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NON-VIRAL RISK FACTORS FOR NASOPHARYNGEAL CARCINOMA IN THE PHILIPPINES: RESULTS FROM A CASE-CONTROL STUDY

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In a case-control study of NPC conducted in the Philippines, 104 predominantly non-Chinese (<10% ethnically Chinese) cases of nasopharyngeal carcinoma (NPC) and 205 hospital and community controls were recruited. Risk factor information was obtained through personal interview. The occupational history of each subject was reviewed "blind" by an industrial hygienist to determine estimates of exposure to formaldehyde, solvents, dusts, exhaust and pesticides. After control for confounding, subjects who were first exposed to formaldehyde 25 or more years prior to diagnosis/interview or who were first exposed before the age of 25 were found, in relation to those never exposed, to be at a 4.0-fold excess risk of disease. Similarly, those first exposed to dust and/or exhaust 35 or more years prior to diagnosis/interview were at a 4.4-fold excess risk of disease and those first exposed before the age of 20 were at a 3.5-fold excess risk of disease. Salted fish consumption was not associated with risk, while consumption of processed meats protected against NPC. Smoking was positively associated with NPC, but only when cases were compared to community controls. Relative to non-smokers, subjects reporting more than 30 years of smoking were at an adjusted 7.2-fold excess risk of disease. Herbal medicine use and burning of anti-mosquito coils were both independently associated with risk of NPC, with ever-users of herbal medicines being at a 2.5-fold excess risk of disease and those reporting daily use of anti-mosquito coils being at a 5.9-fold excess risk of disease relative to never users. Exposure to solvents, pesticides, or use of betel nuts were not associated with NPC risk.

Nasopharyngeal carcinoma (NPC) is a very rare tumor which occurs at a yearly rate of <1 per 100,000 in most countries (Muir *et al.,* 1987). However, in a few geographic regions and among certain ethnic groups, this tumor occurs at relatively high rates. The highest incidence of NPC is reported from South-east Asia. In Hong Kong, the incidence of NPC between 1978 and 1982 was 30.0/100,000 among males and 12.9/100,000 among females (Muir *et al.,* 1987). Ethnic southern Chinese residing outside of the People's Republic of China are at increased risk of disease relative to other ethnic groups (Hildesheim and Levine, 1993). In addition, intermediate incidence rates of NPC have been reported from areas in Northern Africa and the Arctic (Hildesheim and Levine, 1993).

Numerous factors have been postulated to be linked to the development of NPC, including Epstein-Barr virus (EBV), consumption of salted and processed foods, occupational exposure to formaldehyde and dusts, and cigarette smoking (Hildesheim and Levine, 1993). Most studies of NPC have been conducted in China or among individuals of Chinese ethnicity. Notable exceptions are occupational studies which have reported an association between formaldehyde exposure and NPC among Caucasians (Blair *et al.,* 1990).

In Rizal province, The Philippines, the age-standardized incidence of NPC during the period 1978–1982 was 4.7/100,000 among males and 2.6/100,000 among females, rates which are intermediate between those in China and in western countries (Muir *et al.,* 1987). Little is known about the risk factors for NPC in this population, which is composed largely of descendants from peoples of the Malaysian peninsula. To investigate the etiology of NPC among this group of predominantly non-Chinese cases, we have conducted a hospital-based case-control study. As part of this study, information was collected on socio-demographic factors, adult diet, occupational history, smoking, use of betel nut, burning of anti-mosquito coils, and use of herbal medicines. In addition, blood was collected and used to assess EBV antibody titers. EBV results have previously been reported (Hildesheim *et al.,* 1992). In this publication we examine the association between non-viral factors and NPC, with particular emphasis on occupational exposures.

MATERIAL AND METHODS

The design and methods of this study have been previously described (Hildesheim *et al.,* 1992). In brief, 104 (100% response rate) incident cases of histologically confirmed NPC were recruited from the Philippine General Hospital. Two types of controls were selected: hospital and community controls. The 104 hospital controls (100% response rate) were matched to cases for sex, age and hospital ward type (private *vs.* public) and the 101 community controls (77% response rate) were matched to cases for sex, age, and neighborhood.

