International Journal of Epidemiology, 2021, 975–986
doi: 10.1093/ije/dyab060
Advance Access Publication Date: 31 March 2021
Original article

Smoking

Smoking and nasopharyngeal cancer: individual data meta-analysis of six prospective studies on 334 935 men

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Received 2 June 2020; editorial decision 16 February 2021; Accepted 4 March 2021

Abstract

Background: The role of smoking in nasopharyngeal carcinoma (NPC) remains uncertain, especially in endemic regions. We conducted an individual participant data (IPD) meta-analysis of prospective cohort studies to investigate the associations between

smoking exposure and risk of NPC.
Methods: We obtained individual participant data of 334 935 male participants from six eligible population-based cohorts in NPC-endemic regions, including two each in Guangzhou and Taiwan, and one each in Hong Kong and Singapore. We used one- and two-stage approaches IPD meta-analysis and Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of NPC for smoking exposure adjusting for age and drinking status.
Results: During 2 961 315 person-years of follow-up, 399 NPC evens were ascertained. Risks of NPC were higher in ever versus never smokers ($HR_{one\text{-}stage} = 1.32$, 95% CI = 1.07-1.63, $P = 0.0088$; $HR_{two\text{-}stage} = 1.27$, 1.01-1.60, 0.04). These positive associations appeared to be stronger in ever smokers who consumed 16+ cigarettes/day ($HR_{one\text{-}stage} = 1.67$, 95% CI = 1.29-2.16, $P = 0.0001$), and in those who started smoking at age younger than 16 (2.16, 1.33-3.50, 0.0103), with dose-response relationships (*P*-values for trend = 0.0028 and 0.0103, respectively). Quitting (versus daily smoking) showed a small reduced risk (stopped for 5+ years: $HR_{one\text{-}stage} = 0.91$, 95% CI = 0.60-1.39, $P = 0.66$; for former smokers: $HR_{two\text{-}stage} = 0.84$, 0.61-1.14, 0.26).
Conclusions: This first IPD meta-analysis from six prospective cohorts in endemic regions has provided robust observational evidence that smoking increased NPC risk in men. NPC should be added to the 12–16 cancer sites known to be tobacco-related cancers. Strong tobacco control policies, preventing young individuals from smoking, would reduce NPC risk in endemic regions.

Key words: Nasopharyngeal carcinoma, smoking, epidemiology, cohort study, individual data, meta-analysis

Key Messages

- This first individual participant data (IPD) meta-analysis from six population-based prospective cohorts in endemic regions of nasopharyngeal carcinoma (NPC) assessed the associations between smoking exposure and risk of NPC in men.
- Ever smokers had 32% higher risks of NPC than never smokers.
- Smokers who consumed 16+ cigarettes per day had 67% higher risks of NPC.
- Smokers who started smoking younger than age 16 showed the highest HR (hazard rato) of 2.16.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinctive geographical variation,[1,2] with over 70% of 129 000 new cases of NPC in 2018 diagnosed in East and South-East Asia.[3] Despite its similar cell or tissue lineage, NPC presents an epidemiological pattern distinct from most types of head and neck cancer that have been confirmed to be smoking related.[4–6] The 2012 International Agency for Research on Cancer (IARC) Monograph considered cigarette smoking to be causally related to NPC.[7] However, the association between smoking and NPC has not been concluded to be causal in the 2014 US Surgeon General's Report.[8]

Previous epidemiological studies on the association between smoking and NPC have shown inconsistent results. Such association appeared to be stronger in case-control studies[9–34] than cohort studies,[35–39] probably because case-control studies are subject to recall bias. In addition, positive associations were mainly observed in non-endemic regions of NPC, where the major NPC histological type is squamous cell carcinoma.[40,41] Prospective epidemiological data are very limited in endemic regions, where the major histological type is non-keratinizing undifferentiated carcinoma.[42] Only two summary aggregate data meta-analyses have reported that smoking was associated with higher

risks of NPC in non-endemic regions, but not in endemic regions.[43,44] Individual participant data (IPD) meta-analysis is considered to be the 'gold standard' of systematic review and can provide the strongest evidence from observational studies.[45] As smoking may have different roles in different subtypes of NPC, separate analyses would be ideal. However, information on subtypes was rarely collected by previous cohort studies and the numbers of NPC events were small, so pooling individual data restricting to studies in endemic regions, having over 95% of non-keratinizing undifferentiated carcinoma NPC, could reflect the association for non-keratinizing undifferentiated carcinoma. We conducted an IPD meta-analysis to assess the associations between smoking history and risk of NPC in endemic regions.

