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ORIGINAL RESEARCH

The association of the *CYP1A1* Ile462Val polymorphism with head and neck cancer risk: evidence based on a cumulative meta-analysis

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Objective: The aim of this study was to address the association between the Ile462Val polymorphism in the gene encoding cytochrome P450 1A1 (*CYP1A1*) and the risk of head and neck cancer (HNC).

Materials and methods: The Medline/PubMed, EMBASE, and Web of Science databases were searched. The strength of the association was evaluated by calculating the odds ratio (OR) with a 95% confidence interval (CI).

Results: Overall, we observed an increased risk of HNC in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype among the 6,367 cases and 6,395 controls evaluated in the 34 eligible studies, with a pooled OR of 1.284 (95% CI: 1.119–1.473). In addition, we observed an increased risk of HNC in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype in the subgroup analyses (OR =1.362, 95% CI: 1.102–1.685 for laryngeal cancer; OR =1.519, 95% CI: 1.253–1.843 for pharyngeal cancer; OR =1.371, 95% CI: 1.111–1.693 for Asians; and OR =1.329, 95% CI: 1.138–1.551 for patients in studies using hospital-based controls).

Conclusion: This cumulative meta-analysis suggests that the *CYP1A1* Ile462Val polymorphism might contribute to the risk of HNC, particularly for pharyngeal cancer and laryngeal cancer.

Keywords: *CYP1A1*, polymorphism, head and neck cancer, oral cancer, laryngeal cancer, pharyngeal cancer, risk

Introduction

Head and neck cancer (HNC) is a broad term that encompasses epithelial malignancies that arise in the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. HNC is the sixth most common type of cancer, representing ~6% of all cancer cases and accounting for an estimated 650,000 new cases and 350,000 cancer deaths worldwide each year.[1] Tobacco smoking and alcohol intake are considered the major risk factors for HNC;[2] however, only a small proportion of smokers and alcohol users develop HNC in their lifetime, suggesting that individual susceptibility might also be a significant factor in disease etiology. The Cancer Genome Atlas profiled 279 head and neck squamous cell carcinomas and provides a comprehensive landscape of the somatic genomic aberrations associated with HNC.[3]

The gene encoding cytochrome P450 1A1 (*CYP1A1*) maps to chromosome 15 and encodes an aryl hydrocarbon hydrolase that plays a role in the metabolism of the carcinogenic polycyclic aromatic hydrocarbons that are present in tobacco smoke. Previous studies have demonstrated that an amino acid substitution from isoleucine to valine in codon 462 (rs1048943, A4889G) in exon 7 of *CYP1A1* enhances the

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catalytic activity of the cytochrome P450 1A1 protein[4,5] and influences the risk of several cancers.[6–10] To date, a number of epidemiological studies that have explored the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC have been reported.[11–44] However, the results of these studies have been conflicting rather than conclusive. Thus, we conducted a cumulative meta-analysis of eligible published studies to further evaluate the association between the Ile462Val polymorphism and HNC risk.

Materials and methods

Literature source and analytical methods

We searched the Medline/PubMed, EMBASE, and Web of Science databases for articles published until December 31, 2015, using various combinations of the following keywords in the search parameters: HNC, oral cancer, oral cavity cancer, pharyngeal cancer, laryngeal cancer, *CYP1A1*, cytochrome P450 1A1, rs1048943, polymorphism, and variant. In addition, we manually searched the reference list of relevant publications to identify additional studies.

The selection criteria of the eligible publications included the following: 1) the study that evaluated the *CYP1A1* Ile462Val polymorphism and the risk of HNC; 2) the publication that reported a case–control study or cohort study; 3) the publication that reported all data regarding the genotype of the *CYP1A1* Ile462Val polymorphism that was required to calculate the odds ratio (OR) with a 95% confidence interval (CI); and 4) the study that used controls verified to have no clinical evidence of a malignancy. Accordingly, reviews and publications of overlapping studies were excluded. In the context of publications with overlapping data, those that included more data were preferentially used in the study. In total, 45 published studies evaluating the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC were identified. We reviewed all the articles in accordance with the criteria defined earlier and excluded nine reviews and two publications with overlapping data. Ultimately, 34 studies were deemed to be eligible for the present study. One additional article[45] was included in the oral cancer subgroup analysis only.

