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Cigarette smoking and the risk of nasopharyngeal carcinoma: a meta-analysis of epidemiological studies

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ABSTRACT

Objective The role of cigarette smoking as an independent risk factor for patients with nasopharyngeal carcinoma (NPC) is controversial. We attempted to provide evidence of a reliable association between cigarette smoking and the risk of NPC.

Design Meta-analysis.

Data sources PubMed online and the Cochrane Library of relevant studies published up to February 2016.

Eligibility criteria All studies had to evaluate the relationship between NPC and cigarette smoking with never smokers as the reference group.

Outcomes The primary outcome was the adjusted OR, RR or HR of NPC patients comparing smoking with never-smoking; the second was the crude OR, RR or HR.

Results We identified 17 case–control studies and 4 cohort studies including 5960 NPC cases and 429 464 subjects. Compared with never smokers, current smokers and ever smokers had a 59% and a 56% greater risk of NPC, respectively. A dose–response relationship was identified in that the risk estimate rose by 15% (p<0.001) with every additional 10 pack-years of smoking, and risk increased with intensity of cigarette smoking (>30 cigarettes per day). Significantly increased risk was only found among male smokers (OR, 1.36; 95% CI 1.15 to 1.60), not among female smokers (OR, 1.58; 95% CI 0.99 to 2.53). Significantly increased risk also existed in the differentiated (OR, 2.34; 95% CI 1.77 to 3.09) and the undifferentiated type of NPC (OR, 1.15; 95% CI 0.90 to 1.46). Moreover, people who started smoking at younger age (<18 years) had a greater risk than those starting later for developing NPC (OR, 1.78; 95% CI 1.41 to 2.25).

Conclusions Cigarette smoking was associated with increased risk of NPC, especially for young smokers. However, we did not find statistical significant risks of NPC in women and in undifferentiated type, which might warrant further researches.

Strengths and limitations of this study

- Major strengths of our meta-analysis comprise new published studies being included, strict selection criteria, careful literature search, data extraction and analyses by two authors separately.
- The main limitations of our meta-analysis are study design, characteristics and size of study population, different outcome and variables used in eligible studies.

INTRODUCTION

There were approximately 86 691 incident cases of NPC and 50 831 NPC-related deaths in 2012 worldwide.[1] Despite NPC being rare in developed countries, the overall incidence rate in Southeastern Asia is 6.5/100 000 person-years among men and 2.6/100,000 person-years among women.[2] Particularly, an age-standardised incidence rate of 20–50 per 100 000 men in south China presented a remarkably high incidence compared with that among white populations.[3]

Cigarette smoking has been regarded as a risk factor for the occurrence of a wide variety of malignancies, including respiratory tract, gastrointestinal and urogenital systems.[4 5] Over the decades, some reports have suggested that cigarette smoking is associated with NPC risk.[6] However, the association has not been consistently demonstrated, some studies failed to find such a positive association.[7–10] The discrepancies of inconsistent outcome might be owing to variations in study population, methodology, definitions of cigarette smoking and so on. Furthermore, inevitable recall bias and confounding in case–control studies might further complicate the scenario.[11 12]

One recent meta-analysis of 28 case–control studies and 4 cohort studies reported the adverse effect of cigarette smoking on the incidence of NPC.[13] The pooled analysis showed that ever smokers had a 60% greater risk of developing the disease than never smokers. And there was a significant dose-dependent association. However, between-study heterogeneity was strikingly high across the overall analysis and still remained after stratified analyses. Specifically, some included studies might not be appropriate to be combined for synthetic analysis because of their inadequate reports about association between cigarette smoking and NPC risk,[14–17] unclear definition of cigarette smoking and

