Systematic Review and Meta-Analysis

Medicine®

OPEN

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

A meta-analysis based on 43 studies

Xianlu Zhuo, MD[a,b,c,*], Jue Song, MS[b], Jian Liao, MD[b], Wei Zhou, MD[c], Huiping Ye, MD[b], Qi Li, MS[a], Zhaolan Xiang, MS[a], Xueyuan Zhang, MD[a,*]

Abstract

Background: Previous reports showed that CYP2E1 RsaI/PstI polymorphism may be a risk factor for cancers. Published meta-analyses in 2010 and 2011, respectively, on the relationship of CYP2E1 RsaI/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 confidential 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 RsaI/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 = 1.06–1.86) when the data were stratified by ethnicities. Interestingly, increased cancer risk only was shown among never-smokers (c2c2+c1c2 vs c1c1: OR = 1.44; 95%CI = 1.05–1.98) but not ever-smokers.

Conclusion: CYP2E1 RsaI/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 RsaI/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.[1] 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,[2] papilloma virus infection,[3] betel quid chewing,[4] and exposure to toxic substances[5] 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.[6] 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.[7] 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.[8]

It is suggested that Cytochrome P450 (CYP) enzymes catalyze Phase I metabolism reactions. Previously, we found that 2 polymorphic sites of CYP1A1, Ile462Val and MspI, may modify oral cancer susceptibility.[9,10] 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

Editor: Jimmy T. Efird.

Authorship: XZ (Xianlu Zhuo) and HY designed and planned the analysis; XZ (Xianlu Zhuo), WZ, and XZ (Xueyuan Zhang) wrote the manuscript draft; JL, ZX, and QL processed data and prepared the figures and tables. XZ (Xianlu Zhuo) and JS revised and improved the manuscript. All authors reviewed the manuscript.

The authors report no conflicts of interest.

[a] Department of Otolaryngology, Southwest Hospital, Third Military Medical University, Chongqing, [b] Affiliated Hospital of Guiyang Medical University, Guiyang, [c] Post-doctoral Scientific Research Station, Chongqing Cancer Institute, Chongqing, China.

[*] Correspondence: Xianlu Zhuo and Xueyuan Zhang, Department of Otolaryngology, Southwest Hospital, Third Military Medical University, Chongqing, China (e-mails: zhuoxianlu@gmc.edu.cn[Xianlu Zhuo]; sydzxy@aliyun.com [Xueyuan Zhang]).

Medicine (2016) 95:43(e5156)

Received: 1 December 2015 / Received in final form: 14 September 2016 / Accepted: 27 September 2016

http://dx.doi.org/10.1097/MD.0000000000005156

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, RsaI 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 (c1c1), heterozygous (c1c2), and variant homozygous (c2c2) genotypes.

A number of studies have focused on the association between CYP2E1 RsaI/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, *laryngx, pharyngx, napharynx, 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 RsaI/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 RsaI/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)[15]; 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).

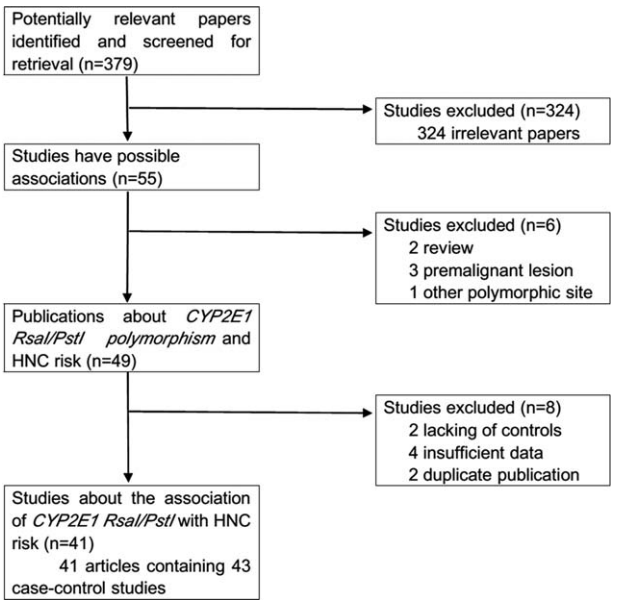

Figure 1. The flow diagram of included/excluded studies.

Table 1

Characteristics of studies included in the meta-analysis.

