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META-ANALYSIS

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Cyclooxygenase-2–1195G>A Polymorphism and Head and Neck Squamous Cell Carcinoma Susceptibility: A Meta-Analysis of 1564 Cases and 2346 Controls

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to investigate the association between cyclooxygenase-2 (COX-2) rs689466 (–1195 G>A) polymorphism and susceptibility to head and neck squamous cell carcinoma (HNSCC) by performing a meta-analysis.

Material/Methods: PubMed and Embase were searched for relevant cohort and case-control studies up to 13 March 2015. After data extraction and methodological quality assessment for eligible studies, the overall, subgroup, sensitivity, and cumulative meta-analyses were conducted using the Comprehensive Meta-Analysis software (version 2.2).

Results: Finally, 5 case-control studies involving 1564 HNSCC patients and 2346 healthy controls were included. For overall population, the results of 3 genetic models showed significant association, while the other 2 presented negative association [A *vs.* G: OR=0.97–1.09, 95%CI=0.97–1.09; AA *vs.* GG: OR=1.26, 95%CI=1.01–1.57; AA *vs.* GA: OR=1.21, 95%CI=1.01–1.45); AA *vs.* (GG+GA): OR=1.20, 95%CI=1.01–1.43; (AA+GA) *vs.* GG: OR=0.98, 95%CI=0.84–1.15]. Publication bias was not assessed due to the limited number of included studies.

Conclusions: This meta-analysis indicated that COX-2 rs689466 polymorphism might be associated with increased susceptibility to HNSCC. We also suggest performing more relevant studies in order to enlarge the sample size and obtain more precise results.

MeSH Keywords: Cyclooxygenase 2 • Head and Neck Neoplasms • Meta-Analysis • Mouth Neoplasms • Polymorphism, Genetic

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Background

Head and neck squamous cell carcinoma (HNSCC), mainly including the oral cavity squamous cell carcinoma (OSCC), oropharynx squamous cell carcinoma (OPSCC), pharynx squamous cell carcinoma (PSCC), and larynx squamous cell carcinoma (LSCC), is one of the most common cancers worldwide [1,2]. Considering the special location and great importance of the head and neck, seeking risk factors associated with HNSCC susceptibility and developing effective strategies to prevent this disease is a significant task. Human papillomavirus (HPV) infection, tooth loss, cigarette smoking, periodontal diseases, and alcohol drinking are commonly accepted risk factors of developing HNSCC [2–7]. Genetic factors also play important roles during the onset and development of HNSCC [8–10], and the cyclooxygenase-2 (COX-2) gene has been reported to be one of those relevant genes [11].

The human COX-2 gene, is 8.3 kb in size, also named the prostaglandin-endoperoxide synthase 2 (PTGS2), is located on chromosome 1q25.2-q25.3; it contains 10 exons and 9 introns and produces an mRNA of 4.6 kb [12]. Published meta-analyses indicated the COX-2 gene plays a vital role in tumor development, metastasis, and inflammation [13–17]. Enhanced biosynthesis of inflammation-promoting prostaglandins via Cox-2 catalysis, resulting in elevated DNA damage, may be the mechanism of the carcinogenesis effects of this gene. [18] The rs689466 polymorphism (–1195 G>A) is one of the most widely investigated Cox-2 polymorphisms. In 2008, a case-control study including 377 OSCC patients and 442 healthy controls found COX-2–1195 G>A polymorphism was a potential genetic risk of OSCC [19]. However, this positive result was not supported in the following case-control study by Peters et al. in 2009 [20]. This situation with different studies showing controversial results is less convincing; therefore, a meta-analysis was necessary to pool evidence for providing a more precise and less uncertain result [21]. Therefore, we conducted this meta-analysis to investigate the association between COX-2 rs689466 polymorphism and HNSCC susceptibility.

Material and Methods

We carried out this meta-analysis according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement [22].

Eligible criteria

A case-control or cohort study would be included if it met all the following criteria: (1) the theme was the association between COX-2 rs689466 polymorphism and human HNSCC susceptibility; (2) the patients were identified as HNSCC, OPSCC, OSCC, PSCC, or LSCC pathologically; (3) the controls were healthy volunteers or cancer-free population; (4) the frequency of genotypes in case and control groups were reported or could be calculated from reported data; (5) the publication language was English or Chinese, and the full text could be obtained.