Data extraction

Data were extracted, analyzed by two investigators, and entered into an electronic database. The following information was collected from each study: author, year of publication, country, ethnicity, the source of control (hospital-based controls, which mean controls from hospital, and population-based controls, which mean controls from randomly selected healthy individuals), study population size, genotype frequency, and tumor type. The key characteristics of the eligible studies are summarized in Table 1.

Quantitative data synthesis

A cumulative meta-analysis was performed to assess the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC.[46] The Cochrane *Q* statistics test was used to examine heterogeneity.[47] The data were combined using either a fixed-effects model or a random-effects model depending on the results of the heterogeneity test. The fixed-effects model was applied if no heterogeneity was detected. In all other cases, the random-effects model was applied.[47] A funnel plot was created to assess publication bias. Begg's test (a linear regression approach used to measure funnel plot asymmetry on the natural logarithm scale of the OR)[48] was used to evaluate the symmetry of the funnel plot. A sensitivity analysis was conducted in which we sequentially removed each eligible study from the pooled data.[46] The pooled OR of all the studies evaluated in this meta-analysis was calculated to evaluate the significance of the Ile/Val+Val/Val vs the Ile/Ile genotype in HNC.

All the statistical analyses were conducted using the STATA 10.0 software package (StataCorp LP, College Station, TX, USA). All the tests were two-sided, and a *P*-value of ≤ 0.05 was considered to be statistically significant.

Results

Meta-analysis databases

Table 1 lists some general information associated with the eligible studies, including the first author, year of publication, country, ethnicity of the patients, source of controls, tumor subtype, and study population size. We identified a total of 34 studies that included 6,367 cases and 6,395 controls that evaluated the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC.

Test of heterogeneity

No heterogeneity was observed for the *CYP1A1* Ile/Val+Val/Val genotype vs the Ile/Ile genotype in the subgroup analyses of patients with pharyngeal cancer and Caucasian patients. Therefore, we calculated the pooled ORs for these two groups using the fixed-effects model. The random-effects model was used to calculate the pooled OR for the remaining subgroup analyses.

Quantitative data synthesis

Table 2 lists the pooled ORs associated with the *CYP1A1* Ile462Val polymorphism and the risk of HNC calculated

Table 1 Characteristics of the selected studies

First author	Year	Country	Ethnicity	Source of controls	Tumor type	Cases	Controls
Park et al[11]	1997	USA	Mixed	HB	Oral and laryngeal cancers	131	131
Matthias et al[12]	1998	Germany	Caucasian	HB	Oral, laryngeal, and pharyngeal cancers	380	193
Oude Ophuis et al[13]	1998	the Netherlands	Mixed	HB	Oral, laryngeal, and pharyngeal cancers	185	207
Katoh et al[14]	1999	Japan	Asian	HB	Oral cancer	92	147
Morita et al[15]	1999	Japan	Asian	HB	Oral, laryngeal, and pharyngeal cancers	145	164
McWilliams et al[16]	2000	USA	Caucasian	PB	Oral, laryngeal, and pharyngeal cancers	139	121
Olshan et al[17]	2000	USA	Mixed	HB	Oral, laryngeal, and pharyngeal cancers	171	189
Sato et al[18]	2000	Japan	Asian	PB	Oral cancer	142	142
Ko et al[19]	2001	Germany	Caucasian	HB	Oral, laryngeal, and pharyngeal cancers	312	300
Sreelekha et al[20]	2001	India	Asian	HB	Oral cancer	98	60
Hahn et al[21]	2002	Germany	Caucasian	HB	Oral cancer	94	92
Kao et al[22]	2002	People's Republic of China	Asian	HB	Oral cancer	106	146
Gronau et al[23]	2003	Germany	Caucasian	HB	Oral, laryngeal, and pharyngeal cancers	187	139
Gronau et al[45,a]	2003	Germany	Caucasian	HB	Oral cancer	73	136
Varzim et al[24]	2003	Portugal	Caucasian	HB	Laryngeal cancer	88	177
Evans et al[25]	2004	USA	Caucasian	PB	Oral, laryngeal, and pharyngeal cancers	281	208
Li et al[26]	2004	People's Republic of China	Asian	HB	Laryngeal cancer	89	164
Xie et al[27]	2004	USA	Mixed	PB	Oral cancer	132	143
Gajecka et al[28]	2005	Poland	Caucasian	HB	Laryngeal cancer	289	316
Leichsenring et al[29]	2006	Brazil	Mixed	PB	Oral cancer	72	60
Marques et al[30]	2006	Brazil	Mixed	HB	Oral cancer	231	212
Sugimura et al[31]	2006	Japan	Asian	HB	Oral cancer	122	241
Reszka et al[32]	2008	Poland	Caucasian	HB	Oral, laryngeal, and pharyngeal cancers	127	145
Sam et al[33]	2008	India	Asian	HB	Oral, laryngeal, and pharyngeal cancers	408	220
Varela-Lema et al[34]	2008	Spain	Caucasian	HB	Oral and pharyngeal cancers	66	92
Amtha et al[35]	2009	Indonesia	Asian	HB	Oral cancer	81	162
Singh et al[36]	2009	India	Asian	HB	Oral, laryngeal, and pharyngeal cancers	200	200
Sabitha et al[37]	2010	India	Asian	HB	Oral, laryngeal, and pharyngeal cancers	205	245
Sharma et al[38]	2010	India	Asian	HB	Oral, laryngeal, and pharyngeal cancers	203	201
Tai et al[39]	2010	People's Republic of China	Asian	HB	Laryngeal and pharyngeal cancers	278	278
Lourenco et al[40]	2011	Brazil	Mixed	HB	Oral, laryngeal, and pharyngeal cancers	142	142
Balaji et al[41]	2012	India	Asian	HB	Oral cancer	157	132
Szanyi et al[42]	2012	Hungary	Caucasian	HB	Laryngeal and pharyngeal cancers	142	150
Singh et al[43]	2014	India	Asian	HB	Oral cancer	122	127
Maurya et al[44]	2015	India	Asian	Unknown	Oral, laryngeal, and pharyngeal cancers	750	749

