Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis

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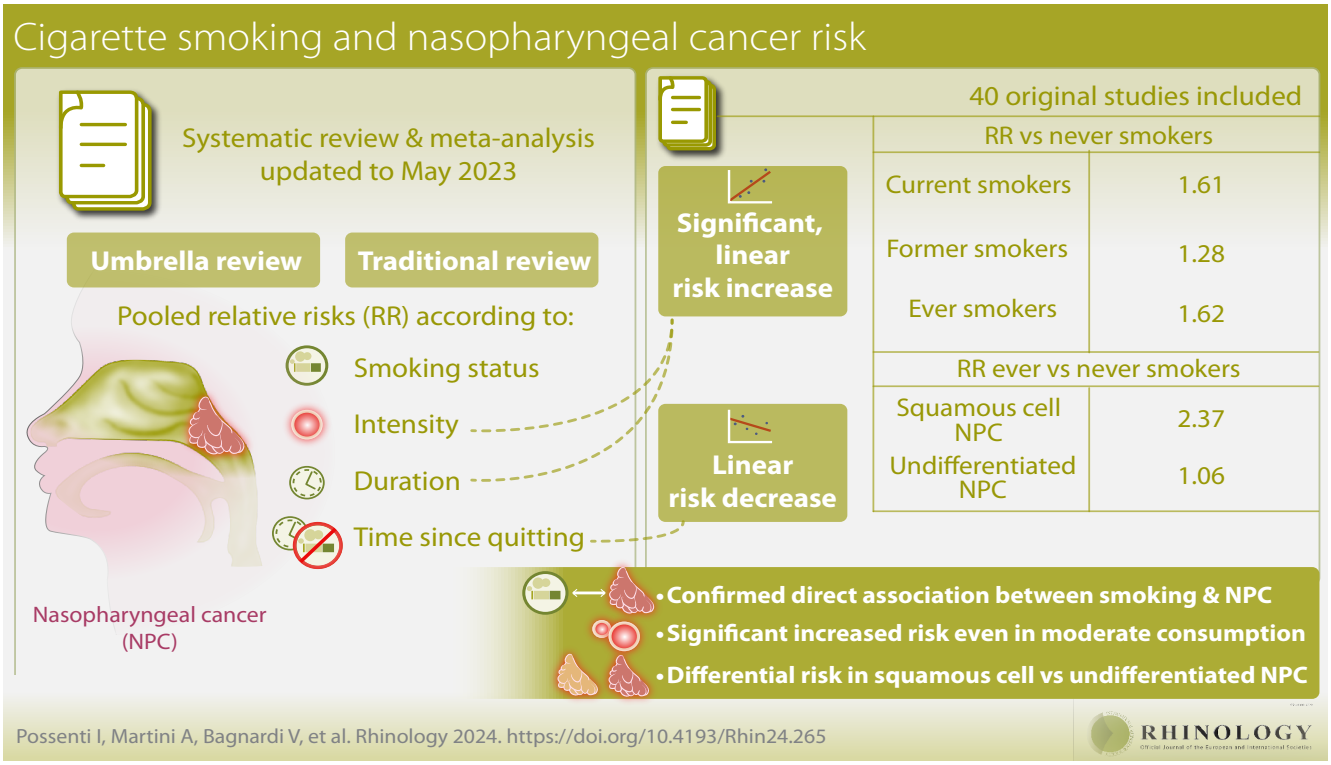

Abstract

Introduction: Nasopharyngeal cancer (NPC) is a relatively rare yet aggressive malignancy, primarily affecting regions of East and Southeast Asia. This study aims at providing an up-to-date quantification of the association between cigarette smoking and NPC risk, overall and by histological subsites.

Methods: We conducted a systematic review and meta-analysis of case-control and cohort studies on the association between cigarette smoking and NPC risk published up to May 2023. The methodology used is original and efficient and includes both a comprehensive umbrella review and a traditional review. We estimated pooled relative risks (RR) of NPC according to smoking status, intensity, duration, and time since quitting.

Results: Among 46 eligible articles, 40 original studies were included in this meta-analysis. Compared with never smokers, the pooled RR of NPC was 1.61 for current, 1.28 for former, and 1.62 for ever smokers. The RR for ever compared with never smokers was 2.37 for squamous cell NPC and 1.06 for undifferentiated NPC. NPC risk significantly increased linearly with smoking intensity and duration, and decreased linearly with increasing time since quitting.

Conclusion: This meta-analysis confirms the link between tobacco smoking and NPC, highlighting the significant risk posed even by moderate cigarette consumption. Additionally, our findings underscore the differential risk between squamous cell and undifferentiated subtypes of NPC, shedding light on the distinct implications for NPC prevention strategies.

Key words: nasopharyngeal cancer, head and neck cancer, cigarette smoking, dose-response relationship, meta-analysis

Introduction

Nasopharyngeal cancer (NPC) is a malignant neoplasm that arises from the epithelial cells of the nasopharynx. Its incidence is relatively limited, with less than two cases diagnosed per 100,000 people per year worldwide [1]. However, its geographical distribution varies widely, with the highest incidence in Southeast Asian regions, where the age-standardized rate stands at 4.7 cases per 100,000 individuals [2]. NPC has a significant impact on patients' quality of life and is known to be quite aggressive, with an estimated 5-year survival rate of 63% [3].

Several risk factors have been identified for the development of NPC. Among these, extensive research has focused on factors such as Epstein-Barr virus infection, genetic predisposition, alcohol consumption, and exposure to environmental toxins [2, 4-6]. In addition, cigarette smoking is recognized as a major risk factor associated with cancers of the respiratory tract, including the nasopharynx [7-9]. The composition of cigarette smoke encompasses several hazardous chemicals, many of which are recognized carcinogens. When inhaled, these substances enter the upper respiratory tract, can induce DNA damage and promote the progression of cancer cells [10].

Despite extensive research, there are still major gaps in the understanding of the etiology of NPC. In addition, although the association between cigarette smoking and cancers of the respiratory tract is well-established, the precise role of smoking in cancers of different sites within the respiratory tract remains unclear. In fact, most of the recent studies investigating cancer risks associated with cigarette smoking treat NPC exclusively as part of the cancers of the head and neck, the upper aerodigestive tract, or the pharynx [11, 12]. The complex aetiology of NPC, which distinguishes it from other cancers, requires separate consideration and investigation, particularly in examining different histological subtypes.

The primary objective of this meta-analysis is to quantify the precise magnitude of the association between cigarette smoking and NPC risk, thus filling the existing gap from recent meta-analyses on this topic. In addition, this meta-analysis aims to unravel the association of interest using dose-response analyses with smoking intensity, duration and time since quitting, and performing stratified analyses, with specific stratifications including sex, geographical area, and cancer subtype.

Materials and methods

The current meta-analysis is part of a series of systematic reviews and meta-analyses investigating the association between cigarette smoking and second-hand smoke (SHS) exposure and cancer risk [13-18]. The present analysis is specifically focused on NPC. This analysis uses an innovative methodology that combines umbrella and traditional review approaches [19]. In our umbrella review, we systematically identified all relevant meta-analyses, pooled analyses and systematic reviews that examined the association between cigarette smoking and the risk of NPC. We then used a traditional review process to identify original studies published after the most recent comprehensive review. Our study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017063991).

Search strategy

In the first stage, we conducted an umbrella review focusing on the association between smoking and SHS exposure and cancer risk across different anatomical sites. Using a thorough literature search of multiple databases, including PubMed/MEDLINE, Embase, the Institute for Scientific Information Web of Science and the Cochrane Database of Systematic Reviews, we identified all relevant meta-analyses, pooled analyses and systematic reviews on the association between cigarette smoking and SHS exposure and cancer risk up to October 12 2022.

The umbrella review identified 57 reports (Supplementary Table 1), which included systematic reviews, meta-analyses, pooled analyses or reports from international agencies, regarding the association between cigarette smoking and SHS exposure and the risk of cancers located anywhere in the upper aero-digestive tract. From these reports, all original articles that specifically addressed NPC were extracted, resulting in the identification of 72 non-duplicate original publications on tobacco smoking and the risk of NPC. These articles were thoroughly screened from their full text using the eligibility criteria described in the following section, resulting in the exclusion of 33 articles that were identified as ineligible (Supplementary Table 2).

In the subsequent phase of our search, we conducted a literature search to encompass all original studies published between January 2016 (i.e., the beginning of the year previous to the publication date of the most recent and comprehensive review available on the topic [8]) and May 31 2023. The search string involved combinations of MeSH and text words related to NPC and tobacco or smoking (Supplementary Box 1). After excluding duplicate publications and ineligible articles, the literature update resulted in 11 additional original publications on cigarette smoking and the risk of NPC.

By merging the original articles identified in the umbrella review and the literature update, a total of 46 non-duplicate publications were considered eligible (Supplementary Figure 1).