Methods

Ethics Approval

The Guangzhou Biobank Cohort Study has ethics approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China (Co-Principal Investigator: Prof. Lam Tai-Hing). The Guangzhou Occupational Cohort Study obtained ethics approval from the Ethics Committee, Faculty of Medicine, and the University of Hong Kong. Permission to use data was granted by Guangzhou Occupational Diseases Prevention and Treatment Centre (Principal Investigator: Prof. Lam Tai-Hing). The Hong Kong Elderly Health Service Cohort Study obtained ethics approval from the University of Hong Kong–Hospital Authority Hong Kong West Cluster Joint Institutional Review Board (Principal Investigator: Prof. Lam Tai-Hing). The Singapore Chinese Health Study was approved by the Institutional Review Boards of the University of Southern California and the National University of Singapore (Principal Investigator: Prof. Yuan Jian-Min). The Taiwan Cohort conducted in 1984 was approved by the institutional review board of the College of Public Health National Taiwan University (Principal Investigator: Prof. Chen Chien-Jen). The Taiwan MJ Cohort was approved at the National Health Research Institutes and at China Medical University Hospital (Principal Investigator: Prof. Wen Chi-Pang).

Search strategy, cohort selection criteria and study sample

We identified prospective cohort studies in endemic regions published in Chinese or English from January 1970 to November 2019 from PubMed, Web of Science, CNKI and Wanfang. An endemic region was defined as having an age-standardized incidence rate (ASIR) greater than 8 per 100 000 person-years in men. Manual search was also done by reviewing references in relevant articles. Three published cohort studies from endemic regions were found in the literature review from Taiwan,[38] Guangzhou[39] and Singapore.[37] Three other cohorts in endemic regions, including Taiwan,[46] Guangzhou[47] and Hong Kong,[48] with ascertainment of NPC and smoking data, were identified by manual search, though they had no publication on NPC. The inclusion criteria were: (i) the cohort study was conducted in NPC-endemic regions with ASIR $\geq$8/100 000 persons-years in men; (ii) selection of participants was not based on history of any previous chronic disease; (iii) the cohort included sufficient NPC events with a male crude mortality $\geq$4/100 000 person-years or male crude event rate $\geq$10/100 000 person-years; (iv) the cohort had baseline information on sex, age and smoking and alcohol consumption; (v) the mean duration of follow-up of the cohort was $\geq$5 years; (vi) participants in the cohort were aged 18+; and (vii) the primary investigator of the eligible study agreed to provide individual-level data.

All the six cohorts identified in the literature search were eligible. Each of the principal investigators has agreed to join the NPC Cohort Study Collaboration (NPC-CSC). With a data request sheet (Supplementary Figure S1, available as Supplementary data at *IJE* online), we obtained information on NPC event (fatal or non-fatal cases), demographic characteristics (sex, age and educational level), smoking and drinking status, medical history at baseline, duration of follow-up, and vital status (Supplementary Figure S2, available as Supplementary data at *IJE* online). All studies had obtained ethics approval and informed consent for their studies. All participants provided informed consent. This paper follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Individual Patient Data reporting guidelines.[49]

Follow-up and outcome

Participants were followed from the baseline in each cohort to the date of first instance of non-fatal or fatal NPC event, or the date of death from other causes or the last follow-up date in each cohort (Table 1). All six studies classified NPC events by the International Classification of Disease (ICD) Revision 9 or 10. Malignant neoplasm of nasopharynx was coded as 147 in ICD-9 or C11 in ICD-10. We excluded deaths that occurred within 2 years from baseline. Missing duration of follow-up (one NPC event in the Taiwan Cohort 1984, 11 NPC events in the Taiwan MJ Cohort, and 104 participants in the Guangzhou Biobank Cohort Study) was imputed using the median follow-up years of each cohort.

Table 1 Baseline characteristics of individual cohorts and the combined cohort in the meta-analyses (men only)

Study	Taiwan Cohort 1984 (included men only)	Guangzhou Occupational Cohort	Singapore Chinese Health Study	Hong Kong Elderly Health Service Cohort	Guangzhou Biobank Cohort Study	Taiwan MJ Cohort	Combined cohort
Cohort reference number	38	39	37	48	47	46	37–39,46–48
Regions	Taiwan	Guangzhou	Singapore	Hong Kong	Guangzhou	Taiwan	Endemic regions
Enrolment/last follow-up date	1984-86/2011	1988-92/1999	1993-99/2008	1998-2001/2012	2003-08/2017	1994-2006/2008	1984-2008/2017
Median baseline survey year	1985	1990	1996	1999	2005	1999	1996
Population source	Population register	Health check-up	Population register	Health check-up	Health check-up	Health check-up	NA
Male participants	9428	87 327	26 654	21 764	6952	182 810	334 935
Mean (SD) age at baseline survey, years	51.6 (12.5)	41.2 (5.9)	56.5 (7.9)	71.9 (5.3)	64.4 (6.7)	40.6 (13.6)	44.8 (14.2)
Mean (SD) follow-up, years	21.4 (7.5)	7.3 (0.7)	12.2 (3.1)	11.0 (3.2)	11.3 (2.6)	8.1 (3.3)	8.8 (4.0)
No. of NPC case	42	30	117	23	20	167	399
Drinking status, no. (%)							
Never	7577 (80.4)	72 205 (82.7)	18 200 (68.3)	15 771 (72.5)	3530 (50.8)	117 371 (64.2)	234 654 (70.1)
Ever	1851 (19.6)	15 122 (17.3)	8454 (31.7)	5993 (27.5)	3422 (49.2)	65 439 (35.8)	100 281 (29.9)
Smoking status, no. (%)							
Never	3277 (34.8)	40 099 (45.9)	11 342 (42.6)	13 125 (60.3)	2190 (31.5)	87 678 (48.0)	157 711 (47.1)
Ever	6151 (65.2)	47 228 (54.1)	15 312 (57.5)	8639 (39.7)	4762 (68.5)	95 132 (52.0)	177 224 (52.9)
Smoking status, no. of NPC deaths							
Never	3	6	16	14	2	12	53
Ever	14	24	28	9	11	37	123
Smoking status, no. of NPC new cases							
Never	9	NA	37	NA	1	47	94
Ever	16	NA	36	NA	6	71	129

