423 (363/60)                 | 219 (175/44)                   | Noncancer controls (PB) | 60.5 (NA/54.0 (NA)                                      | Caucasian     | Combined | Germany     |
| Neuhaus                      | 2004             | 312 (251/61)                 | 299 (176/123)                  | Healthy controls (PB) | 60.0 (NA/47.0 (NA)                                      | Caucasian     | Combined | Germany     |
| Gajacka                      | 2005             | 289 (289/NA)                 | 316 (316/NA)                   | Healthy controls (PB) | 57.9 (38–84/48.9 (40–66)                                | Caucasian     | Larynx    | Poland       |
| Li                           | 2005             | 724 (540/194)                | 1236 (908/323)                 | Noncancer controls (age, sex, smoking, ethnicity-matched; PB) | 57.1 (NA/57.1 (NA)                                      | Caucasian     | Combined | USA          |
| Ryzanecz                     | 2005             | 266 (253/13)                 | 143 (143/0)                    | Noncancer controls (smoking, occupational exposure-matched; HB) | 61.6 (23–84/53.1 (50–66)                                | Caucasian     | Combined | Poland       |
| Yang                         | 2005             | 502 (300/142)                | 194 (97/102)                   | Healthy controls (PB) | 53.0 (NA/49.6 (NA)                                      | Asian         | Combined | China       |
| Gallas                       | 2006             | 103 (90/13)                  | 102 (93/9)                     | Noncancer controls (PB) | 54.0 (NA/53.0 (NA)                                      | Mixed         | Combined | Brazil       |
| Marques                      | 2006             | 231 (193/38)                 | 212 (168/44)                   | Noncancer controls (age, sex, skin color-matched; PB) | NA (15–79/NA (15–79)                                    | Mixed         | Mouth     | Brazil       |
| Sugimura                     | 2006             | 122 (68/54)                  | 241 (118/123)                  | Noncancer controls (PB) | 60.4 (NA/56.8 (NA)                                      | Asian         | Mouth     | Japan        |
| Boccia                       | 2008             | 210 (150/60)                 | 245 (177/68)                   | Noncancer controls (age, gender-matched; PB) | 63.0 (NA/63.3 (NA)                                      | Caucasian     | Combined | Italy        |
| Buch                         | 2008             | 203 (159/44)                 | 416 (302/114)                  | Healthy controls (age, sex, zip code matched; PB) | 58.7 (23–81/58.7 (27–84)                                 | Caucasian     | Combined | USA          |
| Harth                        | 2008             | 312 (251/61)                 | 300 (178/124)                  | Noncancer controls (PB) | 59.7 (NA/52.4 (NA)                                      | Caucasian     | Combined | Germany     |
| Soya                         | 2008             | 408 (269/139)                | 220 (148/72)                   | Noncancer controls (PB) | 52.8 (NA/52.3 (NA)                                      | Asian         | Combined | India        |
| Oliveri                      | 2009             | 153 (139/14)                 | 145 (139/6)                    | Noncancer controls (PB) | 50 (NA/51.5 (NA)                                       | NA/NA         | Mixed     | Brazil       |
| Ruwali                       | 2009             | 350 (350/0)                  | 350 (350/0)                    | Noncancer controls (PB) | 53.0 (NA/52.0 (NA)                                      | Caucasian     | Combined | India        |
| Garcia                       | 2010             | 207 (184/23)                 | 244 (225/19)                   | Noncancer controls (PB) | 54.3 (24–81/53.6 (20–82)                                | Mixed         | Combined | Brazil       |
| Guo                          | 2010             | 358 (239/119)                | 629 (271/358)                  | Noncancer controls (PB) | 45.0 (NA/46.0 (NA)                                      | Asian         | Nasopharynx | China       |
| Tai                          | 2010             | 279 (260/19)                 | 278 (236/22)                   | Noncancer controls (age, sex-matched; PB) | NA/NA                                               | Asian         | Combined | China        |
| Anantharaman                 | 2011             | 665 (476/189)                | 802 (707/95)                   | Noncancer controls (age, sex, smoking-matched; PB) | 50 (NA/43 (NA)                                         | Asian         | Mouth     | India        |
| Balaji                       | 2011             | 157 (98/71)                  | 132 (46/86)                    | Noncancer controls (age, sex, smoking-matched; PB) | 55.1 (NA/53.1 (NA)                                      | Asian         | Mouth     | India        |
3. Results