Note: [a]Included in the oral cancer subgroup analysis only.
Abbreviations: HB, hospital-based control study; PB, population-based control study.

Table 2 Pooled OR of the association between the *CYP1A1* Ile462Val polymorphism and the risk of head and neck cancer

Group	Number of studies	Heterogeneity test		Analysis model	Cumulative OR (95% CI)	Hypothesis test		Begg's test	
		Q	*P*			*Z*	*P*	*Z*	*P*
Overall	34	104.34	0.000	Random-effects model	1.284 (1.119–1.473)	3.561	0.000	0.36	0.722
Tumor subtype									
Oral cancer	21	74.59	0.000	Random-effects model	1.181 (0.930–1.500)	1.364	0.173	0.23	0.820
Laryngeal cancer	11	22.44	0.013	Random-effects model	1.362 (1.102–1.685)	2.854	0.004	0.78	0.436
Pharyngeal cancer	7	6.82	0.338	Fixed-effects model	1.519 (1.253–1.843)	4.250	0.000	0.30	0.764
Ethnicity									
Asians	16	59.89	0.000	Random-effects model	1.371 (1.111–1.693)	2.941	0.003	0.14	0.893
Caucasians	11	14.98	0.135	Fixed-effects model	1.138 (0.941–1.376)	1.329	0.184	0.00	1.000
Source of controls									
Population based	5	14.08	0.007	Random-effects model	1.013 (0.606–1.694)	0.051	0.960	0.73	0.462
Hospital based	28	80.64	0.000	Random-effects model	1.329 (1.138–1.551)	3.603	0.000	1.05	0.295

Abbreviation: OR, odds ratio.

for the 6,367 cases and 6,395 controls evaluated. Overall, we observed an increased risk of HNC in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype, with a pooled OR of 1.284 (95% CI: 1.119–1.473; Figure 1).

In the subgroup analyses of tumor types, we observed an increased risk of laryngeal cancer and pharyngeal cancer in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype. The pooled ORs for laryngeal cancer and pharyngeal cancer were 1.362 (95% CI: 1.102–1.685) and 1.519 (95% CI: 1.253–1.843), respectively (Table 2). No significant association between the *CYP1A1* Ile462Val polymorphism and the risk of oral cancer was observed. The pooled OR associated with the risk of oral cancer was 1.181 (95% CI: 0.930–1.500; Table 2).

In the subgroup analyses of patients stratified by ethnicity, we observed an increased risk of HNC in Asians with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype, with a pooled OR of 1.371 (95% CI: 1.111–1.693; Table 2). No significant association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC in Caucasians was observed. The pooled OR in this subgroup was 1.138 (95% CI: 0.941–1.376; Table 2).