Search strategy

A comprehensive electronic database search in PubMed and Embase was conducted up to 13 March, 2015 by 2 authors independently. The search term was as follows: [(carcinoma OR cancer OR tumor OR neoplasm) AND (head and neck OR oral OR pharyngeal OR oropharynx OR laryngeal OR laryngopharyngeal OR mouth OR tongue) AND (polymorphism OR mutation OR variant OR haplotype) AND (cyclooxygenase-2 OR COX-2 OR PTGs2)]. Moreover, the bibliographies of recent reviews and included studies were retrieved manually.

Data extraction

Two authors independently selected studies and then extracted data from included studies, any disagreements were resolved by discussion. The extracted data were as follow: surname of the first author, publication year, study locations (country), ethnicity of included population, source of control, smoking status, alcohol consumption, sample sizes, frequency of genotype distribution, HPV status, genotyping method, and Hardy-Weinberg equilibrium (HWE) for controls (p>0.05 of control was considered as in accordance with HWE).

Methodological quality assessment

Two authors independently assessed the study methodological quality using the Newcastle-Ottawa scale (NOS) [21,23–26], and the detailed items was clearly described by Leng et al. [27].

Data analysis

The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were chosen as effect size. The A *vs.* G, AA *vs.* GG, AA *vs.* GA, AA *vs.* (GG+GA), and (AA+GA) *vs.* GG genetic models were used to present the strength of associations between COX-2 rs689466 polymorphism and HNSCC susceptibility. Firstly, the Cochran's Q and I^2 test [28] were used to explore the heterogeneity among the involved studies. An I^2 no more than 50% along with corresponding p>0.10 indicates an acceptable heterogeneity and the fixed-effects model was used; otherwise, we used the random-effects model. We performed subgroup analyses according to ethnicity, smoking status, alcohol consumption, and type of study design. Since all included studies conformed to HWE and no HPV-positive patients were involved, no subgroup analysis according to HWE and HPV status was performed. The sensitivity analysis was also carried out to investigate the robustness of overall results. The cumulative meta-analysis was

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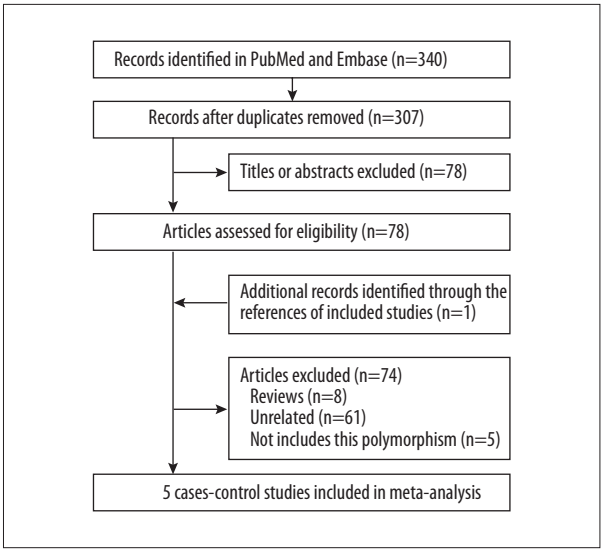

Figure 1. Flow chart from identification of eligible studies to final inclusion.

conducted to observe the trend with sample size enlarged. Because only 5 studies were included in our analyses, publication bias was not assessed. All analyses were carried out using the Comprehensive Meta-Analysis software (version 2.2) [23].

Results

Study characteristics

The electronic searching identified 44 studies from PubMed and 296 studies from Embase, and finally 5 case-control studies involving 1564 HNSCC patients and 2346 healthy controls were included [19,20,29–31]. Figure 1 shows the selection process.

Of them, 3 studies were conducted in China [19,30,31], 1 in the Netherlands [20], and 1 in India [29]; 2 studies exclusively included OSCC patients [19,29], and 1 study [31] reported data for all HNSCC patients, OSCC, and LSCC patients respectively; 1 study [29] focused on smokers and the smoking status of the other 4 studies were mixed; 1 study did not report the alcohol consumption, and the other 4 studies were mixed. All studies conformed to HWE and involved no HPV patients. The methodological quality of all the included studies was high, and the score ranged from 7 to 8. Table 1 presents the main characteristics.