A personal interview was conducted with all subjects by a trained nurse interviewer. Information was collected on socio-demographic factors (education, Chinese ancestry), frequency of usual adult consumption of selected food items (salted fish, fresh fish and processed meats), occupational history, cigarette smoking, and use of herbal medicine, betel nut and anti-mosquito coils. The list of occupations reported by subjects was reviewed "blind" by an industrial hygienist (M.D.) using various sources of exposure information (OSHA, 1987; Gerin *et al.,* 1989; TLV Committee, 1990). Each occupation was classified as likely or unlikely to involve exposure to any of the following factors: formaldehyde, solvents, wood dust, dust and pesticides. A list of occupations classified as likely to involve exposure to these factors is provided in the Appendix. For each subject, this information was combined with the complete occupational history to obtain the following estimates: (1) Overall duration of exposure; (2) duration of exposure excluding exposure in the 10 years immediately preceding diagnosis (for cases) or interview (for controls); (3) number of years since first exposure; and (4) age at first exposure. Estimates of duration of exposure with a 10-year lag (2 above) were calculated in the light of previous evidence suggesting stronger effects when recent exposure was excluded (Vaughan and Davis, 1991). Estimates of number of years since first exposure (3 above) were obtained to examine possible latency effects. Finally, estimates of age at first exposure (4 above) were computed to examine the hypothesis that exposure at young ages is more relevant than adult exposure.

Dietary assessment involved obtaining information on frequency of usual adult consumption of various salted and fresh fish, and of processed meats. The following salted fish items were included in the questionnaire: tuyo, dilis, daing, bagoong, and "other salted fish." Consumption of 2 types of processed

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meat was assessed: ham and longanisa. The frequency of consumption of the different salted fish and processed meats was then summed to yield an overall measure of consumption of salted fish and processed meats. These foods were categorized into tertiles based on the distribution of consumption observed among controls.

The relative risk (RR), as estimated by the odds ratio, was the measure used to assess associations between risk factors and disease. Significance levels were determined by use of the 95% confidence interval (95% CI). Conditional logistic regression was utilized to assess the associations between exposures of interest and disease, while controlling for potential confounding factors (Lubin, 1981). The correlation between exposures was assessed by means of the Spearman correlation coefficient. Analyses were performed comparing cases to all controls, and to hospital and community controls separately. Results from comparisons of cases *versus* all controls are presented throughout. Differences observed when cases were compared separately to hospital and community controls are also presented.

RESULTS

The median age of cases in our study was 46 years (range 11–83 years). Of these patients, 73% (N = 76) were male, giving a male:female ratio of 2.7:1. The vast majority of cases were not of Chinese ethnicity; only 8 (7.7%) cases recruited into the study had a parent or grandparent who was from China or was of pure Chinese ethnicity. These subjects of Chinese ethnicity were found to be at a non-significant 50% excess risk of developing NPC (95% CI = 0.58, 3.8). Education was negatively correlated to NPC risk, with RR estimates for subjects reporting 4–10 years of education and 11 or more years of education relative to those with less than 4 years of education being 0.49 (95% CI = 0.21, 1.1) and 0.25 (95% CI = 0.09, 0.71), respectively.

Table I presents results of the analysis of the association between estimates of occupational exposure to formaldehyde and NPC. After lagging exposure 10 years, those exposed to formaldehyde for 15 or more years were found to be at a non-significant 2.1-fold excess risk of developing NPC (95% CI = 0.70, 6.2). More striking effects were observed when latency since first exposure and age at first exposure were examined. Subjects first exposed to formaldehyde before the age of 25 years were at a 2.7-fold excess risk of disease (95% CI = 1.1, 6.6) and those first exposed 25 or more years preceding diagnosis or interview were at a 2.9-fold excess risk of developing NPC (95% CI = 1.1, 7.6), effects that were independent of the association between exposure to other occupational exposures and NPC. When latency since first exposure was investigated more finely, the 5 cases who were first exposed to formaldehyde 35 or more years preceding diagnosis were found to be at a 5.6-fold greater risk of developing NPC than those never exposed to formaldehyde (95% CI = 0.58, 52.9). A stronger effect was not observed, however, when only those individuals most likely to be exposed, or most likely to be exposed to high doses, were compared to unexposed subjects (see Appendix for list of occupations involving most likely/high doses of exposure). When we examined the joint effect of age at first exposure and years since first exposure there was an indication, despite small number of subjects in each category, that these 2 factors were independently associated with risk of NPC (data not shown).