Eligibility criteria

To be included in the present meta-analysis, studies were required to meet specific eligibility criteria: i) be either case-control studies (including nested case-control studies or pooled analyses of case-control studies) or cohort studies (including case-cohort studies or pooled analyses of cohort studies); ii) be published as original articles in the English language; iii) provide data pertaining to the general population; iv) provide infor-

mation on the association between cigarette smoking and the risk of NPC; v) report risk estimates, including risk ratios, odds ratios, hazard ratios, or mortality rate ratios - all referred to as relative risk (RR) - for at least one variable among smoking status (current, former, and/or ever), intensity, duration, and time since quitting, compared with never or current cigarette smokers, and the corresponding 95% confidence intervals (CI), or provide sufficient information to calculate them.

Data extraction

In the data extraction phase, information was systematically collected from each eligible study, including both general and study-specific details. Data extracted included: general publication information (e.g., first author, year of publication, and journal), study characteristics (e.g., country in which the study was conducted, study name, study design, and sample size), details of the statistical model used for RR estimates (including covariates considered), and RRs with corresponding 95% CIs and, where available, numbers of cases and controls (or persons at risk/person-years for cohort studies) for different exposure categories.

Where appropriate, we used the technique for aggregating non-independent estimates described by Hamling and colleagues [20]. This approach involved modifying the reference category or collapsing RRs from two or more categories in cases where the reference group remained the same across categories.

Statistical analysis

We calculated pooled RRs for current, former, and ever smokers compared with never smokers. These estimates were performed both overall and stratified by study design (i.e., cohort and case-control studies). We used random-effects meta-analytic models to account for the heterogeneity of risk estimates [21].

Study quality was assessed by two authors (AL and IP) using the Newcastle-Ottawa Scale (NOS) [22]. NOS score ranges between 0 (poor quality) and 9 (good quality) and consider information on three broad categories: selection (maximum 4 points), comparability (maximum 2 points) and outcome for case-control or exposure for cohort studies (maximum 3 points). In this meta-analysis, high-quality studies were defined as those with NOS scores ≥7. To ensure the completeness and comprehensiveness of our study, no low-quality study was excluded from the meta-analysis.

Heterogeneity was assessed using the χ^2 test, and inconsistency was quantified using the I^2 statistic, which represents the proportion of total variation attributable to between-study variance [23]. We carried out stratified analyses based on various study and population characteristics, such as cancer subsite, sex, study design, type of control (for case-control studies), endpoint (for cohort studies), tertiles of the number of cases, presence of any adjustment, study quality, geographic area, income group, and year of publication.

To investigate publication bias, we examined funnel plots [24] and employed Egger's test for funnel plot asymmetry [25].

We examined both linear and nonlinear associations between smoking intensity (for current vs. never smokers), smoking duration (for current vs. never smokers), and time since quitting (for former vs. current smokers) and the log RR of NPC. Dose-response relationships were evaluated using a one-stage random-effects dose-response model [26]. Non-linear coefficients were subjected to the Wald test for statistical significance. When linearity was rejected, non-linear relationships were modelled using restricted cubic splines with three knots at fixed percentiles of exposure (10%, 50%, and 90%) [14, 27]. Exposure levels for each category were determined as the midpoint between upper and lower bounds; for open-ended upper categories, exposure levels were set at 1.2 times the lower bound [19, 28, 29].

In cases where the numbers of cases and/or controls in specific exposure categories were not available in the original study publication, we estimated the covariance between log RRs by considering the total number of cases and/or controls in the study, weighted by the average percentage distribution of subjects pooled from all other studies [30].

All statistical analyses were performed using R software version 4.2.2 (R Development Core Team, 2017), particularly leveraging the "meta" and "dosresmeta" packages [30, 31].

Results

Study selection and description

Among the initially identified 46 eligible articles exploring the relationship between cigarette smoking and NPC risk, 38 were identified from existing reviews and meta-analyses identified in the umbrella review and 8 were newly identified studies retrieved in the traditional review [32-39]. From these articles, 6 were excluded during the study selection process due to duplicated data (Supplementary Table 2). Consequently, a total of 40 studies (33 case-control and 7 cohort studies) were included in the present systematic review and meta-analysis (Supplementary Table 3 and Supplementary Table 4). The selected studies covered the period from 1982 to 2021 and included more than 15,000 NPC cases. Among them, 16 studies provided a measure of the association (or data to calculate it) for current smokers, 15 for former smokers, and 37 studies for ever smokers, as compared with never smokers. Additionally, 17 studies reported RR estimates for smoking intensity (including 5 among current smokers), 15 for smoking duration (including 5 among current smokers), and 8 for time since quitting. Publications containing data that were partially excluded from the present meta-analysis, with the corresponding reasons of exclusion, are described in Supplementary Table 5. The quality score of included case-control and cohort studies are shown in Supplementary Table 6 and Supplementary Table 7, respectively. Overall, 11 (33%)

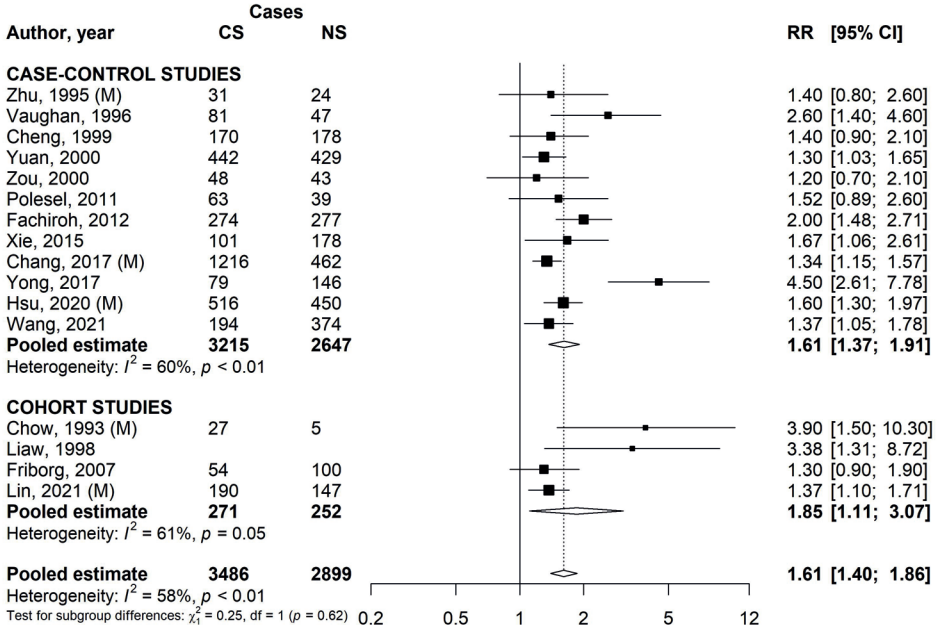

Figure 1. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer (NPC) for current cigarette smokers (CS) versus never smokers (NS), by study design. CI: confidence interval; M: males.

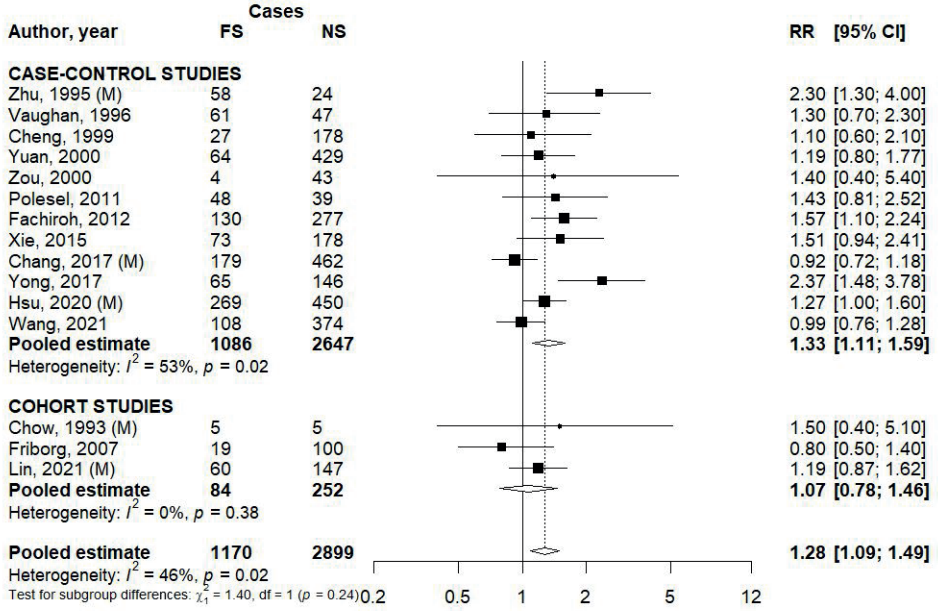

Figure 2. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer (NPC) for former cigarette smokers (FS) versus never smokers (NS), by study design. CI: confidence interval; M: males.

case-control and 5 (71%) cohort studies were scored as of high quality (i.e., NOS≥7).