Meta-analysis

Table 2 presents results of overall and subgroup analyses. Overall, the meta-analysis showed significantly increased risk in 3 genetic models: AA *vs.* GG (OR=1.26, 95%CI=1.01–1.57, Figure 2), AA *vs.* GA (OR=1.21, 95%CI=1.01–1.45), AA *vs.* (GG+GA) (OR=1.20, 95%CI=1.01–1.43). When stratified by smoking status, a significantly increased risk was also found in these 3 genetic models (AA *vs.* GG, AA *vs.* GA, and AA *vs.* (GG+GA)) in mixed populations. When stratified by ethnicity, only the allele genetic model showed an increased risk, with marginal significance in Asians population (OR=1.12, 95%CI=1.00–1.25). The other results of overall and subgroup population all revealed non-significant association.

Because all included studies conformed to HWE and involved no HPV-positive patients, no subgroup analysis according to

Table 1. Characteristics of included studies in the meta-analysis.

Study	Country (Ethnicity)	Form of disease	Sample size (Ca/Co)	Genotyping method	Genotype distribution (Ca/Co)			P for HWE	Smoking status	Alcohol status	NOS
					GG	GA	AA				
Chiang 2008	China (Asian)	OSCC	368/441	PCR-RFLP	80/114	187/235	101/92	0.17	Mixed	Mixed	7
Peters 2009	Netherlands (Caucasian)	HNSCC	431/438	PCR	275/260	134/163	22/15	0.08	Mixed	Mixed	7
Mittal 2010	India (Asian)	OSCC	193/137	PCR-RFLP	3/5	57/32	133/100	0.24	Smokers	Unclear	8
Chang 2013	China (Asian)	HNSCC	313/295	Taqman	93/90	146/148	74/57	0.78	Mixed	Mixed	8
Niu 2014	China (Asian)	HSNCC	259/1035	Taqman	61/222	126/542	72/271	0.11	Mixed	Mixed	7
		OSCC	149/1035	Taqman	44/222	80/542	25/271	0.11	Mixed	Mixed	
		LSCC	90/1035	Taqman	17/222	46/542	27/271	0.11	Mixed	Mixed	

Ca/Co – Case/Control; HNSCC – head and neck squamous cell carcinoma; OSCC – oral cavity squamous cell carcinoma; LSCC – larynx squamous cell carcinoma; HWE – Hardy-Weinberg equilibrium; Mixed – smokers and non-smokers; NOS – Newcastle-Ottawa scale.

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Table 2. Results of overall and subgroups analyses of pooled ORs and 95% CIs.

Overall and subgroups	No. of studies	Heterogeneity (I^2/p)	Effect model	OR(95%CI)	
A *vs.* G					
Overall	5	7%/0.37	Fixed	1.08	(0.97–1.09)
Smoker (mixed)	4	21%/0.28	Fixed	1.09	(0.98–1.21)
Smoker (yes)	1	NA	NA	0.93	(0.61–1.42)
Asians	4	0%/0.56	Fixed	1.12	(1.00–1.25)
Caucasian	1	NA	NA	0.92	(0.73–1.16)
OSCC	3	80%/<0.10	Random	1.01	(0.87–1.16)
LSCC	1	NA	NA	0.96	(0.72–1.32)
AA *vs.* GG					
Overall	5	0%/0.46	Fixed	1.26	(1.01–1.57)
Smoker (mixed)	4	0%/0.39	Fixed	1.24	(1.00–1.55)
Smoker (yes)	1	NA	NA	2.22	(0.52–2.49)
Asians	4	14%/0.32	Fixed	1.25	(0.99–1.57)
Caucasian	1	NA	NA	1.39	(0.70–2.73)
OSCC	3	86%/<0.10	Random	1.07	(0.40–2.86)
LSCC	1	NA	NA	1.30	(0.69–2.45)
AA *vs.* GA					
Overall	5	28%/0.23	Fixed	1.21	(1.01–1.45)
Smoker (mixed)	4	0%/0.68	Fixed	1.30	(1.07–1.58)
Smoker (yes)	1	NA	NA	0.75	(0.45–1.24)
Asians	4	30%/0.23	Fixed	1.17	(0.97–1.42)
Caucasian	1	NA	NA	1.78	(0.89–3.57)
OSCC	3	76%/<0.10	Random	0.88	(0.53–1.48)
LSCC	1	NA	NA	1.17	(0.71–1.93)
AA *vs.* (GG+GA)					
Overall	5	12%/0.34	Fixed	1.20	(1.01–1.43)
Smoker (mixed)	4	0%/0.61	Fixed	1.27	(1.06–1.53)
Smoker (yes)	1	NA	NA	0.82	(0.51–1.33)
Asians	4	26%/0.26	Fixed	1.18	(0.99–1.41)
Caucasian	1	NA	NA	1.52	(0.78–2.96)
OSCC	3	83%/<0.10	Random	0.89	(0.50–1.58)
LSCC	1	NA	NA	1.21	(0.75–1.94)
(AA+GA) *vs.* GG					
Overall	5	28%/0.23	Fixed	0.98	(0.84–1.15)
Smoker (mixed)	4	27%/0.25	Fixed	0.97	(0.83–1.14)
Smoker (yes)	1	NA	NA	2.40	(0.56–10.21)
Asians	4	13%/0.33	Fixed	1.07	(0.88–1.29)
Caucasian	1	NA	NA	0.83	(0.63–1.09)
OSCC	3	75%/<0.10	Random	1.03	(0.57–1.88)
LSCC	1	NA	NA	1.17	(0.68–2.03)