We next investigated the effect of other occupational exposures on risk of NPC. Estimates of exposure to overall wood dust, dust, exhaust fumes, solvents and pesticides were evaluated. This analysis was complicated by the fact that these exposures were highly correlated. Among controls, the correlation between these factors ranged from 0.72 to 0.92. Interestingly, these exposures were not highly correlated with exposure

TABLE I – RISK OF NPC BY EXPOSURE TO FORMALDEHYDE, DUSTS AND EXHAUST FUMES, AS ESTIMATED FROM JOB TITLES

	Cases (n)	Controls (n)	Crude RR	Adj. RR[1]	95% CI
Formaldehyde					
Never	75	171	1.0	1.0	
< 15 yrs	19	8	4.6	2.7	[1.1,6.6]
15+ yrs	8	14	1.4	1.2	[0.48,3.2]
No[2]	83	174	1.0	1.0	
< 15 yrs (10 yrs lag)	11	11	2.1	1.6	[0.65,3.8]
15+ yrs (10 yrs lag)	8	8	2.4	2.1	[0.70,6.2]
Never	75	171	1.0	1.0	
< 25 yrs since 1st exp.	12	12	2.2	1.3	[0.55,3.2]
25+ yrs since 1st exp.	14	10	3.5	2.9	[1.1,7.6]
Never	75	171	1.0	1.0	
25+ yrs at 1st exp.	11	10	2.3	1.2	[0.47,3.3]
< 25 yrs at 1st exp.	16	12	3.2	2.7	[1.1,6.6]
Dust and/or exhaust					
Never	22	94	1.0	1.0	
< 25 yrs	42	42	4.7	4.2	[2.1,8.7]
25+ yrs	38	57	3.9	3.2	[1.4,7.3]
No[3]	33	101	1.0	1.0	
< 20 yrs (10 yrs lag)	37	44	4.1	3.7	[1.7,8.0]
20+ yrs (10 yrs lag)	32	48	3.8	3.2	[1.3,7.9]
Never	22	94	1.0	1.0	
< 35 yrs since 1st exp.	49	59	4.0	3.6	[1.8,7.2]
35+ yrs since 1st exp.	30	40	5.8	5.5	[1.9,16.0]
Never	22	94	1.0	1.0	
20+ yrs at 1st exp.	28	47	3.2	2.8	[1.3,6.0]
< 20 yrs at 1st exp.	52	52	5.5	5.0	[2.4,10.4]

[1]Formaldehyde estimates adjusted for years since first exposure to dust and/or exhaust fumes. Dust/exhaust estimates adjusted for years since first formaldehyde exposure.–[2]Includes 8 cases and 3 controls exposed only in the 10 years immediately preceding diagnosis/interview.–[3]Includes 11 cases and 7 controls exposed only in the 10 years immediately preceding diagnosis/interview.

to formaldehyde (Spearman correlation coefficients ranging from −0.04 to 0.24). The association observed between wood-dust exposure and NPC (RR = 1.3 and 2.1 for <35 or 35+ years since first exposure, relative to never-exposed subjects) was weaker than that observed between overall dust exposure and NPC. In fact, those first exposed to dusts less than 35 years before diagnosis or interview were at a 3.4-fold excess risk of disease (95% CI = 1.8, 6.2) and those first exposed 35 or more years preceding diagnosis or interview were at 4.7-fold excess risk of disease (95% CI = 1.8, 12.5). Exposure to wood dust was therefore not considered separately in further analysis. Exposure to pesticides was also more weakly associated with NPC than exposure to dust (RR = 1.4 and 1.7 for <35 and 35+ years since first exposure, relative to never-exposed subjects). As with wood-dust exposure, since all subjects exposed to pesticides were also exposed to dust, pesticide exposure was not considered separately in further analysis.