Ever smokers included daily smokers and former smokers, and occasional smokers were excluded. Guangzhou Occupational Cohort and Hong Kong Elderly Health Service Cohort had mortality data only.
SD, standard deviation; NPC, nasopharyngeal carcinoma; NA, not applicable.

Smoking exposure assessment

Information on smoking was obtained from the baseline questionnaire. Smoking exposure in ever smokers (including daily smokers and former smokers) was classified into different categories and compared with never smokers. Cumulative consumption (pack-years) was calculated by multiplying the number of packs (20 cigarettes per pack) smoked per day by the number of years smoked. Smoking categories were first grouped into five-unit (e.g. five cigarettes per day/years/pack-years) intervals, then the intervals were regrouped if the number of events in a five-unit interval was too small for analysis. In the analyses of quitting, time since quitting was classified into four groups: daily smokers (reference group), quitters who had stopped smoking for <5, 5+ years and never smokers.

Statistical analyses

Participants with missing data on cigarette smoking or alcohol drinking at baseline were excluded. We also excluded participants with prevalent NPC or cancer at baseline because the disease status might have changed the subjects' smoking habits. Due to the small number of ever smokers among women (7.6%; Supplementary Table S1, available as Supplementary data at *IJE* online) and missing data (95%) on occasional smokers, the present analysis excluded female participants and occasional smokers.

We examined the association between smoking exposure and NPC events by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard models adjusting for age and drinking status. The Cox proportional hazard assumption was checked using Schoenfeld residuals, and no evidence of violation of the assumption was found. We conducted one-stage meta-analyses that analysed IPD from all cohorts simultaneously, and also used the two-stage random-effect approach to compare the associations for smoking (ever smokers versus never smokers) and quitting status (former smokers versus daily smokers).[50] Smoking cumulative consumption (pack-years) was selected to examine any threshold of a great increase in the HR for smoking as it included both smoking amount and smoking duration. Never smokers were used as the referent to compare with 30 consecutive cut-off points (>1, >2, ... >29, >30 pack-years) in smoking cumulative consumption, and 30 HRs were calculated. The heterogeneity of HRs across the studies was measured by the I^2 and Q statistics. Funnel plots were used to check for publication bias. Missing values for smoking exposure were coded as separate categories and included as indicator variables in the models, except for in dose-response analyses. To assess dose-response effects of smoking duration, smoking cumulative consumption, age at starting smoking and quitting duration, a test for trend was examined treating these factors as ordinal variables among ever smokers only. Statistical interactions by alcohol were assessed based on the likelihood ratio test that compared nested models with and without interaction terms.

Several sensitivity analyses were conducted. We repeated analyses in daily smokers (versus never smokers). We also conducted a sensitivity analysis excluding 116 participants with missing follow-up data for the associations between smoking exposure and NPC events, which did not substantially affect our results (Supplementary Table S2, available as Supplementary data at *IJE* online). Because the association of smoking with NPC mortality and incidence outcomes may be different, we examined the associations with fatal (NPC mortality) and non-fatal (NPC incidence) events separately, and the results were similar. All statistical analyses were conducted with Stata version 15.0 (StataCorp LLC, College Station, TX), and all tests were two-sided.

Results

Of 334 935 male participants (median follow-up of 8.8 years, standard deviation of 4.0) from six studies in regions endemic for NPC, 399 NPC events were ascertained (Table 1).

Risks of NPC were consistently higher in ever smokers, daily smokers and former smokers (versus never smokers) (Table 2). The corresponding adjusted HRs were, respectively, 1.44 (95% CI = 1.17-1.76, $P = 0.0005$), 1.49 (1.20-1.85, 0.0003) and 1.28 (0.94-1.74, 0.11) in Model 1 (adjusted for age), and 1.32 (1.07-1.63, 0.0088), 1.37 (1.10-1.71, 0.0058) and 1.19 (0.87-1.62, 0.28) in Model 2 (adjusted for age and drinking status). The risks of NPC for smoking were stronger in ever smokers (versus never) who consumed 16+ cigarettes per day (adjusted HR = 1.67, 95% CI = 1.29-2.16, $P = 0.0001$) and who started smoking at age younger than 16 (2.16, 1.33-3.50, 0.0103) with dose-response relationships (both *P*-values for trend < 0.05). The associations of smoking exposure with NPC incidence and mortality were similar (Supplementary Table S3, available as Supplementary data at *IJE* online) and remained in daily smokers (Supplementary Table S4, available as Supplementary data at *IJE* online). Quitting (versus daily smoking) showed a small reduced risk (for quitting duration < 5 years: adjusted HR = 1.22, 95% CI = 0.78-1.90, $P = 0.38$; 5+ years: 0.91, 0.60-1.39, 0.66). Figure 1 shows that HRs were consistently >1 and steadily