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 (342/56)	219 (175/44)	Noncancer controls (HB)	61.1 (NA)/54.1 (NA)	Caucasian	Combined	Germany
He	1999	105 (77/28)	93 (64/29)	Healthy controls (age-, sex-matched; PB)	47.7 (23–70)/40.8 (22–65)	Asian	Nasopharynx	China
Katoh	1999	92 (56/36)	147 (91/56)	Noncancer controls (HB)	62.4 (30–88)/69.9 (34–91)	Asian	Mouth	Japan
Morita	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 (HB)	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)	Healthy controls (PB)	NA/NA	Asian	Nasopharynx	Thailand
Liu (Caucasian)	2001	113 (80/33)	226 (146/80)	Noncancer controls (age-, sex-, hospital-matched; HB)	62.0 (28–91)/59.9 (25–91)	Caucasian	Mouth	USA
Liu (African-American)	2001	58 (42/16)	173 (107/66)	Noncancer controls (age-, sex-, hospital-matched; HB)	58.6 (39–84)/59.6 (34–88)	African-American	Mouth	USA
Zavras	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 (HB)	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
Gajecka	2005	289 (289/NA)	316 (316/NA)	Healthy controls (PB)	57.9 (38–84)/45.9 (40–66)	Caucasian	Larynx	Poland
Li	2005	724 (540/184)	1226 (906/320)	Noncancer controls (age-, sex-, smoking, ethnicity-matched; HB)	57.1 (NA)/57.1 (NA)	Caucasian	Combined	USA
Rydzanicz	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 (360/142)	1942 (917/1025)	Healthy controls (PB)	51.6 (NA)/46.5 (NA)	Asian	Combined	China
Gattas	2006	103 (90/13)	102 (93/9)	Noncancer controls (HB)	54.0 (NA)/53.0 (NA)	Mixed	Combined	Brazil
Marques	2006	231 (193/38)	212 (168/44)	Noncancer controls (age-, sex-, skin color-matched; HB)	NA (15–79)/NA (15–79)	Mixed	Mouth	Brazil
Sugimura	2006	122 (68/54)	241 (118/123)	Noncancer controls (HB)	60.4 (NA)/56.8 (NA)	Asian	Mouth	Japan
Boccia	2008	210 (150/60)	245 (177/68)	Noncancer controls (age-, gender-matched; HB)	63.6 (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 (176/124)	Noncancer controls (HB)	59.7 (NA)/47.2 (NA)	Caucasian	Combined	Germany
Soya	2008	408 (269/139)	220 (148/72)	Noncancer controls (HB)	52.8 (NA)/52.3 (NA)	Asian	Combined	India
Olivieri	2009	153 (139/14)	145 (139/6)	Noncancer controls (HB)	NA/NA	Mixed	Combined	Brazil
Ruwali	2009	350 (350/0)	350 (350/0)	Noncancer controls (HB)	53.0 (NA)/52.0 (NA)	Caucasian	Combined	India
Garcia	2010	207 (184/23)	244 (225/19)	Noncancer controls (HB)	54.3 (24–81)/53.6 (20–82)	Mixed	Combined	Brazil
Guo	2010	358 (239/119)	629 (271/358)	Noncancer controls (HB)	45.0 (NA)/46.0 (NA)	Asian	Nasopharynx	China
Tai	2010	278 (260/18)	278 (256/22)	Noncancer controls (age-, sex-matched; HB)	NA/NA	Asian	Combined	China
Anantharaman	2011	665 (476/189)	802 (707/95)	Noncancer controls (age-, sex-, smoking-matched; HB)	50 (NA)/43 (NA)	Asian	Mouth	India
Balaji	2011	157 (86/71)	132 (46/86)		55.1 (NA)/53.1 (NA)	Asian	Mouth	India

Table 1 (Continued).

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
				Healthy controls (age-, sex-, smoking-matched; PB)				
Brocic	2011	123 (91/32)	177 (135/42)	Healthy control (age-, gender-matched; PB)	58 (36–80)/58 (36–80)	Caucasian	Mouth	Serbia
Hakenewerth	2011	172 (NA/NA)	1325 (924/401)	Healthy control (age-, sex-, race-matched; PB)	NA (20–80)/NA (20–80)	Mixed	Combined	USA
Cury	2012	217 (NA/NA)	334 (NA/NA)	Healthy control (PB)	49.0 (NA)/49.0 (NA)	Mixed	Combined	Brazil
Pandey	2012	50 (50/0)	50 (50/0)	Noncancer controls (HB)	NA/NA	Caucasian	Mouth	India
Jin	2014	552 (534/18)	666 (641/25)	Healthy controls (age-, gender-matched; PB)	63.5 (NA)/62.3 (NA)	Asian	Larynx	China
Maurya	2014	750 (750/0)	750 (750/0)	Healthy controls (PB)	54.0 (NA)/53.0 (NA)	Caucasian	Combined	India
Bedlaga	2015	84 (67/17)	242 (150/92)	Healthy controls (PB)	61.8 (NA)/42.9 (NA)	Caucasian	Combined	Spain
Lourembam	2015	105 (72/33)	115 (71/44)	Healthy control (age-, sex, ethnicity-matched; PB)	48.9 (NA)/44.0 (NA)	Mixed	Nasopharynx	India
Ben Chaaben	2015	124 (77/47)	166 (88/78)	Healthy controls (PB)	44.4 (NA)/42.8 (NA)	Mixed	Nasopharynx	Tunisia

HB = hospital-based, NA = not available, PB = population-based.

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,[19,20] 3 papers[21–23] on precancerous lesions, and 1 study[24] on other polymorphic sites of CYP2E1 rather than RsaI/PstI were discarded. Next, 2 studies[25,26] lacking of controls and 4 studies[27–30] providing insufficient data were also eliminated. As a result, 43 publications were selected for data extraction and assessment. However, 2 duplicate publications [31,32] were further excluded during the data extraction process. As a result, a total of 41 publications were selected for analysis. Notably, there were 2 papers [33,34] that contained 2 solitary studies, respectively, and these sub-studies were considered as independent studies for data assessment. Therefore, 41 publications [33–73] containing 43 independent case-control studies were lastly 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.[34,35,45,55,73] The genetic distributions of variant c2c2 and c1c2 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), but not the homozygote comparison model (c2c2 vs c1c1: $P = 0.115$ for Q-test). 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 = 1.53–2.53), 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%

Table 2

Distribution of CYP2E1 RsaI/PstI genotype among HNC cases and controls included in the meta-analysis.