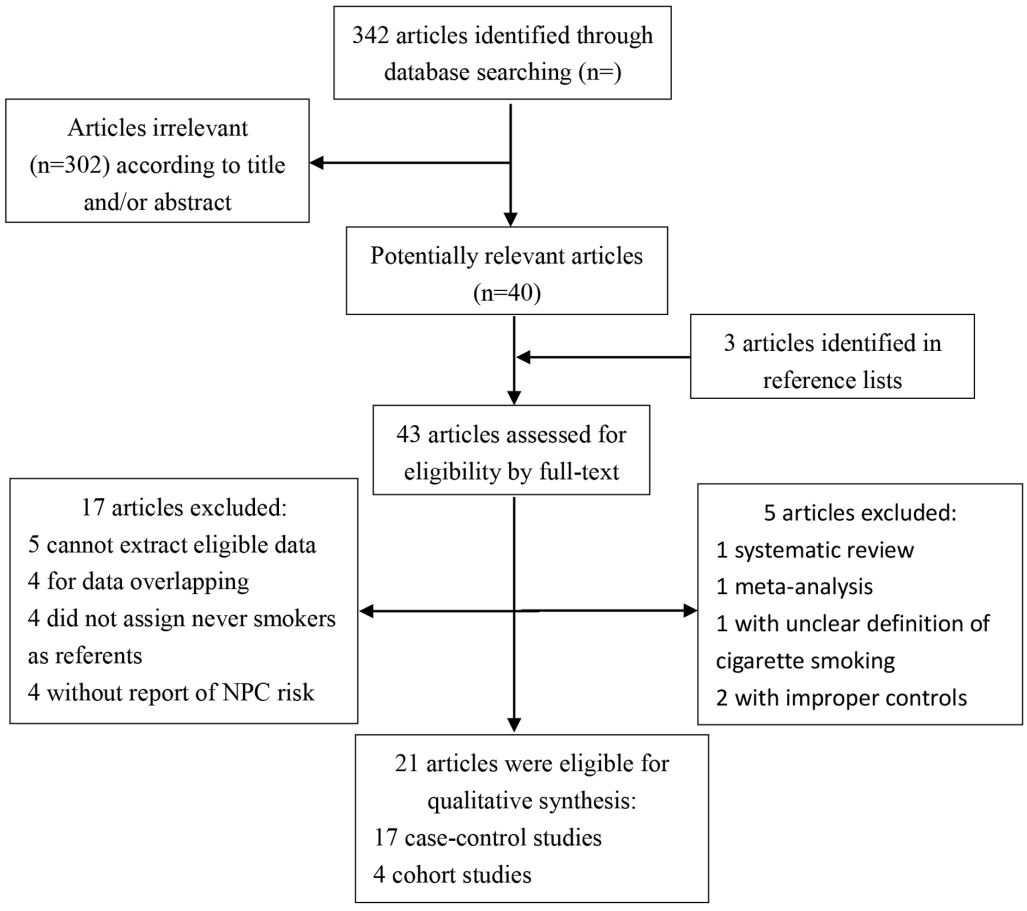

Figure 1 Summary of literature search.

health condition of controls,[18 19] controls with a history of cancer[20] and inappropriate reference group.[21 22] These might result in overestimating or underestimating the association of cigarette smoking on NPC risk, and thus the conclusions might be hard to interpret. In addition, new studies have been published recently which warrant an up-to-date analysis.[23–26]

In this meta-analysis, we sought to provide a summary of available literature to examine the association between cigarette smoking and the risk of NPC, we also assessed the gender and histological type differences in effects of cigarette smoking on the NPC risk.

METHODS

Literature search

This meta-analysis was performed on the basis of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[27] To identify all relevant publications on NPC and cigarette smoking, first, we used the engine 'Windows Internet Explorer 10.0' to search the PubMed and Cochrane Library databases with terms '(nasopharyngeal carcinoma OR nasopharyngeal cancer OR cancer of nasopharynx) AND (smoking OR cigarette OR tobacco OR nicotine) AND (etiology OR epidemiology OR environment OR risk factor) AND (Humans (Mesh))', then we scrutinised the references of articles obtained from the database search for additional studies. Only publications in English were included.

Selection criteria

The following criteria were applied for literature selection: (1) the study was case–control or cohort design; (2) controls were cancer-free; (3) cases were patients who were histopathologically confirmed NPC and had no other malignancies; (4) the study evaluated the relationship between NPC and one of various aspects of cigarette smoking, including cigarette smoking status, smoking intensity, cumulative amount of cigarette smoking, age at onset and duration of smoking; (5) studies used never smokers as the reference group; (6) studies provided enough information to estimate the ORs or the relative risk (RR) or HRs with 95% CI for cigarette smoking variable. If multiple articles were on the same study population, the one with adequate information or most related or largest sample size was finally selected; furthermore, when there were separate data for gender or histological type of NPC in one study, they were considered for additional subgroup analysis.

Data extraction

The following data were extracted from eligible studies: first author, publication year, study region, study design, sample size, control source, age of participants (range,

Table 1 General characteristics of case–control studies used for meta-analysis

Study	Region	Period	Incidence rate	Cases /Controls	Man /Woman	Age range (years old)	Quality score	Source of controls	Matching factors	Adjusting factors
Mabuchi *et al*[34]	USA	–	Low	39/39	–	–	7	Hospital-based	Age, sex, race, Education, occupation, marital status	—
Yu *et al*[37]	Guangzhou	1983–1985	High	306/306	209/97	Under 45	7	Population-based	Age, sex, residence, education	Birth place, marital status, dietary risk
Nam *et al*[35]	USA	1983–1986	Low	204/408	141/63	<65	5	Hospital-based	Age, sex	By multiple logistic regression analysis
Sriamporn *et al*[36]	Thailand	1987–1990	Moderate	120/120	81/39	Mean 47.2	6	Hospital-based	Age, sex	Age, sex, education, residence, occupation, consumption of salted fish and alcohol
Zhu *et al*[38]	USA	1984–1988	Low	113/1910	Man	–	8	Population-based	—	Birth, education, background, medical history, occupation, alcohol intake
Vaughan *et al*[39]	USA	1987–1993	Low	231/244	154/77	Mean 55.2	9	Population-based	Age, sex, region	Age, sex, alcohol use, education
Cheng *et al*[7]	Taiwan	1991–1994	Moderate	375/327	260/115	Mean 46 (15–74)	7	Population-based	Age, sex, residence, education, marital status	Age, sex, race, education, family history of NPC, drinking status
Chelleng *et al*[40]	India	1996–1997	Moderate	47/94	34/13	Mean 43.7	6	Population-based	Age, sex, ethnicity	—
Yuan *et al*[41]	Shanghai	1987–1991	Moderate	935/1032	668/267	Mean 50	8	Population-based	Age, sex, residence	Age, gender, education, intake frequencies of preserved foods, occupational exposure history of chronic ear and nose condition, family history of NPC
Zou *et al*[51]	Yangjiang	1987–1995	High	97/192	83/14	Mean 52.6 (30–82)	7	Population-based	Age, sex, occupation	—
Feng *et al*[42]	North Africa	2002–2005	Moderate	440/409	Man	–	7	Hospital-based	Age, sex, ethnicity, centre, childhood household type	Age, socioeconomic status, dietary risk factors
Ji *et al*[44]	Wuhan	1991–2009	Moderate	1044/1095	755/289	–	5	—	Age, sex, ethnicity	Age, gender, cigarette, alcohol intake, family history
Polesel *et al*[9]	Italy	1992–2008	Low	150/450	119/31	Median 52 (18–76)	6	Hospital-based	Age, sex, residence	Age, sex, place of residence, education, alcohol intake
Turkoz *et al*[45]	Turkey	–	Moderate	183/183	122/61	Mean 44.9 (18–75)	6	Hospital-based	Age, sex	Age, sex
Fachiroh *et al*[23]	Thailand	2005–2010	Moderate	681/1078	504/177	Mean 49.8	6	Hospital-based	Age, sex, residence	Age group, sex, centre, education, alcohol drinking
Lye *et al*[25]	Malaysia	2007	Moderate	356/356	276/80	Mean 53.2	6	Hospital-based	Age, sex, ethnicity	Age, sex, ethnicity, salted fish and alcohol intake
Xie *et al*[26]	Hong Kong	2010–2012	High	352/410	253/99	Mean 51.6	8	Population-based	Age, sex, ethnicity, residence district	Age, sex, education, house type, family history of NPC, environmental tobacco smoke exposure, dietary risk, occupational exposure and cooking experience