Table 2 Hazard ratios of NPC in male ever smokers in the one-stage approach IPD meta-analysis of the combined cohort

Exposures and categories	Person-years (Total: 2 961 315)	NPC events ($n = 399$)	Event rate of NPC per 100 000 person-years (95% CI)			Model 1 (95% CI)				Model 2 (95% CI)			
Never smokers	1 360 051	147	10.8	(9.2-	12.7)	Ref				Ref			
Smoking status 1													
Ever smokers	1 601 263	252	15.7	(13.9-	17.8)	1.44	(1.17-	1.76)	***	1.32	(1.07-	1.63)	**
Smoking status 2													
Daily smokers	1 250 684	190	15.2	(13.2-	17.5)	1.49	(1.20-	1.85)	***	1.37	(1.10-	1.71)	**
Former smokers	345 257	60	17.4	(13.5-	22.4)	1.28	(0.94-	1.74)		1.19	(0.87-	1.62)	
Smoking amount in ever smokers, cigarettes/day													
1-15	912 741	116	12.7	(10.6-	12.2)	1.20	(0.94-	1.53)		1.11	(0.87-	1.43)	
16+	496 559	105	21.1	(17.5-	25.6)	1.82	(1.42-	2.34)	****	1.67	(1.29-	2.16)	***
P for trend[a]							0.0022				0.0028		
Smoking duration in ever smokers, years													
Never	1 213 532	133	11.0	(9.2-	13.0)		Ref				Ref		
1-15	572 694	43	7.5	(5.6-	10.1)	0.83	(0.58-	1.18)		0.78	(0.55-	1.12)	
16-35	429 234	88	20.5	(16.6-	25.3)	1.72	(1.32-	2.26)	***	1.59	(1.20-	2.09)	**
36+	280 254	72	25.7	(20.4-	32.4)	1.66	(1.22-	2.27)	**	1.50	(1.09-	2.05)	*
P for trend[a]							0.19				0.31		
Smoking cumulative consumption in ever smokers, pack-years													
Never	1 213 532	133	11.0	(9.2-	13.0)		Ref				Ref		
1-5	337 593	25	7.4	(5.0-	11.0)	0.82	(0.53-	1.26)		0.78	(0.51-	1.21)	
6-25	619 062	93	15.0	(12.3-	18.4)	1.36	(1.05-	1.78)	*	1.26	(0.96-	1.65)	
26+	301 034	82	27.2	(21.9-	33.8)	1.80	(1.35-	2.42)	***	1.63	(1.21-	2.20)	**
P for trend[a]							0.05				0.10		
Age at starting smoking in ever smokers, years													
Never	1 213 532	133	11.0	(9.2-	13.0)		Ref				Ref		
26+	353 338	37	10.5	(7.6-	14.5)	1.00	(0.69-	1.44)		0.96	(0.66-	1.38)	
16-25	991 233	165	16.6	(14.3-	19.4)	1.40	(1.11-	1.76)	**	1.28	(1.01-	1.62)	*
<16	58 881	19	32.3	(20.6-	50.6)	2.31	(1.42-	3.75)	**	2.16	(1.33-	3.50)	**
P for trend[a]							0.0069				0.0103		
Quitting duration in former smokers, years													
Daily smokers	1 229 548	187	15.2	(13.2-	17.6)		Ref				Ref		
<5	98 864	22	22.3	(14.7-	33.8)	1.22	(0.78-	1.91)		1.22	(0.78-	1.90)	
≥5	124 624	26	20.9	(14.2-	30.6)	0.90	(0.59-	1.38)		0.91	(0.60-	1.36)	
Never smokers	1 213 532	133	11.0	(9.2-	13.0)	0.73	(0.59-	0.91)	**	0.79	(0.63-	0.99)	*
P for trend[a]							0.60				0.61		

Model 1 adjusted for age, Model 2 adjusted for age and drinking status.

IPD, individual participant data; NPC, nasopharyngeal carcinoma; CI, confidence interval.

[a]Trend test in ever smokers, excluding never smokers; if trend tests in this table included never smokers, both would have yielded $p < 0.05$. Missing values for exposure were coded as separate categories and included as indicator variables in the models, except for in dose-response analyses.

*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

increased with greater cut-off points of pack-year, suggesting no threshold effect.

