

# Environmental Risk Factors for Nasopharyngeal Carcinoma: A Case-Control Study in Northeastern Thailand<sup>1</sup>

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## Abstract

**A case-control study of nasopharyngeal carcinoma was conducted in northeast Thailand, a region which shows an intermediate risk for this neoplasm. The study was conducted to investigate the importance of environmental exposures, particularly salted fish consumption, cigarette smoking, alcohol drinking, and occupational exposure to smoke or dust, as risk factors for the disease. Data from 120 nasopharyngeal cancer cases and the same number of hospital-matched controls indicated that consumption of sea-salted fish at least once a week was a significant risk factor (odds ratio, 2.5; 95% confidence interval, 1.2-5.2). Agricultural workers were also at significantly higher risk (odds ratio, 2.8; 95% confidence interval, 1.3-6.2), and working in agriculture or as a woodcutter was associated with an even higher risk (odds ratio, 8.0; 95% confidence interval, 2.3-28.2). There was no association between nasopharyngeal carcinoma and alcohol drinking or cigarette smoking.**

## Introduction

NPC<sup>3</sup> is a rare tumor in most countries; the cumulative incidence rates up to age 74 rarely exceed 0.1% (1). Populations of southern Chinese origin, however, usually exhibit high rates of NPC, the Hong Kong population reaching cumulative incidence rates of 3.1% and 1.3% in males and females, respectively. Genetic susceptibility is strongly supported by studies comparing blood genetic markers of patients and controls (2-4) and by a recent linkage study on NPC sibling pairs (5). However, the existence of significant environmental cofactors is suggested by the change in risk which is observed in Chinese populations migrating from high- to low-risk areas (6-7). Epstein-Barr virus infection is accepted as a cause of undifferentiated NPC, but infection with this virus is

universal and by itself could not account for the occurrence of rare tumors in limited geographical areas or ethnic groups without postulating its interaction with other factors (8-9).

Two environmental factors were repeatedly associated with the occurrence of NPC: the consumption, especially during childhood, of some salted food items, particularly fish (10-15), and occupational or domestic exposures to dusts and fumes (4, 11, 14-17). Tobacco smoking and alcohol consumption were also addressed as possible causal factors, although contradictory results were reported (4, 11, 14-19).

We conducted a case-control study on NPC in northeast Thailand, the population of which is characterized by an intermediate risk for the disease: according to data from the population-based cancer registry of Khon Kaen province, the cumulative incidence (age 0-74 years) in 1988-89 was 0.4% in males and 0.2% in females (20). The incidence rates standardized to the world population, per 100,000 inhabitants, were 3.0 and 2.1 for males and females, respectively.

## Materials and Methods

In 1990, 120 histologically confirmed NPC cases were interviewed at Srinagarind Hospital, Khon Kaen, the only hospital offering radiation therapy in northeastern Thailand. All the cases were diagnosed in the same hospital between 1987 and 1990 and were attending for radiation therapy; 67% of the cases were males.

An equal number of controls was recruited among patients admitted to the same hospital for other diseases, excluding any neoplasms and respiratory diseases. Controls were matched to the cases by sex and age ( $\pm 5$  years).

Cases and controls were interviewed in the hospital by one of the authors using a standard questionnaire. Information was collected on the following characteristics: residential history, marital status, race, education, income, current and past occupation, family history of NPC, tobacco smoking, and current usual intake of alcoholic beverages and of the most popular types of salted fish. Three groups of salted fish consumed in this region can be distinguished according to the type of the fish (fresh-water or sea fish) and the curing process used for its preservation. *Pla-ra* is a freshwater fish left to ferment in salted water for at least 1 month; it is the traditional salted-fish dish of northeast Thailand, which is home-prepared and is kept wet. Other freshwater fish are also home preserved after a short fermentation period (usually 1 week) and may be kept wet or dried. The third type comprises sea fish fermented with salt for several weeks and allowed to dry. This typical Chinese-style fish is purchased in markets rather than being prepared at

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<sup>3</sup> The abbreviations used are: NPC, nasopharyngeal cancer; CI, confidence interval; OR, odds ratio.

Table 1 Demographic characteristics of cases and controls

	Cases	Controls
No. of subjects	120	120
% males (81)	67.5	67.5
Age (years): mean $\pm$ SD	47.2 $\pm$ 13.5	45.9 $\pm$ 13.7
% illiterate or primary school	86.7	75.8 <sup>a</sup>
% family income >1500 bahts/month	42.5	50.8
% ethnic group (Thai)	92.5	97.5
% religion (Buddhist)	99.2	100.0
Marital status (% married)	84.2	75.8
Place of birth (Khon Kaen and provinces)	66.7	75.0
Area of residence (% Khon Kaen provinces)	61.7	75.8 <sup>a</sup>

<sup>a</sup>  $P < 0.05$ .

home. The current usual frequency of consumption and the cooking method of each type of fish were collected during the interview.