NPC, nasopharyngeal carcinoma.

mean), gender distribution, categories of smoking (status, intensity, pack-years, age at onset of smoking and so on), method of questionnaire survey, duration of follow-up, endpoint (for cohort study), covariates for adjustment, OR, RR or HR with their 95% CIs for each category of smoking exposure. In case the above effect sizes were not available, crude effect estimates and 95% CIs were calculated by provided number of subjects. All data were independently extracted and analysed by two investigators; any inconsistency was resolved by consensus.

Quality assessment

The qualities of eligible studies were assessed by using the Newcastle-Ottawa Scale (NOS),[28] which comprised three parts assigned with a maximum of nine points: selection, comparability, exposures and outcome condition. Two investigators evaluated all eligible publications separately and discrepancies were resolved by discussion.

Data integration

Not all studies included in this meta-analysis provided consistent information about cigarette smoking, so we stipulated smoking status as follows: never smokers (people who did not smoke any tobacco product), ever smokers, current smokers and former smokers. With regard to smoking quantity, we combined data extracted from all eligible publications into new categories: subjects with cigarettes consumption of <30 pack-years were assigned to light smokers, while those who consumed ≥30 pack-years were designated to heavy smokers. Similarly, for age at smoking onset, early group meant that subjects began smoking at <18 years age while later group defined as smoking at ≥18 years age. We also defined that regions with NPC incidence <1 per 100 000 person-years was low incidence rate group, 1–10 per 100 000 person-years was intermediate incidence rate group and >10 per 100 000 was high incidence rate group.

Statistical analysis

Since NPC is considered as a relatively rare outcome, RR and OR were not differentiated, the ORs were used as effect size for all studies. We conducted fixed and random effects meta-analyses and the synthetic estimates did not differ substantially between the two models. Therefore, random-effects (Der Simonian-Laird) model,[29] generally regarded as the more conservative method, was applied to calculate point estimates for all analyses. Heterogeneity among articles was estimated by using the I^2 statistic and p value associated with Q statistics.[30]

We conducted dose–response meta-analyses using the generalised least-squares method for trend estimation of summary dose–response data, as described by Greenland and Longnecker.[31] For non-linearity relationship, restricted cubic splines with four knots at percentiles 5%, 35%, 65% and 95% of the distribution were created and p value for non-linearity was computed by testing the null hypothesis that the coefficients of the second and the third splines were equal to zero.[32]

Table 2 General characteristics of cohort studies used for meta-analysis

Study	Region	Period	Incidence rate	Cohort size	No. of cases	Years of follow-up	Endpoint	Quality score	Source of cohort	Adjusting factors
Chow *et al*[46]	USA	1954–1980	Low	248 046	48	26	Mortality	6	Veterans	Age, calendar year
Friborg *et al*[10]	Singapore	1993–2005	High	61 320	173	12	Morbidity	9	Population-based	Age, sex, dialect group, year of interview, education
Hsu *et al*[43]	Taiwan	1984–2006	Moderate	9622	32	Mean 18.1	Incidence	9	Population-based	Age, two anti-EBV viral serum-markers
Lin *et al*[24]	Guangzhou	1988–1999	High	101 823	34	Mean 7.3	Incidence	8	Factory workers and drivers	Age, sex, education, drinking status, occupation

EBV, Epstein-Barr virus.