Risks of NPC were higher in ever smokers (versus never) in four individual cohorts, including the Taiwan Cohort (adjusted HR = 1.28, 95% CI = 0.64-2.53), Guangzhou Occupational Cohort 1988 (2.54, 1.00-6.50), Taiwan MJ Cohort 1994 (1.37, 0.98-1.91) and Guangzhou Biobank Cohort 2003 (2.57, 0.74-8.98), and in the pooled estimation (1.27, 1.01-1.60, $P = 0.04$). No heterogeneity was found in this meta-analysis ($I^2 = 7\%$, $P_{\text{heterogeneity}} = 0.37$) (Figure 2). These positive associations remained in daily smokers (versus never) (Supplementary Figure S3, available as Supplementary data at *IJE* online). However, no clear association was observed in former smokers (versus daily smokers) in each individual cohort or in the pooled analyses (adjusted HR = 0.84, 95%

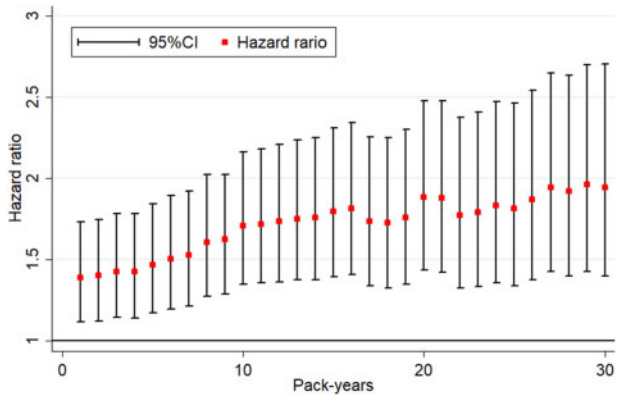

Figure 1 Adjusted hazard ratios of nasopharyngeal carcinoma for smoking cumulative consumption (pack-years) at each of 30 consecutive cut-off points in male ever smokers (daily smokers and former smokers combined)

CI = 0.61-1.14, $P = 0.26$). No heterogeneity was found ($I^2 = 0\%$, $P_{heterogeneity} = 0{\cdot}97$) (Figure 3). Visual inspection of funnel plots showed no publication bias in our overall analyses (Figure 4; Supplementary Figure S4, available as Supplementary data at *IJE* online).

Discussion

This is the first IPD meta-analysis of prospective cohort studies in endemic regions to evaluate the association between smoking exposure and NPC with detailed information on smoking. We found smoking consistently associated with increased risk of NPC. Ever smokers had 32% higher risks of NPC than never smokers. Smokers who consumed 16+ cigarettes per day had 67% higher risks of NPC. Smokers who started smoking younger than age 16 had over twice the risk of NPC compared with never smokers. Quitting was associated with a small reduced risk of NPC in this cohort. This is the largest study to show the harm of smoking and NPC, with dose-response relationships by different exposure indicators.

The findings from this IPD meta-analysis support previous research demonstrating an increased risk of NPC in ever smokers (versus never). Xue *et al.al.*[43] reported an increased risk of NPC (odds ratio = 1.38, 95% CI = 0.96-1.98, $P = 0.18$) in an aggregate data-based meta-analysis of 399 975 participants with 328 NPC events including three cohorts from endemic regions (Guangzhou,[51] Singapore[37] and Taiwan[38]) and one cohort in a low-risk region of NPC (USA).[35] They also reported a higher HR of 1.63 (95% CI = 1.38-1.92, $P < 0.01$) based on 28 case-control studies. Long *et al.*[44] updated the meta-analysis including fofur recent studies (three case-control[29–31] and one cohort[39]) and showed that ever smokers (versus never) had a 56% higher risk of NPC, based on 17 case-control studies and four cohort studies. Whereas Long *et al.*[44] reported a null association based on two cohort studies[37,38] (OR for ever versus never smoking = 1.11, 95% CI = 0.84-1.48, $P = 0.83$), an increased risk of NPC was observed in current smokers (2.19, 1.02-4.72) based on three cohort studies[37–39] including our recent study.[39] Another cohort study in 34 439 male British doctors with four NPC deaths also showed a positive association for smoking.[36]

A dose-response effect for age at starting smoking was first observed in our study. Participants who started smoking younger than 16 years showed the highest HR of 2.16. A relative risk (RR) of greater than 2 means that the attributable fraction in the exposed is greater than 50% [(RR-1)/RR]. This indicates that in NPC patients who started smoking at a young age, about half of the NPC cases can be attributed to smoking. Friborg *et al.* reported a suggestive association between age at smoking initiation and NPC (smokers started smoking at age <15 years: RR = 1.5, 95% CI = 0.8-2.8, P for trend = 0.08). Our findings of increased risk of NPC associated with heavy and chronic smoking (higher smoking amount, smoking duration and cumulative consumption in ever smokers) are consistent with previous studies in Singapore,[37] Taiwan[38] and Guangzhou.[39] We did not find dose-response relationships for smoking duration and cumulative consumption in ever smokers. Dose-response relationships were observed for smoking duration in Singapore ($P = 0.04$)[37] and for smoking cumulative consumption in Guangzhou ($P = 0.014$),[39] but they both included never smokers in the trend test, which would also have shown dose-response relationships in our analyses.

