

Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan

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Abstract

Objectives: Nasopharyngeal carcinoma (NPC) is rare in most countries but occurs with relatively high frequency among southern Chinese populations throughout the world. A case-control study of NPC was conducted in Taiwan to investigate the importance of active and passive cigarette exposure and alcohol consumption as risk factors for this disease.

Methods: 375 histologically confirmed incident NPC cases (99% response rate) were prospectively identified from two hospitals in Taipei between July 1991 and December 1994 and administered a detailed questionnaire. 327 healthy community controls individually matched to cases on sex, age and residence were selected (88% response rate).

Results: After multivariate adjustment, the odds ratio (OR) and 95% confidence interval (CI) was 1.7 (1.1–2.9 with $p = 0.03$ for increasing dose-response) for those who smoked for ≥ 25 years compared with non-smokers. Passive smoking during childhood or adult life was not associated with an increased risk of disease. Alcohol consumption was not associated with NPC risk. The OR for subjects with ≥ 15 grams of ethanol per day compared to non-drinkers was 1.1 (95% CI = 0.7–1.7).

Conclusions: Our results suggest that long term cigarette smoking is associated with NPC but that low level exposure to cigarette smoke via passive exposure and alcohol consumption are not associated with disease risk.

Introduction

Nasopharyngeal carcinoma (NPC) is rare in most countries with an age-standardized incidence of less than 1 per 100,000 person-years [1]. In contrast, the exceptionally high rate of NPC, among the southern Chinese population throughout the world, has been known for many years [1–3]. In Taiwan, NPC is the seventh most common malignant neoplasm in males and the thirteenth most common malignant neoplasm in females, with an age-standardized annual incidence of 6.6 for males and 2.8 for females per 100,000 [4].

Cigarette smoking has been shown to be a major risk factor for cancers of various organ systems and consti-

tuents of cigarettes, including nitrosamines and formaldehyde, have been shown to have carcinogenic potential [5]. Given that the inhalation of cigarette smoke directly exposes the nasopharynx to carcinogens present in tobacco smoke [6], an association between cigarette smoking and NPC is biologically plausible. Results from studies, which have examined the association between cigarette smoking and NPC, have been conflicting. However, Lin *et al.* (1973) [7], in a study conducted in Taiwan, reported a significant increase in risk of NPC with increasing duration of cigarette smoking. This initial finding was supported by numerous subsequent studies [8–15], but other studies failed to observe an association between cigarette smoking and NPC [16–24].

Few studies have evaluated the risk of NPC associated with passive smoking. Among the three case-control studies that have evaluated risk associated with exposure to passive smoking, only one conducted in Guangxi, China [10] observed a significant association, while the other two studies conducted in Guangzhou, China [11] and Taiwan [25] did not observe an association between passive smoking and disease.

Numerous studies have investigated the association between alcohol consumption and NPC. No significant association was found in most studies [7, 9, 16, 22, 23, 25, 26]. However, two studies conducted in Malaysia [19] and the United States [13] reported an increased NPC risk associated with alcohol consumption.

The present study was carried out to further explore the associations with NPC of active and passive cigarette smoking and alcohol consumption.

Material and methods

Incident cases of histologically confirmed NPC were prospectively ascertained from two teaching hospitals in Taipei City, the National Taiwan University Hospital and Mackay Memorial Hospital, between July 15, 1991 and December 31, 1994. The eligibility criteria of NPC cases included age less than 75 years, no previous diagnosis and/or treatment for NPC, and a residence in Taipei City or County for at least 6 months. 378 eligible cases were identified. One individually matched community control who had no history of NPC was randomly selected *via* the National Household Registration System for each eligible NPC case. Controls were matched to cases on sex, age (same 5-year group) and residence (same district or township).

No interviews were sought from next of kin, and refusals or non-respondents were not replaced. Interviews were conducted by standardly trained interviewers using a structured questionnaire. Double-entry and verification of all data was performed to avoid keying errors. There were 375 NPC cases (99% response rate) and 327 community controls (88% response rate) included in the analyses.

Information on tobacco use included age at which smoking began and ended, intensity and duration of smoking, and degree of inhalation into the lungs. Former smokers were defined as those subjects who stopped smoking more than 1–2 years prior to NPC diagnosis (cases) or interview (controls). Current smokers were defined as those who were active smokers at the time of interview or who reported having quit in the 1–2 years preceding diagnosis (cases) or interview (controls). Cumulative exposure in pack-years was derived using data on intensity and duration of use. Information on house-

hold passive smoking during childhood and adult life included number of smokers in the household, duration of exposure to passive smoking (person-years) and cumulative exposure to passive smoking (pack-person-years). The latter two variables were derived from information obtained on intensity and duration of smoking for each member reported to have smoked in the household.

