

Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat

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Background	During 1990–1992, 282 Chinese residents of Selangor and the Federal Territory, Malaysia with histologically confirmed nasopharyngeal carcinoma (NPC) were interviewed about occupational history, diet, alcohol consumption, and tobacco use, as were an equal number of Malaysian Chinese population controls, pair-matched to cases by age and sex.
Methods	Exposures to 20 kinds of workplace substances, solar and industrial heat, and cigarette smoke, were analysed by univariate and multivariate methods.
Results	Nasopharyngeal carcinoma was associated with occupational exposures to construction, metal and wood dusts; motor fuel and oil; paints and varnishes; certain other chemicals; industrial heat; solar heat from outdoor occupations; certain smokes; cigarette smoking; and childhood exposure to parental smoking. After adjustment for risk from diet and cigarette smoke, only wood dust (OR = 2.36; 95% CI : 1.33–4.19), and industrial heat (OR = 2.21; 95% CI : 1.12–4.33) remained clearly associated. Wood dust remained statistically significant after further adjustment for social class. No significant crude or adjusted association was found between NPC and formaldehyde (adjusted OR = 0.71; 95% CI : 0.34–1.43).
Conclusions	This study supports previous findings that some occupational inhalants are risk factors for NPC. The statistical effect of wood dust remained substantial after adjustment for diet, cigarette smoke, and social class. Intense industrial heat emerged as a previously unreported risk factor, statistically significant even after adjustment for diet and cigarette smoke. No association was found between NPC and formaldehyde.
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Although comparatively rare worldwide, nasopharyngeal carcinoma (NPC) has substantial incidence and mortality in populations of southern Chinese ancestry in China and Southeast Asia. Nasopharyngeal carcinoma in southern Chinese is believed to result from a combination of genetic susceptibility,

infection with Epstein-Barr virus, and regular consumption of salted fish beginning in childhood.¹ Nasopharyngeal carcinoma has been associated with salted foods,^{2–7} with alcohol consumption,^{3,8} cigarette smoking,⁸ and occupational exposures.^{2,4,7,9–12} The epidemiology of NPC has been reviewed by Yu and Henderson.¹³ We report a case-control study of NPC in Chinese of the Federal Territory (Kuala Lumpur), and State of Selangor, Malaysia. The primary objective was to pursue indications from smaller studies of this population,^{2,14} and of others, that NPC risk rises with work-site inhalation of dust and smoke particles, formaldehyde, and certain aromatic hydrocarbons. We examined associations of NPC with occupational exposure histories, active and passive cigarette smoking, and consumption of alcohol and various dietary components. Results on dietary exposures including alcohol have been reported.³ Here we focus on associations with occupational exposures and cigarette smoke.

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Methods

Cases were ascertained through records of NPC diagnosis and/or treatment at four centres with radiotherapy in the study area of Selangor and the Federal Territory: General Hospital, Tung Shin Hospital, Pantai Medical Centre, and Computer Radionics Centre, Kuala Lumpur.

Between 1 July 1990 and 30 June 1992 we identified 530 Chinese cases with histologically confirmed NPC who had resided in the study area for at least 5 years, and been diagnosed between 1 January 1987 and 30 June 1992. Of these, 121 (23%) had died, 63 (12%) could not be located, 4 (1%) were too ill for interview, and 60 (11%) declined participation, leaving 282 cases (53%) for study. Of the 530 eligible cases, 282 were prevalent (diagnosed before 1990) and 245 were incident cases (1990 to mid-1992). The 282 NPC cases for study comprised 119 (42%) prevalent and 163 (58%) incident cases. The modest participation rate was largely due to the attempt to obtain a population-based sample, including non-hospitalized cases and prevalent cases with onset as much as 3.5 years prior to initiation of data collection. Specifically, of the 125 cases who could not be interviewed because they were too ill or had died, 104 (83%) were prevalent cases when ascertained. So were 41 (65%) of those who could not be located, some of whom may also have died.