First author	Year	Genotyping method	Cases			Controls			HWE (control)	
			c2c2	c1c2	c1c1	c2c2	c1c2	c1c1	Chi-squre	*P*
Lucas	1996	PCR-RFLP	0	6	98	1	11	248	4.540	<0.05
Hildesheim	1997	PCR-RFLP	27	108	229	9	113	198	2.290	>0.05
Hung	1997	PCR	2	19	20	4	42	76	0.389	>0.05
Gonzalez	1998	PCR-RFLP	1	6	68	0	21	179	0.614	>0.05
Matthias	1998	PCR-RFLP	1	23	355	0	10	165	0.151	>0.05
He	1999	PCR-RFLP	6	27	72	1	33	59	2.422	>0.05
Katoh	1999	PCR	3	36	53	7	45	95	0.308	>0.05
Morita	1999	PCR	8	46	91	7	52	105	0.031	>0.05
Bouchardy	2000	PCR	1	20	229	0	8	164	0.098	>0.05
Kongruttanachok (Chinese)	2001	PCR-RFLP	5	24	27	4	51	43	5.489	<0.05
Kongruttanachok (Thai)	2001	PCR-RFLP	2	37	93	1	28	70	0.990	>0.05
Liu (Caucasian)	2001	PCR-RFLP	0	7	105	0	14	210	0.233	>0.05
Liu (African-American)	2001	PCR-RFLP	0	0	55	0	1	155	0.002	>0.05
Zavras	2002	PCR-RFLP	0	1	92	0	1	98	0.003	>0.05
Matthias	2003	PCR	1	21	342	0	10	165	0.151	
Neuhaus	2004	Real-time PCR	0	8	304	2	13	282	13.445	<0.05
Gajecka	2005	PCR-RFLP	0	9	279	0	18	305	0.265	>0.05
Li	2005	PCR-RFLP	3	37	684	3	86	1137	1.015	>0.05
Rydzanicz	2005	PCR-RFLP	0	10	314	0	7	135	0.091	>0.05
Yang	2005	PCR-RFLP	3	43	57	31	191	331	0.247	>0.05
Gattas	2006	PCR-RFLP	0	13	90	0	6	96	0.094	>0.05
Marques	2006	PCR-RFLP	0	31	200	0	25	187	0.832	>0.05
Sugimura	2006	PCR-RFLP	11	39	72	7	70	164	0.020	>0.05
Boccia	2008	PCR-RFLP	10*	–	200	16*		229	–	–
Buch	2008	PCR-RFLP	0	14	176	0	39	364	1.042	>0.05
Harth	2008	Real-time PCR	0	8	304	2	13	285	13.610	<0.05
Soya	2008	PCR-RFLP	14*	–	394	8*	–	212	–	–
Olivieri	2009	PCR-RFLP	1	24	99	1	16	105	0.198	>0.05
Ruwali	2009	PCR-RFLP	23*	–	327	7*	–	343	–	–
Garcia	2010	PCR-RFLP	0	19	188	0	17	227	0.318	>0.05
Guo	2010	Sequencing	20	108	228	26	186	412	0.735	>0.05
Tai	2010	PCR-RFLP	13	81	184	12	84	182	0.335	>0.05
Anantharaman	2011	PCR-RFLP	9*	–	414	35*	–	665	–	–
Balaji	2011	Taqman	0	6	151	0	7	125	0.098	>0.05
Brocic	2011	PCR-RFLP	5	13	105	1	16	160	0.399	>0.05
Hakenewerth	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	>0.05
Maurya	2014	PCR-RFLP	59*	–	691	20*	–	730	–	–
Bediaga	2015	Taqman	0	2	82	0	16	226	0.283	>0.05
Lourembam	2015	PCR-RFLP	0	19	86	0	20	95	1.043	>0.05
Ben Chaaben	2015	PCR-RFLP	6	3	115	1	5	160	12.130	<0.05

* c2c2+ c1c2.

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.

3.4. Sensitivity analysis

To test the stability of the overall results, we changed the effect models and reanalyzed the data for the 3 genetic models (data not shown). The results showed that the results were not statistically changed. Besides, we removed the studies whose distribution of controls were not in line with HWE and reanalyzed the data.

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*	*P* (Q-test)	OR (95%CI)	*P*	*P* (Q-test)	OR (95%CI)	*P*	*P* (Q-test)
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 (0.80–1.39)	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 (1.40–2.83)	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 (0.96–2.12)	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.