Information on alcohol drinking included current and past alcohol drinking status, age at which drinking began and ended, duration of alcohol drinking, and cumulative alcohol consumption (gram-years), which was derived from frequency and intensity of consumption reported for the type of alcoholic beverage most frequently consumed. As was done for smoking, former alcohol drinkers were defined as those who stopped drinking for more than 1–2 years prior to NPC diagnosis (cases) or interview (controls). Current drinkers were defined as those who reported drinking at the time of interview or who reported having quit in the 1–2 years preceding diagnosis (cases) or interview (controls).

Unconditional logistic regression was used to estimate odds ratios (ORs) both before and after controlling for potential confounders with change-in-estimate methods [27]. In addition to active smoking, passive smoking, and alcohol consumption, factors considered as potential confounders in our analyses included age, gender, ethnicity, educational level, and family history of NPC. Potential confounding by dietary factors was also considered and found not to affect the estimates of risk associated with cigarette smoking (both active and passive) and alcohol consumption. Conditional logistic regression was also performed and results were similar to those observed when unconditional logistic regression was used. ORs and their 95% corresponding confidence intervals (CIs) from the multivariate unconditional regression analysis are presented. The statistical software used in data analysis were SAS and EGRET.

Results

Sociodemographic characteristics

375 cases and 327 controls were included in the analyses (Table 1). The age and sex distribution was very comparable between cases and community controls, as expected due to the matching criteria used. Cases were more likely than controls to be of Fukkienese or Hakka origin and less likely to be of other Han origin. Compared to Fukkienese subjects, those of Hakka origin had an OR of disease of 1.2 (95% CI = 0.7–2.2) and those of Guangdong/Aboriginal and other Han origin had ORs of 0.8 (95% CI = 0.4–1.7) and 0.3

Table 1. Sociodemographic characteristics of 375 nasopharyngeal carcinoma cases and 327 community controls

Sociodemographic characteristics	Frequency distribution		Age/Sex adjusted OR (95% CI)
	Cases No. (%)	Controls No. (%)	
Sample size	375	327	
Age Mean (SD ^a)	46 (11.6)	46 (11.8)	
Range	15–74	19–74	
Age < 35	65 (17.3)	57 (17.4)	
35–44	121 (32.3)	102 (31.2)	
45–54	96 (25.6)	85 (26.0)	
55–64	73 (19.5)	64 (19.6)	
65+	20 (5.3)	19 (5.8)	
Sex Female	115 (30.7)	104 (31.8)	
Male	260 (69.3)	223 (68.2)	
Race ^b Fukienese	308 (82.1)	238 (73.0)	1.0
Hakka	32 (8.5)	20 (6.1)	1.2 (0.8–2.2)
Guangdong/Aboriginal	16 (4.3)	15 (4.6)	0.8 (0.4–1.7)
Other Han	19 (5.1)	53 (16.3)	0.3 (0.2–0.5)
Educational level			
Junior high or below	225 (60.0)	164 (50.2)	1.0
Senior high or above	150 (40.0)	163 (49.8)	0.6 (0.4–0.9)
Marital status			
Married	311 (82.9)	283 (86.5)	1.0
Others	64 (17.1)	44 (13.5)	1.3 (0.9–2.0)
Religion Childhood			
None	137 (36.5)	101 (30.9)	1.0
Buddhist/Taoist	225 (60.0)	203 (62.1)	0.8 (0.6–1.1)
Christian/other	13 (3.5)	23 (7.0)	0.4 (0.2–0.9)
Religion Adulthood ^c			
None	85 (22.8)	65 (19.9)	1.0
Buddhist/Taoist	276 (74.0)	240 (73.4)	0.9 (0.6–1.3)
Christian/other	12 (3.2)	22 (6.7)	0.4 (0.2–0.9)

^a Standard deviation.

^b Race was not available for 1 control.

^c Adult religion was not available for 2 cases.