Each case was matched by sex and age (within 3 years) to one control participant in good health with no history of cancer of the head, neck, or respiratory system, selected from the general Chinese population of the study area using a standard procedure of multistage area sampling. For each case, an interviewer began at a randomly chosen house in a randomly selected postal code district of a Chinese neighbourhood, and proceeded house-to-house by a standard algorithm¹⁵ until a qualified control, also resident in the study area for at least 5 years, was found. The overall refusal rate among eligible controls was 10%, but in affluent neighbourhoods it was 20%. Data were collected from each participant during two 40–50-minute in-home, structured interviews by specially trained full-time Chinese interviewers fluent in all local dialects. The interviews requested complete residential and occupational history, information on use of alcohol and tobacco, and frequencies of consumption of 55 food items at age 10 and at 5 years prior to diagnosis of NPC for the case (for matched controls, same calendar year as the index case). For each job in the occupational history, the interview covered job description, work performed, calendar time, machines, tools and substances used, size and type of workplace, exposure to dusts, smoke, gases and chemicals. Exposures to 20 inhalants and heat from two sources were recorded by trade or profession with calendar years, frequency (days per week), and duration (hours per day) of exposure. Questions followed the format of Gerin *et al.*¹⁶ and Gerin and Siemietycki.¹⁷ Inhalant selection was limited to those dusts, smoke, and gases associated with deposition or absorption in the nasopharynx, with special attention to formaldehyde.

Exposure to inhalants was subsequently coded by one of us (RWA) who is familiar with Malaysian industries and hygiene. Coding was conducted blind to case-control status. Codes were adapted from Hoar *et al.*,¹⁸ Gerin *et al.*¹⁶ and Gerin *et al.*¹⁹ Jobs were classified using official Malaysian occupational codes.²⁰ Level of exposure to inhalants (ever/never, low, medium, high)

was assessed with reference to kind of job, work performed, mode of contact (respiratory and/or cutaneous), respondent's reporting of exposure to particular inhalants, years of exposure, frequency, and duration.

Participants were asked about history of active smoking and exposure to cigarette smoke from spouse and other family members, and from parents while growing up. They were also asked about educational level, occupation, job status (employed, retired, etc.), spouse's and parental occupation, and house type as a basis for establishing social class.

Data analysis

Consistent with most other studies, we focus on duration of exposure. Estimated hours of each work-site exposure was calculated by subject by summing $52 \times (\text{calendar years in job}) \times (\text{workdays per week}) \times (\text{hours per day})$ over jobs where the exposure was present.

Statistical significance of each exposure's crude association with NPC was examined by sign test of estimated hours exposed, excluding tied pairs. The sign test was used because of its robustness and good performance with heavy-tailed distributions.^{21,22} Cigarette smoking was studied by multiple logistic regression. Cigarette smoking history was defined as present if the subject reported ever having smoked for a period of 6 months or more, and absent otherwise. For subjects with smoking histories, cumulative pack-years were estimated as reported years of smoking multiplied by scores of 0.25, 0.75, 1.25, and 2.00 for smokers, respectively, averaging <10, 11–20, 21–30 and >30 cigarettes daily. We examined models using dichotomous variables for cigarette smoking history >6 months, exposure to parental cigarette smoking in childhood, and exposure to cigarette smoking by spouse or other household member. We considered estimated accumulated pack-years of smoking, years of living with smoking parents, and years of living with smoking spouse or other household member as crude indices of dose, and these were also evaluated as quantitative predictors. Social class categories (poor, lower middle, upper middle, high) based on Liberatos *et al.*²³ were constructed for each participant for time of interview, and childhood (age 10). Social class coding was blind to case-control status.

To account for possible confounding, a dietary and cigarette risk-adjusted sign test (Appendix) was obtained from a conditional logistic regression model with linear predictor $(\beta_D z_D + \beta_C z_C + \beta_S s)$, where z_D is a dietary risk index derived previously from these data³ which summarizes past consumption of salted fish, salted egg, pork or beef liver, shrimp, Chinese flowering cabbage, oranges or tangerines, and beer; z_C is a cigarette smoke risk index, where $z_C = 1$ if the case or control had smoked cigarettes for >6 months and/or had been exposed to parental smoking, and $z_C = 0$ if neither; and $s = 1$ or 0 is an indicator variable identifying the member of each matched pair with highest estimated hours of past exposure. The likelihood ratio test of $H_0: \beta_S = 0$ from the model-based conditional likelihood gives the adjusted test.

To indicate the strength of observed statistical relationships, the median case-control difference in hourly exposures was calculated after excluding unexposed pairs. The maximum (conditional) likelihood point estimate of the odds ratio (OR) for any exposure versus none, with exact 95% CI, was obtained from the subset of pairs with exactly one exposed subject.