3.1. Study characteristics

Relevant publications were obtained by retrieving the keywords in the databases. As shown in Fig. 1, 379 publications were originally identified, among which 324 irrelevant papers were excluded. Thus, 55 publications were eligible. Then, 2 review articles,[20,21] 3 papers on precancerous lesions, and 1 study on other polymorphic sites of CYP2E1 rather than RsaI/PstI were discarded. Next, 2 studies lacking of controls and 4 studies providing insufficient data were also eliminated. As a result, 43 publications were selected for data extraction and assessment. However, 2 duplicate publications containing 2 solitary studies, respectively, and these sub-studies were considered as independent studies for data assessment. Therefore, 41 publications containing 43 independent case-control studies were finally included in the present meta-analysis.

All publications were written in English, except for 1 in Chinese,[72] 1 in French[73] and 1 in Germany.[44] The relevant information such as the first author, the number and characteristics of cases and controls for each study was listed in Table 1. The selected articles included 16 groups of Caucasians, 18 of Asians, 1 of African-American, and 8 of mixed ethnicities. Table 2 displayed the distributions of the CYP2E1 RsaI/PstI genotypes and the genotyping methods of the included studies. The genetic distributions of the control groups in all studies were consistent with the HWE except for 5 studies.[33,34,45,55,73] The genetic distributions of variant c2c2 in 8 included studies [53,54,57,62,64,65,67,70] were combined as c2c2+c1c2. Thus, they were only included in the dominant model for data pooling.

3.2. Test of heterogeneity

We analyzed the heterogeneity for the 3 models, respectively. Studies that provided the combined genetic distributions (c2c2+c1c2) but not the detailed genotypes were only included in the dominant model for assessment. As a result, marked heterogeneities were found in 2 models (c2 vs c1: P=0.004 for Q-test; c2c2+c1c2 vs c1c1: P=0.000 for Q-test); respectively (Table 3), indicating that homozygote comparison (OR=1.97; 95% CI=1.33–2.53), indicating that homozygote c2c2 genotypes may be a risk factor for HNC. Therefore, the random-effect models were chosen in the former 2 genetic models, whereas the fixed-effect models were used in the ladder model.

3.3. Meta-analysis results

The main results of the meta-analysis are listed in Table 3. For the overall data including 10,817 cases and 13,039 controls, the pooled ORs for the allelic contrast (OR=1.12; 95% CI=0.99–1.27) and dominant model (OR=1.06; 95% CI=0.92–1.22) (Fig. 2) failed to indicate a relationship. Nevertheless, increased HNC risk was observed in the homozygote comparison (OR=1.97; 95% CI=1.33–2.53), indicating that homozygote c2c2 genotypes may be a risk factor for HNC.

Given that the confounding factors might exert impact on the overall results, we further performed subgroup analyses. In the subgroup analysis on ethnicity, increased risk was shown in Asians under the allelic contrast (OR=1.20; 95% CI=1.03–1.39) and the homozygote comparison (OR=1.98; 95% CI=1.47–2.63).
CI = 1.51–2.60), respectively, and in mixed population under the allelic contrast model (OR = 1.41; 95% CI = 1.06–1.86) (Fig. 3).

In the subgroup analysis regarding source of controls, increased risk was found in the population-based subgroup under the homozygote comparison (OR = 2.59; 95% CI = 1.84–3.65), in agreement with the overall data. The significance of the results in the subgroup analyses about sample size and genotyping method, respectively, were in line with the overall data, suggesting that these factors exert little impact on the overall data.

We tried to extract data regarding smoking and drinking status and found that there were 11 studies provided data on smoking status and 7 studies on drinking status. As shown in Table 3, increased risk could be observed in either the never drinking group or the ever drinking group, indicating that drinking status might not interact with CYP2E1 polymorphisms for HNC risk.

For smoking status, an interesting result was observed. As shown in Fig. 4, increased cancer risk was shown among individuals who had no smoking history (OR = 1.44; 95% CI = 1.05–1.98), whereas this statistical significance was not observed for people who have a smoking history (OR = 1.42; 95% CI = 0.96–2.12), indicating that c2 allele might only increase HNC risk among never-smokers, and an interaction between CYP2E1 polymorphism and smoking might lower the HNC risk.