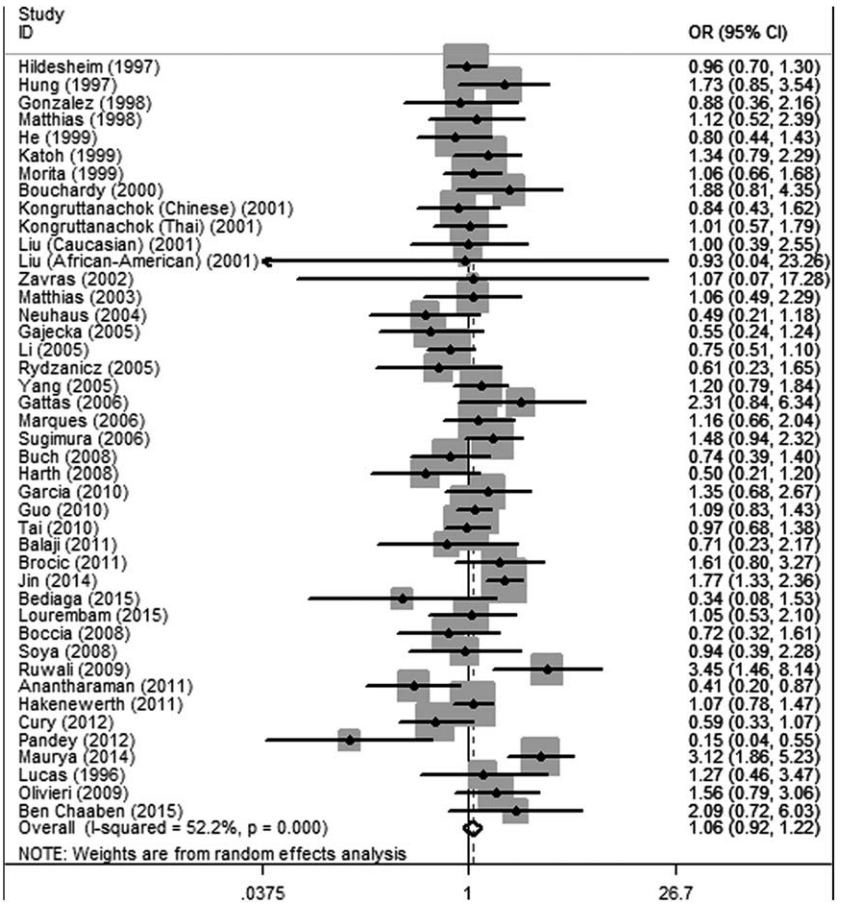

Figure 2. Meta-analysis for the association of HNC risk with CYP2E1 RsaI/PstI polymorphism for the overall data (c2c2+c1c2 vs c1c1). HNC = head and neck cancer.

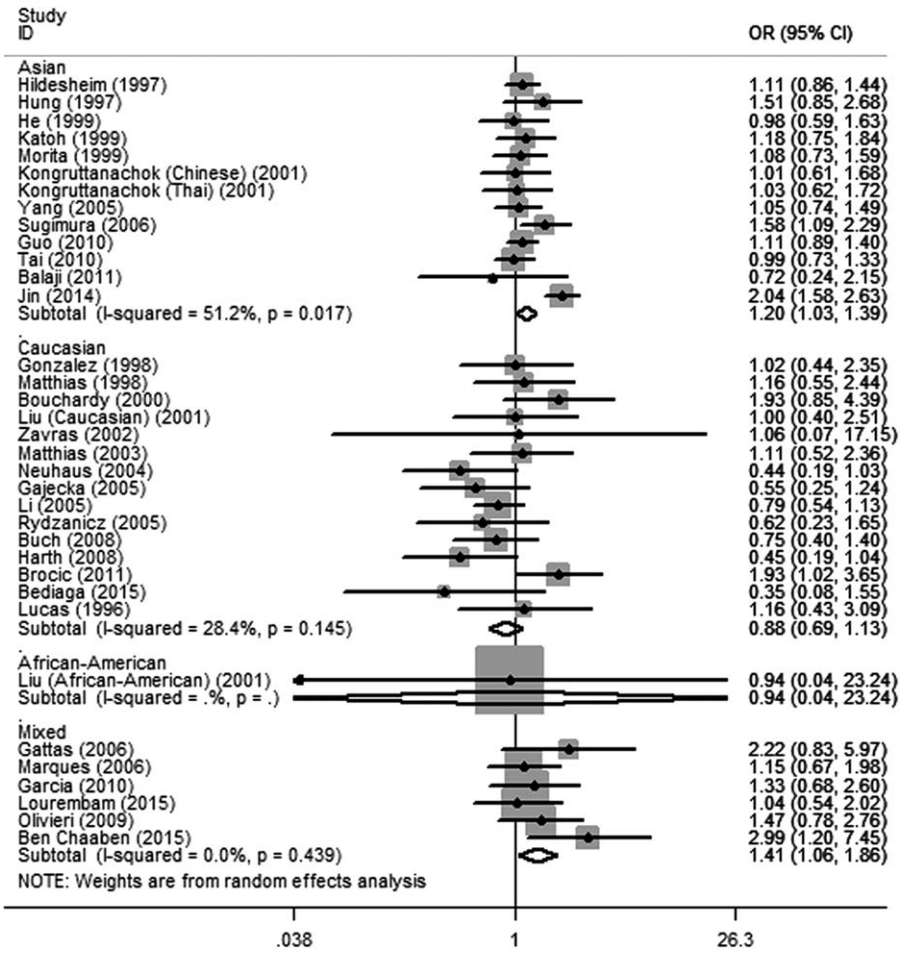

Figure 3. Meta-analysis for the association of HNC risk with CYP2E1 RsaI/PstI polymorphism (c2 vs c1; stratified by ethnicity). HNC = head and neck cancer.

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 c2c2 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[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[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,[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[14] there were also 6 studies[43,44,49,55,61,72] 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 confidential estimate.

