

Salted Fish and Inhalants as Risk Factors for Nasopharyngeal Carcinoma in Malaysian Chinese¹

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ABSTRACT

We conducted a case-control study of nasopharyngeal carcinoma among Malaysian Chinese to test inhalants, salted fish consumption, and use of tobacco, alcohol, and nasal ointments as risk factors for the disease. Interviews with 100 cases and 100 controls indicated that salted fish consumption during childhood was a significant risk factor (relative risk, 3.0; $p = 0.04$); childhood daily consumption of this food item compared to nonconsumption carried a relative risk of 17.4 [95% confidence interval = (2.7, 111.1)]. Occupational exposure to smokes (relative risk, 6.0; $p = 0.006$) and to dusts (relative risk, 4.0; $p < 0.001$) was also significantly associated with nasopharyngeal carcinoma. The two risk factors (consumption of salted fish and exposure to smoke and/or dust) were independent of each other. There was no association between nasopharyngeal carcinoma and tobacco, alcohol, or nasal ointments.

INTRODUCTION

Although the nature of the environmental etiology of NPC³ continues to be elusive, recent results from experimental and epidemiological studies in Hong Kong (9, 15), California (11), and Alaska (18) point toward dust and smoke inhalants and the eating of salted fish as being risk factors for this disease. NPC is a major cancer in southeastern China and is significant wherever there is a sizable Chinese population with ancestry from this region (2). This paper reports on a case-control study of NPC in Chinese of Selangor, Malaysia. The objective of the study was to follow up on previous work in the same population (1) and specifically to test hypotheses that inhalation of smoke and dust, eating of salted fish, and use of nasal medications, tobacco, and alcohol were risk factors for NPC.

MATERIALS AND METHODS

During 1980, we conducted a case-control study among 100 Chinese NPC patients and 100 Chinese control participants, all of whom were residents of 27 census districts of central Selangor. The study area had a population of 1.5 million in 1980. Most of the population is resident in the urban centers of Kuala Lumpur, Petaling Jaya, and Klang; the rest are in intervening suburban and rural areas.

Cases were NPC patients, diagnosed between 1973 and 1980, and treated with radiotherapy at the Institute for Radiotherapy, General Hospital, Kuala Lumpur, the only hospital offering radiotherapy treatment for NPC in Malaysia. Only histologically confirmed cases who had resided in the study area for at least 5 years were included.

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³ The abbreviation used is: NPC, nasopharyngeal carcinoma.

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For each case interviewed, we sought persons of the same sex who lived in the immediate neighborhood of the patient's residence and who had lived in the study area for the last 5 years. From this group of neighbors we sought as control the person closest in age to the case.

All interviews were conducted in the homes of the participants by 2 full-time Chinese interviewers. The interview schedule requested information on use of alcohol, tobacco, and nasal ointments; dietary habits, including the consumption of salted fish in childhood and in adolescence; and a complete occupational, residential, and medical history.

Standard matched-pair methods (4, 16) were used to analyze the interview data. The data were also analyzed by stratifying on sex and age since, for a number of case-control pairs, close matching in age was not achieved. Results from the stratified analysis were similar to those from the matched analysis. In this report, we present odds ratios and their corresponding significance levels (p values) from the matched analysis. Pairs in which data were missing for either the case or the control were eliminated from analysis. All p values quoted are one sided, unless stated otherwise.

RESULTS

Our case group consisted of 65 males (mean age, 44.8 years) and 35 females (mean age, 44.7 years). The histology of all cases was squamous cell carcinoma. The male controls had a mean age of 41.5 years; the female controls had a mean age of 40.2 years. The case and the control groups were similar in distribution with respect to the following variables: place of birth; marital status; ethnic subgroup [Cantonese, Khek (Hakka), Hokkien, Teochiu, Hainanese, and Hokchiu]; and social class.

A history of salted fish intake in childhood was a significant risk factor for NPC (relative risk, 3.0; $p = 0.04$) (Table 1). The relative risk for daily consumption of this food item in childhood compared to noneaters was 17.4 [95% confidence interval = (2.7, 111.1)]. All 14 cases (and all 3 controls) who ate salted fish daily in childhood continued to eat this food daily in adolescence. Similarly, 66 of the 70 cases who claimed they ate salted fish less frequently than daily during childhood (and 71 of the 73 controls) reported the same consumption frequency in adolescence. Most of the other participants had salted fish at some time in their adolescent years; only 3 cases and 3 controls claimed they never ate salted fish during that time. The relative risk of daily consumption of salted fish compared to less frequent than weekly consumption in adolescence was 3.5 [95% confidence interval = (1.2, 10.7)]. There was no significant difference between NPC cases and controls in the kinds of salted fish eaten. Results were similar when we adjusted for ethnic subgroup variation between cases and controls.