Individuals exposed to solvents were found to be at increased risk of disease. Those first exposed to solvents less than 35 years before diagnosis or interview were at 1.7-fold excess risk of disease (95% CI = 0.93, 3.2) and those first exposed 35 or more years preceding diagnosis or interview were at 2.6-fold excess risk of disease (95% CI = 1.1, 6.3). However, when exposures to solvents and dust were examined jointly, no consistent association between solvent exposure and NPC was observed within strata of dust exposure (data not shown). Exposure to exhaust fumes was also found to be associated with NPC risk. The RR estimates were 2.7 (95% CI = 1.5, 5.1) and 2.8 (95% CI = 1.1, 7.0) for those first exposed to exhaust less than 35 years and 35 or more years before diagnosis or interview, respectively, relative to unexposed subjects. When the joint effects of dust and exhaust fume exposure were investigated, the highest risk was observed for individuals who were first exposed to dusts and to exhaust fumes 35 or more years preceding diagnosis compared to subjects never exposed to either (RR = 5.7; 95% CI = 1.9, 17.4). Since dust and exhaust exposures were highly correlated (Spearman correlation coefficient between the latency variables for exhaust and dust exposure was 0.72), it was not possible to disentangle their independent effects. Rather, we combined the 2 highly correlated variables into one (Table I). Latency since first exposure was found to be the strongest determinant of risk, as was previously observed for formaldehyde exposure. After controlling for formaldehyde exposure, subjects who were first exposed to dust or exhaust fumes less than 35 years preceding diagnosis or interview were at a 3.6-fold excess risk of disease (95% CI = 1.8, 7.2) and those first exposed 35 or more years preceding diagnosis were at a 5.5-fold excess risk of disease (95% CI = 1.9, 16.0). Age at first exposure was also strongly associated with risk of disease; those first exposed to dust or exhaust prior to the age of 20 were at a 5.0-fold excess risk of developing NPC (95% CI = 2.4, 10.4), relative to those never exposed. As observed with formaldehyde exposure, age at first exposure and latency since first exposure to dust or exhaust fumes seemed to be independently associated with NPC (data not shown).

When exposures to formaldehyde and dust/exhaust were examined jointly, the 2 exposures appeared to have independent effects on risk. Those first exposed to formaldehyde 25 or more years preceding diagnosis and first exposed to dust/exhaust 35 or more years preceding diagnosis were at the highest risk, relative to those unexposed to both factors (RR = 15.7; 95% CI = 2.7, 91.2).

We next examined the effect on risk of consumption of selected dietary factors (Table II). Adult consumption of salted fish was not associated with disease risk, with subjects classified in the highest tertile of consumption being at only a 30% excess risk of disease (95% CI = 0.69, 2.6). In contrast, consumption of processed meats was inversely associated with risk, those in the highest tertile of consumption being at lowest risk (RR = 0.33; 95% CI = 0.17, 0.66). An increase in risk of disease was also observed among subjects in the highest tertile of consumption of fresh fish (RR = 2.7; 95% CI = 1.2, 6.1).

Overall, no dose-response relationship was observed between cigarette smoking and NPC, although subjects who reported smoking for more than 30 years were at a 2.4 fold excess risk of disease (95% CI = 0.95, 5.9) (Table III). When cases were compared to community controls only, an association between cigarette smoking and NPC was observed. In fact, we observed that the RR estimates for subjects who reported smoking for 1–20 years, 21–30 years, and 31+ years relative to never-smokers were 0.60 (95% CI = 0.21, 1.8), 2.4 (95% CI = 0.55, 10.5), and 4.9 (95% CI = 1.6, 15.4), respectively. No consistent association between cigarette smoking and NPC was observed when cases were compared to hospital controls.

Burning of anti-mosquito coils was found to be strongly associated with NPC. Subjects who reported daily use of these coils were at a 7.8-fold excess risk of disease relative to those who reported never using coils (95% CI = 2.7, 22.8). As we previously reported (Hildesheim *et al.*, 1992), herbal medicine use was also found to be significantly associated with disease; ever-users of herbal medicines were at a 2.7-fold excess risk of disease (95% CI = 1.4, 5.2). Very few subjects reported use of betel nut and no significant association with risk was detected (Table III).

Education and the exposures found to be important in Tables I–III were included in a final logistic model to assess the independent effects of these factors (Table IV). All the factors found to be significantly associated with NPC in the more restricted models remained important after more extensive control for confounding, with the exception of education, whose association with NPC was greatly reduced by adjustment. In addition to latency since first exposure to formalde-

TABLE II – RISK OF NPC BY EXPOSURE TO DIETARY FACTORS

Factor	Cases (n)	Controls (n)	Crude RR	Adj. RR[1]	95% CI
Salted fish					
Low tertile	32	70	1.0	1.0	
Mid tertile	28	70	0.91	1.1	[.57,2.3]
High tertile	44	65	1.6	1.3	[.69,2.6]
Processed meats					
Low tertile	61	66	1.0	1.0	
Mid tertile	22	61	0.37	0.41	[.21,.80]
High tertile	21	78	0.28	0.33	[.17,.66]
Fresh fish					
Low tertile	24	69	1.0	1.0	
Mid tertile	27	69	1.4	1.2	[.59,2.5]
High tertile	53	67	3.6	2.7	[1.2,6.1]

[1]Adjusted for all variables listed in the Table.