A dietary and cigarette risk-adjusted OR and asymptotic 95% CI were obtained from the conditional logistic regression model with linear predictor $\beta_D z_D + \beta_C z_C + \beta_{S^*} s^*$, where $s^* = 1$ or 0 depending on whether the subject was ever or never exposed.

To examine possible dose-response relationships, occupational exposure was represented by $x = \log_{10}(t + 1)$, where t = estimated hours exposed, since t is a surrogate for cumulative dose of an hypothetically toxic agent, and the logistic tolerance distribution is typically more successful in describing quantal responses to log rather than absolute doses of toxic agents.²⁴ Logistic regression models were then fit using x , with and without the dietary index z_D and cigarette smoke index z_C as covariates. Non-linearity was examined by sequential addition of quadratic and, as necessary, cubic terms in x to the model. Likelihood ratio tests were used for these and other logistic model comparisons. Upon choice of a dose-response curve of order $k = 1, 2$ or 3 as described, effect modification by diet and cigarette smoke were examined by separate sequential addition of interaction terms $z_D x^i$ and $z_C x^i$, $i = 1, \dots, k$, until the first non-significant interaction term of each type was reached. In these models, a one unit increase in the exposure measure $x = \log_{10}(t + 1)$ represents, to a very close approximation, a tenfold increase in the estimated hours exposed, and estimated OR from logistic regressions are presented corresponding to this exposure ratio.

Because an association of wood dust with NPC has previously been reported and is supported by our data, other occupational exposures with OR > 1.5 after adjustment for diet and cigarette smoke were also simultaneously adjusted for diet, cigarette smoke, and wood dust. This was done by adding z_W , the log-transformed hours of exposure to wood dust to the models derived above. We also checked for confounding of each occupational exposure by social class by adding three dummy variables for social class to the diet and cigarette adjustment models.

To account for a possible long NPC latency, cumulative exposures were restricted to each of five time frames: >1, 5, 10, 15 and 20 years prior to NPC diagnosis. We also classified participants by exposures above each of three thresholds: 10+ years of exposure, 5+ years of high level exposure, and 20+ years of low level exposure, at any time in working life. The impacts of latency and exposure thresholds were examined by calculating unadjusted OR for NPC using each of the eight risk dichotomies implied by the five latency periods and three thresholds defined above, and screening for trends with time frame or exposure threshold.

Results

All 282 NPC cases were squamous cell carcinomas. Cases included 195 males aged 19–72 years (mean 45.6 versus 45.1 for controls), and 87 females aged 24–74 (mean 44.6 versus 44.2 for controls). Case and control groups had similar distributions of birthplace and marital status, but differed in social class, Chinese subethnicity, and education. Twenty per cent of cases and 8% of controls belonged to the 'poor' social class ($P < 0.00005$), reflecting among other factors fewer years of education among cases ($P = 0.011$). The NPC OR for poor versus all others was 4.1 ($P < 0.01$). Childhood social class was not significantly related to NPC after adjustment for current social class. Hokkien Chinese were underrepresented among cases (23%) as compared to controls (32%), with Khek and smaller subethnicities moderately

overrepresented ($P = 0.05$), but the association of subethnicity with NPC vanished after adjustment for diet.³

Table 1 compares cases with controls for each occupational exposure, including results of crude and diet-adjusted sign tests for statistically significant association. Although 282 case-control pairs were studied, the number of informative pairs relative to each individual exposure (pairs with at least one exposed subject), varied widely from a low of 11 (dyes) to a high of 157 (other fumes), with median of 45 pairs. The power to detect existing associations with NPC thus varied substantially among the exposures. Exposures to construction, metal and wood dusts, solar heat from outdoor occupations, industrial heat (from furnaces, rolling mills, welding machines, etc.), motor fuel and oil, paints and varnishes, other chemicals (primarily acids, bases, solvents, detergents, and soaps), and other smoke (from oil, tars, grass and other non-metallic sources), show statistically significant ($\alpha = 5\%$) excesses among cases. The median hourly case-control differences in exposure were between 1000 and 8000, with the exception of motor fuel and oil where the difference was 460 hours. However, only wood dust, other chemicals, and industrial heat remain statistically significant ($\alpha = 5\%$) after adjustment for risk from diet and cigarette smoke.