In the subgroup analysis on ethnicity, significant association was only found among Asians and mixed-ethnicity, but not

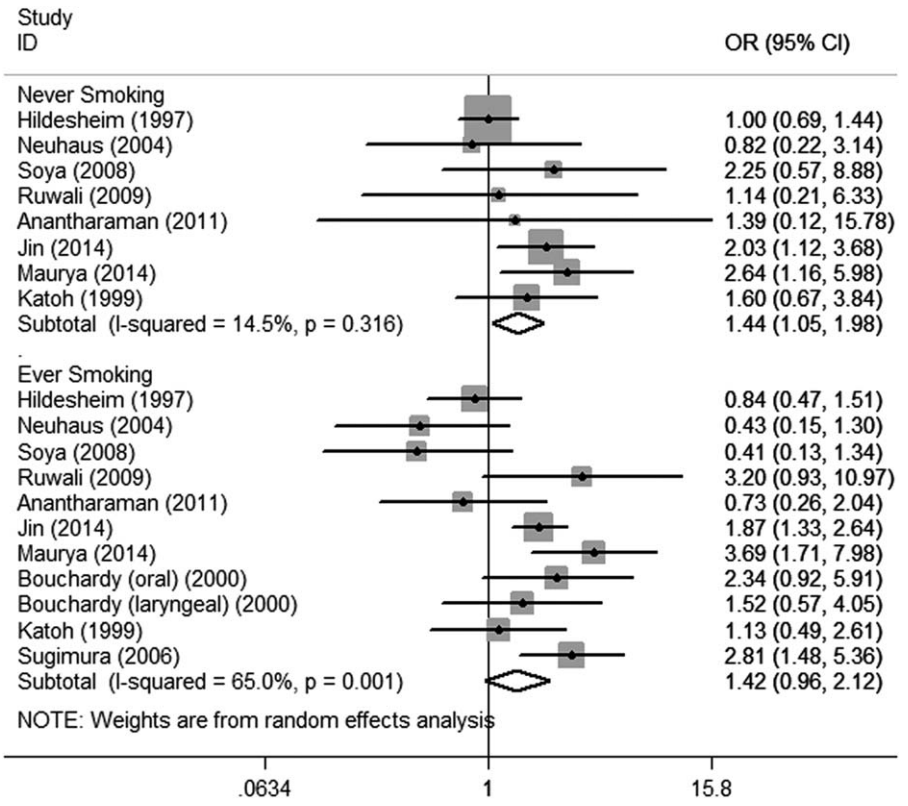

Figure 4. Meta-analysis for the association of HNC risk with CYP2E1 RsaI/PstI polymorphism (c2c2+c1c2 vs c1c1; stratified by smoking status). HNC = head and neck cancer.

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

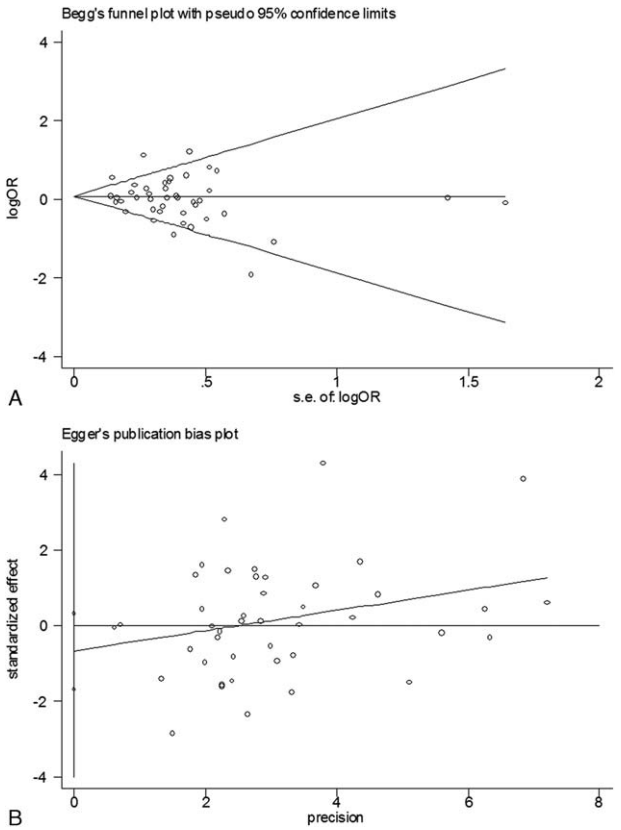

Figure 5. Publication bias test for the overall data (c2c2+c1c2 vs c1c1): (A) funnel plot; (B) Egger's linear regression test.

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 possible publications without a language limitation as we could in the databases. Another limitation concerned the ethnicity. The number of the included studies for African-American was only one, and thus, the results were underpowered to address an association for this ethnicity. Moreover, stratified analyses regarding other confounding factors such as age, gender, HPV infection, and tumor stages were not assessed in this meta-analysis because relevant information was insufficient in the 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 RsaI/PstI polymorphism has a correlation with increased HNC risk. Particularly, the variant c2 of CYP2E1 RsaI/PstI may confer HNC risk among Asians, mixed populations, and never-smokers. More future research is required to verify the results.

References

[1] Specenier P, Vermorken JB. Cetuximab: its unique place in head and neck cancer treatment. Biologics 2013;7:77–90.

[2] Toporcov TN, Znaor A, Zhang ZF, et al. Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium. Int J Epidemiol 2015;44:169–85.

[3] Field N, Lechner M. Exploring the implications of HPV infection for head and neck cancer. Sex Transm Infect 2015;91:229–30.

[4] Little MA, Pokhrel P, Murphy KL, et al. The reasons for betel-quid chewing scale: assessment of factor structure, reliability, and validity. BMC Oral Health 2014;14:62.