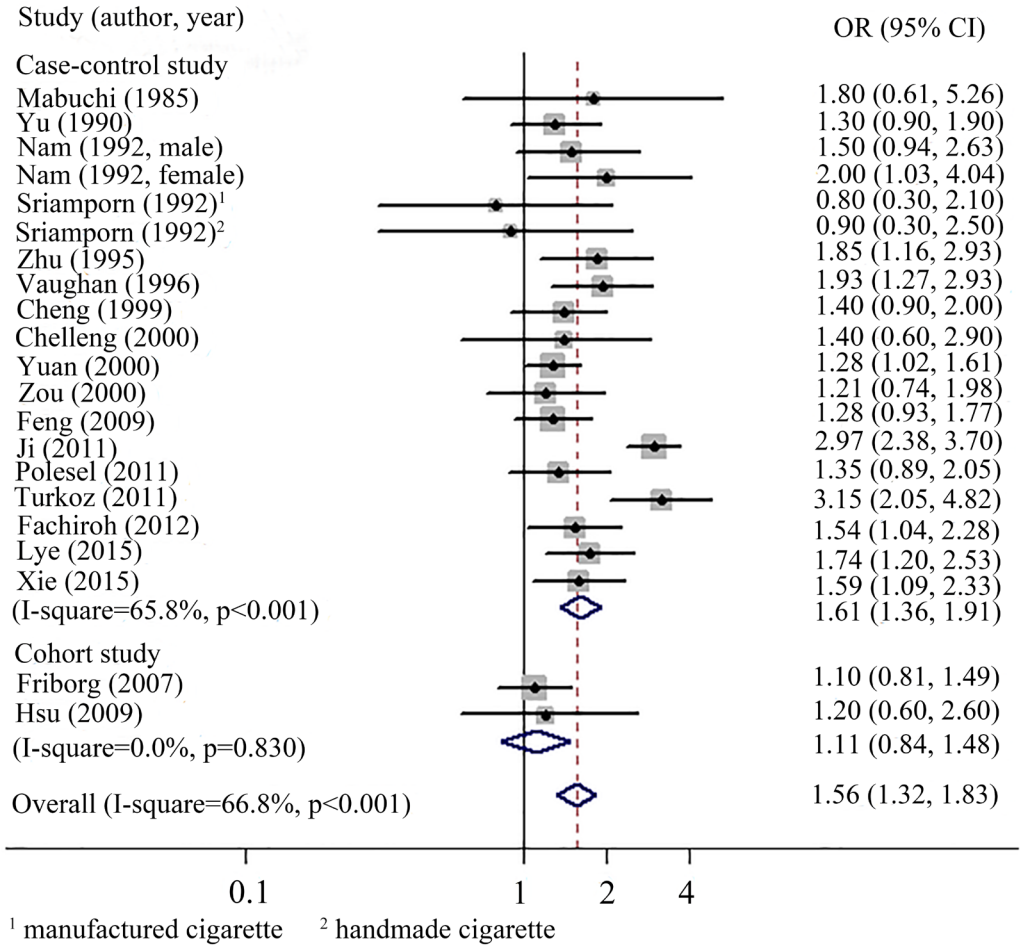

Figure 2 Forest plots for comparing the risk for NPC between ever smokers versus never smokers.

To assess the robustness of our findings and the source of heterogeneity, meta-regression methods and stratified analyses were performed according to study design, incidence rate of regions, adjustment, score of eligible studies, categories of cigarette smoking, gender and NPC histological type (the latter three were only evaluated in stratified analysis). Sensitivity analysis was also conducted by deleting each study in turn to reflect the influence of every single study to the overall estimate. In addition, we evaluated the publication bias in the pooled analysis by Egger's test and the trim-and-fill method.[33] All statistical analyses were performed with Stata SE V.12.0 software, and p value <0.05 (two sides) was considered statistically significant.

Patient involvement

No patients were involved in this study.

RESULTS

Study characteristics

Figure 1 shows the flow chart describing the sequential selection procedures of eligible studies. A total of 342 articles were identified, of which 302 articles were deemed irrelevant after reviewing the titles and abstracts. Subsequently, 40 articles were further scanned by full text. Meanwhile, by searching all references of relevant articles, three additional articles were considered as potentially eligible. Among them, 22 were excluded because of following reasons: 5 studies with inadequate information for data extraction, 4 studies without report of the association between cigarette smoking and NPC risk, 4 studies with overlapped data, 4 studies did not designate never smokers as reference group, 2 studies included improper controls (eg, controls with malignancies or without description of health conditions), 1 without clear definition of cigarette smoking, 1 systematic review and 1 meta-analysis. Finally, 21 articles were eligible for qualitative synthesis, including 17 case–control studies (5673 cases and 8653 controls) and 4 cohort studies (287 cases and 420 811 participants).

All of the studies in the overall analysis were published between 1985 and 2015. Of these included studies, not all studies reported the estimates for all risk estimates. Nineteen studies reported on ever smoking,[7–10 23 25 26 34–45] 10 on former smoking,[7–9 23 26 38 39 41 46] 11 on current smoking,[7–10 23 24 26 38 39 41 46] 10 on pack-years of smoking[7 23 24 26 35 37–39 41 43] and 6 on age at onset of smoking.[7 9 10 23 26 46] Additionally, five studies provided separate data of gender[35 38 41–43] and five studies reported the risk of NPC histological type associated with cigarette

Table 3 Subgroup analysis on pooled ORs for the association between cigarette smoking and nasopharyngeal carcinoma

Subgroup	No. of studies	Effect estimate (95% CI)	Heterogeneity I^2, p	Egger's test p *Value*	Adjusted for publication bias
Smoking status					
Ever smokers	19	1.56 (1.32 to 1.83)	66.8%, <0.01	0.29	1.56 (1.32–1.84)
Current smokers	11	1.59 (1.35 to 1.89)	32.5%, 0.14	0.10	
Former smokers	10	1.36 (1.15 to 1.61)	2.3%, 0.42	0.97	
Design					
Case–control					
Current smokers	8	1.67 (1.06 to 2.61)	22.6%, 0.25	0.58	
Former smokers	8	1.45 (1.21 to 1.73)	0.0%, 0.70	0.98	
Cohort					
Current smokers	3	2.19 (1.02 to 4.72)	65%, 0.06	0.16	
Former smokers	2	0.87 (0.54 to 1.41)	0.0%, 0.37	—	
Pack-years					
<30	7	1.34 (1.13 to 1.58)	0.0%, 0.73	0.54	
≥30	6	2.03 (1.57 to 2.61)	0.0%, 0.45	<0.01	1.80 (1.37–2.36)
Age at onset of smoking (years)					
<18	5	1.78 (1.41 to 2.25)	0.0%, 0.94	0.46	
≥18	5	1.28 (1.00 to 1.64)	0.0%, 0.86	0.93	
Incidence rate					
Low	5	1.68 (1.36 to 2.07)	0.0%, 0.84	0.64	
Intermediate	10	1.59 (1.21 to 2.09)	78.8%, <0.01	0.29	
High	4	1.27 (1.05 to 1.53)	0.0%, 0.52	0.63	
Gender					
Man	5	1.36 (1.15 to 1.60)	0.0%, 0.68	0.48	
Woman	2	1.58 (0.99 to 2.53)	0.0%, 0.64	—	
Histological type					
Differentiated	5	2.34 (1.77 to 3.09)	0.0%, 0.72	0.64	
Undifferentiated	4	1.15 (0.90 to 1.46)	0.0%, 0.02	0.28	
Adjustment					
Adjusted	13	1.55 (1.26 to 1.91)	75.4%, <0.01	0.33	
Unadjusted	6	1.57 (1.27 to 1.93)	0.0%, 0.68	0.93	