(95% CI = 0.2–0.5), respectively. Subjects with a senior high school education or beyond were at significantly lower risk of disease than those with less education (OR = 0.6, 95% CI = 0.4–0.9). Marital status was not significantly associated with NPC risk. Individuals who reported being either Christians or of a religious belief other than Buddhism and Taoism were found to be at a reduced risk of NPC compared to Buddhists, Taoists and those who espoused no religious beliefs during childhood or adult life.

Active cigarette smoking

Ever cigarette smoking was associated with a weak increased odds of NPC (OR = 1.4, 95% CI = 0.9–2.0) (Table 2). Compared to never smokers, current smokers had an OR of disease of 1.4 (95% CI = 0.9–2.1) and former smokers had an OR of 1.1 (95% CI = 0.6–2.1). The risk of NPC tended to increase with increasing duration of cigarette smoking (p for trend = 0.03), with

multivariate-adjusted ORs of 1.1 (95% CI = 0.7–1.8) and 1.7 (95% CI = 1.1–2.9) for those who had smoked cigarettes for less than 25 years and for 25 or more years, respectively. No significant effect of smoking intensity, pack-years of smoking, inhalation into the lungs and age at which smoking began was observed in our study.

Passive smoking

Exposure to passive smoking during childhood was associated with a non-significant decrease in odds of disease (OR = 0.7, 95% CI = 0.5–1.0) (Table 3). No significant effect was observed when number of smokers in the household during childhood was examined. A non-significant trend of decreasing odds of disease with increasing person-years of exposure to passive smoking was observed (p for trend = 0.07), with ORs of 0.7 (95% CI = 0.5–1.0) and 0.7 (95% CI = 0.4–1.1) for those exposed to passive smoking for 18 or less person-

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for the effects of active cigarette smoking on nasopharyngeal carcinoma risk

Active smoking variable	No. of cases/No. of controls	Age/Sex adjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Smoking habit			
Never	178/173	1.0	1.0
Ever	197/152	1.3 (0.9–1.7)	1.4 (0.9–2.0)
Smoking status			
Never	178/173	1.0	1.0
Former	27/29	1.0 (0.5–1.8)	1.1 (0.6–2.1)
Current	170/123	1.5 (1.0–2.1)	1.4 (0.9–2.1)
	<i>p</i> for trend =	0.04	0.09
Inhalation			
Never smoked	178/173	1.0	1.0
No	49/34	1.6 (0.9–2.6)	1.5 (0.9–2.6)
Yes	148/117	1.3 (0.9–2.0)	1.3 (0.9–2.0)
	<i>p</i> for trend =	0.2	0.20
Age starting smoking			
Never	178/173	1.0	1.0
< 20	84/70	1.3 (0.8–2.0)	1.3 (0.8–2.0)
≥ 20	113/82	1.5 (1.0–2.2)	1.4 (0.9–2.2)
	<i>p</i> for trend =	0.07	0.1
Intensity of smoking (cigarettes/day)			
None	178/173	1.0	1.0
< 20	93/69	1.4 (0.9–2.2)	1.4 (0.9–2.1)
≥ 20	104/81	1.4 (0.9–2.1)	1.4 (0.9–2.2)
	<i>p</i> for trend =	0.1	0.2
Duration of smoking (years)			
None	178/173	1.0	1.0
< 25	104/89	1.2 (0.8–1.8)	1.1 (0.7–1.8)
≥ 25	93/63	1.7 (1.1–2.7)	1.7 (1.1–2.9)
	<i>p</i> for trend =	0.03	0.03
Cumulative exposure to active smoking (pack-years)			
None	178/173	1.0	1.0
< 20	100/77	1.4 (0.9–2.1)	1.3 (0.8–2.0)
≥ 20	97/73	1.4 (0.9–2.2)	1.5 (0.9–2.4)
	<i>p</i> for trend =	0.1	0.1

^a Adjusted for age, sex, race, educational level, family history of NPC, drinking status.

years and for those exposed for more than 18 person-years, respectively. After multivariate adjustment a trend of decreasing NPC risk was indicated ($p = 0.03$) for cumulative exposure to passive cigarette smoking in pack-person-years, but the ORs were not monotonically decreasing. Stratification by active cigarette smoking status indicated that the trend observed for passive cigarette smoking exposure in childhood remained among non-smokers, but not among former or current smokers. Among non-smokers after multivariate adjustment, a trend of decreasing NPC risk was indicated ($p = 0.03$ and $p = 0.02$) for cumulative exposure to passive cigarette smoking in person-years and in pack-person-years, respectively. For duration of passive smoking (person-years), the ORs were 0.6 (95% CI = 0.4–1.0) and 0.5 (95% CI = 0.2–1.2) for those exposed to passive smoking for 18 or less person-years and for those exposed for more than 18 person-years,

respectively. For cumulative exposure to passive smoking in pack-person-years, the ORs were not monotonically decreasing. Exposure to passive cigarette smoking during adulthood was not found to be significantly associated with risk of NPC, either when overall analysis or analysis stratified by active cigarette smoking status was performed.