Quantitative data synthesis

The pooled RR of NPC for current smokers compared to never smokers was 1.61 (95% CI: 1.40-1.86), and was non-significantly lower in case-control (RR: 1.61; 95% CI: 1.37-1.91) than in cohort (RR: 1.85; 95% CI: 1.11-3.07) studies (Figure 1). Corresponding RR estimates for former smokers compared to never smokers were 1.28 (95% CI: 1.09-1.49) overall, 1.33 (95% CI: 1.11-1.59) in case-control studies, and 1.07 (95% CI: 0.78-1.46) in cohort studies (Figure 2). The pooled RR for ever smokers compared to never smokers was 1.62 (95% CI: 1.41-1.87) overall, 1.64 (95% CI: 1.41-1.91) in case control and 1.46 (95% CI: 1.00-2.12) in cohort studies (Supplementary Figure 2).

The pooled RRs for specific cancer subsites are detailed in Table

Table 1. Pooled relative risk (RR) and corresponding 95% confidence interval (CI) for nasopharyngeal cancer (NPC) risk for current, former, and ever cigarette smokers vs. never cigarette smokers, overall and in strata of selected characteristics.

	Current smokers				Former smokers				Ever smokers			
Strata	**N. studies**	**Pooled RR (95% CI)**	**p-value***	**p-value#**	**N. studies**	**Pooled RR (95% CI)**	**p-value***	**p-value#**	**N. studies**	**Pooled RR (95% CI)**	**p-value***	**p-value#**
Total	16	1.61 (1.40-1.86)	-	<0.01	15	1.28 (1.09-1.49)	-	0.03	37	1.62 (1.41-1.87)	-	<0.01
Type of study												
Case-control	12	1.61 (1.37-1.91)	<0.01	<0.01	12	1.33 (1.11-1.59)	0.24	0.02	33	1.64 (1.41-1.91)	0.57	<0.01
Cohort	4	1.85 (1.11-3.07)		0.05	3	1.07 (0.78-1.46)		0.38	4	1.46 (1.00-2.12)		0.09
Histological Type												
SQC NPC	2	4.79 (2.50-9.20)	-	0.45	2	1.75 (0.91-3.34)	-	0.63	5	2.37 (1.69-3.32)	-	0.85
UD NPC	2	0.92 (0.36-2.34)		0.11	2	1.36 (0.88-2.10)		0.83	4	1.06 (0.78-1.44)		0.23
Sex												
Men	5	1.43 (1.28-1.61)	0.89	0.59	5	1.23 (1.06-1.42)	0.32	0.54	9	1.41 (1.29-1.53)	0.46	0.55
Women	2	1.38 (0.79-2.40)		0.94	2	0.88 (0.46-1.68)		0.17	4	1.95 (0.82-4.62)		0.02
Type of controls [a]												
Hospital	4	1.53 (1.33-1.77)	0.46	0.79	4	1.24 (1.03-1.48)	0.38	0.44	9	1.33 (1.17-1.52)	0.02	0.24
Population	8	1.77 (1.24-2.53)		<0.01	8	1.41 (1.12-1.77)		0.20	22	1.77 (1.46-2.13)		<0.01
Endpoint [b]												
Incidence	2	1.35 (1.12-1.63)	<0.01	0.81	2	1.03 (0.71-1.50)	0.38	0.20	3	1.48 (0.91-2.41)	0.85	0.04
Mortality	3	3.42 (1.93-6.06)		0.93	1	1.50 (0.42-5.36)		-	1	1.64 (0.64-4.20)		-
Number of cases [c]												
<151	4	1.52 (1.12-2.06)	0.15	0.22	4	1.75 (1.22-2.53)	0.03	0.67	14	1.93 (1.41-2.62)	0.31	<0.01
151-700	6	1.97 (1.41-2.76)		<0.01	6	1.40 (1.07-1.83)		0.03	14	1.61 (1.33-1.96)		<0.01
≥701	6	1.40 (1.27-1.54)		0.33	5	1.09 (0.92-1.29)		0.26	9	1.41 (1.10-1.81)		<0.01
Adjustements [d]												
Non-adequate	4	2.80 (1.43-5.46)	0.07	<0.01	3	2.14 (1.41-3.24)	0.01	0.64	7	1.64 (0.99-2.74)	0.99	<0.01
Adequate	12	1.49 (1.35-1.64)		0.01	12	1.28 (1.09-1.49)		0.18	30	1.64 (1.44-1.87)		<0.01
Study Quality												
Low (NOS<7)	7	1.86 (1.40-2.47)	0.07	<0.01	7	1.42 (1.13-1.77)	0.27	0.13	22	1.55 (1.29-1.87)	0.37	<0.01
High (NOS≥7)	9	1.41 (1.28-1.55)		<0.01	8	1.20 (1.01-1.44)		0.15	15	1.75 (1.46-2.10)		<0.01
Geographic area [e]												
North America	3	2.24 (1.28-3.90)	0.46	0.14	3	1.72 (1.09-2.71)	0.03	0.38	6	1.99 (1.56-2.53)	0.10	0.81
Europe	1	1.52 (0.89-2.60)		-	1	1.43 (0.81-2.52)		-	2	1.46 (1.46-2.23)		<0.01
Asia	12	1.56 (1.34-1.81)		<0.01	11	1.22 (1.03-1.44)		0.03	27	1.64 (1.37-1.96)		<0.01
Africa	-	-		-	-	-		-	2	1.23 (0.91-1.65)		0.54
Income group [f]												
High income	7	1.70 (1.38-2.10)	0.67	0.16	7	1.36 (1.04-1.78)	0.54	0.20	11	1.63 (1.35-1.97)	0.98	0.32
Middle or low income	9	1.59 (1.28-1.98)		<0.01	8	1.23 (1.01-1.50)		0.03	26	1.63 (1.35-1.96)		<0.01
Year of publication												
≤2000	7	1.66 (1.25-2.21)	0.99	<0.01	6	1.39 (1.05-1.83)	0.03	0.51	13	1.58 (1.32-1.89)	0.76	0.20
2001-2014	3	1.62 (1.62-2.17)		0.33	3	1.24 (0.82-1.88)		0.10	12	1.57 (1.13-2.17)		<0.01
≥2015	6	1.66 (1.24-2.23)		<0.01	6	1.25 (0.98-1.58)		<0.01	12	1.75 (1.39-2.21)		<0.01

* p-value for heterogeneity across strata. # p-value for heterogeneity within strata. [a] Type of controls for case-control studies only. Studies considering both studies with hospital and with population controls were not included. [b] Endpoint for cohort studies only. Studies providing RRs for both incidence and mortality were considered in both categories. [c] Studies in which the number of cases was not reported were excluded. [d] Estimates adjusted for, at least, age, sex, and at least one of the following variables: alcohol consumption, Epstein-Barr Virus infection, race, diet, and family history of NPC, and exposure to pollutants (e.g., air pollution, radon, asbestos). [e] Studies conducted in multiple countries from different geographic areas were not included. No studies from South America or Oceania. [f] Studies conducted in multiple countries with different income groups were not included. NOS: Newcastle Ottawa Scale; SQC: squamous cell; UD: undifferentiated.

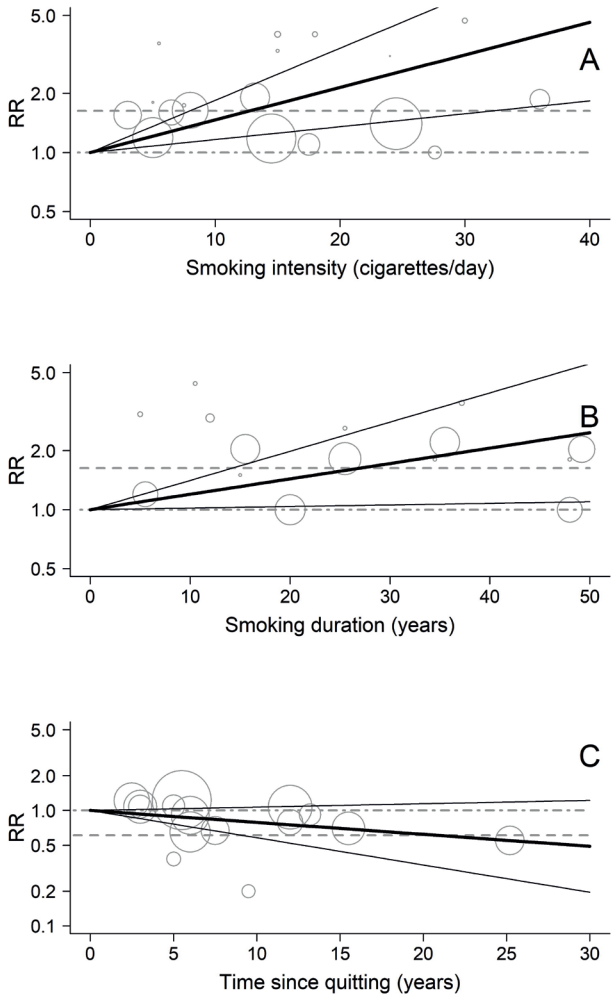

Figure 3. Relative risk (RR) for the dose-response relationships between cigarette smoking intensity, duration, and time since quitting and nasopharyngeal cancer. A) cigarette smoking intensity (based on 5 studies); B) cigarette smoking duration (based on 5 studies); C) time since quitting (based on 8 studies).