History of active cigarette smoking (>6 months) was associated with NPC (OR = 1.66, $P = 0.012$). After adjustment for such history, exposure to passive parental smoking during childhood was associated with NPC as well (OR = 1.54, $P = 0.040$). In this multiple logistic regression model, non-smokers exposed to parental smoking in childhood exhibited similar excess risk of NPC as did active smokers, whether the latter were passively exposed in childhood or not. Table 2 shows these results with and without adjustment for diet. Passive exposure to smoke from spouse or other household member showed no association with NPC after adjustment for active smoking. Models including estimated pack-years of active smoking and years of exposure to parental smoking (not reported) added no significant predictive power to the models in Table 2.

Table 3 shows crude and diet/smoking-adjusted OR for any versus no history of each occupational exposure. Wood dust (OR = 2.36), other chemicals (OR = 2.36), and industrial heat (OR = 2.21) have the highest apparent diet-adjusted OR, followed by metal, textile, and tin dusts, and wood smoke, with essentially equal OR between 1.65 and 1.77. Only wood dust and industrial heat achieve statistical significance after adjustment.

Table 4 represents dose-response relationships in terms of OR associated with a tenfold ratio of hours exposed. Wood dust, industrial heat, and other chemicals again have the highest crude and diet/smoking-adjusted OR. Adjusted OR for metal, tin, and textile dusts, and for other smoke, form a lower tier. Based on adjusted dose-response relationship, only wood dust (observed median case-control difference of 4610 h) and industrial heat (observed median difference of 3740 h) retain statistically significant positive associations with NPC. Exposure to resins was moderately negatively associated with NPC (OR = 0.74), with a marginally statistically significant P -value. Neither effect modification by diet or cigarette smoke nor non-linear dose-response relationships were found for these variables. A quadratic effect of exposure to wood smoke was found in exploratory analysis. This is likely artifactual, as it occurs without a statistically significant linear trend and suggests a biologically implausible decline in impact of progressively larger increases in

Table 1 Associations of nasopharyngeal cancer with histories of 22 occupational exposures

Substance	Exposure (%)		Exposed pairs	Median difference in hours exposed (100s)	P-value (sign test)	P-value (diet and cigarette smoke adjusted sign test) ^a
	Cases	Controls				
Dusts						
Construction	22.0	14.2	93	72.5	0.012	0.30
Fertilizer	1.4	1.4	8	-2.0	1.00	0.44
Metal	16.0	9.6	65	11.0	0.025	0.06
Talc	3.6	2.5	17	6.0	0.63	0.26
Tin	3.2	1.8	14	76.6	0.42	0.43
Textile	7.8	5.0	34	46.1	0.12	0.12
Wood	24.8	12.1	92	46.1	0.000014	0.0028
Other ^b	39.7	31.2	157	11.5	0.07	0.31
Fumes						
Cooking	6.7	4.6	31	20.7	0.47	0.82
Engine exhaust	20.9	19.9	98	-6.1	0.92	0.72
Wood	9.6	5.3	37	3.5	0.099	0.54
Other ^c	10.3	5.3	43	28.5	0.031	0.27
Chemicals						
Biocides	6.7	6.7	37	-0.4	1.00	0.63
Dyes	2.1	1.8	11	2.3	1.00	0.97
Formaldehyde	9.9	8.2	49	0.6	0.57	0.25
Glues	11.0	6.7	47	5.8	0.09	0.43
Other chemicals ^d	7.1	3.2	28	16.2	0.036	0.05
Motor fuel and oil	29.4	19.9	117	4.6	0.0053	0.36
Paints and varnishes	16.0	9.6	63	17.3	0.023	0.46
Resins	2.8	4.6	21	-20.2	.38	0.10
Heat						
Solar	18.1	11.0	75	29.8	0.037	0.75
Industrial	17.0	6.7	62	37.4	0.00050	0.027

^a Adjusted for diet using $z_D \equiv 0.66 \times (f_1 + f_2 - f_3) + 0.23 \times (f_4 - f_5) - 0.86 \times f_6 + 0.29 \times f_7$, where $f_1 = -1, 0, \text{ or } 1$ according to whether subject consumed salted fish less than monthly, monthly but less than weekly, or at least weekly 5 years prior to diagnosis of the case; f_2 is defined similarly to f_1 , but for pork and/or beef liver; $f_3 = 0, 1 \text{ or } 2$ according to whether Chinese flowering cabbage was consumed less than weekly both 5 years prior to diagnosis and at age 10, at least weekly at one of those times, and at least weekly at both of those times; $f_4 = f_{41} + f_{42}$, where f_{41} is defined as f_1 for salted eggs 5 years prior to diagnosis and f_{42} is defined similarly at age 10; f_5 is defined as f_4 , but for fresh shrimp; $f_6 = 1 \text{ or } 0$ according to whether or not oranges and/or tangerines were consumed at least monthly at either time; and $f_7 = 1, \dots, 5$ depending on frequency and amount of beer consumption 5 years prior to diagnosis of the case, as described in Armstrong *et al.*³ Adjusted for cigarette smoke using $z_C = 1$ if subject ever smoked for at least 6 months or was exposed to parental smoking in the home during childhood, and 0 otherwise.