TABLE III – RISK OF NPC BY OTHER FACTORS

Factor	Cases (n)	Controls (n)	Crude RR	Adj. RR[1]	95% CI
Smoking (yrs)[2]					
Never	30	66	1.0	1.0	
1–20	18	48	0.62	0.53	[.22,1.3]
21–30	22	46	1.0	0.95	[.32,2.8]
31+	34	45	2.5	2.4	[.95,5.9]
Anti-mosquito coils					
Never	59	163	1.0	1.0	
< daily	24	36	1.7	1.8	[.94,3.5]
Daily	21	6	8.9	7.8	[2.7,22.8]
Herbal medicines					
Never	64	161	1.0	1.0	
Ever	40	44	2.5	2.7	[1.4,5.2]
Betel nut					
No	99	191	1.0	1.0	
Yes	5	14	0.69	0.56	[.18,1.8]

[1]Adjusted for all variables listed in the Table.–[2]When cases were compared to community controls, adjusted RR estimates were as follows: Never 1.0; 1–20 yrs 0.60 (95% CI = 0.21,1.8); 21–30 yrs 2.4 (95% CI = 0.55,10.5); 31+ yrs 4.9 (95% CI = 1.6,15.4).

TABLE IV – RISK OF NPC BY INDEPENDENT FACTORS—FINAL MODEL

Factor	Cases (n)	Controls (n)	Adj. RR[1]	95% CI
Education				
<4 yrs	16	19	1.0	
4–10 yrs	70	130	0.78	[.27,2.3]
11+ yrs	18	56	0.75	[.19,3.0]
Formaldehyde				
Never	75	171	1.0	
<25 since 1st exp.	12	12	1.2	[.41,3.6]
25+ since 1st exp.	14	10	4.0	[1.3,12.3]
Dust/exhaust				
Never	22	94	1.0	
<35 since 1st exp.	49	59	2.5	[1.1,5.9]
35+ since 1st exp.	30	40	4.4	[1.1,17.5]
Processed meats				
Low tertile	61	66	1.0	
Mid tertile	22	61	0.43	[.19,.99]
High tertile	21	78	0.46	[.20,1.0]
Fresh fish				
Low tertile	24	69	1.0	
Mid tertile	27	69	1.1	[.47,2.7]
High tertile	53	67	2.5	[.90,7.2]
Smoking (yrs)[2]				
Never	30	66	1.0	
1–20	18	48	0.48	[.15,1.5]
21–30	22	46	0.87	[.26,3.0]
31+	34	45	2.3	[.73,7.3]
Anti-mosquito coils				
Never	59	163	1.0	
≤Daily	24	36	1.4	[.64,2.8]
Daily	21	6	5.9	[1.7,20.1]
Herbal medicines				
Never	64	161	1.0	
Ever	40	44	2.5	[1.1,5.3]

[1]Adjusted for all variables listed in the Table.–[2]When cases were compared to community controls, adjusted RR estimates were as follows: Never 1.0; 1–20 yrs 0.80 (95% CI = 0.14,4.4); 21–30 yrs 2.9 (95% CI = 0.45,18.2); 31+ yrs 7.2 (95% CI = 1.5,34.4).

hyde and dust/exhaust, age at first exposure to these occupational factors was also found to be associated with NPC after control for confounding. Subjects first exposed to formaldehyde before the age of 25 were at a 4.0-fold excess risk of disease (95% CI = 1.3, 12.0) and those first exposed to dust/exhaust before the age of 20 were at a 3.5-fold excess risk of disease (95% CI = 1.4, 8.6).