In the subgroup analysis in which the data were stratified according to the source of controls used in the study, we observed an increased risk of HNC associated with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype in patients from studies that used hospital-based controls (OR =1.329, 95% CI: 1.138–1.551), but no significant association was observed in patients from studies that used population-based controls (OR =1.013, 95% CI: 0.606–1.694; Table 2).

Bias diagnosis

The publication bias was evaluated using a funnel plot analysis. The shape of the funnel plot appeared roughly symmetrical (Figure 2), and the results of Begg's test suggested that publication bias would not significantly affect the summary estimates.

Sensitivity analysis

To determine the impact of the individual data sets on the pooled OR, we conducted a sensitivity analysis in which each eligible study was consecutively omitted from the pooled data. The pooled OR was not significantly affected by the sequential deletion of individual studies, indicating that the results of this study are reliable and robust (Figure 3).

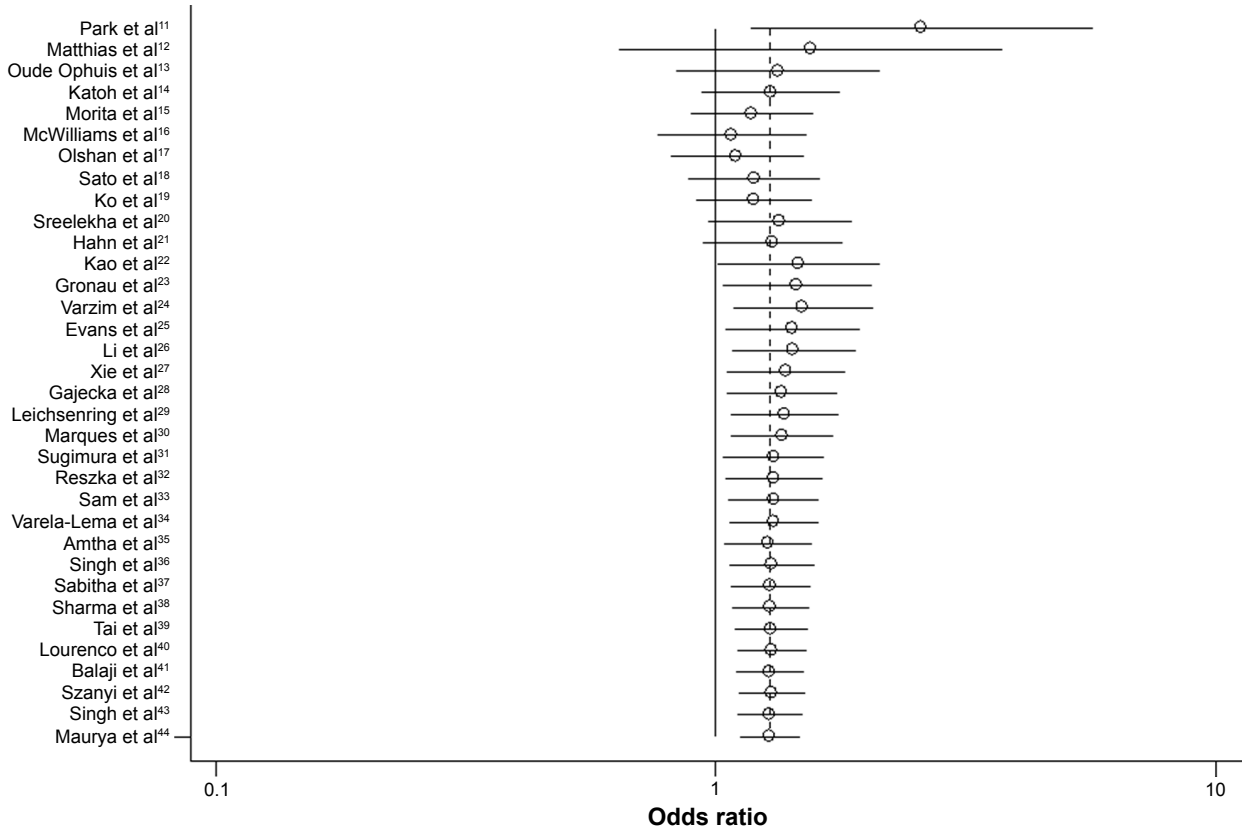

Figure 1 The cumulative meta-analysis of the association between the *CYP1A1* Ile462Val polymorphism and the risk of head and neck cancer (Ile/Val+Val/Val vs Ile/Ile).