Tobacco has been classified as a group 1 carcinogen by the IARC since 1992.[52] As tobacco can cause laryngeal cancer[53] and pharyngeal cancer,[54] there is no plausible explanation why it cannot cause cancer in the nasopharyngeal region, which is also directly exposed to the carcinogens from smoking, and all were not associated with ionizing radiation exposure.[55–57] The main reason for the limited evidence to support causation is probably because NPC is rare and individual cohort studies did not have sufficient number of NPC events.

There may be several explanations for our findings of increased risk of NPC associated with smoking exposure in men. One possibility is that the association between smoking and NPC was mediated through Epstein-Barr virus (EBV) reactivation.[34,58,59] EBV is closely associated with the occurrence and development of NPC, and its reactivation is associated with smoking. Whereas one study in subjects with elevated IgA antibodies against EBV viral capsid antigen (VCA/IgA) found a null association between smoking and EBV,[60] several large studies in healthy subjects

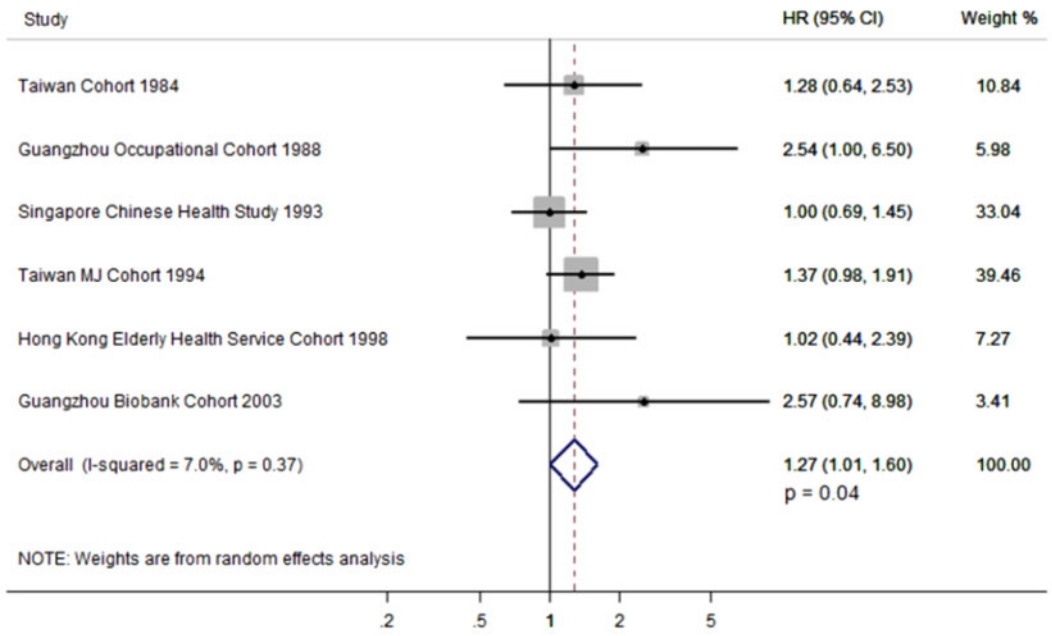

Figure 2 Adjusted hazard ratios of nasopharyngeal carcinoma in male ever smokers (daily smokers and former smokers combined) versus never smokers in individual cohort studies and two-stage approach individual participant data meta-analysis in random-effects model

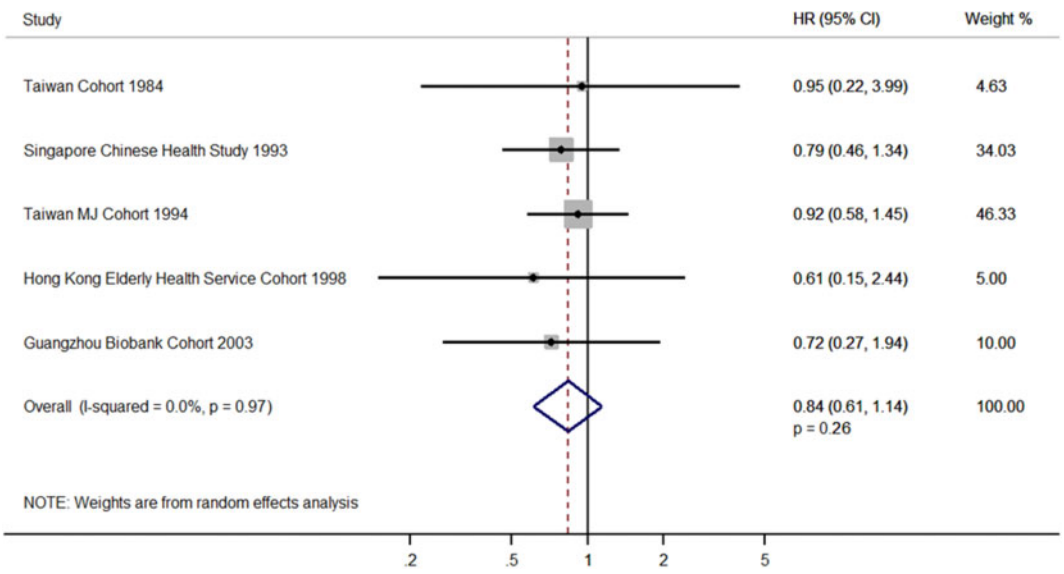

Figure 3 Adjusted hazard ratios of nasopharyngeal carcinoma in male former smokers (daily smokers and former smokers combined) versus daily smokers in individual cohort studies and two-stage approach individual participant data meta-analysis in random-effects model