Alcohol drinking

Alcohol drinking was not associated with NPC risk (OR = 0.9, 95% CI = 0.6–1.3) as shown in Table 4. No measure of alcohol drinking examined was significantly associated with risk of NPC (Table 4).

Analyses were also performed, restricted to subjects of Fukkienese origin. Results obtained were similar to those reported herein (data not shown). The number of subjects of Hakka, Guangdong, Aboriginal, or other

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for the effects of passive cigarette smoking on nasopharyngeal carcinoma risk among all subjects and among none active smokers

Passive smoking variable	All subjects		None active smokers	
	No. of cases/ No. of controls	Adjusted OR ^a (95% CI)	No. of cases/ No. of controls	Adjusted OR ^a (95% CI)
Childhood Passive smoking				
No	142/106	1.0	86/64	1.0
Yes	233/218	0.7 (0.5–1.0)	92/108	0.6 (0.4–1.0)
Number of smokers In the household				
None	142/106	1.0	86/64	1.0
= 1	168/162	0.7 (0.5–1.0)	66/84	0.6 (0.4–0.9)
> 1	65/55	0.8 (0.5–1.3)	26/23	0.8 (0.4–1.5)
	<i>p</i> for trend =	0.2	<i>p</i> for trend =	0.1
Duration of exposure to passive smoking (person-years)				
None	142/106	1.0	86/64	1.0
≤ 18	178/171	0.7 (0.5–1.0)	72/87	0.6 (0.4–1.0)
> 18	45/45	0.7 (0.4–1.1)	16/19	0.5 (0.2–1.2)
	<i>p</i> for trend =	0.1	<i>p</i> for trend =	0.0
Cumulative exposure to passive smoking (pack-person-years)				
None	142/106	1.0	86/64	1.0
< 10	66/72	0.6 (0.4–1.0)	36/47	0.5 (0.3–0.9)
10–18	77/69	0.8 (0.5–1.2)	22/23	0.7 (0.4–1.4)
> 18	30/41	0.5 (0.3–0.9)	10/18	0.4 (0.2–0.9)
	<i>p</i> for trend =	0.0	<i>p</i> for trend =	0.0
Adulthood Passive smoking				
No	182/149	1.0	80/69	1.0
Yes	193/176	0.8 (0.6–1.1)	98/104	0.7 (0.5–1.2)
Number of smokers in the household				
None	182/149	1.0	80/69	1.0
= 1	106/125	0.6 (0.4–0.8)	57/73	0.6 (0.4–1.0)
> 1	84/51	1.3 (0.8–2.0)	40/31	1.1 (0.6–2.1)
	<i>p</i> for trend =	0.8	<i>p</i> for trend =	0.9
Duration of exposure to passive smoking (person-years)				
None	182/149	1.0	80/69	1.0
≤ 18	115/116	0.7 (0.5–1.0)	54/66	0.6 (0.4–1.1)
> 18	75/58	0.9 (0.6–1.4)	43/36	1.0 (0.5–2.0)
	<i>p</i> for trend =	0.3	<i>p</i> for trend =	0.7
Cumulative exposure to passive smoking (pack-person-years)				
None	182/149	1.0	80/69	1.0
< 10	80/78	0.8 (0.5–1.1)	43/45	0.8 (0.4–1.3)
10–18	50/37	1.0 (0.6–1.7)	20/18	0.8 (0.4–1.8)
> 18	46/38	0.8 (0.5–1.3)	25/25	0.8 (0.4–1.6)
	<i>p</i> for trend =	0.4	<i>p</i> for trend =	0.5

^a Adjusted for age, sex, race, educational level, family history of NPC.

Han origin was too small to warrant stratified analysis. Analyses stratified by age (<45 years and ≥45 years) revealed findings that were consistent with the overall findings reported here.

Discussion

Results from the present study indicate that long term active smoking is associated with risk of NPC. In

contrast, alcohol consumption and passive smoking during childhood or adult life were not related to increased risk of this disease.