Similar results were obtained when cases were compared separately to hospital and community controls, with 2 notable exceptions. Smoking was found to be a risk factor only when cases were compared to community controls (RR estimates for individuals who reported smoking for 1–20 years, 21–30 years, and 30+ years, relative to non-smokers were 0.80, 2.9, and 7.2, respectively) but not when cases were compared to hospital controls (RR estimates for individuals who reported smoking for 1–20 years, 21–30 years, and 30+ years, relative to non-smokers were 0.35, 0.42, and 1.5, respectively). Similarly, fresh fish consumption was associated with NPC only when cases were compared to community controls (RR estimates for individuals in the middle and high tertiles of consumption, relative to those in the lowest tertile were 1.7 and 5.1, respectively, for community controls and 0.87 and 1.1, respectively, for hospital controls).

DISCUSSION

Results from this study suggest that Filipino NPC cases share a number of risk factors with their high-risk Chinese neighbors, including occupational exposure to dusts, cigarette smoking, and herbal medicine use. However, we did not observe any association between risk and adult consumption of salted fish. In addition, several risk factors not previously found to be associated with disease among high-risk Chinese emerged, including occupational exposure to formaldehyde and exhaust fumes, and burning of anti-mosquito coils.

We were able to assess the association between occupational exposures and NPC. Complete occupational histories were obtained from each study participant and reviewed "blind" by an experienced industrial hygienist using various sources of exposure information (OSHA, 1987; Gerin *et al.*, 1989; TLV Committee, 1990). Although estimates of occupational exposures obtained from job titles alone are prone to misclassification, it is unlikely that misclassification varies by case-control status; risk estimates for occupational exposures obtained from this study are therefore likely to be biased towards rather than away from the null.

In concordance with numerous (Blair *et al.*, 1990; Hildesheim and Levine, 1993) but not all studies (Purchase and Paddle, 1989) which have examined formaldehyde, we observed a strong association between our estimates of formaldehyde exposure and NPC. In particular, individuals who were first exposed to formaldehyde 25 or more years prior to diagnosis/interview or who were first exposed to formaldehyde before the age of 25 were found to be at a 4.0-fold excess risk of

developing NPC. Our finding of a stronger association between exposure and disease among those exposed at an early age is in agreement with previous reports which have observed that dietary patterns at early ages are more important determinants of risk of NPC than adult dietary patterns (Yu, 1990). It is unclear at this time, however, whether these findings reflect increased susceptibility at younger ages, a long latency between exposure and disease, or both.

Dust and exhaust exposure were also found to be significantly associated with NPC. As with formaldehyde, latency of exposure and age at first exposure were the measures most strongly associated with risk. The effect of dust exposure did not appear to be limited to exposure to wood dust, since exposure to wood dust was not as strongly associated with NPC as overall dust exposure. This argues against the association with NPC of a specific chemical present in dust, and suggests that physical irritation of the nasopharynx by dust particles might account for the increase in risk among dust-exposed subjects.

Previous studies which examined occupational exposure to dust have been largely negative (Hildesheim and Levine, 1993), although a few studies have reported a positive association between disease and occupational exposure to dust (Armstrong *et al.,* 1983; Henderson *et al.,* 1976). None of these studies, however, have examined the association between risk and latency or age at first exposure. Although little is known about the effect of exposure to exhaust fumes on NPC risk, a few studies have suggested that vehicle mechanics (Vaughan, 1989) and individuals exposed to combustion products (Yu *et al.,* 1990; Zheng *et al.,* 1992) are at excess risk of developing NPC.

In contrast to most studies which have examined the effect of diet on NPC risk (Hildesheim and Levine, 1993), we did not observe an association between NPC and adult consumption of salted fish. Our failure to observe such an association might be due to the lack of data on salted fish consumption at young ages, which has previously been shown to be a more important risk factor for NPC than adult consumption (Yu, 1990). Alternatively, consumption of salted fish in the Philippines might indeed not be associated with NPC, indicating the need to further investigate differences in methods of preparation in future studies.

We did observe a positive association between fresh fish consumption and NPC, and a negative association between processed meat consumption and NPC. The interpretation of these findings is unclear, particularly in view of the presence of precursors to nitrosamines, which are thought to be linked to NPC (Poirier *et al.,* 1989), in processed meats. Our dietary findings, however, should be interpreted with care, since our questionnaire did not obtain complete dietary information from study participants.