showed that both smoking[61,62] and cotinine[63] were associated with higher seropositivity for several biomarkers of EBV reactivation and subsequently with higher risk of NPC.[34,59] Another possibility is formaldehyde, a constituent of cigarette smoke which causes squamous cell carcinoma of the nasal cavities upon inhalation exposure of rats, and formaldehyde is considered a cause of nasopharyngeal cancer in humans by IARC.[64] A study demonstrated a 10-fold higher level of the formaldehyde-DNA adduct N6-hydroxymethyl deoxyadenosine in leukocytes of smokers than never smokers, suggesting its possible involvement in NPC in smokers.[65] Moreover, tobacco smoke contains more than 70 carcinogens[66] and some of them may also contribute to the mechanism of how tobacco causes NPC.

By using the IPD meta-analysis design, our study has the largest number of NPC events ($n = 399$) and of total participants ($n = 334\ 935$) in NPC-endemic regions and the world. With the IPD data, we have provided more reliable and robust results and improved the potentially

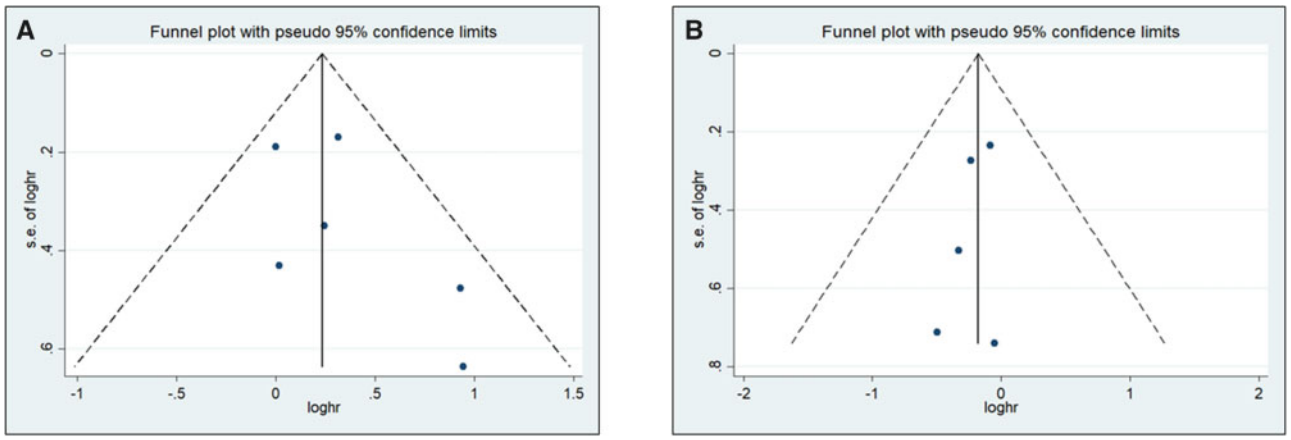

Figure 4 Funnel plots of the risk of nasopharyngeal carcinoma (log-adjusted hazard ratios) associated with A: ever smokers; B: former smokers (both versus never) in the two-stage approach individual participant data meta-analysis (men only)

important limitations of reviews based on published aggregated data. We used one- and two-stage approach meta-analysis to evaluate the reliability of the results.[50] IPD allowed us to conduct sensitivity and subgroup analyses by sex, cohorts and smoking status categories of each individual cohort, and used the same adjustment for potential confounders before the combined analysis. Compared with previous studies, we have enhanced generalizability by combining findings from all six eligible cohort studies across NPC endemic regions.[67]

We recognize the limitations of the short follow-up (<10 years), lack of detailed information on alcohol consumption, and missing data of smoking duration, age at starting smoking and quitting duration in one cohort.[48] More NPC events would be available if all cohorts can further follow up and update the data. Limited by the data we collected, another concern is confounding since our analyses have only adjusted for age and alcohol consumption, but not other potential confounders, such as salted fish intake and EBV reactivation. Previous studies in Guangdong and Guangxi, China, showed that associations between smoking and NPC did not alter substantially after adjusting for consumption of salted fish.[32,34] Our case-control study in Hong Kong, China, also reported similar association between smoking and NPC with and without adjusting for salted fish intake (data not shown).[68] Although our results may be influenced by EBV infection and activation, EBV may not be a confounder but a mediator of the association between smoking and NPC. We did not collect information on reasons for quitting (whether stopped by choice or because of illness). The protective effects of quitting cannot be assessed straightforwardly.[69] Cessation for 5 years or longer appeared to reduce NPC risk, but a larger dataset in future research is needed for confirmation. As the present analysis included Chinese men only, our findings may not be generalized to women and non-Chinese who are not in endemic regions. Future studies with detailed information on quitting and in women are recommended.