OSCC – oral cavity squamous cell carcinoma; LSCC – larynx squamous cell carcinoma; NA – not available.

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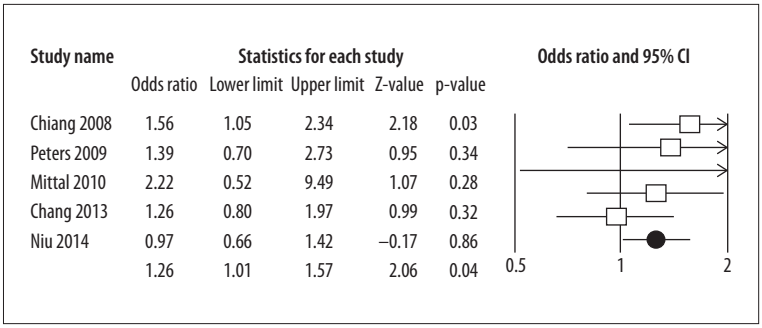

Figure 2. Forest plot for AA *vs.* GG comparison (fixed effect model).

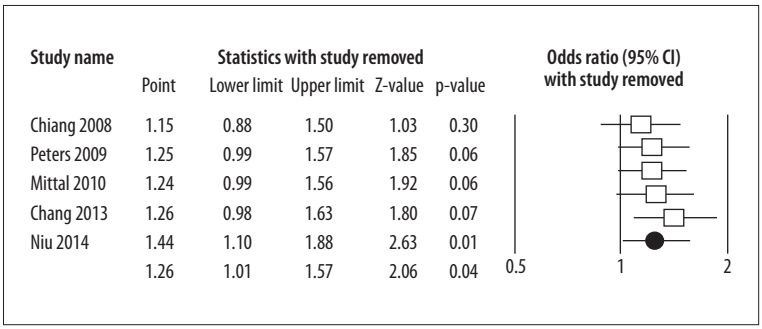

Figure 3. Sensitivity forest plot for AA *vs.* GG comparison (fixed effect model).

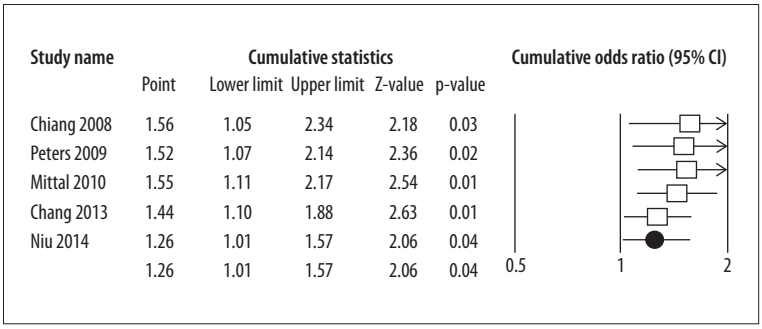

Figure 4. Cumulative forest plot for AA *vs.* GG comparison (fixed effect model).

HWE or HPV status was performed. When omitting each included study sequentially, the results of sensitivity analyses all showed the overall results were unstable (Figure 3 for AA *vs.* GG). The results of cumulative analyses by publication year also failed to detect a significant change (Figure 4 for AA *vs.* GG).

Publication bias

Because only 5 case-control studies were included [32], publication bias was not assessed.