[5] Choudhury JH, Ghosh SK. Gene-environment interaction and susceptibility in head and neck cancer patients and in their first-degree relatives: a study of Northeast Indian population. J Oral Pathol Med 2015;44: 495–501.

[6] Enomoto M, Tierney WJ, Nozaki K. Risk of human health by particulate matter as a source of air pollution—comparison with tobacco smoking. J Toxicol Sci 2008;33:251–67.

[7] Singh S, Arcaroli J, Thompson DC, et al. Acetaldehyde and retinaldehyde-metabolizing enzymes in colon and pancreatic cancers. Adv Exp Med Biol 2015;815:281–94.

[8] Chen BH, Wang CC, Hou YH, et al. Mechanism of sulfotransferase pharmacogenetics in altered xenobiotic metabolism. Expert Opin Drug Metab Toxicol 2015;11:1053–71.

[9] Zhuo X, Zhao H, Chang A, et al. Cytochrome P450 1A1 Ile462Val polymorphism and oral carcinoma risk: an updated meta-analysis including 1,515 cases and 2,233 controls. Tumour Biol 2012;33:2079–89.

[10] Zhuo X, Zhao H, Chang A, et al. Quantitative assessment of CYP1A1*2A variations with oral carcinoma susceptibility: evidence from 1,438 cases and 2,086 controls. Cancer Invest 2012;30:552–9.

[11] Seitz HK, Wang XD. The role of cytochrome P450 2E1 in ethanol-mediated carcinogenesis. Subcell Biochem 2013;67:131–43.

[12] Hayashi S, Watanabe J, Kawajiri K. Genetic polymorphisms in the 5′-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J Biochem 1991;110:559–65.

[13] Tang K, Li Y, Zhang Z, et al. The PstI/RsaI and DraI polymorphisms of CYP2E1 and head and neck cancer risk: a meta-analysis based on 21 case-control studies. BMC Cancer 2010;10:575.

[14] Lu D, Yu X, Du Y. Meta-analyses of the effect of cytochrome P450 2E1 gene polymorphism on the risk of head and neck cancer. Mol Biol Rep 2011;38:2409–16.

[15] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.

[16] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[17] Munafo MR, Clark TG, Flint J. Assessing publication bias in genetic association studies: evidence from a recent meta-analysis. Psychiatry Res 2004;129:39–44.

[18] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[19] Khlifi R, Messaoud O, Rebai A, et al. Polymorphisms in the human cytochrome P450 and arylamine N-acetyltransferase: susceptibility to head and neck cancers. BioMed Res Int 2013;2013:582768.

[20] Daly AK. Polymorphic Vvriants of cytochrome P450: relevance to cancer and other diseases. Adv Pharmacol 2015;74:85–111.

[21] Sikdar N, Mahmud SA, Paul RR, et al. Polymorphism in CYP1A1 and CYP2E1 genes and susceptibility to leukoplakia in Indian tobacco users. Cancer Lett 2003;195:33–42.

[22] Duarte EC, Ribeiro DC, Gomez MV, et al. Genetic polymorphisms of carcinogen metabolizing enzymes are associated with oral leukoplakia development and p53 overexpression. Anticancer Res 2008;28 (2A):1101–6.

[23] Gupta S, Gupta OP, Srivastava S. Role of CYP2E1 genetic polymorphism in the development of oral leukoplakia among tobacco users in North Indian population. Indian J Cancer 2014;51:154–8.

[24] Jia WH, Pan QH, Qin HD, et al. A case-control and a family-based association study revealing an association between CYP2E1 polymorphisms and nasopharyngeal carcinoma risk in Cantonese. Carcinogenesis 2009;30:2031–6.

[25] Tanabe H, Ohhira M, Ohtsubo T, et al. Genetic polymorphism of aldehyde dehydrogenase 2 in patients with upper aerodigestive tract cancer. Alcohol Clin Exp Res 1999;23(4 suppl):17S–20S.

[26] Matthias C, Jahnke V, Jones PW, et al. Cyclin D1, glutathione S-transferase, and cytochrome P450 genotypes and outcome in patients with upper aerodigestive tract cancers: assessment of the importance of individual genes using multivariate analysis. Cancer Epidemiol Biomarkers Prev 1999;8:815–23.

[27] Jahnke V, Matthias C, Fryer A, et al. Glutathione S-transferase and cytochrome-P-450 polymorphism as risk factors for squamous cell carcinoma of the larynx. Am J Surg 1996;172:671–3.