smoking.[9 38 39 42 44] As regarding to geographic region, eight studies were conducted in China,[7 8 24 26 37 41 43 44] five in the USA,[34 35 38 39 46] five in Southeast Asia region,[10 23 25 36 40] two in Europe[9 45] and one in Africa.[42] The summarised characteristics of the 21 studies are presented in tables 1 and 2.

Association between cigarette smoking status and NPC

The pooled analysis of nineteen studies revealed a modest but significant increased risk of NPC among ever smokers against never smokers (OR, 1.56; 95% CI 1.32 to 1.83). Heterogeneity was obviously observed across the studies (I^2=66.8%, p<0.01). The pooled estimate for case–control studies was 1.61 (95% CI 1.36 to 1.91; heterogeneity: I^2=65.8%, p<0.01), whereas cohort studies presented a null association (OR, 1.11; 95% CI 0.84 to 1.48; heterogeneity: I^2=0.0%, p=0.83) (figure 2).

Similarly, 11 studies identified for the comparison of current smokers with NPC risk demonstrated positive result (OR, 1.59; 95% CI 1.35 to 1.89; heterogeneity: I^2=32.5%, p=0.14). When analysed by study design, the risk estimates were both statistically significant for case–control and cohort studies. The pooled ORs were 1.67 (95% CI 1.06 to 2.61; heterogeneity: I^2=22.6%, p=0.25) and 2.19 (95% CI 1.02 to 4.72; heterogeneity: I^2=65.0%, p=0.06), respectively (table 3).

When compared with never smokers, former smokers from 10 studies exhibited an increased risk of NPC (OR, 1.36; 95% CI 1.15 to 1.61; heterogeneity: I^2=2.3%, p=0.42). However, stratified analysis presented a void association

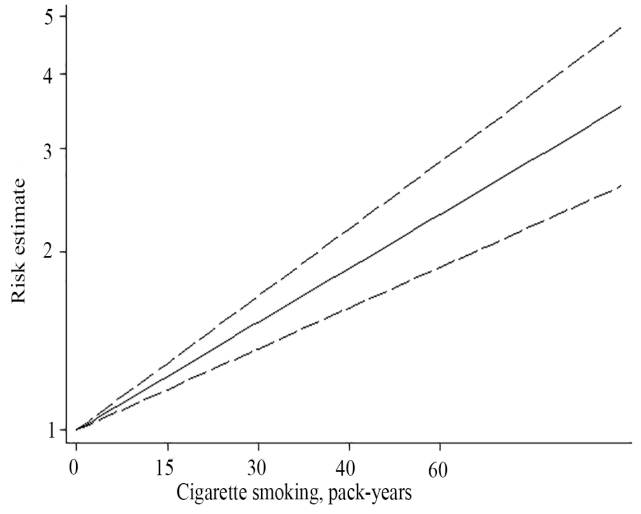

Figure 3 A linear relationship between the cumulative number of pack-years and NPC risk (p for linearity=0.83), with a 15% (95% CI 1.11 to 1.19, p<0.001) increasing risk of NPC for every additional 10 pack-years smoked in comparison with never smokers (the solid line depicts the pooled risk estimate of NPC associated with each 1 pack-year increment of cigarette smoking, the dashed line depicts the upper CI, the dot line depicts the lower CI). NPC, nasopharyngeal carcinoma.

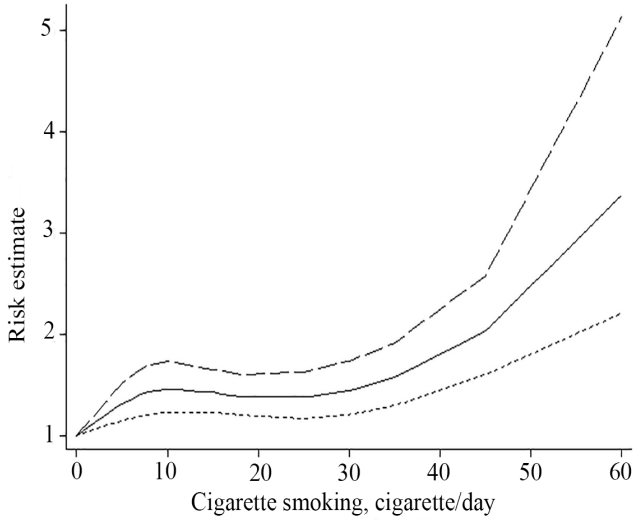

Figure 4 A non-linear association between intensity of cigarette smoking and NPC risk (p for non-linearity <0.05) (the solid line depicts the pooled risk estimate of NPC associated with each 1 cigarette/day increment, the dashed lines depict the upper and the lower CI, respectively). NPC, nasopharyngeal carcinoma.

in cohort studies (OR, 0.87; 95% CI 0.54 to 1.41; heterogeneity: I^2=0.0%, p=0.37) but a significant association in case–control studies (OR, 1.45; 95% CI 1.21 to 1.73; heterogeneity: I^2=0.0%, p=0.70) (table 3).