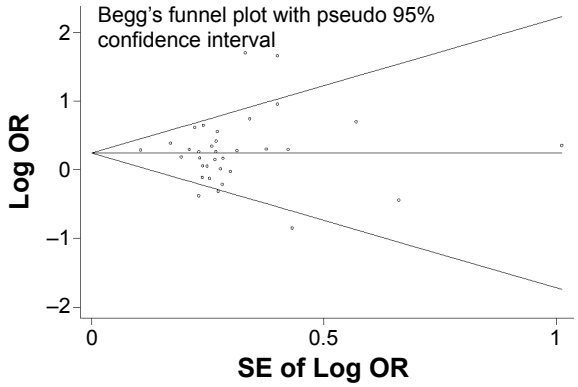

Figure 2 Funnel plot of the publication bias detected using Begg's test (Ile/Val+Val/Val vs Ile/Ile).
Notes: The *x*-axis represents the standard error of the log of the odds ratio, and the *y*-axis represents the log of the odds ratio.
Abbreviations: SE, standard error; OR, odds ratio.

Discussion

Although two previously published meta-analyses evaluated the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC,[49,50] careful examination of these data reveals several key issues worth noting. First, Qin et al mistakenly included a study published by Cascorbi et al[51] that evaluated the association between the –463G/A variant of the myeloperoxidase gene and the risk of cancer of the aerodigestive tract in their meta-analysis (supplemental Table 1 and supplemental references in the study of Qin et al[50]). Similarly, Qin et al also mistakenly included a study published by Bufalo et al[52] that evaluated the association between the *CYP1A1* Ile462Val polymorphism and the susceptibility of thyroid cancer in their meta-analysis (supplemental Table 1 and supplemental references in Qin et al[50]). Furthermore, Qin et al[50] included one article with overlapping data.[53]

In the second meta-analysis, Liu et al[49] reported data from a study by Katoh et al[14] that were inconsistent with the data reported by Katoh et al[14] in their original publication. Katoh et al reported that they evaluated 92 cases and 147 controls (Table 3 in Katoh et al[14]); however, Liu et al reported that 147 cases and 92 controls had been evaluated in that study (Table 1 in Liu et al[49]). Similarly, Liu et al reported that Reszka et al's study evaluated 151 controls (Table 1 in Liu et al[49]), whereas Reszka et al reported that they evaluated