Occupations reported were grouped into a few broad categories, but employment in sawmills and jobs such as wood cutting or rice husking were investigated specifically, since these entail high exposures to dust.

The statistical significance of the difference between two proportions was assessed by the  $\chi^2$  test after the arcsin transformation. Mean age difference between cases and controls was tested through Student's *t* test. The association between the factors described and risk of NPC was assessed by OR. Univariate ORs, adjusted for sex and age to allow for the sampling design, were estimated through the Mantel-Haenszel procedure (21). Conditional logistic regression was subsequently used to obtain OR estimates adjusted for reciprocal confounding. Approximately 95% confidence intervals were computed, based on the logistic parameters and their estimated SE (22). The computational package used was EGRET (23).

## Results

Table 1 shows the main characteristics of cases and controls. The two series were similar with respect to race and religion; the prevalence of Chinese-speaking people in this region is very low, about 4.6%. Some differences were observed for the other variables: cases showed lower education and income and were more frequently resident and born in provinces far from Khon Kaen.

Five cases, but no controls, were Chinese, and three cases (no controls) reported having had a first-degree relative affected by NPC. All the Chinese cases belonged to the high-income class and were more educated: 3 of 5 attended at least secondary school versus a corresponding ratio of 3 of 111 observed among Thai cases.

The distribution of histological types of the cases was 57.5% squamous cell carcinomas and 42.5% undifferentiated carcinomas. About 80% of the cases were diagnosed between 1989 and 1990; the rest were detected in 1987–1988. Most cases were at an advanced stage, 77.5% being stage IV (24).

Among the 81 male controls, 53.1% were surgical patients (39.5% of whom were affected by kidney stones), 34.6% were orthopedic cases, and 12.4% were medical cases. Among the female controls, 43.6% were affected by gynecological disorders, 12.8% were recruited in the orthopedic department, and the remainder

Table 2 Factors associated with nasopharyngeal carcinoma

Factors	Cases	Controls	M-H <sup>a</sup>	OR <sup>b</sup>	95% CI
Alcohol intake					
No	40	50	1	1	
Yes	80	70	1.7	1.5	0.7 3.4
Type of cigarette					
Nonsmoker	50	54	1	1	
Manufactured cigarette	23	34	0.7	0.8	0.3 2.1
Handmade cigarette	47	32	1.9	0.9	0.3 2.5
Salted fish consumption					
Only fresh-water fish	69	74	1	1	
Sea-salted fish, less than once a week	16	22	0.7	1.5	0.6 3.5
Sea-salted fish, at least once a week	35	24	1.6	2.5	1.2 5.2
Occupation					
Not agriculture, not wood cutting	20	47	1	1	
Wood cutting, not agriculture	5	3	4.3	4.1	0.8 22.1
Agriculture, not wood cutting	76	64	3.0 <sup>c</sup>	2.8	1.3 6.2
Agriculture and wood cutting	19	6	11.0 <sup>d</sup>	8.0	2.3 28.2

<sup>a</sup> Mantel-Haenszel estimates adjusted for sex and age.

<sup>b</sup> Logistic estimates adjusted for all factors in the table plus education and area of residence.

<sup>c</sup>  $P < 0.05$ .

<sup>d</sup>  $P < 0.01$ .

were medical cases. None of the reasons for admission to hospital represented more than 25% of all diagnoses among either male or female controls. Nevertheless, the prevalence of the factors under study occurring in the main pathological groups of the controls did not differ substantially.

Table 2 shows the results of the stratified and multivariate analyses. Only four of the study subjects were nonconsumers of any kind of salted fish. All the others shared the common habit of eating the traditional *pla-ra* fish with similar frequency among cases and controls; thus the consumption of *pla-ra* fish could not be evaluated. After adjustment for sex and age by the Mantel-Haenszel procedure two factors were significantly associated with an increased risk of NPC: agricultural work (OR, 3.0;  $P < 0.05$ ) and agricultural work associated with frequent exposure to wood-cutting tasks (OR, 11.0;  $P < 0.01$ ). Consumption of salted Chinese-style fish appeared to be very weakly associated with the risk of the disease, the OR for consumers at least once a week being 1.6 (not significant) compared to that for nonconsumers. Some excess risk, not statistically significant, was associated with alcohol consumption (OR, 1.7) and with smoking of handmade cigarettes (OR, 1.9).