### Table 2

| First author               | Year | Genotyping method | Cases c2c2 | c1c2 | c1c1 | Controls c2c2 | c1c2 | c1c1 | HWE (control) |
|----------------------------|------|-------------------|------------|------|------|---------------|------|------|--------------|
| Lucas                     | 1996 | PCR-RFLP          | 0          | 6    | 98   | 1             | 11   | 248  | 4.540        |
| Hildesheim                | 1997 | PCR-RFLP          | 27         | 108  | 234  | 9             | 113  | 198  | 2.290        |
| Hung                      | 1997 | PCR               | 2           | 19   | 20   | 4             | 42   | 76   | 0.389        |
| Gonzalez                  | 1998 | PCR-RFLP          | 1           | 6    | 68   | 0             | 21   | 179  | 0.614        |
| Matthias                  | 1998 | PCR-RFLP          | 1           | 23   | 355  | 0             | 10   | 165  | 0.151        |
| He                        | 1999 | PCR-RFLP          | 6           | 27   | 72   | 1             | 33   | 59   | 2.422        |
| Kato                      | 1999 | PCR               | 3           | 36   | 53   | 7             | 45   | 95   | 0.308        |
| Monta                     | 1999 | PCR               | 8           | 46   | 91   | 7             | 52   | 105  | 0.031        |
| Bouchardy                 | 2000 | PCR               | 1           | 20   | 229  | 0             | 8    | 164  | 0.098        |
| Kongruttanachok (Chinese) | 2001 | PCR-RFLP          | 5           | 24   | 27   | 4             | 51   | 43   | 5.480        |
| Kongruttanachok (Thai)    | 2001 | PCR-RFLP          | 2           | 37   | 93   | 1             | 28   | 70   | 0.990        |
| Liu (Caucasian)           | 2001 | PCR-RFLP          | 0           | 7    | 105  | 0             | 14   | 210  | 0.233        |
| Liu (African-American)    | 2001 | PCR-RFLP          | 0           | 0    | 55   | 0             | 1    | 155  | 0.002        |
| Zavras                    | 2002 | PCR-RFLP          | 0           | 1    | 92   | 0             | 1    | 98   | 0.003        |
| Matthias                  | 2003 | PCR-RFLP          | 1           | 21   | 342  | 0             | 10   | 165  | 0.151        |
| Neuhau                    | 2004 | Real-time PCR     | 0           | 8    | 304  | 3             | 12   | 282  | 13.445       |
| Gajacka                   | 2005 | PCR-RFLP          | 0           | 9    | 279  | 0             | 18   | 305  | 0.265        |
| Li                        | 2005 | PCR-RFLP          | 3           | 37   | 684  | 3             | 86   | 1137 | 1.015        |
| Rydzanicz                 | 2005 | PCR-RFLP          | 0           | 10   | 314  | 0             | 7    | 135  | 0.091        |
| Yang                      | 2005 | PCR-RFLP          | 3           | 43   | 57   | 31            | 191  | 331  | 0.247        |
| Guttas                    | 2006 | PCR-RFLP          | 0           | 13   | 90   | 0             | 6    | 96   | 0.094        |
| Rauwala                   | 2006 | PCR-RFLP          | 0           | 31   | 290  | 0             | 25   | 187  | 0.032        |
| Sugimura                  | 2006 | PCR-RFLP          | 11          | 39   | 72   | 7             | 70   | 164  | 0.020        |
| Boccia                    | 2008 | PCR-RFLP          | 10*         | –    | 200  | 16*          | –    | 229  | –            |
| Buch                      | 2008 | PCR-RFLP          | 0           | 14   | 176  | 0             | 39   | 364  | 1.042        |
| Harth                     | 2008 | Real-time PCR     | 0           | 8    | 304  | 2             | 13   | 285  | 13.610       |
| Soja                      | 2008 | PCR-RFLP          | 14*         | –    | 394  | 8*           | –    | 212  | –            |
| Olivieri                  | 2009 | PCR-RFLP          | 1           | 24   | 99   | 1             | 16   | 105  | 0.198        |
| Ruswali                   | 2009 | PCR-RFLP          | 23          | –    | 327  | 7*           | –    | 343  | –            |
| Garcia                    | 2010 | PCR-RFLP          | 0           | 19   | 188  | 0             | 17   | 227  | 0.318        |
| Guo                       | 2010 | Sequencing        | 20          | 108  | 228  | 26            | 186  | 412  | 0.735        |
| Tai                       | 2010 | PCR-RFLP          | 13          | 81   | 184  | 12            | 84   | 182  | 0.335        |
| Anantharaman              | 2011 | PCR-RFLP          | 9*          | –    | 414  | 35*          | –    | 665  | –            |
| Balaji                    | 2011 | Taqman            | 0           | 6    | 151  | 0             | 7    | 125  | 0.098        |
| Brocic                    | 2011 | PCR-RFLP          | 5           | 13   | 105  | 1             | 16   | 160  | 0.399        |
| Hakumewerth               | 2011 | Illumina          | 83*         | –    | 1139 | 84*          | –    | 1237 | –            |
| Cury                      | 2012 | PCR-RFLP          | 17*         | –    | 200  | 42*          | –    | 292  | –            |
| Pandey                    | 2012 | PCR-RFLP          | 3*          | –    | 47   | 15*          | –    | 35   | –            |
| Jin                       | 2014 | PCR               | 37          | 97   | 418  | 8             | 94   | 564  | 3.128        |
| Maurya                    | 2014 | PCR-RFLP          | 59*         | –    | 691  | 20*          | –    | 730  | –            |
| Bediaga                   | 2015 | Taqman            | 0           | 2    | 82   | 0             | 16   | 226  | 0.283        |
| Lourenbam                 | 2015 | PCR-RFLP          | 0           | 19   | 86   | 0             | 20   | 95   | 1.043        |
| Ben Chaibon               | 2015 | PCR-RFLP          | 6           | 3    | 115  | 1             | 5    | 160  | 12.130       |