——— Linear model;

——— 95% confidence interval of the linear models;

---------- RR for the reference category (never smokers in A and B, current smokers in C);

- - - - - RR for current vs. never cigarette smokers (A and B) former vs. current cigarette smokers (C);

o RR for various exposure categories in each study included in the analysis. The area of the circle is proportional to the precision (i.e. to the inverse variance) of the RR.

1 and in Supplementary Tables 3 and 4. Compared with never smokers, the RR for differentiated squamous cell carcinoma of the nasopharynx was 4.79 (95% CI: 2.50-9.20; n=2) for current smokers, 1.75 (95% CI: 0.91-3.34; n=2) for former smokers, and 2.37 (95% CI: 1.69-3.32; n=5) for ever smokers. The RR for undifferentiated NPC was 0.92 (95% CI: 0.36-2.34; n=2) for current smokers, 1.36 (95% CI: 0.88-2.10; n=2) for former smokers, and 1.06 (95% CI: 0.78-1.44; n=4) for ever smokers.

Possible sources of heterogeneity were investigated through stratified analyses (Table 1 and Supplementary Figure 5). Among current smokers, significant differences have been observed according to endpoint (RRs of NPC were 1.35 in cohort studies on incidence and 3.42 in cohort studies on mortality, p<0.01). Among former smokers, significant differences were observed according to number of cases (RRs of NPC were 1.75 for studies with less than 151 cases, 1.40 in studies with a number of cases between 150 and 700, and 1.09 in studies with more than 700 cases; p=0.03), adjustments (RRs of NPC were 2.14 for studies with non-adequate adjustments and 1.28 for studies with adequate adjustments; p=0.01), and geographic area (RRs of NPC were 1.72 in studies conducted in North America, 1.43 in a study conducted in Europe, and 1.22 in studies conducted in Asia; p=0.03). Among ever smokers, a significant difference was observed according to type of controls in case-control studies (RRs of NPC were 1.33 for studies with hospital controls and 1.77 for studies with population controls; p=0.02).

Publication bias

Evidence of possible publication bias emerged for the analysis of current compared with never smokers both from the visual inspection of the funnel plot (Supplementary Figure 6, panel A) and from the Egger's test (p=0.02), while there was no evidence of publication bias in either former or ever smokers (Supplementary Figure 6, panels B and C; p=0.15 and p=0.11, respectively).

Dose-response analysis

Figure 3 shows the dose-response relationships between smoking intensity, duration, and time since quitting in relation to the risk of NPC. A linear increase in NPC risk was observed with increasing smoking intensity among current smokers (RRs were 1.47; 95% CI: 1.16-1.84 for 10 cigarettes per day and 2.14; 95% CI: 1.35-3.40 for 20 cigarettes per day; Figure 3, panel A). The risk of NPC also increased linearly with increasing duration of smoking: RRs were 1.44 (95% CI: 1.04-1.99) for 20 years and 2.06 (95% CI: 1.08-3.94) for 40 years of smoking (Figure 3, panel B). A non-significant inverse linear association was observed between time since quitting smoking and the risk of NPC, with the RR for former smokers compared with current smokers being 0.79 (95% CI: 0.58-1.06) after 10 years and 0.62 (95% CI: 0.34-1.14; Figure 3, panel C) after 20 years. Thus, the risk for former compared current smokers after 20 years since smoking cessation is equivalent to the risk for never compared to current smokers (RR=0.62).

Discussion

This systematic review and meta-analysis provides up-to-date and comprehensive evidence on the association between cigarette smoking and NPC risk. It includes 46 eligible articles

and uses data from 40 original articles and more than 15,000 NPC cancer cases. Pooled risk estimates showed a 61% and 28% increased NPC risk in current and former smokers, respectively. Dose-response analyses revealed that the risk of NPC increased linearly with the intensity and duration of the smoking habit. The most recent meta-analysis focusing on NPC alone, and not as part of the head and neck or the upper aerodigestive tract, found a 59% excess risk of NPC cancer associated with smoking [8]. Notably, our study, which included twice as many articles, strengthens the robustness of these findings.

Our analysis revealed a significant association only between smoking and differentiated squamous cell NPC, whereas no such association was observed for undifferentiated NPC. This finding, which is consistent with previous meta-analyses on NPC [8, 9], is also aligned with patterns observed for other cancer sites, such as lung and oesophageal cancer, for which higher RRs of cancer associated with smoking were observed for squamous cell carcinoma compared with other histological subtypes [40]. Undifferentiated carcinoma accounts for more than 95% of the NPC cases in high-incidence regions, such as Asia, whereas squamous cell NPC is predominant in low-incidence regions, such as North America [41]. Furthermore, undifferentiated NPC is more strongly correlated with Epstein-Barr virus infection [42], suggesting distinct etiological pathways for this subtype. Despite potential limitations in our stratified analyses due to the limited number of studies providing stratified analyses for histological subtypes, the results suggest different risk profiles across NPC histologies, highlighting the need for further research to elucidate these complex interactions.

Most of the studies included in the meta-analysis were from Asian countries, where the incidence of NPC is 4 to 5 times higher than those observed in Europe or North America [1]. Significant heterogeneity in risk estimates across geographic area emerged among former smokers, with the lowest risk found in the studies conducted in Asia. Non-significantly lower RRs for studies conducted in Asia compared to studies conducted in North America were also observed among current and ever smokers. This phenomenon, previously noted by Xue and colleagues [9], may be attributed to the varying histological subtypes in high- and low-risk areas, particularly to the higher prevalence of undifferentiated NPC, which appears to be less associated with smoking, in high-risk areas, such as Asia. These results also suggest that smoking does not act synergistically with factors contributing to the higher occurrence of NPC in Eastern populations, such as Epstein-Barr Virus infection.

The dose-response analyses carried out showed linear associations for smoking intensity and duration with NPC risk. These findings are generally consistent with those emerging from previously published meta-analyses, which were however based on smaller numbers of studies [8, 9]. A non-significant inverse linear dose-response association between time since quitting smoking and NPC risk emerged, with the risk of a former smoker reaching that of a never smoker after 20 years since quitting smoking. This result, which was not analysed in previous meta-analyses, sheds light on the beneficial impact of smoking cessation on NPC risk. Given the limited number of studies contributing to this analysis, its interpretation underscores the need for further research to clarify the role of smoking cessation in reducing NPC risk.

Our systematic review and meta-analysis has several strengths. The innovative methodology used to identify original articles based on a combination of umbrella and traditional reviews [15] allowed the inclusion of more than 40 epidemiological studies investigating the association between cigarette smoking and NPC risk, making this meta-analysis the most comprehensive on the topic. The screening process of all the retrieved publications was carefully carried out to avoid data overlap. A comprehensive quality assessment of the included studies was performed using the NOS [22]. No significant differences in NPC cancer among current, former, and never smokers were found according to study quality as measured by the NOS.

The limitations of this work are those typical of meta-analyses of epidemiological studies. Case-control and cohort studies are prone to selection and recall bias. Differential misclassification of exposure may have occurred since information on smoking status, smoking intensity and duration, and time since quitting was self-reported in all studies. We assumed that the impact of these biases was limited. In fact, the risk estimates were not significantly heterogeneous across study design. It has also been observed that smokers may be over-represented among hospital-based controls, biasing the association towards the null [43]. Our results support this hypothesis, showing a weaker association in hospital-based studies compared with population-based case-control studies.

Consistent heterogeneity between studies was found for each smoking status. This may be the result of pooling data from studies conducted with different methodologies, using different definitions of smoking, and including subjects with different characteristics and background risk levels. We accounted for heterogeneity between studies using random-effects models, although these models did not completely resolve heterogeneity. We examined possible sources of heterogeneity in risk estimates through stratified analyses according to histological subtype of cancer, socioeconomic status, and study characteristics. However, these variables only partially explained the observed heterogeneity.

Conclusion

This meta-analysis confirms the association between cigarette smoking and NPC, and shows that even moderate cigarette consumption can significantly increase the risk. These findings underscore the need for continued research to identify risk factors

associated with the high prevalence of undifferentiated NPC in high-incidence regions, such as Eastern Asia. In addition, these results are important to reduce the burden of NPC and highlight the importance of distinguishing between histological subtypes in NPC risk assessment and prevention. People should avoid smoking, and current smokers should quit to reduce the risk.

Authorship contribution

SG and AL: concept of study, study design, interpretation of results, writing of manuscript, supervision. VB and CS: concept of study, study design. AM: collection of data, statistical analysis. IP: collection of data, statistical analysis, interpretation of results, writing of manuscript. WG, LS and AO: supervision. All authors critically reviewed all contents of the manuscript.

Conflict of interest

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. List of 57 included meta-analysis, pooled-analyses, systematic reviews, and reports on the association between smoking and upper aerodigestive cancer risk.