As for age at cigarette smoking onset, six studies reported the association with NPC risk. The pooled analysis revealed that early group (smoking at <18 years age) had significantly increased risk of NPC (OR, 1.78; 95% CI 1.41 to 2.25; heterogeneity: I^2=0.0%, p=0.94), whereas later group (smoking at ≥18 years age) had slightly increased risk of NPC (OR, 1.28; 95% CI 1.00 to 1.64; heterogeneity: I^2=0.0%, p=0.86) (table 3).

Dose–response analysis

For the cumulative amount of cigarette smoking, no between-study heterogeneity was found (I^2=0.0%, p>0.05) with a pooled OR of 1.34 (95% CI 1.13 to 1.58) for light smokers and 2.03 (95% CI 1.57 to 2.61) for heavy smokers, respectively (table 3). The dose–response analysis showed statistical linear relationship between the number of pack-years and NPC risk ($P_{\text{for linearity}}$=0.83) (figure 3). Smokers had a 15% (OR, 1.15; 95% CI, 1.11 to 1.19, p<0.001) increasing risk of NPC for every additional 10 pack-years smoked in comparison with never smokers (data not shown). When comparing the NPC risk for intensity of cigarettes smoked per day with never smokers, the non-linear dose–response relationship indicated that smokers with high exposure (>30 cigarettes/day) other than with low exposure have higher risk estimate, which presented an upward tendency in steeply rising trend ($P_{\text{for non-linearity}}$ <0.05) (figure 4).

Stratified analysis

When conducted stratified analysis by regions with different incidence rate, there were 19 studies compared NPC risk for ever smokers with that for never smokers. Among them, five studies carried out in regions with low NPC incidence rate yielded the highest risk (OR, 1.68; 95% CI 1.36 to 2.07; heterogeneity: I^2=0.0%, p=0.84). The pooled estimates were 1.59 (95% CI 1.21 to 2.09; heterogeneity: I^2=78.8%, p<0.01) for regions (10 studies) with intermediate NPC incidence rate and 1.27 (95% CI 1.05 to 1.53; heterogeneity: I^2=0.0%, p=0.52) for regions (4 studies) with high incidence rate, respectively (table 3).

We also performed stratified analysis by status of adjustment for confounding variables. Thirteen studies provided adjusted ORs for pooled analysis. But six studies either reported unadjusted ORs or reported the number of cases and controls which could be used to calculate the ORs. The estimates for the association of cigarette smoking and NPC risk in adjusted group (OR, 1.55; 95% CI 1.26 to 1.91; heterogeneity: I^2=75.3%, p<0.01) and in unadjusted group (OR, 1.57, 95% CI 1.27 to 1.93; heterogeneity: I^2=0.0%, p=0.68) were similar (table 3).

When the meta-regression analyses were applied to assess the sources of heterogeneity and their impacts on the NPC risk, we found that the publication year, study design, regions of different incidence rate and quality of studies were not significant sources of heterogeneity (p=0.55, data not shown).

Association between cigarette smoking and histological type of NPC

Specifically, the effects of cigarette smoking on NPC histological types were different. We found that significant association was only noted for differentiated squamous-cell