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*c2c2 + c1c2.*
Table 3
Main results of the pooled data in the meta-analysis.

|                          | No of studies | c2 vs c1 |       |       |       | c2c2 vs c1c1 |       |       |       | (c2c2 +c1c2) vs c1c1 |       |       |
|--------------------------|---------------|----------|-------|-------|-------|-------------|-------|-------|-------|---------------------|-------|-------|
|                          |               | OR (95%CI)| P     | PP    | (Q-test) OR (95%CI) | P     | PP    | (Q-test) OR (95%CI) | P     | PP    |
| Total                    | 43            | 1.12 (0.99–1.27) | 0.070 | 0.004 | 1.97 (1.53–2.53) | 0.000 | 0.115 | 1.06 (0.92–1.22) | 0.412 | 0.000 |
| Ethnicity                |               |          |       |       |       |             |       |       |       |                     |       |       |
| Asian                    | 15            | 1.20 (1.03–1.39) | 0.020 | 0.017 | 1.98 (1.51–2.60) | 0.000 | 0.033 | 1.10 (0.93–1.29) | 0.265 | 0.036 |
| Caucasian                | 19            | 0.88 (0.69–1.13) | 0.315 | 0.145 | 1.48 (0.70–3.14) | 0.304 | 0.536 | 0.94 (0.68–1.29) | 0.689 | 0.000 |
| African-American         | 1             | 0.94 (0.04–23.24) | 0.970 | –     | –     | –     | –     | 0.93 (0.04–23.26) | 0.967 | –     |
| Mixed                    | 8             | 1.41 (1.06–1.86) | 0.017 | 0.439 | 4.41 (0.92–21.01) | 0.063 | 0.245 | 1.15 (0.90–1.48) | 0.270 | 0.244 |
| Source of controls       |               |          |       |       |       |             |       |       |       |                     |       |       |
| PB                       | 21            | 1.11 (0.90–1.35) | 0.332 | 0.001 | 2.59 (1.84–3.65) | 0.000 | 0.082 | 1.07 (0.88–1.30) | 0.516 | 0.000 |
| HB                       | 22            | 1.11 (0.97–1.28) | 0.134 | 0.318 | 1.39 (0.95–2.02) | 0.090 | 0.695 | 1.05 (0.86–1.28) | 0.652 | 0.009 |
| Sample size              |               |          |       |       |       |             |       |       |       |                     |       |       |
| >600                     | 13            | 0.95 (0.70–1.29) | 0.746 | 0.000 | 2.00 (1.44–2.80) | 0.000 | 0.004 | 1.05 (0.83–1.39) | 0.717 | 0.000 |
| <300                     | 14            | 1.19 (0.99–1.43) | 0.063 | 0.708 | 2.18 (1.16–4.09) | 0.015 | 0.632 | 1.09 (0.84–1.41) | 0.530 | 0.147 |
| 300–600                  | 16            | 1.15 (0.98–1.35) | 0.082 | 0.377 | 1.77 (1.09–2.88) | 0.020 | 0.571 | 1.04 (0.89–1.22) | 0.615 | 0.423 |
| Genotyping method        |               |          |       |       |       |             |       |       |       |                     |       |       |
| PCR-RFLP                 | 31            | 1.09 (0.98–1.22) | 0.115 | 0.401 | 1.99 (1.40–2.63) | 0.000 | 0.417 | 1.04 (0.87–1.24) | 0.674 | 0.000 |
| PCR                      | 8             | 1.15 (0.80–1.65) | 0.463 | 0.001 | 2.31 (1.47–3.65) | 0.000 | 0.033 | 1.19 (0.86–1.64) | 0.295 | 0.025 |
| Others                   | 4             | 0.91 (0.54–1.53) | 0.721 | 0.247 | 1.39 (0.76–2.55) | 0.286 | –     | 1.05 (0.86–1.28) | 0.656 | 0.437 |
| Smoking status           |               |          |       |       |       |             |       |       |       |                     |       |       |
| Never smoking            | 8             | –       | –     | –     | –     | –     | –     | 1.44 (1.05–1.98) | 0.023 | 0.316 |
| Ever smoking             | 11            | –       | –     | –     | –     | –     | –     | 1.42 (1.06–2.12) | 0.083 | 0.001 |
| Drinking status          |               |          |       |       |       |             |       |       |       |                     |       |       |
| Never drinking           | 4             | –       | –     | –     | –     | –     | –     | 2.86 (1.98–4.12) | 0.000 | 0.786 |
| Ever drinking            | 7             | –       | –     | –     | –     | –     | –     | 1.76 (1.14–2.72) | 0.011 | 0.041 |