First Autor, Year (Ref)	Type of analysis
Ansary-Moghaddam, 2009 (1)	Meta-analysis
Ansary-Moghaddam, 2009 (2)	Pooled-analysis
Asombang, 2019 (3)	Review
Berthiller, 2016 (4)	Pooled-analysis
Carter, 2015 (5)	Pooled-analysis
Castellsagué, 1999 (6)	Pooled-analysis
Castellsagué, 2000 (7)	Pooled-analysis
Castro, 2018 (8)	Meta-analysis
Chang, 2019 (9)	Pooled-analysis
Chetwood, 2019 (10)	Review
Cook, 2010 (11)	Pooled-analysis
Di Credico, 2019 (12)	Pooled-analysis
Drahos, 2016 (13)	Pooled-analysis
Du, 2018 (14)	Review
Fahey, 2015 (15)	Meta-analysis
Gandini, 2008 (16)	Meta-analysis
Hashibe, 2007 (17)	Pooled-analysis
Hashibe, 2009 (18)	Pooled-analysis
IARC, 2004 (19)	Report
IARC, 2012 (20)	Report
Ishikawa, 2006 (21)	Pooled-analysis
Jia, 2012 (22)	Review
Jones, 2013 (23)	Meta-analysis
Katanoda, 2008 (24)	Pooled-analysis
Khani, 2018 (25)	Review
Koyanagi, 2016 (26)	Meta-analysis
Lin, 2021 (27)	Pooled-analysis
Long, 2017 (28)	Meta-analysis
Lubin, 2009 (29)	Pooled-analysis
Lubin, 2012 (30)	Pooled-analysis
Macfarlane, 1995 (31)	Pooled-analysis
Mello, 2019 (32)	Meta-analysis
Miyazaki, 2017 (33)	Meta-analysis
Nakamura, 2009 (34)	Meta-analysis
Ordóñez-Mena, 2016 (35)	Pooled-analysis
Oze, 2012 (36)	Meta-analysis
Oze, 2019 (37)	Pooled-analysis
Park, 2014 (38)	Meta-analysis
Petti, 2013 (39)	Meta-analysis
Prabhu, 2013 (40)	Meta-analysis
Prabhu, 2014 (41)	Meta-analysis
Prasad, 2019 (42)	Meta-analysis
Sadri, 2007 (43)	Meta-analysis
Saito, 2017 (44)	Pooled-analysis
t Mannetje, 1999 (45)	Pooled-analysis
Toporcov, 2015 (46)	Pooled-analysis
Tramacere, 2011 (47)	Meta-analysis
SGR, 2001 (48)	Report
SGR, 2004 (49)	Report
Wang, 2017 (50)	Meta-analysis
Wyss, 2013 (51)	Pooled-analysis
Xue, 2013 (52)	Meta-analysis
Yu, 2014 (53)	Meta-analysis
Zeka, 2003 (54)	Meta-analysis
Zhang, 2011 (55)	Meta-analysis
Zheng, 2014 (56)	Pooled-analysis
Zuo, 2017 (57)	Meta-analysis

IARC: International Agency for Research on Cancer; SGR: Surgeon General Report.

Supplementary Table 2. List of 39 excluded publications (33 ineligible and 6 with duplicated results) for the review and meta-analysis and reason for exclusion.

First Author, Year (Ref)	Study design	Reason
Ineligible articles		
Amtha, 2009 (58)	CC	Non inherent
Armstrong, 1983 (59)	CC	Non inherent
Bendjemana, 2011 (60)	CC	Not in English
Bolm-Audorff, 1989 (61)	CC	Not in English
Cai, 1996 (62)	CC	Not in English
Cao, 2000 (63)	CC	Not in English
Chelleng, 2000 (64)	CC	Wrong reference category
Chen, 1997 (65)	CC	Non inherent
Doll, 2005 (66)	CO	No RR available
Henderson, 1976 (67)	CC	Wrong reference category
Hsu, 2015 (68)	CC	Book or symposyum
Huang, 2002 (69)	CC	Not in English
Jayaprakash, 2006 (70)	CC	No RR available
Kurniawan, 2019 (71)	CC	Wrong reference category
Lanier, 1980 (72)	CC	Non inherent
Liao, 2005 (73)	CC	Not in English
Lin Y-H, 1997 (74)	CO	Not in English
Lin, 1973 (75)	CC	No CI 95%
Liu, 2017 (76)	CC	No RR available
Lourembam, 2015 (77)	CC	No RR available
Ma, 2011 (78)	CC	No RR available
Mirabelli, 2000 (79)	CC	No RR available
Nesic, 2010 (80)	CC	No RR available
Ng, 1986 (81)	CC	No RR available
Ning, 1990 (82)	CC	No RR available
Ruan, 2013 (83)	CC	Wrong reference category
Tsai, 2016 (84)	CC	Non inherent
Ye, 1995 (85)	CC	Not in English
Yu, 1986 (86)	CC	Non inherent
Yu, 1988 (87)	CC	SHS only
Zhang, 2004 (88)	CO	Not in English
Zheng, 1994 (89)	CC	Non inherent
Zou, 2014 (90)	CC	Non inherent
Eligible articles		**Included in**
Ekburanawat, 2010 (91)	CC	Fachiroh, 2012 (92)
He, 2015 (93)	CC	Xu, 2012 (94)
Hsu, 2009 (95)	CO	Lin, 2021 (27)
Lin, 1979 (96)	CC	Lin, 1973 (75)
Singh, 2016 (97)	CC	Singh, 2019 (98)
Zhu, 1997 (99)	CC	Zhu, 1995 (100)

CC: case-control study; CO: cohort study.

Supplementary Table 3. Main characteristics of the 33 case-control studies on the association between cigarette smoking and nasopharyngeal risk included in the review, and information contributing to the meta-analysis for nasopharyngeal cancer.

First author, year (Ref)	Country	Sex	Type of controls	N. Cases	N. Controls	Status			Intensity		Duration		TSQ
						Current	Former	Ever	Current	Ever	Current	Ever	Former
Armstrong, 2000 (101)	Malaysia	MF	P	282	282			X					
Ban, 2017 (102)	Malaysia	MF	P	300	533			X					
Chang, 2017 (103)	China	M	P	2554	2648	X	X	O		X		X	O
Cheng, 1999 (104)	Taiwan	MF	P	375	327	X	X	X		X		X	
Fachiroh, 2012 (92)	Thailand	MF	P	681	1078	X	X	O		X	X		X
Feng, 2009 (105)	North Africa (Algeria, Morocco, Tunisia)	M	HP	636	615			X		X		X	
Ghosh, 2014 (106)	India	MF	P	64	100			X					
Guo, 2009 (107)	China	MF	P	1049	785			X		X			
Hardell, 1982 (108)	Sweden	MF	P	27	541			O					
Hsu, 2020 (109)	China	M	H	1235	1262	X	X	O		X		X	X
Ji, 2011 (110)	China	MF	P	1044	1095			X		X		X	
Lye, 2015 (111)	Malaysia	MF	H	356	356			X					
Mabuchi, 1985 (112)	USA	MF	H	39	39			X		X			
Nam, 1992 (113)	USA	MF	P	204	408			O					
Nor Hashim, 2012 (114)	Malaysia	MF	P	96	96			X					
Nuaba, 2020 (115)	Indonesia	MF	P	46	46			X					
Oudjehih, 2020 (116)	Algeria	MF	HP	192	384			O					
Polesel, 2011 (117)	Italy and France	MF	H	150	450	X	X	O					
Ren, 2010 (118)	China	MF	P	1845	2381			X					
Singh, 2019 (98)	India	MF	P	123	189			O		X			
Sriamporn, 1992 (119)	Thailand	MF	H	120	120			X					
Turkoz, 2011 (120)	Turkey	MF	HP	183	183			X					
Vaughan, 1996 (121)	USA	MF	P	294	244	X	X	O					X
Wang, 2021 (122)	Hong Kong	MF	H	676	1285	O	O	O					X
West, 1993 (123)	The Philippines	MF	HP	104	205			O				X	
Xie, 2015 (124)	Hong Kong	MF	H	352	410	X	X	X		X		X	X
Xu, 2012 (94)	China	M	P	1316[b]	1571[b]								
Yang, 2005 (125)	Taiwan	MF	P	502	1944			X				X	
Yong, 2017 (126)	Singapore	MF	P	300	310	X	X	O					
Yu, 1990 (127)	China	MF	P	250	250			X					
Yuan, 2000 (128)	China	MF	P	935	1032	X	X	X	X				
Zhu, 1995 (100)	USA	M	P	113	1899	X	X	O		X		X	
Zou, 2000 (129)	China	MF	P	95	190	X	X	O					
Total (1982-2021) [a]				**15222**	**21687**	**12**	**12**	**33**	**1**	**11**	**1**	**9**	**6**

F: females; H: hospital; M: males; P: population; TSQ: time-since-quitting; X symbol indicates that estimates were provided in the original study publication; O symbol indicates that estimates were derived from the information provided in the original study publication. [a] For status, intensity, duration, and TSQ, numbers represent the number of studies providing information; [b] Number of subjects not included in the total, because overall estimates are already included in other articles.