In conclusion, this first IPD meta-analysis from six prospective cohorts in endemic regions has provided robust observational evidence that smoking increased NPC risk in men. NPC should be added to the 12–16 cancer sites known to be tobacco-related cancers. Strong tobacco control policies, preventing young individuals from smoking, would reduce NPC risk in endemic regions.

Data Availability

Due to ethical restrictions protecting patient privacy, data may be available on request from the Guangzhou Biobank Cohort Study Data Access Committee. Please contact us at [gbcsdata@hku.hk] for fielding data accession requests. The data of the Guangzhou Occupational Cohort and the Hong Kong Elderly Health Service Cohort Study underlying this article will be shared on reasonable request to the corresponding author, and the principal investigator Prof. Tai-Hing Lam [hrmrlth@hku.hk]. Data are from the Singapore Chinese Health Study, and the authors did not seek approval from the IRB to make the data publicly available. According to the Singapore Personal Data Protection Act, the authors could not release the data without approval from IRB. Researchers who meet the criteria for access to confidential data may contact the principal investigators of Singapore Chinese Health Study at Prof. Jian-Min Yuan [yuanj@upmc.edu] and Prof. Woon Puay Koh [woonpuay.koh@duke-nus.edu.sg] to seek approval from the National University of Singapore IRB. The Taiwan Cohort (conducted in 1984) data underlying this article will be shared on reasonable request to the principal investigator at Prof. Chen Chien-Jen [cjchen@ntu.edu.tw]. The data that support the findings of this study are

available from MJ Health Research Foundation, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of MJ Health Research Foundation.

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

This study was funded by the Hong Kong RGC Area of Excellence Scheme (AoE/M-06/08), World Cancer Research Fund UK (WCRF UK) and Wereld Kanker Onderzoek Fonds (WCRF NL), as part of the WCRF International grant programme (2011/460). This revision was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. The Guangzhou Biobank Cohort Study was funded by the University of Hong Kong Foundation for Educational Development and Research, Hong Kong, the Guangzhou Public Health Bureau and the Guangzhou Science and Technology Bureau, Guangzhou, China, and the University of Birmingham, UK. The Guangzhou Occupational Cohort was funded by the Hong Kong Research Grants Council (HKU 466/96 M), Hong Kong Health Services Research Committee (531036), Guangdong Province Public Health Bureau Five One Project (96–186), Guangzhou Municipal Science and Technology Commission (96-Z-65). The Hong Kong Elderly Health Service Cohort Study was funded by the Health Services Research Fund in Hong Kong (grant no. HSRF#S111016). The Singapore Chinese Health Study was funded by National Institutes of Health grants RO1 CA55069, R35 CA53890, and R01 CA80205, from the National Cancer Institute, Bethesda, MD. The Taiwan Cohort conducted in 1984 was funded by DOH 75–0203-18 and DOH 76–0203-17 from the Department of Health, Executive Yuan, Taipei, Taiwan. The Taiwan MJ Cohort was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212–114004), MOST Clinical Trial Consortium for Stroke (MOST 109–2321-B-039–002), China Medical University Hospital (DMR-109–231), Tseng-Lien Lin Foundation, Taichung, Taiwan.

Acknowledgements

The chief acknowledgments are to the participants who provided information for these studies and the research staff. We thank the Guangzhou Centre for Disease Control and Prevention (Professors G Z Lin, H Z Liu and M Wang), the Medical Insurance Administration Bureau of Guangzhou, and the Guangzhou Municipal Public Security Bureau for assisting follow-up and record linkage. We also thank the Guangzhou Health and Happiness Association for the Respectable Elders for convoking the subjects. We thank Dr Ye Guo-Xiong, Director of Guangzhou Public Health Bureau, adviser of the study, Guangzhou Public Security Bureau Population Information Centre and street police stations, District Public Health Bureaux, Guangzhou Funeral Home and other staff of the Guangzhou Occupational Diseases Prevention and Treatment Centre. We wish to thank the staff of the Elderly Health Service, Department of Health, particularly Shelley Chan, and the Hospital Authority, the Government of Hong Kong Special Administrative Region, for their assistance in data collection and entry. We would also like to acknowledge the contribution of Dr P Y Leung, when at the Department of Health, in facilitating the creation of the cohort. We thank Siew-Hong Low of the National University of Singapore for overseeing the fieldwork of the Singapore Chinese Health Study and Renwei Wang for the development and maintenance of the cohort study database. We also thank Mimi C Yu for being the founding and longstanding principal investigator of the Singapore Chinese Health Study. We thank Dr Elizabeth K Cahoon and Dr Lindsay M Morton for revising the manuscript.

Author Contributions

All the authors participated in individual cohort design, data collection and data cleaning. J.H.L. conducted the combined statistical analysis and drafted the manuscript under T.H.L.'s and C.P.W.'s supervision. Z.M.M. re-analysed the data, conducted additionally analyses and revised the manuscript substantially based on reviewers' comments, and is the guarantor for the paper. All authors helped to draft the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest

None declared.

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