^b Includes cement, rice, flour, fertilizer and gypsum dusts.

^c Includes smokes from oil, tars, grass and other non-metallic sources; excludes smokes from wood burning and cooking, engine exhaust, and cigarette smoke.

^d Includes a variety of acids, bases, solvents, detergents and soaps.

Table 2 Unadjusted and diet-adjusted simultaneously estimated odds ratios (OR) for smoking and parental smoking among smokers and non-smokers, with P-values and 95% CI

Exposed pairs	Unadjusted for dietary index			Adjusted for dietary index		
	OR	P	95% CI	OR	P	95% CI
Cigarette smoking history >6 months	2.86	0.002	1.42-5.76	1.82	0.16	0.78-4.23
Parental smoking for smokers ^a	0.88	0.70	0.47-1.65	0.74	0.43	0.34-1.59
Parental smoking for non-smokers ^a	2.27	0.002	1.32-3.88	2.28	0.008	1.21-4.28

^a Overall P-values for the full models containing smoking, parental smoking and their interaction were 0.001 and 0.040 in the unadjusted and adjusted models respectively, with corresponding P-values for interaction (effect modification of smoking and parental smoking) of 0.018 and 0.028.

absolute dose. It does not remain significant after Bonferroni correction for multiple comparisons.

Dose-response effects of industrial heat and other chemicals, metal, tin and textile dusts, and wood smoke were further adjusted to account for possible simultaneous confounding

by wood dust, dietary, and cigarette smoke exposures. Only industrial heat retained a statistically significant adjusted dose-response effect (OR = 1.23, P = 0.021). Simultaneous adjustment of all dose response effects for dietary and cigarette smoke risks, and current social class produced little change

Table 3 Estimated odds ratios for any versus no history of 22 occupational exposures with and without adjustment for diet and cigarette smoke indices

Substances	Unadjusted	Logistic regression adjusted
Dusts		
Construction	1.71 (1.07–2.76)	1.31 (0.77–2.24)
Fertilizer	1.00 (0.18–5.37)	0.52 (0.10–2.71)
Metal	1.90 (1.07–3.45)	1.67 (0.90–3.08)
Talc	1.43 (0.49–4.43)	0.49 (0.14–1.66)
Tin	1.80 (0.54–6.84)	1.69 (0.45–6.30)
Textile	1.66 (0.77–3.74)	1.77 (0.76–4.11)
Wood	2.64 (1.58–4.53)	2.36 (1.33–4.19)
Other ^b	1.53 (1.03–2.29)	1.39 (0.88–2.16)
Fumes		
Cooking	1.50 (0.68–3.42)	0.93 (0.38–2.27)
Engine exhaust	1.08 (0.67–1.71)	1.05 (0.61–1.79)
Wood	2.20 (0.99–5.21)	1.65 (0.69–3.92)
Other ^c	2.00 (1.01–4.11)	1.46 (0.66–3.23)
Chemicals		
Biocides	1.00 (0.49–2.04)	0.91 (0.42–1.98)
Dyes	1.20 (0.30–4.98)	1.03 (0.26–4.02)
Formaldehyde	1.24 (0.67–2.32)	0.71 (0.34–1.43)
Glues	1.75 (0.91–3.47)	1.30 (0.61–2.76)
Other chemicals ^d	2.37 (0.99–6.28)	2.36 (0.92–6.08)
Motor fuel and oil	1.79 (1.16–2.82)	1.33 (0.81–2.20)
Paints and varnishes	2.00 (1.10–3.74)	1.32 (0.67–2.57)
Resins	0.62 (0.22–1.61)	0.41 (0.14–1.21)
Heat		
Solar	1.83 (1.09–3.16)	1.20 (0.67–2.14)
Industrial	3.07 (1.64–6.08)	2.21 (1.12–4.33)

^{b c d} See Table 1 for definitions.

in results. In particular, wood dust results were essentially unaffected (OR = 1.22, $P = 0.0057$, 95% CI: 1.05–1.42), while the estimated effect size for industrial heat was slightly attenuated, with concomitant increase in P -value to a conventionally suggestive level (OR = 1.18, $P = 0.071$, 95% CI: 0.98–1.41).