Supplementary Table 4. Main characteristics of the 7 cohort studies on the association between cigarette smoking and nasopharyngeal cancer risk included in the review and corresponding information contributing to the meta-analysis.

First author, year (Ref)	Country	Sex	Type of controls	N. Cases	N. Controls	Status			Intensity		Duration		TSQ
						Current	Former	Ever	Current	Ever	Current	Ever	Former
Chow, 1993 (130)	USA (US Veterans)	M	m	48	X	X	O	X		X			
Friborg, 2007 (131)	Singapore (SCHS)	MF	i	173	X	X	O	X		X		O	
Hu, 2019 (132)	China (screening project in Sihui County)	MF	i	71			X						
Liaw, 1998 (133)	Taiwan (12 townships)	MF	m	16	X			X		X			
Lin, 2015 (134)	China (GOC)	MF	m	34[b]	X			X		X			
Lin, 2021 (27)	China (GBCS)	M	i	399	X	X	X		X		X	X	
Marsh, 2009 (135)	USA (WWC)	M	m	7			X						
Total (1993-2021) [a]				**714**	**5**	**3**	**5**	**4**	**1**	**4**	**1**	**2**	

F: females; GBSC: Guangzhou Biobank Cohort Study; GOC: Guangzhou Occupational Cohort; i: incidence; m:mortality; M: males; TSQ: time-since-quitting; X symbol indicates that estimates were provided in the original study publication; O symbol indicates that estimates were derived from the information provided in the original study publication; SCHS: Singapore Chinese health Study; WWC: Walingford Workers Cohort. [a] For status, intensity, duration, and TSQ, numbers represent the number of studies providing information; [b] Number of subjects not included in the total, because overall estimates are already included in other articles.

Supplementary Table 5. List of publications containing data that was partially excluded from the meta-analysis and reason for exclusion.

First Author, Year (Ref)	Excluded estimate	Reason for exclusion
Lin, 2015 (134)	Status (ex, curr, ev) for nasopharyngeal cancer	Men are included in Lin, 2021 (27)
Xu, 2012 (94)	Status (ev) for nasopharyngeal cancer	Included in Ren, 2010 (118)

Supplementary Table 6. Quality evaluation of the 33 case-control studies included in the present meta-analysis using the New-Castle Ottawa (NOS) scale.

First author, year [Ref]	SELECTION				COMPARABLITY	EXPOSURE			TOTAL NOS SCORE
	Adequate definition of cases	Representiveness of cases	Selection of Controls	Definition of controls	Comparability of cases and controls [b]	Ascertainment of exposure	Same methods of ascertainment of exposure	Non-response rate	
Armstrong, 2000 [101]	★	★	★	★	★★	-	★	★	8
Ban, 2017 [102]	★	-	★	★	★★	-	★	★	7
Chang, 2017 [103]	★	★	★	-	★★	-	★	★	7
Cheng, 1999 [104]	★	-	★	★	★★	-	★	★	7
Fachiroh, 2012 [92]	★	★	★	-	★★	-	★	-	6
Feng, 2009 [105]	★	★	-	-	★★	-	★	★	6
Ghosh, 2014 [106]	★	-	★	-	-	-	-	-	2
Guo, 2009 [107]	★	★	-	-	★★	-	★	★	6
Hardell, 1982 [108]	★	★	★	-	-	★	★	-	5
Hsu, 2020 [109]	★	-	-	★	★★	-	★	★	6
Ji, 2011 [110]	★	★	★	★	★★	★	★	★	9
Lye, 2015 [111]	★	-	-	★	★★	-	-	★	5
Mabuchi, 1985 [112]	★	★	-	-	★★	-	-	-	4
Nam, 1992 [113]	★	-	★	-	★★	-	★	★	6
Nor Hashim, 2012 [114]	★	-	-	★	★★	-	★	-	5
Nuaba, 2020 [115]	★	-	-	-	★★	-	★	★	5
Oudjehih, 2020 [116]	★	★	-	-	★★	-	★	-	5
Polesel, 2011 [117]	★	-	-	-	★★	-	★	★	5
Ren, 2010 [118]	★	★	-	★	★★	-	★	★	7
Singh, 2019 [98]	★	-	★	-	★★	-	★	★	6
Sriamporn, 1992 [119]	★	-	-	-	★★	-	★	-	4
Turkoz, 2011 [120]	★	★	-	-	★★	-	★	★	6
Vaughan, 1996 [121]	★	★	★	-	★★	-	★	★	7
Wang, 2021 [122]	★	-	-	★	★★	-	★	★	6
West, 1993 [123]	★	-	-	-	★	-	★	-	3
Xie, 2015 [124]	★	★	-	★	★★	-	★	★	7
Xu, 2012 [94]	★	-	-	-	★★	-	★	-	4
Yang, 2005 [125]	-	★	★	★	★	-	★	-	5
Yong, 2017 [126]	★	-	★	★	★	-	★	★	6
Yu, 1990 [127]	★	★	★	-	★★	-	★	★	7
Yuan, 2000 [128]	★	★	★	-	★★	-	★	★	7
Zhu, 1995 [100]	★	★	★	-	★★	-	★	★	7
Zou, 2000 [129]	★	★	★	-	★	-	★	★	6

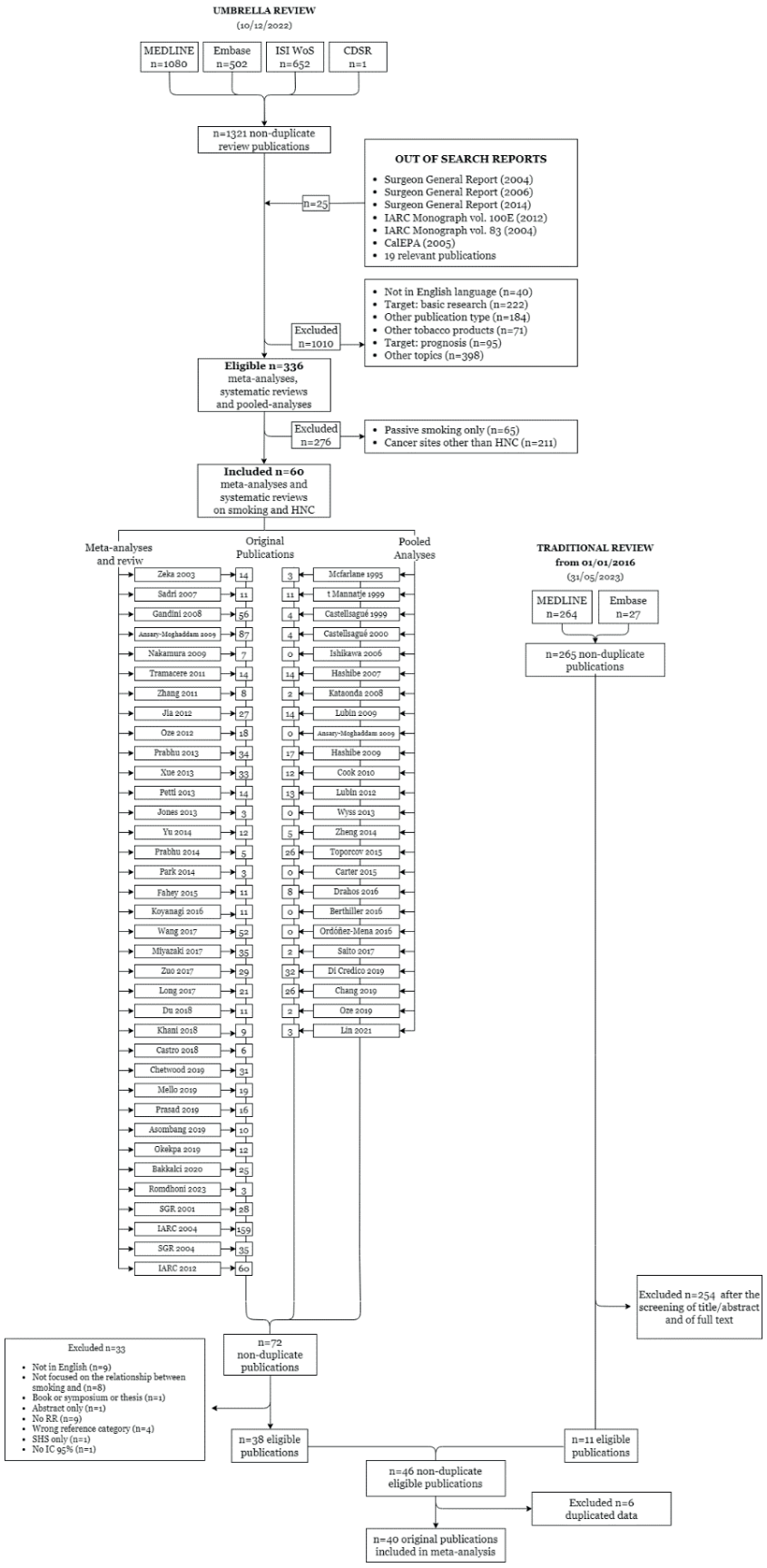
[a] Each item could be scored with a maximum of one star, except for the item "Comparability of cases and controls" which could receive a maximum of two stars; [b] Studies controlling for age or sex in the design or in the analysis received one star. Studies with all the previous variables and at least one of the following variables: alcohol consumption, Epstein-Barr Virus infection, race, diet, and family history of nasopharyngeal cancer, and exposure to pollutants (e.g., air pollution, radon, asbestos) received two stars.