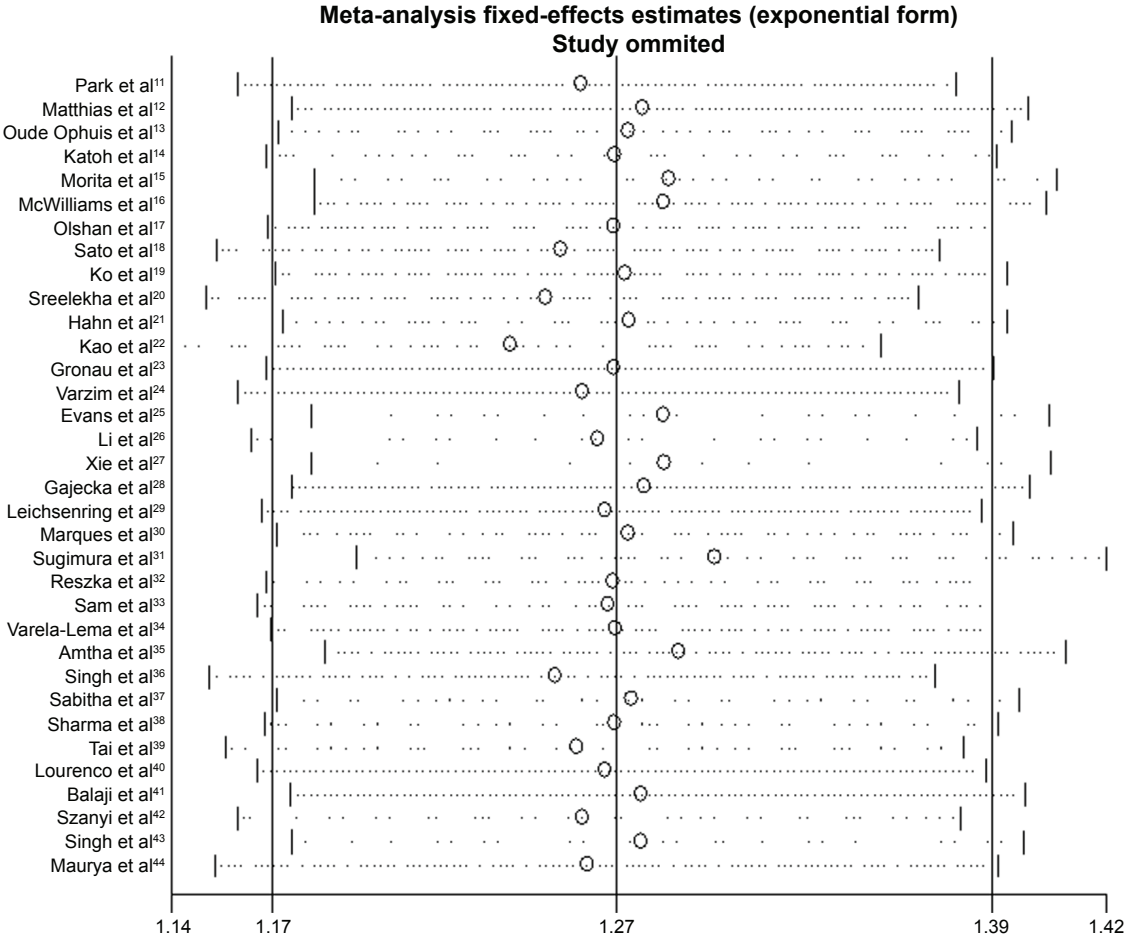

Figure 3 Sensitivity analysis of the association between the *CYP1A1* Ile462Val polymorphism and the risk of head and neck cancer (Ile/Val+Val/Val vs Ile/Ile).

145 controls (Table 2 in Reszka et al[32]). Furthermore, Liu et al[49] reported that the study by McWilliams et al[16] evaluated 160 cases and 149 controls (Table 1 in Liu et al[49]). However, McWilliams et al reported that they evaluated 139 cases and 121 controls (Table 4 in McWilliams et al[16]). In addition, three eligible articles[12,13,27] were not included in the study by Liu et al.[49] Finally, although Sato et al reported that the *CYP1A1* Ile462Val polymorphism was associated with an increased risk of oral cancer,[18] these data were not included in the oral cancer subgroup analysis in the Liu et al's study (Figure 2A in Liu et al[49]).

Together, these observations indicate that current data describing the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC are not entirely reliable. Three recent studies[41,43,44] on this topic have been subsequently published; however, further verification of the association between the *CYP1A1* Ile462Val polymorphism and the risk of HNC is still required. The cumulative meta-analysis reported here was conducted to verify the association of the *CYP1A1* Ile462Val polymorphism with the risk of HNC using data from a total of 34 studies that evaluated 6,367 cases and 6,395 controls. The goal of this study was to provide comprehensive and conclusive evidence regarding the association of the *CYP1A1* Ile462Val polymorphism with the risk of HNC. Overall, we observed an increased risk of HNC in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype. We also observed an increased risk of HNC in patients with the Ile/Val+Val/Val genotype compared to those with the Ile/Ile genotype in various subgroups (laryngeal cancer, pharyngeal cancer, Asians, and patients in studies that used hospital-based controls).

The potential limitations of this meta-analysis should also be acknowledged. First, only published articles were selected in this study; therefore, publication bias might have influenced the results. To address this issue, we evaluated the eligible studies using Begg's test and determined that the likelihood of publication bias was negligible. Second, although some confounding variables were well balanced between studies, different studies might have used different inclusion criteria and different sources of controls. These factors should be taken into account when interpreting the pooled data. To address this issue, we conducted subgroup analyses of patients in studies that used hospital-based controls and those that used population-based controls. Third, this cumulative meta-analysis is based on an unadjusted estimate; therefore, a more precise analysis accounting for adjusted factors should be carried out in the future.

Conclusion

Our results suggest that the *CYP1A1* Ile462Val polymorphism is associated with an increased risk of HNC, particularly in laryngeal cancer and pharyngeal cancer. The verification of our findings requires additional well-designed studies evaluating large sample sizes.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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