There was a significant association between occupational exposure to smoke and NPC (relative risk, 6.0; $p = 0.006$). The risk for NPC was elevated for wood, paper, and grass smoke as well as "other smoke," which includes oil and tar (Table 1). Exposure to dusts was also a highly significant risk factor

Table 1
Risk factors for NPC
The total number of cases (or controls) does not necessarily add up to 100, due to missing values.

| Factor | | Cases | Controls | Relative risk | One-sided p value |
|-------------------------------------|--------|-------|----------|---------------|-------------------|
| Salted fish intake during childhood | | | | | |
| Ever eaten | Yes | 87 | 79 | 3.0 | 0.04 |
| | No | 5 | 13 | | |
| Frequency | Never | 5 | 13 | 1.0 | <0.001 |
| | <Daily | 70 | 73 | 2.8 | |
| | Daily | 14 | 3 | 17.4 | |
| Occupational exposure | | | | | |
| Smoke | Yes | 13 | 3 | 6.0 | 0.006 |
| | No | 87 | 97 | | |
| Wood, paper, grass smoke | Yes | 8 | 2 | 7.0 | 0.04 |
| | No | 92 | 98 | | |
| Other smoke | Yes | 5 | 1 | 5.0 | 0.11 |
| | No | 95 | 99 | | |
| Dust | Yes | 52 | 25 | 4.0 | <0.001 |
| | No | 48 | 75 | | |
| Wood dust, sawdust | Yes | 17 | 10 | 2.2 | 0.08 |
| | No | 83 | 90 | | |
| Construction-related dust | Yes | 15 | 9 | 1.9 | 0.13 |
| | No | 85 | 91 | | |
| Quarry dust | Yes | 10 | 1 | ∞^a | 0.002 |
| | No | 90 | 99 | | |
| Road dust | Yes | 11 | 2 | 5.5 | 0.01 |
| | No | 89 | 98 | | |
| Other dust | Yes | 17 | 8 | 2.3 | 0.05 |
| | No | 83 | 92 | | |
| Smoke and/or dust | Yes | 58 | 26 | 5.0 | <0.001 |
| | No | 42 | 74 | | |

^a The single positive control was matched to a positive case.

(relative risk, 4.0; $p < 0.001$), and excess risks were observed with all kinds of dust. Table 2 shows the duration of exposure to dust and/or smoke by sex and by age. There was a strong dose-response relationship with increasing duration of exposure in all subgroups, that is, in the male and female patients and in younger and older patients. The overall relative risks for 1 to 9 years and 10+ years of exposure were 3.4 and 11.4, respectively [p (linear trend) < 0.001]. Rubber processing (which includes exposure to latex, formic acid coagulant, chalk dust, and wood smoke) was associated with an increased risk for NPC (relative risk, 3.2; $p = 0.01$). However, 15 of the 19 positive cases (and 3 of the 8 positive controls) reported exposure to dust and/or smoke. There were no independent effects of rubber processing after exposure to dust and/or smoke was taken into account. There was no association between NPC and occupational exposure to petroleum oils, industrial gases and fumes, paints, textiles, and industrial chemicals. Similar results were obtained when we took ethnic subgroup into account.

Table 3 shows the relative risk of NPC according to the level of occupational exposure to dust and/or smoke and salted fish intake during childhood. The 2 risk factors displayed a multiplicative effect on risk [2-sided p (goodness of fit of the multiplicative model) = 0.96]. However, these risk estimates possessed large S.E.s due to the small number of cases and controls in most of the statistical cells.

There was no significant difference between case and control participants in the use of tobacco (as cigarettes, pipe, or snuff), alcohol, or nasal ointments. Besides nasal ointments, the use of Tiger Balm, a patent balm made chiefly of Vaseline petroleum jelly, camphor, and menthol, was explored especially, but no elevated risk for NPC emerged. This study also examined general medical history and use of the Western, Chinese, Malay, and

Indian medical services available in Malaysia but found no associations with NPC.

DISCUSSION

An association between consumption of salted fish and NPC was proposed by Ho (13) in Hong Kong, who observed that eating "Cantonese salted marine fish" was common among the Cantonese at high risk of the disease and uncommon among Chinese populations in northern provinces at low risk of the disease. Fong and Chan (6) provided evidence of a carcinogenic mechanism to support Ho's proposition in their analysis of nitrosamines in Cantonese salt-dried fish. Nitrosamine compounds have been found to cause cancers of the nasal cavity in laboratory animals (10, 12), and a recent paper reported that rats fed Cantonese salted fish have developed nasal cavity carcinomas (17).