Supplementary Table 7. Quality evaluation of the 7 cohort studies included in the present meta-analysis using the New-Castle Ottawa (NOS) scale.

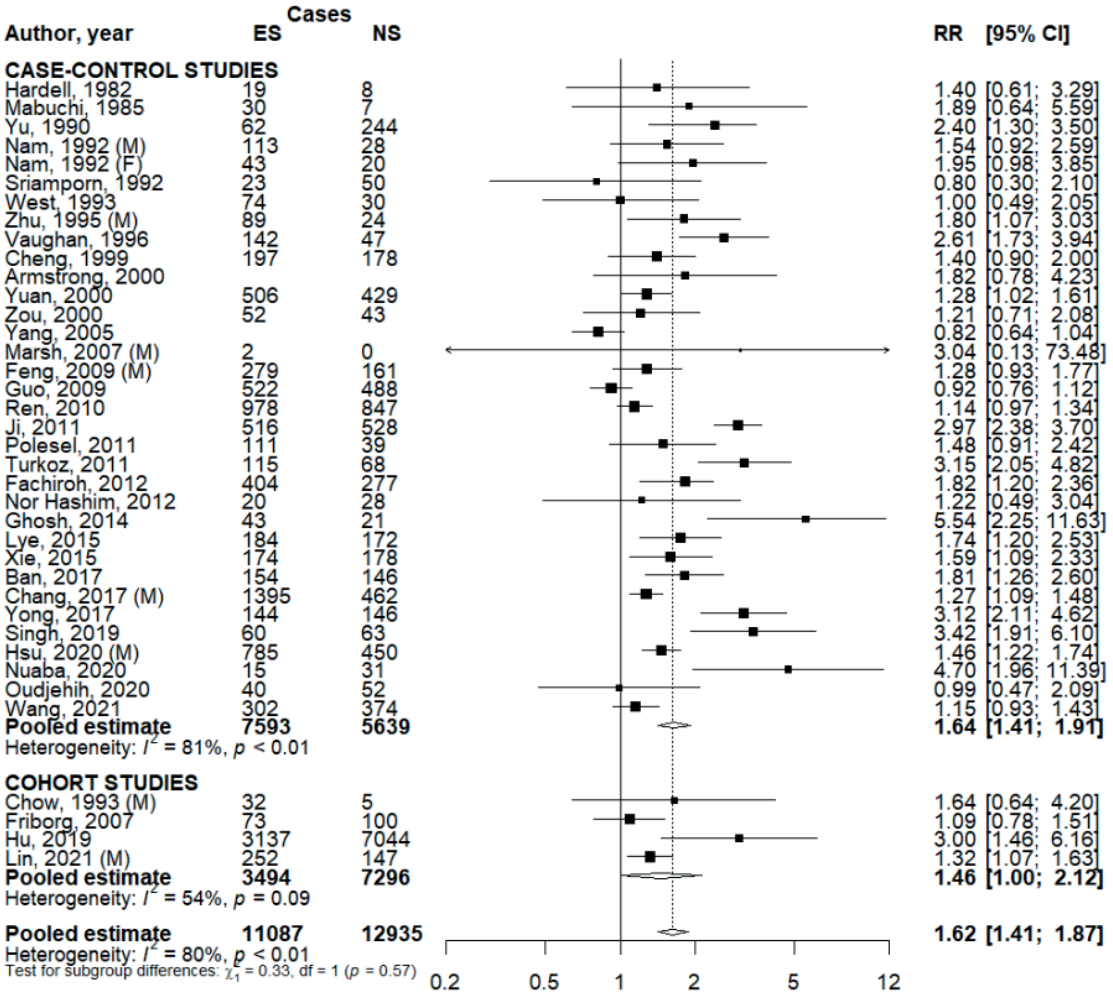
First author, year (Ref)	SELECTION				COMPA-RABLITY	EXPOSURE			
	Repre-senta-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascer-tainment of exposure	Outcome of inter-est not present at start of study	Compa-rability of cohorts [b]	Ascertain-ment of outcome	Follow-up long enough for outcome to occur [c]	Adequacy of follow-up cohorts [d]	TOTAL NOS SCORE
Chow, 1993 (130)	★	★	★	★	★★	-	★	★	8
Friborg, 2007 (131)	★	★	★	★	★★	★	★	★	9
Hu, 2019 (132)	★	★	★	★	★★	★	-	-	7
Liaw, 1998 (133)	★	★	★	★	★	★	★	★	8
Lin, 2015 (134)	★	★	★	★	★★	★	-	-	6
Lin, 2021 (27)	★	★	★	★	★★	★	-	★	8
Marsh, 2007 (135)	-	★	★	-	★★	★	★	★	7

[a] Each item could be scored with a maximum of one star, except for the item "Comparability of cases and controls" which could receive a maximum of two stars; [b] Studies controlling for age or sex in the design or in the analysis received one star. Studies with all the previous variables and at least one of the following variables: alcohol consumption, Epstein-Barr Virus infection, race, diet, and family history of nasopharyngeal cancer, and exposure to pollutants (e.g., air pollution, radon, asbestos) received two stars; [c] Studies with follow-up time ≥10 years received one star; [d] Studies with follow-up rate ≥80% or with a description of those lost at follow-up received one star.

Supplementary Figure 1. Flowchart for the selection of the original studies on the association between cigarette smoking and nasopharyngeal cancer risk included in the review and meta-analysis.

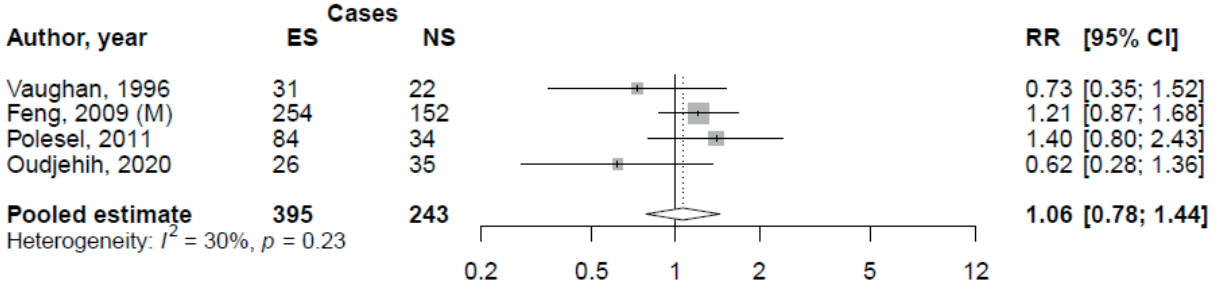


Supplementary Figure 2. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer for ever smokers (ES) versus never smokers (NS), overall and by study design.

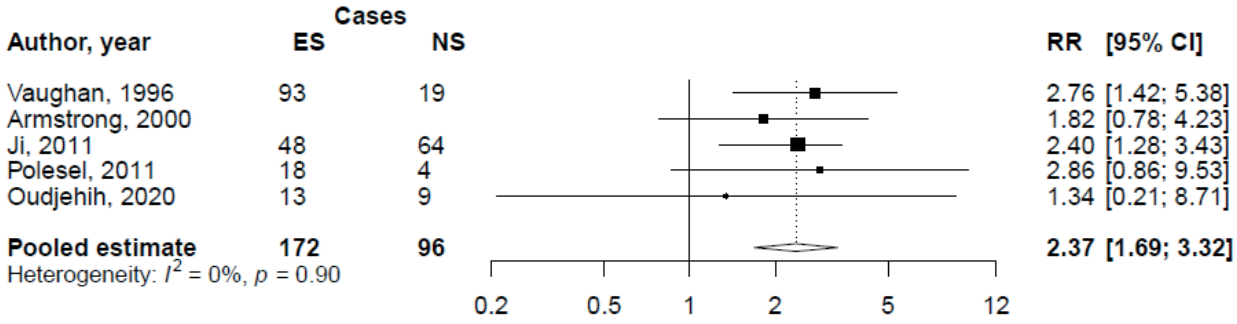


CI: confidence interval; F: females; M: males.