CI = confidence interval, HB = hospital-based, OR = odds ratio, PB = population-based.

Figure 2. Meta-analysis for the association of HNC risk with CYP2E1 RsaI/PstI polymorphism for the overall data (c2c2+c1c2 vs c1c1). HNC = head and neck cancer.
Moreover, we also deleted 1 study from the database in the repeated analyses. The results showed that the overall results was not altered in the above analysis process (data not shown), indicating that the overall results of the present study were stable.

3.5. Bias diagnostics

Publication bias was an unavoidable problem that needs to be addressed. For the overall data, the funnel plots were generated and their symmetries were further assessed by Egger’s linear regression tests. As expected, the data showed that the plots for the 3 genetic models were relatively stable (c2 vs c1: \( t = -1.33, P = 0.194 \); c2c2 vs c1c1: \( t = -0.48, P = 0.638 \); c2c2+c1c2 vs c1c1: \( t = -1.33, P = 0.190 \)), suggesting that the publication bias was not evident to influence the credibility of the results (Fig. 5).

4. Discussion

CYP2E1 RsaI/PstI polymorphism has been suggested to correlate with susceptibilities to a variety of cancers. The present meta-analysis revealed that c2 alleles of CYP2E1 RsaI/PstI polymorphism might increase HNC risk, particularly among Asians, mixed population, and never-smokers.

Previously, a meta-analysis by Tang et al\(^\text{[13]}\) in 2010 including 21 studies showed that increased HNC risk among Asians was possibly associated with c2 homozygotes. However, information regarding mixed population as well as African was missed. Besides, subgroup analysis on smoking and drinking status were based on limited number of studies (2–5 studies), which did not reveal an association in these subgroups, inconsistent with the present meta-analysis. In another meta-analysis by Lu et al\(^\text{[14]}\) in 2011, a total of 24 studies were included. The paper showed that the increased risk was presented among mixed population in addition to Asians. Moreover, subgroup analysis regarding confounding factors such as smoking and drinking had not been reported in this paper. Notably, any selection bias might also be considered in their 2 meta-analyses. For example, in the paper by Tang et al\(^\text{[13]}\) there were 6 studies\(^{43,44,47,49,55,72}\) that might meet the inclusion criteria missed, whereas in the article by Lu et al\(^\text{[14]}\) there were also 6 studies\(^{43,44,49,53,61,72}\) ignored. Therefore, compared to these 2 published meta-analyses\(^{13,14}\) the present updated one involved both the missed studies and the recent published studies, thus markedly minimizing the selection bias. Moreover, subgroup analyses regarding more confounding factors such as ethnicity, source of controls, and genotyping methods were conducted, and strict sensitivity analysis and bias tests were carried out. This might help increase the statistical power and get a more confident estimate.