Our finding that long-term cigarette smokers are at increased risk of NPC is consistent with previous studies conducted in Taiwan [7, 12, 25]. Several studies in other high and low risk areas have also observed a positive association between cigarette smoking and NPC [9, 11, 13–15], although some studies failed to detect such an

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) for the effects of alcohol consumption on nasopharyngeal carcinoma risk

Alcohol consumption variable	No. of cases/No. of controls	Age/Sex adjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Drinking habit			
Never	270/231	1.0	1.0
Ever	105/94	0.9 (0.7–1.3)	0.9 (0.6–1.3)
Drinking status			
Never	270/231	1.0	1.0
Former	13/8	1.4 (0.6–3.5)	1.6 (0.6–4.5)
Current	92/86	0.9 (0.6–1.3)	0.8 (0.6–1.2)
	<i>p</i> for trend =	0.6	0.3
Age starting alcohol drinking			
Never	270/231	1.0	1.0
< 25	61/49	1.1 (0.7–1.6)	1.0 (0.6–1.6)
≥ 25	43/44	0.8 (0.5–1.3)	0.8 (0.5–1.3)
	<i>p</i> for trend =	0.5	0.4
Duration of alcohol drinking (years)			
None	270/231	1.0	1.0
< 15	35/38	0.8 (0.5–1.3)	0.7 (0.4–1.2)
≥ 15	68/54	1.1 (0.7–1.6)	1.1 (0.7–1.6)
	<i>p</i> for trend =	0.9	0.9
Alcohol consumption quantity (gram of ethanol/day)			
None	270/231	1.0	1.0
< 15	47/51	0.8 (0.5–1.2)	0.7 (0.5–1.2)
≥ 15	57/42	1.2 (0.7–1.8)	1.1 (0.7–1.7)
	<i>p</i> for trend =	0.8	0.9
Cumulative alcohol consumption (g-years)			
None	270/231	1.0	1.0
< 100	33/31	0.9 (0.5–1.5)	0.8 (0.5–1.4)
100–499	32/34	0.8 (0.5–1.4)	0.7 (0.4–1.3)
≥ 500	38/26	1.3 (0.7–2.2)	1.2 (0.7–2.2)
	<i>p</i> for trend =	0.8	1.0

^a Adjusted for age, sex, race, educational level, family history of NPC, smoking status.

association [16–23]. It is of note that most studies which have failed to detect an association between cigarette smoking and NPC were conducted in high risk populations [17–21]. This suggests the possibility that a smoking effect is more difficult to detect in populations in which other exposures strongly linked to NPC development may be common. An etiological link between cigarette smoking and NPC risk is biologically plausible. First, the nasopharynx is a site directly exposed to smoke during cigarette smoking. Also, cigarette smoking has been demonstrated to be an important risk factor for numerous other cancers of the upper and lower respiratory tract and constituents of cigarettes have been shown to have carcinogenic potential [5].

In concordance with most previous studies which have examined the association between passive smoking and NPC, we did not observe a positive association between passive smoking and NPC risk, either during childhood or during adult life [11, 25]. The decrease in risk

associated with exposure to passive smoking during childhood in our study is an unexpected finding. Interpretation of this finding is unclear. It is possible that our finding is due to unmeasured confounding by other childhood sociodemographic and/or lifestyle factors which are negatively associated with NPC development. Alternatively, since no clear dose response pattern was observed between cumulative exposure to passive smoking during childhood and NPC, our observations might reflect a chance finding.

Results from our study failed to support an association between alcohol consumption and NPC. No evidence for an association between alcohol consumption and NPC was observed when measures of duration or intensity of drinking were examined. Our findings are consistent with those from most [7, 9, 12, 16, 22, 23, 25, 26] but not all [13, 19] previous studies.

Several strengths of the present investigation warrant mention. First, all cases had incident disease and were

recruited and interviewed prior to final diagnosis and treatment, thus avoiding the problem of survival bias. Second, histological confirmation of all cases also reduced the likelihood of misclassification of disease. Third, the high participation rate observed for cases and controls (99 and 88%, respectively) reduces the potential for non-response bias. Finally, in our study, no interviews were sought from next of kin, increasing the accuracy of data.

In summary, the present study identified long term active smoking as a risk factor for NPC, while exposure to cigarette smoke *via* passive exposure and alcohol consumption were not associated with risk of this disease.

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