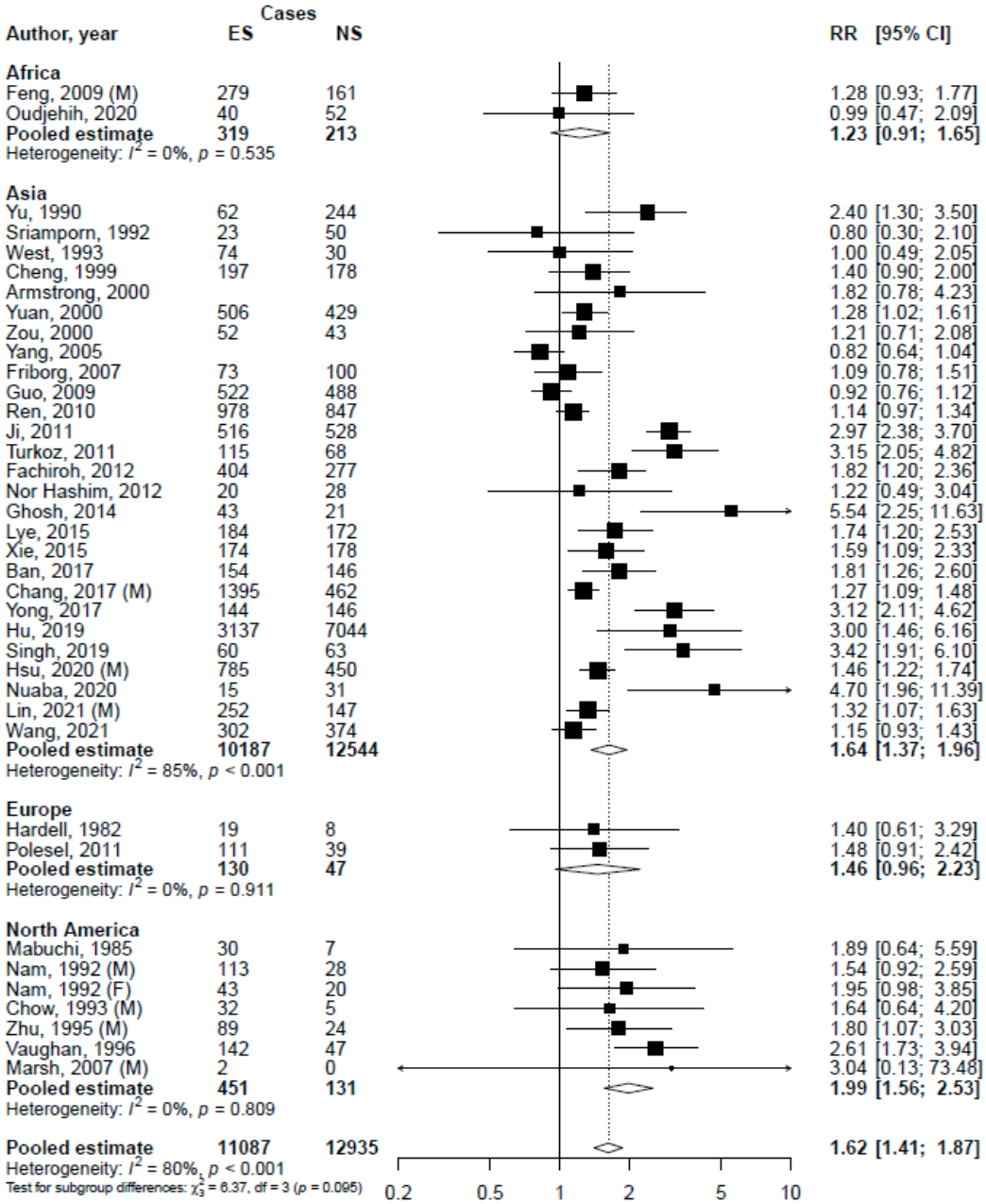
Supplementary Figure 3. Forest plot of study-specific and pooled relative risk (RR) of undifferentiated nasopharyngeal cancer for ever smokers (ES) versus never smokers (NS).



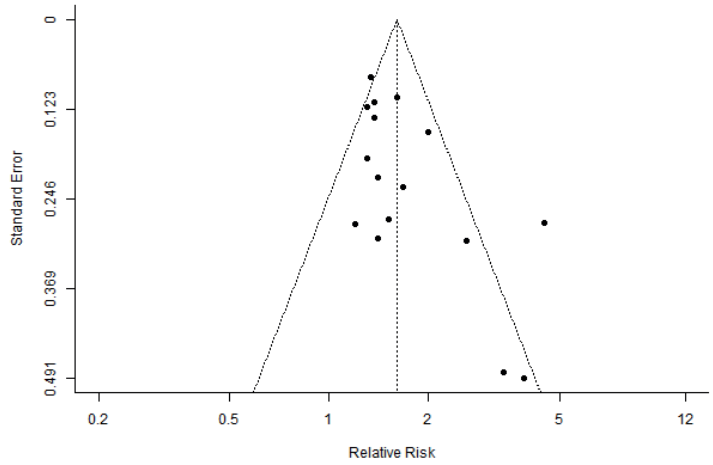
Supplementary Figure 4. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal squamous cell carcinoma for ever smokers (ES) versus never smokers (NS).

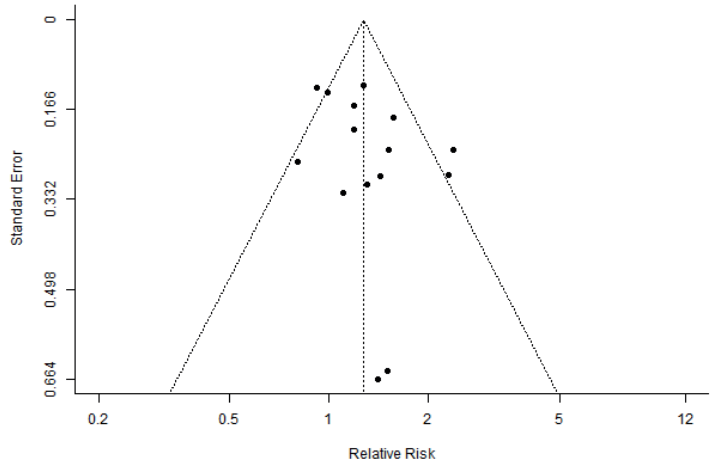


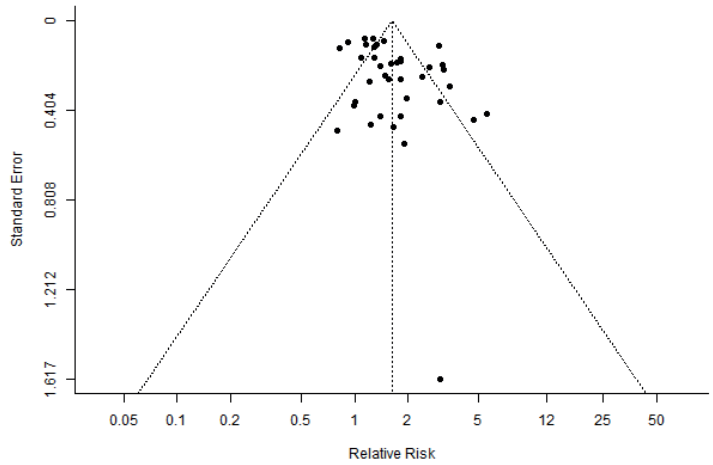
Supplementary Figure 5. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer for ever smokers (ES) versus never smokers (NS), overall and by geographic area.



Supplementary Figure 6. Funnel plot of studies on the association between current (panel A), former (panel B), and ever (panel C) cigarette smokers versus never smokers and nasopharyngeal cancer risk.







Supplementary Box 1. Literature search strings for the update of the last available comprehensive review on the association between smoking and nasopharyngeal cancer risk used in MEDLINE and Embase.

Source	Date	Search string	N
PubMed	31/5/2023	(nasopharynx OR nasopharyngeal) AND (cancer OR neoplasm OR carcinoma OR adenocarcinoma OR Neoplasms [MeSH Terms]) AND (cigarette OR cigarettes OR tobacco OR smoking OR smokers OR smoking [MeSH Terms]) AND (English [Language]) AND ("2016"[Date - Publication] : "2023"[Date - Publication])	264
Embase	31/5/2023	cigarette:ti OR cigarettes:ti OR tobacco:ti OR smoking:ti OR smokers:ti AND nasopharynx:ab,ti OR nasopharyngeal:ab,ti) AND (cancer:ab,ti OR neoplasm:ab,ti OR carcinoma:ab,ti OR adenocarcinoma:ab,ti) AND (article:it OR review:it) AND [english]/lim AND [2016-2023]/py	27
		Duplicates	26
Total	31/5/2023	-	**265 non duplicates**

Supplementary Box 2. Functions of the linear models used to estimate the associations between smoking intensity (current vs. never smokers), duration (current vs. never smokers) and time since quitting (former vs. current smokers) and the risk of nasopharyngeal cancer.

Smoking intensity among current smokers (cigarettes/day)	f(x)= 0.03819357x
Smoking duration among current smokers (years)	f(x)= 0.0180665x
Time since quitting (years)	f(x)= -0.02384517x

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