Discussion

Since the nasopharynx serves to trap primarily medium size particles (5–10 μm) in inspired air²⁵ and absorbs soluble chemicals, inhaled carcinogens are biologically plausible risk factors for NPC. Dust particles from wood, metal, construction sites, tin mining, talc, and textiles, and smoke particles from incomplete combustion of wood and other materials, all occur frequently in Malaysian occupational environments and are of sizes and weights deposited mostly in the nasopharynx. Several studies¹³ have associated wood dust with adenocarcinoma of the nasal cavities and paranasal sinuses, and in 1994 the International Agency for Research on Cancer (IARC)²⁶ classified wood dust as a human carcinogen. Demers *et al.*²⁷ performed a pooled analysis of data from one UK and four US cohort studies on wood dust, and found excess NPC among furniture and plywood workers. But evidence relating NPC to other occupational risk factors has remained less clear. In California, Henderson *et al.*⁹ found NPC significantly associated with fumes, smoke,

and chemicals, but not with dusts. In Malaysia, Armstrong *et al.*² found dose-response relationships of NPC to dust and smoke, but not to chemicals. In China, Ning *et al.*⁷ associated NPC with smoke, dust, and chemical fumes, as did Yu *et al.*⁴ in Hong Kong residents <35 years of age. Chen *et al.*¹⁰ found an association in Taiwan with smoke but not dust, as did Yu *et al.*¹¹ in China. West *et al.*¹² found an association in the Philippines with dust and engine exhaust. Domestic exposures to smoke from burning wood, incense, or anti-mosquito coils are suggested risk factors for which case-control studies provide little support.¹³ An exception is the finding by West *et al.*¹² in the Philippines of an association with anti-mosquito coils.

Our results confirm earlier observations that NPC in Malaysia is crudely associated with occupational exposures to chemical fumes, smoke and dusts, particularly from wood and metals. The persistence of the association with wood dust after adjustment for cigarette smoke, diet, and social class, strengthens the epidemiologic plausibility of a causal pathway involving that exposure. However, cigarette smoke and diet partially confounded the relationships of NPC to other inhalants. We did not find dose-response effects of other inhalants with substantial explanatory power beyond that of presence or absence. This leaves open the question of whether these inhalants are biologically active contributors or simply common companions of other active agents.

Formaldehyde has been suggested as a possible cause of NPC since 1980, when animal studies showed that high doses cause nasal and paranasal cancers in rats. Epidemiological studies have since sought associations between occupational exposure to formaldehyde and various cancers in low-risk NPC populations in Europe and North America. Most of these found an elevated risk for NPC in association with formaldehyde,^{19,28–30} but not all.³¹ The evidence for an association between NPC and formaldehyde has recently been reviewed by the US Agency for Toxic Substances and Disease Registry.³² In 1987, the US Environmental Protection Agency,³² and in 1995 the IARC,²⁶ classified formaldehyde as probably carcinogenic for humans.

In moderate-risk populations, to date the only case-control study to report an association between NPC and formaldehyde is that by West *et al.*,¹² in a non-Chinese Filipino population. Using occupational histories of 257 subjects, of whom 60 (23.3%) were exposed to formaldehyde, they found OR of 3.5 for cases first exposed 25 or more years prior to NPC diagnosis, and 3.2 for cases first exposed before the age of 25, relative to those never exposed. These analyses incorporated a 10-year latency period. In contrast, our study in Malaysia is the largest case-control investigation of the formaldehyde-NPC relationship in a high-risk population, and conveys no suggestion that occupational exposure confers NPC risk. Other differences between our data and those of West *et al.*, e.g. regarding consumption of salted and fresh fish, suggest that these populations may indeed differ with respect to NPC risk factors. However, we identified formaldehyde exposure in only 51 of 564 subjects (9.0%) of our Malaysian Chinese sample, of whom only eight had accumulated ≥ 10 years of exposure outside a 10-year latency period. The Malaysian occupations included those where exposure to formaldehyde would be expected, namely: adhesives, foundries, latex processing, metalworking and welding, plywood manufacture, rubber tire manufacture, sawmilling, shoe making (glues), and textiles (permanent press fabrics). Furthermore,