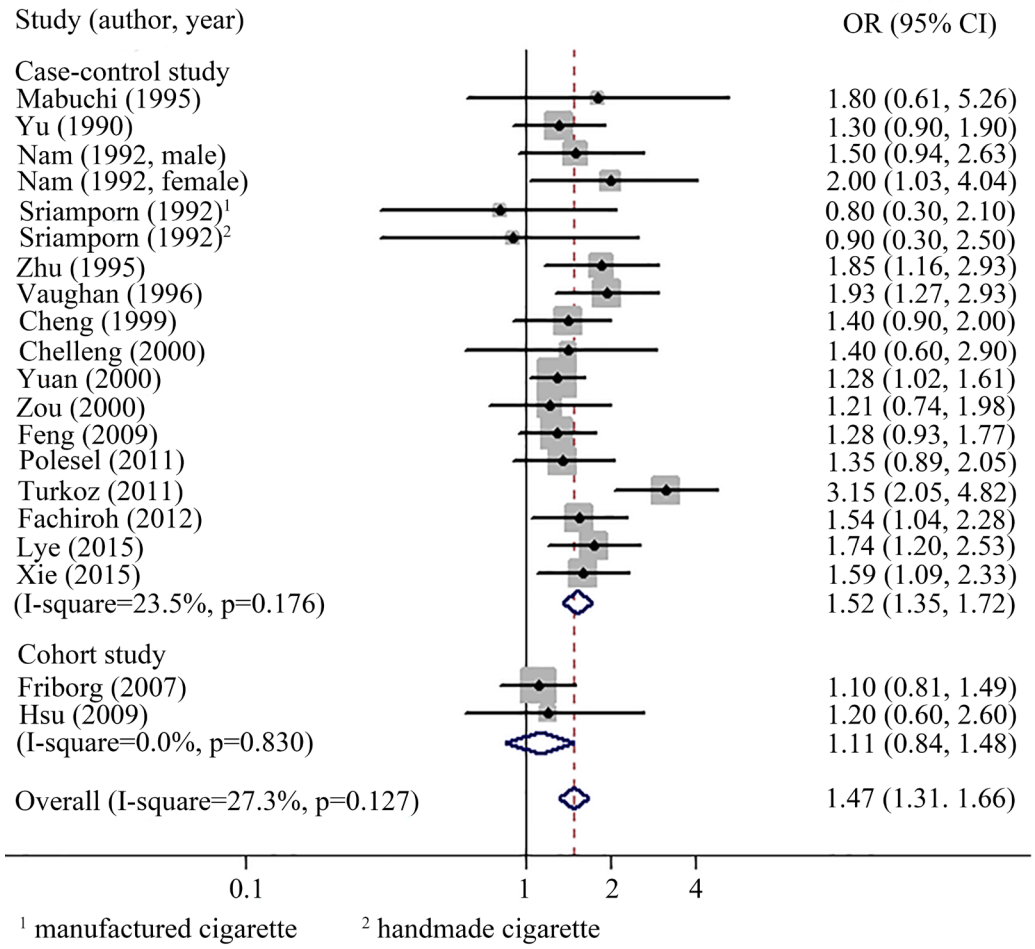

Figure 5 Forest plots for comparing the risk for NPC between ever smokers versus never smokers after deleting the Ji *et al* study.

NPC (OR, 2.34; 95% CI 1.77 to 3.09; heterogeneity: I^2=0.0%, p=0.72). Contrarily, the risk estimate for undifferentiated carcinoma of NPC in smokers was statistically insignificant though the OR was 1.15 (95% CI 0.90 to 1.46; heterogeneity: I^2=0.0%, p=0.02) (table 3).

Association between cigarette smoking of gender and NPC

Seven studies addressed the association between cigarette smoking and NPC risk by gender, including five in males and two in women. Compared with never smokers, increased risk for male smokers was noted (OR, 1.36; 95% CI, 1.15 to 1.60). However, an insignificant association (OR, 1.58; 95% CI, 0.99 to 2.53) was observed for female smokers (table 3).

Sensitivity analysis and publication bias

Sensitivity analysis revealed that[44] study[42] was the source of statistical heterogeneity in the pooled analysis for ever smokers. When this outlier study was removed, between-study heterogeneity dropped strikingly to 27.3% in the remaining studies, whereas the ORs (OR, 1.47; 95% CI 1.31 to 1.66) changed moderately but remained significant. As for case–control studies, the OR changed from 1.61 (95% CI 1.36 to 1.91) to 1.52 (95% CI 1.35 to 1.72) with heterogeneity fallen from 65.8% to 23.5% (figure 5).

The findings were further verified in the intermediated incidence rate group (OR, 1.49, 95% CI 1.21 to 1.82; heterogeneity: I^2=49.6%, p=0.04) and in the adjusted group (OR, 1.45; 95% CI 1.25 to 1.69; heterogeneity: I^2=41.8%, p=0.05) (data not shown). However, the heterogeneity reduced partly when the study of Turkoz *et al* was removed (OR, 1.50; 95% CI 1.28 to 1.76; heterogeneity: I2=62.4%, p<0.01) (data not shown).

Publication bias was evaluated by Egger test and Trim-and-Fill method. Except for subgroup analyses with ever smokers and heavy smokers, no prominently significant publication bias (with p>0.05 in Egger test) was observed in our meta-analysis. After adjusted for publication bias, the risk of NPC remained stable with an OR of 1.56 (95% CI 1.32 to 1.84) for ever smokers, but changed slightly (OR, 1.80, 95% CI 1.37 to 2.36) for heavy smokers (table 3).

DISCUSSION

The results from this meta-analysis, based on 17 case–control studies and 4 cohort studies, supported that there was moderate association between cigarette smoking and nasopharyngeal carcinoma risk, which was consistent with the result of previous meta-analysis.[13]

Interpretation

The pooled risk estimate for cohort studies comparing ever smokers to never smokers was not statistically significant. When conducted similar stratified analyses for current smokers and former smokers, we found that current smoking was significantly related to the risk of NPC while former smoking had an insignificant association with NPC risk. Considering the findings of stratified analyses, it might be the result from former smoking that contributed to the discrepancy between pooled analysis for cohort studies and overall analysis. In addition, this meta-analysis demonstrated relatively high heterogeneity both for the overall analysis and subgroup analyses. When the Ji *et al* study[44] was removed from the synthetic analysis, heterogeneity was strikingly reduced in stratified analysis by study design and regions with different NPC incidence rate. Furthermore, the meta-regression analyses indicated that heterogeneity did not prominently result from publication year, study design, regions of different incident rate and quality of studies. To our knowledge, multiple lines of epidemiological studies had found that the development of NPC could be influenced by varieties of aetiologies including Epstein-Barr virus (EBV), genetic components and other environmental factors, like preserved food, socioeconomic status, occupation, so on and so forth.[6 47–50] Therefore, it might be its inappropriate subjects that contributed to selection bias which resulted in the high heterogeneity in the[44] Ji *et al's* study, though it had a large sample size with risk estimates adjusted by age, gender, alcohol intake and family history.