[28] Jahnke V, Strange R, Matthias C, et al. Glutathione S-transferase and cytochrome P450 genotypes as risk factors for laryngeal carcinoma. Eur Arch Otorhinolaryngol 1997;254(suppl 1):S147–9.
[29] Sam SS, Thomas V, Reddy KS, et al. Gene–gene interactions of drug metabolizing enzymes and transporter protein in the risk of upper aerodigestive tract cancers among Indians. Cancer Epidemiol 2010; 34:626–33.
[30] Guo LK, Zhang CX, Guo XF. Association of genetic polymorphisms of aldehyde dehydrogenase-2 and cytochrome P450 2E1-RsaI and alcohol consumption with oral squamous cell carcinoma. Acta Academiae Medicinae Sinicae 2012;34:390–5.
[31] Hildesheim A, Chen CJ, Caporaso NE, et al. Cytochrome P4502E1 genetic polymorphisms and risk of nasopharyngeal carcinoma: results from a case-control study conducted in Taiwan. Cancer Epidemiol Biomarkers Prev 1995;4:607–10.
[32] Maurya SS, Katiyar T, Dhawan A, et al. Gene–environment interactions in determining differences in genetic susceptibility to cancer in subsites of the head and neck. Environ Mol Mutagen 2015;56:313–21.
[33] Liu S, Park JY, Schantz SP, et al. Elucidation of CYP2E1 5′ regulatory RsaI/PstI allelic variants and their role in risk for oral cancer. Oral Oncol 2001;37:437–45.
[34] Kongruttanachok N, Sukdikul S, Setavarin S, et al. Cytochrome P450 2E1 polymorphism and nasopharyngeal carcinoma development in Thailand: a correlative study. BMC Cancer 2001;1:4.
[35] Lucas D, Menez C, Floch F, et al. Cytochromes P4502E1 and P4501A1 genotypes and susceptibility to cirrhosis or upper aerodigestive tract cancer in alcoholic caucasians. Alcohol Clin Exp Res 1996;20:1033–7.
[36] Hildesheim A, Anderson LM, Chen CJ, et al. CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 1997;89:1207–12.
[37] Hung HC, Chuang J, Chien YC, et al. Genetic polymorphisms of CYP2E1, GSTM1, and GSTT1; environmental factors and risk of oral cancer. Cancer Epidemiol Biomarkers Prev 1997;6:901–5.
[38] Gonzalez MV, Alvarez V, Pello MF, et al. Genetic polymorphism of *N*-acetyltransferase-2, glutathione S-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. J Clin Pathol 1998;51:294–8.
[39] Matthias C, Bockmuhl U, Jahnke V, et al. Polymorphism in cytochrome P450 CYP2D6, CYP1A1, CYP2E1 and glutathione S-transferase, GSTM1, GSTM3, GSTT1 and susceptibility to tobacco-related cancers: studies in upper aerodigestive tract cancers. Pharmacogenetics 1998; 8:91–100.
[40] Morita S, Yano M, Tsujinaka T, et al. Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma. Int J Cancer 1999;80:685–8.
[41] Katoh T, Kaneko S, Kohshi K, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and oral cavity cancer. Int J Cancer 1999;83:606–9.
[42] Bouchardy C, Hirvonen A, Coutelle C, et al. Role of alcohol dehydrogenase 3 and cytochrome P-4502E1 genotypes in susceptibility to cancers of the upper aerodigestive tract. Int J Cancer 2000;87:734–40.
[43] Zavras AI, Wu T, Laskaris G, et al. Interaction between a single nucleotide polymorphism in the alcohol dehydrogenase 3 gene, alcohol consumption and oral cancer risk. Int J Cancer 2002;97:526–30.
[44] Matthias C, Jahnke V, Fryer AA, et al. First results on the influence of polymorphisms at glutathione S-transferase, cytochrome P450, and tumor necrosis factor gene loci on the development of multiple head and neck cancer. Laryngo rhinootologie 2003;82:25–30.
[45] Neuhaus T, Ko YD, Lorenzen K, et al. Association of cytochrome P450 2E1 polymorphisms and head and neck squamous cell cancer. Toxicol Lett 2004;151:273–82.
[46] Li G, Liu Z, Sturgis EM, et al. CYP2E1 G1532C, NQO1 Pro187Ser, and CYP1B1 Val432Leu polymorphisms are not associated with risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14:1034–6.
[47] Yang XR, Diehl S, Pfeiffer R, et al. Evaluation of risk factors for nasopharyngeal carcinoma in high-risk nasopharyngeal carcinoma families in Taiwan. Cancer Epidemiol Biomarkers Prev 2005;14:900–5.
[48] Gajecka M, Rydzanicz M, Jaskula-Sztul R, et al. CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1 and GSTT1 polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. Mutat Res 2005;574:112–23.
[49] Rydzanicz M, Wierzbicka M, Gajecka M, et al. The impact of genetic factors on the incidence of multiple primary tumors (MPT) of the head and neck. Cancer Lett 2005;224:263–78.
[50] Sugimura T, Kumimoto H, Tohnai I, et al. Gene–environment interaction involved in oral carcinogenesis: molecular epidemiological study for metabolic and DNA repair gene polymorphisms. J Oral Pathol Med 2006;35:11–8.
[51] Marques CF, Koifman S, Koifman RJ, et al. Influence of CYP1A1, CYP2E1, GSTM3 and NAT2 genetic polymorphisms in oral cancer susceptibility: results from a case-control study in Rio de Janeiro. Oral Oncol 2006;42:632–7.
[52] Gattas GJ, de Carvalho MB, Siraque MS, et al. Genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 associated with head and neck cancer. Head Neck 2006;28:819–26.
[53] Boccia S, Cadoni G, Sayed-Tabatabaei FA, et al. CYP1A1, CYP2E1, GSTM1, GSTT1, EPHX1 exons 3 and 4, and NAT2 polymorphisms, smoking, consumption of alcohol and fruit and vegetables and risk of head and neck cancer. J Cancer Res Clin Oncol 2008;134:93–100.
[54] Soya SS, Vinod T, Reddy KS, et al. CYP2E1 polymorphisms and gene-environment interactions in the risk of upper aerodigestive tract cancers among Indians. Pharmacogenomics 2008;9:551–60.
[55] Harth V, Schafer M, Abel J, et al. Head and neck squamous-cell cancer and its association with polymorphic enzymes of xenobiotic metabolism and repair. J Toxicol Environ Health A 2008;71:887–97.
[56] Buch SC, Nazar-Stewart V, Weissfeld JL, et al. Case-control study of oral and oropharyngeal cancer in whites and genetic variation in eight metabolic enzymes. Head Neck 2008;30:1139–47.
[57] Ruwali M, Khan AJ, Shah PP, et al. Cytochrome P450 2E1 and head and neck cancer: interaction with genetic and environmental risk factors. Environ Mol Mutagen 2009;50:473–82.
[58] Olivieri EH, da Silva SD, Mendonca FF, et al. CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictors of risk and poor outcome in head and neck squamous cell carcinoma patients. Oral Oncol 2009;45:e73–9.
[59] Garcia SM, Curioni OA, de Carvalho MB, et al. Polymorphisms in alcohol metabolizing genes and the risk of head and neck cancer in a Brazilian population. Alcohol Alcohol 2010;45:6–12.
[60] Tai J, Yang M, Ni X, et al. Genetic polymorphisms in cytochrome P450 genes are associated with an increased risk of squamous cell carcinoma of the larynx and hypopharynx in a Chinese population. Cancer Genet Cytogenet 2010;196:76–82.
[61] Guo X, Zeng Y, Deng H, et al. Genetic polymorphisms of CYP2E1, GSTP1, NQO1 and MPO and the risk of nasopharyngeal carcinoma in a Han Chinese Population of Southern China. BMC Res Notes 2010;3:212.
[62] Cury NM, Russo A, Galbiatti AL, et al. Polymorphisms of the CYP1A1 and CYP2E1 genes in head and neck squamous cell carcinoma risk. Mol Biol Rep 2012;39:1055–63.
[63] Brocic M, Supic G, Zeljic K, et al. Genetic polymorphisms of ADH1C and CYP2E1 and risk of oral squamous cell carcinoma. Otolaryngol Head Neck Surg 2011;145:586–93.
[64] Anantharaman D, Samant TA, Sen S, et al. Polymorphisms in tobacco metabolism and DNA repair genes modulate oral precancer and cancer risk. Oral Oncol 2011;47:866–72.
[65] Hakenewerth AM, Millikan RC, Rusyn I, et al. Joint effects of alcohol consumption and polymorphisms in alcohol and oxidative stress metabolism genes on risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2011;20:2438–49.
[66] Balaji L, Singh KB, Bhaskar LV. Genetic polymorphisms of the CYP2E1 gene do not contribute to oral cancer susceptibility in south Indians. Asian Pac J Cancer Prev 2011;12:1523–7.
[67] Maurya SS, Anand G, Dhawan A, et al. Polymorphisms in drug-metabolizing enzymes and risk to head and neck cancer: evidence for gene-gene and gene-environment interaction. Environ Mol Mutagen 2014;55:134–44.
[68] Jin J, Lin F, Liao S, et al. Effects of SNPs (CYP1B1*2 G355T, CYP1B1*3 C4326G, and CYP2E1*5 G-1293C), smoking, and drinking on susceptibility to laryngeal cancer among Han Chinese. PloS One 2014;9:e106580.
[69] Bediaga NG, Marichalar-Mendia X, Rey-Barja N, et al. Polymorphisms in alcohol and tobacco metabolism genes in head and neck cancer in the Basque Country. J Oral Pathol Med 2015;44:769–75.
[70] Pandey R, Mehrotra D, Catapano C, et al. Association of mitochondrial deoxyribonucleic acid mutation with polymorphism in CYP2E1 gene in oral carcinogenesis. J Oral Biol Craniofac Res 2012;2:4–9.
[71] Lourembam DS, Singh AR, Sharma TD, et al. Evaluation of risk factors for nasopharyngeal carcinoma in a high-risk area of India, the Northeastern Region. Asian Pac J Cancer Prev 2015;16:4927–35.
[72] He Z, Yuan J, Wang S, et al. Association between genetic polymorphism of human cytochrome P450 2El gene and susceptibility to nasopharyngeal carcinoma. Chin J Cancer 1999;18:517–9.