Table 4 Logistic regression odds ratios (OR) for tenfold exposure increase with and without adjustment for diet and cigarette smoke indices

Agent	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P for diet and cigarette smoke adjusted OR ^a
Dusts			
Construction	1.14 (1.02–1.26)	1.06 (0.93–1.20)	0.37
Fertilizer	0.98 (0.64–1.49)	0.82 (0.51–1.32)	0.41
Metal	1.18 (1.02–1.37)	1.14 (0.96–1.35)	0.11
Talc	1.14 (0.86–1.51)	0.86 (0.61–1.21)	0.39
Tin	1.19 (0.90–1.56)	1.16 (0.83–1.61)	0.37
Textile	1.14 (0.96–1.36)	1.16 (0.94–1.42)	0.16
Wood	1.29 (1.13–1.46)	1.24 (1.07–1.44)	0.0018
Other ^b	1.09 (1.00–1.20)	1.07 (0.96–1.19)	0.23
Fumes			
Cooking	1.09 (0.91–1.31)	0.97 (0.78–1.21)	0.80
Engine exhaust	1.01 (0.91–1.12)	1.00 (0.88–1.14)	0.96
Wood	1.20 (0.97–1.49)	1.08 (0.84–1.38)	0.54 ^e
Other ^c	1.22 (1.02–1.45)	1.12 (0.91–1.39)	0.27
Chemicals			
Biocides	0.98 (0.80–1.20)	0.93 (0.74–1.17)	0.40
Dyes	1.13 (0.80–1.58)	1.07 (0.73–1.58)	0.71
Formaldehyde	1.04 (0.86–1.27)	0.88 (0.70–1.12)	0.29
Glues	1.16 (0.97–1.38)	1.09 (0.88–1.34)	0.40
Other chemicals ^d	1.24 (0.99–1.55)	1.20 (0.92–1.56)	0.15
Motor fuel and oil	1.15 (1.02–1.30)	1.05 (0.91–1.22)	0.50
Paints and varnishes	1.19 (1.03–1.38)	1.08 (0.91–1.29)	0.35
Resins	0.84 (0.65–1.08)	0.74 (0.54–1.01)	0.047
Heat			
Solar	1.14 (1.01–1.29)	1.02 (0.89–1.18)	0.74
Industrial	1.33 (1.13–1.56)	1.21 (1.01–1.45)	0.025

^{a b c d} See Table 1 for definitions.

^e Statistically significant quadratic effect; see text.

confidence intervals for formaldehyde OR from these two studies overlap substantially, so the apparent differences may not be material. Considerably more data are needed to resolve the formaldehyde question.

In 1991–1992, we carried out baseline sampling of ambient air in 42 work sites in 10 industries in the study area. The industries were selected on the basis of occupational histories of NPC cases recorded in this and two previous Malaysian studies.^{2,14} Air particle sampling confirmed the presence of high-risk pollution for the nasopharynx of particles with diameter <10 µm in adhesives, metalworking, ricemills, sawmilling, and shoemaking, with mean values exceeding 150 µg/m³ which is the US Environmental Protection Agency's³³ 24-hour ambient air quality standard for PM-10. Formaldehyde levels exceeded the American Conference of Governmental Industrial Hygienists (ACGIH)³⁴ threshold limit value (TLV-Ceiling) of 0.37 mg/m³ in only the adhesives industry but all others had mean 8-hour concentrations between 0.16 and 0.35 mg/m³.

To our knowledge, intense industrial heat has not previously been examined in relation to NPC. Dry heat from sources such as furnaces, welding machines, and rolling mills, combined with the tropical Malaysian climate, yields high working temperatures that may intensify the vulnerability of the nasopharynx to inspired dusts and fumes. The strength of the OR, and the

persistent association after adjustment for other risk factors, indicate that this exposure warrants further investigation.

Analyses of our data by latency time frames of 5, 10, 15 and 20 years prior to diagnosis showed little difference in OR from those based on all exposure at least one year prior to diagnosis. Nor were there important differences by length of exposure (<10 versus ≥10 years), by age of worker (quartiles, and <45 versus ≥45 years), or by Chinese subethnicity. This may indicate short latency and that acute high-level exposures are more dangerous than chronic low-level exposures. Alternatively, this could be due to small numbers of participating pairs in stratified comparisons, or to measurement problems.