In the subgroup analysis on ethnicity, significant association was only found among Asians and mixed-ethnicity, but not
Caucasians and African-Americans, suggesting that c2 allele might increase HNC cancer risk among Asians and mixed populations. The racial disparity might be owing to a possible role of ethnic differences in genetic backgrounds, and different socioeconomic status that might exert an effect on HNC cancer risk.\[^{[74]}\] Besides, CYP2E1 variations may exert different influences on HNC risk among different races because CYP2E1 variations differ among various ethnicities.\[^{[75]}\] For instance, the heterozygous c1c2 displayed low-level enzyme activities of CYP2E1 among Caucasians.\[^{[76]}\] By contrast, the CYP2E1 mRNA levels were higher in the presence of c2 than c1 among Asians.\[^{[77]}\] This might help explain the reason why increased HNC risk could be shown among Asians but not Caucasians. In addition, infection of microorganism, such as human papillomavirus (HPV), might alter host gene expression and thus influence the ethnic health disparities for HNC patients.\[^{[78]}\] However, the information regarding HPV infection in the primary literature is limited and thus their associations could not be further assessed in the present meta-analysis. It is worthy of noting that only 1 group of African-American was involved. Thus, the results might also be due to chance because the limited number of included studies and small sample sizes may result in insufficient statistical power to assess a minor effect. Hence, the results should be interpreted with care. Further investigations with large sample sizes regarding different ethnicities are needed to increase power determining the possible effects of CYP2E1 ethnic variations on HNC risk.

Smoking and alcohol consumption are important established HNC risk factors. In the above mentioned meta-analysis by Tang et al,\[^{[13]}\] no increased cancer risk was observed in either the smoking group or the never-smoking group, inconsistent with the present meta-analysis. The data of the present one showed that increased HNC risk could only be seen in the never-smoking group rather than the ever-smoking group, indicating that CYP2E1 polymorphisms might interact with smoking and decrease HNC risk to any extent. The precise mechanisms are not known. For people who never smoke, the increased HNC risk was not difficult to be understood because this is in agreement with the overall results. Nevertheless, for people who have a smoking history, the risk was lowered. The interesting discrepancy might be due to several possibilities. Tobacco-specific nitrosamines are preferentially metabolized by the CYP2E1. Little evidence suggests that the variant alleles are related to enhanced CYP2E1 activity.\[^{[42]}\] Thus, reduced enzyme activity by the variant allele reduces cancer risk owing to limited metabolic activation, particularly among the exposed population.\[^{[64]}\] Moreover, it is worth noting that significant heterogeneity could be observed in the subgroup analysis regarding ever smoking (\(P = 0.001\)), but not never smoking (\(P = 0.316\)). Both the sample sizes and the number of included studies are different between these 2 subgroups. Therefore, the discrepancy may be due to chance because of the existed imparity and the marked heterogeneity. Future studies concerning this issue are needed to clarify the association. For drinking status, the significances of these 2 subgroups were statistically similar because increased HNC risk can be observed in both groups. In addition, the OR value in the ever-drinking subgroup (1.76) is not evidently higher than that in the never-drinking subgroup (2.86). Thus, the data failed to suggest an interaction of drinking with c2 of CYP2E1 in the increase of HNC susceptibility. However, the above results

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**Figure 4.** Meta-analysis for the association of HNC risk with CYP2E1 RsaI/PstI polymorphism (c2c2+c1c2 vs c1c1; stratified by smoking status). HNC = head and neck cancer.
should be interpreted with caution because the sample sizes of the gene-smoking and gene-drinking analyses were rather limited. Several limitations should be noted in this meta-analysis. One limitation is the potential effect of the selection bias on the results. Since only the popular bio-databases were searched, papers that published in other languages were missed though we included primary literature. Furthermore, the controls in some primary studies were not well-matched to the cases, and therefore, any inevitable bias may existed. Hence, future well-designed investigations are warranted to evaluate the relationship.

In conclusion, through conduction of an updated quantitative meta-analysis, we found that CYP2E1 Rsal/PstI polymorphism has a correlation with increased HNC risk. Particularly, the variant c2 of CYP2E1 Rsal/PstI may confer HNC risk among Asians, mixed populations, and never-smokers. More future research is required to verify the results.

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