[73] Ben Chaaben A, Abaza H, Douik H, et al. Genetic polymorphism of cytochrome P450 2E1 and the risk of nasopharyngeal carcinoma. Bulletin Cancer 2015;102:967–72.
[74] Du XL, Liu CC. Racial/Ethnic disparities in socioeconomic status, diagnosis, treatment and survival among medicare-insured men and women with head and neck cancer. J Health Care Poor Underserved 2010;21:913–30.
[75] Stephens EA, Taylor JA, Kaplan N, et al. Ethnic variation in the CYP2E1 gene: polymorphism analysis of 695 African-Americans, European-Americans and Taiwanese. Pharmacogenetics 1994;4:185–92.
[76] Lucas D, Menez C, Girre C, et al. Cytochrome P450 2E1 genotype and chlorzoxazone metabolism in healthy and alcoholic Caucasian subjects. Pharmacogenetics 1995;5:298–304.
[77] Uematsu F, Kikuchi H, Motomiya M, et al. Association between restriction fragment length polymorphism of the human cytochrome P450IIE1 gene and susceptibility to lung cancer. Jpn J Cancer Res 1991;82:254–6.
[78] Weinberger PM, Merkley MA, Khichi SS, et al. Human papillomavirus-active head and neck cancer and ethnic health disparities. Laryngoscope 2010;120:1531–7.