In the multivariate analysis, adjustment for education and place of residence was introduced to control for the potential selection bias.

The ORs associated with consumption of Chinese-style fish, taking as reference nonconsumers, were 2.5 (95% CI, 1.2–5.2) with a frequency of at least once a week and 1.5 (0.6, 3.5) for less frequent consumption.

Agricultural workers still exhibit a significant excess risk of NPC (OR, 2.8; CI, 1.3–6.2), which appears to be

very high for those reporting exposure to wood cutting (OR, 8.0; CI, 2.3–28.2).

The multivariate analysis revealed a positive confounding between education and occupation and smoking of handmade cigarettes; the slight excess risk for the latter disappeared after adjustment.

An index of alcohol consumption per day was computed, based on frequency of intake of a variety of beverages and their alcohol content. No excess risk or dose-response trend was detected for increasing intake of alcohol.

None of the other factors investigated (in particular, the usual cooking method and the method of fermentation of home-preserved fish) were associated with any excess risk.

## Discussion

Our study supports the hypothesis that adult consumption of Chinese-style salted fish entails an excess risk of NPC. Agricultural workers and those exposed to wood dust due to wood cutting also have an excess risk of NPC. No excess risk is provided by alcohol consumption, cigarette smoking, or usual method of cooking food.

The hospital-based design of the study might have introduced some selection bias; this is suggested by the different distribution by area of residence observed among cases and controls: cases are more likely to attend this hospital, which offers good facilities for the treatment of NPC, even if they live far from it. The possibility of the presence of a relatively high proportion of controls affected by diseases which may be related to diet and which may have introduced some spurious associations was not supported by the comparison of this control set with the remaining controls; the prevalence of the factors investigated was not substantially different from that observed among nonsurgical controls. Moreover, exclusion of these controls would give lower estimates for the OR associated with alcohol consumption, since these controls report themselves to be nonconsumers more frequently than the others. Selection bias was controlled through stratification by place of residence and education. Such adjustment resulted in increased estimates for fish consumption and only a slight decrease of the ORs associated with agricultural work. The striking difference between cases and controls as regards the prevalence of Chinese people (5 cases *versus* no controls) could well reflect the importance of genetic factors in etiology but could also be an artifact due to selection bias: the few Chinese people living in this region are of higher economic class and it is possible that they elect to go outside the region (e.g., to Bangkok) for treatment of diseases other than NPC. It is worth noting that, whatever the reason for the high prevalence of Chinese-speaking cases (real genetic determinant or selection bias), their inclusion in the study followed a conservative approach.

The most interesting result of this study is the observation of an excess risk associated with the consumption of salted fish in adult life; most of the studies conducted so far have demonstrated that exposure to this food item in childhood entails a very high risk, but only a few of them detected an excess risk for consumption at adult ages (11, 14), although the risk attributable to this factor, according to Bruzzi's formula (25), could be only 22% of all incident cases. Experimental studies (26–27) suggested

that the volatile nitrosamine content of salted fish (and other preserved foods) might be the etiologically important factor; analysis of the various kinds of salted fish consumed in northeast Thailand would therefore be of interest, since different preservation methods may result in differing types and quantities of nitrosamines in the food (28–29).

Agricultural workers in Thailand are exposed to organic dust during harvesting, winnowing, and threshing of rice; the unspecific exposure to dust was reported as important in several other retrospective studies (4, 11, 15–17). Unfortunately, the definition of the exposure varied from study to study and was still too ill defined to allow any conclusion on specific substances or their carcinogenic effect.

The failure to find any association with alcohol consumption is in agreement with the literature, since all the studies investigating the subject reported negative results. The case of tobacco smoking is less clear, since a significant excess risk was reported in four studies (16–19), but other reports were negative (4, 11, 14, 15). In our data, the apparent weak association detected only for handmade cigarettes was the result of confounding due to occupation, but overestimation of the habit among controls may have occurred due to the hospital-based design.

In summary, our study identified some risk factors for NPC in a Thai population, showing an intermediate risk level for this neoplasm. Further investigation is suggested in order to evaluate the role of environmental exposure to smoke and dust and to explain the high risk detected for agricultural workers. Genetic characterization would also be highly valuable in order to estimate the proportion of the case attributable to the various factors. The role of viral infection would be better described in a prospective design, since the retrospective one is intrinsically incapable of distinguishing an etiologic factor from an early marker of the presence of disease (30).

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