Discussion

Head and neck carcinogenesis is a complex and multi-step process, with which dysregulation involving many oncogenes and/or tumor suppressor genes have been considered as associated [33]. COX-2 is considered to be relevant in inflammation and cancer via being upregulated by cytokines, growth factors, and tumor promoters. Various nuclear regulatory factors such as NF-κB and c-myb are located in the promoter region of COX-2, hence its expression is transcriptionally regulated [29,34]. Different published studies reported consistent results that COX-2 is overexpressed in multiple cancers, including HNSCC and premalignant lesions [35–37], suggesting its important role in tumor development and dissemination [38]. There are some studies evaluating the effects of single-nucleotide polymorphism (SNPs) in COX-2 gene on the predisposition of HNSCC. In this meta-analysis, we investigated the association between COX-2 rs689466 polymorphism and HNSCC susceptibility based on 5 case-control studies. All studies were confirmed to be consistent with HWE and the results of 5 genetic models showed that COX-2 rs689466 polymorphism might be associated with increased susceptibility of HNSCC; however, the ORs were not large and not all the genetic models showed significant association.

As smoking and alcohol consumption are well accepted risk factors of HNSCC [5], we extracted the smoking and alcohol status of included population. Because the alcohol consumption

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was unclear in 1 study and mixed in the other 4 studies, we only conducted a subgroup analysis of smoking status. Only 1 study investigated exclusively the smokers [29], and the other 4 studies both included smokers and non-smokers but did not reported relevant data separately; hence, we did not extract more information about smoking status from included studies. The results of the mixed smoking status subgroup were similar to overall population, while a non-significant association was shown for smokers. We also considered the influence of different ethnicities and performed a subgroup analysis according to the ethnicity; the results showed a non-significant increasing trend for both Asians and whites. The subgroup analysis based on different cancer sites was also considered in this meta-analysis and yielded similar results as ethnicity for OSCC and LSCC.

For the overall population, the heterogeneity of all genetic models was good and only the fixed-effects model was used to pool data. Acceptable heterogeneity was revealed in all the subgroup analyses except for the OSCC subgroup. The reason why obvious heterogeneity emerged in the OSCC group is hard to explain with the obtained information, and real statistical heterogeneity is a possible explanation. Moreover, the small sample size may have been a source of heterogeneity, since only 5 case-control studies involving 1564 HNSCC patients and 2346 healthy controls were included. Other potential sources include mixed smoking status, different detection technology, or concomitant diseases, which need to be examined in further research.

Our study is the first meta-analysis on this topic, and more details should be investigated in the future. Firstly, many confirmed risk factors, such as periodontal diseases, tooth loss, and HPV infection [3–7], of HNSCC are necessary to report in the study and should be adjusted so we can judge whether the polymorphism is a risk factor or just a marker. Secondly, only 5 studies were included and the results were not consistent in the 5 genetic models, and this may indicate that the sample size was too small and further relevant studies are needed. The results of sensitivity and cumulative analyses also support that more studies are needed. Thirdly, if the COX-2 rs689466 polymorphism is a risk factor for HNSCC, the mechanism needs to be explored. If the COX-2 rs689466 polymorphism is only a marker of other risk factors, the role that this polymorphism plays and the associated risk factors should be determined.

Some limitations in this meta-analysis should be pointed out. Obviously, the sample size is small. Although we did our best to search for more eligible studies, only 4 single-center and 1 multiple-center case-control studies met the inclusion criteria. The small sample size might influence the statistic power and provide a biased result. Because we lacked enough studies, the publication bias was not assessed. Hence, we could not examine the existence of publication bias through qualitative or quantitative detection. Due to the restricted accessibility and language barriers, we did not search databases in other languages (e.g. Russian, Japanese, French, or German) for relevant studies; accordingly, certain eligible studies were possibly not included in this work. Secondly, since the included population consisted of Asians and whites only, the result of this meta-analysis might not be reasonably extended to other ethnicities. As we know, different ethnicity may possess its own genetic background by which the onset, development, or outcome of certain diseases could be influenced. Thirdly, the results of five genetic models did not converge and the sensitivity analyses indicated unstable results. This might be partially explained by the absence of sufficient sample size, on which a conclusive result depends. On the other hand, this also suggests relevant studies should be conducted in the future.

Conclusions

Our meta-analysis indicated that COX-2 rs689466 polymorphism might be associated with increased susceptibility to HNSCC. In the future, 3 points should be taken into consideration: relevant studies reporting more details should be performed for further investigation; whether COX-2 rs689466 polymorphism is a risk factor or just a marker needs to be verified; and the underlying mechanisms of COX-2 rs689466 polymorphism's effects on HNSCC onset, development, or outcome need to be investigated.

Conflict of interest

The authors declare that they have no conflict of interest.

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