One large cohort study,[10] conducted in high-incidence region and comprised the majority of undifferentiated NPC (nearly 90% cases), did not reported statistically increased risk of NPC among current smokers compared with never smokers. The difference in the effect of current smoking on NPC risk may be due to its histological type of NPC because undifferentiated carcinoma in high-risk areas seemed more strongly related to EBV infection other than cigarette smoking.[48] Meanwhile, some case–control studies with small sample size of current smokers also had null results,[7–9 38 39] of which two studies pointed out that significantly higher risk only existed for smokers with considerable levels of cigarette smoking (>20 cigarettes/day or >30 pack-years).[38 39] Nonetheless, the result of our integrated analysis for current smokers versus never smokers was generally consistent with that of the previous meta-analyses.[13]

For former smokers, the less consistent risk estimates might result from small number of studies with adequate sample size. The estimates for former smokers in eight studies[7–10 26 39 41 46] presented null association on NPC risk which was parallel to the results of stratified analysis by study design, and only two studies[23 38] demonstrated statistically positive results. The discrepancies in the effects of former cigarette smoking on NPC risk might arise from the following aspects: the group of former smokers may have included people who had quit for a long time, and thus their risk might diminish or even reach the level of never smokers; the minimum period of time since quitting smoking in former smokers varied by study, which could result in judgement bias on the interviewed subjects in some studies.

This meta-analysis revealed that there was a clear dose–response relationship between cigarette smoking and the risk of NPC. That is, the more cigarette smoking (intensity of cigarettes smoked per day and the amount of pack-years), the higher risk for the development of NPC. Note that similar results have been widely observed for pancreatic cancer, liver cancer, renal carcinoma and gall bladder disease.[51–54] The exact explanation of this dose-dependent effect remains vague, it could be hypothesised that the more cigarette smoking, the greater impact on the epithelial cells of nasopharynx. Therefore, the risk of NPC would be higher in those who smoked more cigarettes. The actual mechanism about the relationship of the amount of smoking and NPC risk had been searched by molecular studies,[55 56] which pointed out that smoking is a factor for tumour growth and acts as a mutagen and DNA damaging agent that drives tumour initiation in normal epithelial cells of nasopharynx.

In this analysis, a statistically significant effect of smoking on NPC risk was observed in males but not in women. The gender difference in response to smoking might be related to interaction between protective endogenous or exogenous oestrogens among women compared with men,[57] and could also be explained by maturity of smoking trends among men and but not among women. Men might have exposure to smoking for a longer duration as compared with women (34% of the men vs 11% of the women had started smoking before the age of 15 years).[58] However, the result of women being ever smokers might not be adequately stable because only two studies reported the association between cigarette smoking and the risk of NPC for women.[35 41]

Additionally, we found that the younger age people began to smoke, the higher risk they developed NPC. Our results showed that the pooled ORs were 1.78 (95% CI 1.41 to 2.25) for smokers in early group and 1.28 (95% CI 1.00 to 1.64) in later group, respectively. Interestingly, the findings of previous meta-analysis appeared totally opposite with ORs of 1.17 (95% CI 0.78 to 1.75) for early group and 1.58 (95% CI 1.10 to 2.26) for later group.[13] Like many other cancers, NPC may take decades to develop from premalignant cells to detectable solid tumour. Thus, the exposure to carcinogenic agents early in life could have substantial impacts on the development of NPC.[6 59] Moreover, the incidence of NPC peaks at age of 50–59 years in high-risk regions, whereas in western countries, the incidence of NPC peaks somewhat later (≥65 years old).[59] As a result, the number of NPC patients in terms of age distribution could considerably vary in our eligible studies that were conducted in different countries.

When stratified by histological type of NPC, the pooled analysis presented a higher risk of differentiated NPC than that of undifferentiated NPC, and the later had an insignificant risk estimate. This difference might be

owing to fewer studies included in the pooled analysis for undifferentiated NPC because we excluded those ineligible studies either for no report of the association between cigarette smoking and NPC risk[16] or for overlapped data.[60] It might avoid incorrect estimation of smoking effects on NPC risk. Moreover, we found that the risk estimates adversely associated with the NPC incidence rate. For example, the pooled OR for high incidence rate areas to low incidence rate areas ranged from 1.27 to 1.68. This might suggest there are substantial heterogeneity between NPC risk and smoking by histological types and geographical variations. Undifferentiated carcinoma of the nasopharynx is the predominant type in high-risk areas, and it is consistently associated with EBV infection, which may increase the carcinogenic effect of cigarette smoking.[48]

Generalisability

The magnitude of association between cigarette smoking and the NPC risk was not as big as those for other smoking-related cancers like lung cancer and gastrointestinal malignancies.[4] However, NPC was quite epidemic in Southeastern Asia especially in cities in southern China, and China was one of the largest tobacco producing and consuming countries in the world.[61] Besides, we found current smokers are more related to the development of NPC with a higher risk estimate as compared with former smokers. These emphasised the importance and urgency of efforts to initiate the control of cigarette smoking to improve public health. Any efficient tobacco control programme would be helpful to reduce morbidity and mortality of smoking-related cancers worldwide.

Limitations

The results of this meta-analysis should be explicated in the context of several limitations. For example, the design of included studies varied in source of subjects recruited, standardisation for categories of cigarette smoking, ambiguous definition of tobacco products and adjusted factors. Additionally, our meta-analysis was a mix of retrospective studies and prospective studies, and was lack of individual participant data for adjustment of potential confounders. Generally, EBV infection was thought to be highly related to NPC risk.[62] However, a 22-year follow-up study carried out by Hsu *et al* revealed that EBV was less likely to modify the estimate for smoking associated with NPC risk.[43] And the links of other risk factors like dietary and social practices were often inconsistent between studies.[62] Moreover, the risk estimates of NPC resembled both in the group with adjusted OR and in the group with unadjusted OR in our meta-analysis.

CONCLUSIONS

This meta-analysis demonstrated that cigarette smoking is associated with a modest, but statistically significant increased risk of NPC. Yet, further prospective studies are needed to elucidate the NPC risk in terms of gender, histological type and for former smokers and smoking onset age.

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