The finding that salted fish consumption is a significant risk factor for NPC in southern Chinese is consistent with the social class distribution of the disease in this population. Salted fish is traditionally one of the lowest priced foods available to supplement rice in south China. Thus, it is probable that salted fish is eaten more often by poorer members of this population, who are at higher risk for this disease. Among the high-risk southern Chinese, NPC is the most common cancer in young people between the ages 15 and 34 (14). This suggests that exposure to the etiological agent(s) occurs early in life, which is compatible with our finding of salted fish intake in childhood as a risk factor. Furthermore, childhood consumption of salted fish as a risk factor for NPC in Chinese could explain the high rates observed among migrants residing in low-risk areas, such as the United States (21) and Canada (8). It also could explain the decrease in

Table 2
Occupational exposure to dust and/or smoke in cases and controls

| | Males | | Females | | Under age 45 | | Age 45+ | | Total | |
|--------|--------------|---------------|--------------|----------------|--------------|---------------|--------------|---------------|--------------|-------------------|
| | Case/Control | Relative risk | Case/Control | Relative risk | Case/Control | Relative risk | Case/Control | Relative risk | Case/Control | Relative risk |
| Never | 24/46 | 1.0 | 18/28 | 1.0 | 19/43 | 1.0 | 23/31 | 1.0 | 42/74 | 1.0 |
| 1-9 yr | 19/11 | 3.3 | 8/4 | 3.5 | 20/11 | 4.3 | 7/4 | 2.7 | 27/15 | 3.4 |
| 10+ yr | 22/8 | 8.4 | 9/3 | ∞ ^a | 17/2 | ∞ | 14/9 | 3.3 | 31/11 | 11.4 ^b |

^a All controls were matched to cases in the same exposure category.

^b $p < 0.001$, test for linear trend.

Table 3

Relative risk of NPC according to level of salted fish intake during childhood and occupational exposure to dust and smoke

| Dust and smoke | Salted fish | | | Total ^a |
|----------------|-------------------------|-------------|-------------|--------------------|
| | Never | <Daily | Daily | |
| Never | 1.0 (3/10) ^b | 2.4 (33/55) | 7.8 (3/2) | 1.0 |
| Ever | 3.4 (2/3) | 9.0 (37/18) | 47.1 (11/1) | 3.9 |
| Total | 1.0 | 2.5 | 10.9 | |

^a Adjusted relative risk estimates, assuming the 2 risk factors were independent.

^b Numbers in parentheses, number of cases/number of controls.

risk for NPC in succeeding generations of Chinese Americans in Calif. (5, 21), who are more likely to give up their traditional way of life than are their southeast Asian counterparts. However, it is uncertain if the apparent high risk is specific for this food item in childhood. Other foods, or other kinds of environmental factors that are associated with eating salted fish, could also be important, and the time of life surrounding childhood may not necessarily be the critical period for carcinogenesis (3).

The hypothesis that inhaled carcinogens are an important risk factor in NPC has logic in known physiology, in that the nasopharynx serves to trap the larger particulate matter in inspired air. Incomplete combustion of fossil fuels and other materials, as occurs in wood fires used in cooking, food roasting, and industrial processes, yields smokes with medium to large particles (median diameter of 5 to 10 μm), which are trapped principally in the nasopharynx (19). Dusts from stone quarries, opencut and sluice tin mines, brick works, roads, wood working trades, and chalk in rubber trades (all important in Malaysia) are also of the size and weight that are deposited mostly in the nasopharynx (median diameter of 10 to 15 μm). The chemical composition of such inhaled particulates is complex, but there are established examples of the probable carcinogenic substance in risk material. For example, unsaturated aldehydes in sawdust and wood-smoke may be the origin of nasal cancers observed in woodworkers (20).

In the case of rubber tappers in Malaysia, workers are exposed to formic acid in the process of congealing latex into crude rubber sheets, both as an inhalant and in skin contact when the sheets are pressed flat with bare feet on a concrete floor (7). Formic acid is highly volatile and pungent in the 5% solution used in this process. The same workers are often further exposed to woodsmoke in the smokehouses for curing rubber sheets and to talc powder which is dusted on the sheets (7).

All the exposures to smoke and dust inhalants in this study were in association with occupations that would explain the type and duration of exposure. There are no important differences in exposure between males and females. Women in Malaysia work in tin mines, rubber estates, sawmills, and brickworks, as road-

side hawkers, and in most other occupational settings, sometimes as unpaid companions to their husbands. In this study, 70% of female participants had worked at some time of their working lives in industrial or agricultural jobs, compared to 55% of the males.

In summary, a childhood and adolescent history of eating salted fish is a major risk factor for NPC in Selangor Chinese, and one in agreement with incidence data and experimental studies based in Hong Kong (21). Occupational exposure to smoke and dusts is significantly related to the development of NPC in Selangor Chinese, and these are associated with particular industrial and agricultural occupations, namely carpentry and other woodworking, tin mining, cement and quarry operations, brick manufacture, roadside hawking, rubber tapping, and agricultural labor. In combination, these 2 independent risk factors demonstrate a multiplicative effect on risk to NPC. Despite the consistency of the results, they should be confirmed by repeating the study in other high-risk Chinese populations, preferably using a larger number of cases and controls. Laboratory investigations are needed into the chemical nature of the smoke, dusts, and salted fish involved and into mechanisms that could explain the associations between these environmental factors and NPC. The strong association between dusts and smoke and this disease could be used as a public health directive to support the general need to improve air quality in occupational settings in Southeast Asia.

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