Previous studies which have examined the association between smoking and NPC have had conflicting results. Numerous studies have observed an association between cigarette smoking and NPC, but others have failed to observe such an association (Hildesheim and Levine, 1993). There is a strong biological rationale for the association between smoking and NPC. First, the nasopharynx is almost certainly a site of exposure to fumes during smoking. Second, cigarette smoking has been linked to the etiology of numerous cancers of the upper and lower respiratory tract. Finally, constituents found in cigarette smoke are known to have carcinogenic potential (Hecht and Hoffmann, 1988). In our study, although no significant association between smoking and NPC was observed when cases were compared to all controls, we observed a strong association between smoking and NPC when cases were compared to community controls. The absence of an association between smoking and NPC when cases were compared to hospital controls is probably explained by the fact that subjects diagnosed with smoking-related diseases were not excluded from participation in the study as hospital controls.

Results from our study also suggest a potential influence on NPC of herbal medicine use and burning of anti-mosquito coil. The association between herbal medicine use and NPC in this study has previously been reported and discussed (Hildesheim *et al.,* 1992). The finding of an association between anti-mosquito coil and NPC, a primary hypothesis of the present study, is provocative. Most previous studies which have examined this relationship have reported negative findings (Hildesheim and Levine, 1993), with the possible exception of one study which reported a non-significant 2.4-fold excess risk of NPC among users of anti-mosquito coils 3 years preceding diagnosis (Yu *et al.,* 1986). The observed strength of the association between anti-mosquito coil use and NPC in the present study suggests the need to further investigate the possible role of these coils in NPC development. In particular, it would be of interest to define the compounds present in the smoke produced by burning anti-mosquito coils, which might account for an association between coil use and NPC.

In summary, results from our study suggest a strong effect of occupational exposure to formaldehyde, dusts and exhaust on risk of developing NPC. In addition, smoking, use of herbal medicines and anti-mosquito coils were found to be significantly associated with NPC, while salted fish consumption was not associated with the disease in our population. The association observed between formaldehyde and disease in our intermediate-risk population is particularly interesting and confirms previous studies conducted among low-risk Caucasian subjects. Future studies should attempt to determine whether this same association is observed among high-risk Chinese. Additional effort is also warranted to dissociate the effect of latency and age at first exposure on risk of NPC.

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APPENDIX – LIKELIHOOD OF OCCUPATIONAL EXPOSURE BY JOB CLASSIFICATION

Title	Formaldehyde	Wood	Dust	Solvent	Exhaust	Pesticide
Animal caretakers, except farm	+		+	+		
Assemblers				+		
Automobile mechanics			++	++	++	
Automobile mechanic apprentices			++	++	++	
Bakers			+			
Bus drivers				+	++	
Carpenters	++	++	++	+		
Cement and concrete finishers			+			
Chemistry teacher	+		+			
Clinical laboratory technologist	+			++		
Compositors and typesetters	+		++	+		
Deliverymen and routemen					++	
Electricians			+			
Excavating, grading, road machine operators			+		+	
Farm managers	+	++	++	++	++	++
Farmers	+	++	++	++	++	++
Fishermen and Oystermen					++	
Forgemen and hammermen			+			
Freight and material handler			+		++	
Garage workers and gas station attendants				++	++	
Garbage collectors			++		++	
Gardeners and groundskeepers, except farm	+		++	++	++	++
Hairdressers and cosmetologists	+			++		
Hucksters, peddlers, street sellers, newsboys			+		+	
Jeepney and tricycle drivers				+	++	
Jewelers and watchmakers				+		
Knitters, loopers, toppers	+		++			
Lumbermen, raftsmen, woodchoppers	+	++	++	+		
Mail carriers/handlers, Post Office			+		+	
Millers; grain, flower and feed			+	++		
Mine operatives, n.e.c.[1]			++		+	
Painter apprentices	+		+	++		
Painters, construction, maintenance	+		+	++		
Painters, manufactured articles	+			++		
Photoengravers and lithographers				+		
Plumbers and pipe fitters			++			
Pressmen apprentices	+		+	++		
Private drivers				+	++	
Radio and television repairmen				+		
Registered nurses	+			+		
Roofers and slaters			+	++		
Shoe repairmen			+	++		
Stock handlers			++		+	
Stone cutters and stone carvers			+			
Tailors, sew girls	+			+	++	
Taxicab drivers			+		+	
Teamsters			+			
Telephone installers and repairmen			++			
Telephone linemen and splicers			++			
Textile operatives, n.e.c.	+			++		
Tile setters				+	++	
Truck drivers						

+ = Exposure likely; ++ = exposure highly likely and/or likely to be of high dose.–[1]n.e.c., not elsewhere classified.