Cigarette smoke has been associated with cancers of the oral cavity, respiratory tract, and distant organs. Our data add to an accumulation of evidence associating cigarettes with NPC, and confirm the finding of Yu *et al.*⁵ that exposure to parental smoking during childhood plays a role. Social class has previously been associated with NPC.¹³ In this study, social class does not substantially confound the diet/smoking adjusted relationships to NPC of any of the occupational exposures examined.

Our study, as earlier case-control studies in high-risk NPC populations, is limited by the fairly small numbers of cases and controls reporting various uncommon occupational exposures.

Combined with random exposure measurement and occasional misclassification errors, this may have produced low power to detect statistically significant dose-response relationships. Also, in view of limited power, we did not adjust our significance testing for multiple comparisons; thus, occasional Type I errors would not be surprising. (However, the result for wood dust in Table 4 persists even after Bonferroni adjustment.) On the other hand, although standardized interviews were carried out by trained professional interviewers using structured questionnaires, recall and exposure-suspicion biases may have contributed to the predominance of positive over negative associations in our results. In addition, it should be noted that it is relatively easy to assess wood dust exposure in population-based case-control studies while it is much more difficult to assess formaldehyde exposure, and this may be a factor in our negative findings for the latter. Finally, 24% of the cases we ascertained had died or were too ill for interview at time of contact, most of these being prevalent cases, contributing to a 47% non-participation rate among diagnosed cases. Therefore, we cannot exclude the possibility of prevalence-incidence (Neyman) or other selection biases, though we are unaware of any specific presumptive rationale or evidence for their presence.

In summary, our data support previous findings that some occupational inhalants are risk factors for NPC. The statistical effect of wood dust remained substantial after adjustment for diet, cigarette smoke, and social class. Intense industrial heat emerged as a previously unreported risk factor, statistically significant even after adjustment for diet and cigarette smoke. No association was found between NPC and formaldehyde. Baseline sampling of ambient air conditions in Malaysian worksites confirms the presence of potentially high-risk particle pollution.

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Appendix

In the context of this paper, a conditional logistic regression model adjusting for diet and cigarette smoke, while incorporating exposure time quantitatively, employs a linear predictor $\beta_D z_D + \beta_C z_C + \beta_S x$, where x is an exposure measure (e.g., $\log_{10}(t+1)$), as used for Table 3). Such a model has likelihood function

$$L(\beta) = \prod_{i=1}^n [1 + \exp(\beta_D(z_{iD} - z_{i0D}) + \beta_C(z_{iC} - z_{i0C}) + \beta_S(x_{i1} - x_{i0}))]^{-1}$$

for matched pairs $i = 1$ to n (here $n = 282$), where i indexes the matched pairs, and 1 or 0 in the subscript distinguishes cases from controls.³⁵ Statistical inference for this model is based on the permutation distribution of $L(\beta)$ obtained from joint exchanges, within each of the 2^n possible subsets of pairs, of observed values of the predictor values z_{iD} , z_{iC} , and x_{i1} for a case

with the predictor values z_{i0C} , z_{i0C} , and x_{i0} for the corresponding matched control. The adjusted sign test is obtained by simply replacing $\beta_S(x_{i1} - x_{i0})$ in $L(\beta)$ by $\beta_S s_i$, where $s_i = \text{sign}(x_{i1} - x_{i0})$, and $\text{sign}(x_{i1} - x_{i0}) = 1$ if $x_{i1} > x_{i0}$, $= 0$ if $x_{i1} = x_{i0}$, and $= -1$ if $x_{i1} < x_{i0}$. Note then that if $L(\beta)$ is the correct specification of the conditional likelihood, then $\beta_S = 0$ implies that $\beta_S = 0$ in the modified likelihood

$$L^*(\beta) = \prod_{i=1}^n [1 + \exp(\beta_D(z_{iD} - z_{i0D}) + \beta_C(z_{iC} - z_{i0C}) + \beta_S s_i)]^{-1},$$

which then is identical to $L(\beta)$. Thus, a test of $\beta_S = 0$ in $L^*(\beta)$ is also a test of $\beta_S = 0$ in $L(\beta)$. The usual null large-sample chi-square distribution of the likelihood ratio statistic applies because its derivation is conditional on the values of the predictors, and does not depend on the manner of their assignment.