Acta Oncologica Vol. 33, No. 8, pp. 867–872, 1994

EPSTEIN-BARR VIRUS INFECTION, SALTED FISH AND NASOPHARYNGEAL CARCINOMA

A case–control study in Southern China

XI ZHENG, LUO YAN, BO NILSSON, GUNNAR EKLUND and BÖRJE DRETTNER

Two hundred and five histologically confirmed cases of nasopharyngeal carcinoma (NPC) in southern China, and an equal number of matched controls, were investigated for their dietary habits, occupational exposure, use of tobacco and alcohol, history of relatives with NPC, and IgA against Epstein-Barr virus (EBV) capsid antigen (IgA/VCA). Positive IgA/VCA and intake of salted fish were associated with a strong excess risk of NPC. The association persisted after adjustment for other factors. The combination of salted fish and EBV was strongly associated with NPC, and more so than EBV or salted fish per se. Multivariate analyses showed that IgA/VCA was the most important predictor of NPC, and salted fish the second most important. These results suggest that EBV has a strong effect on the development of NPC. The exclusion of EBV and genetic factors in earlier epidemiological studies may have resulted in an overestimation of salted fish as important etiological factor causing NPC.

Nasopharyngeal carcinoma (NPC) shows great variations between different ethnic populations (1). It is a rare cancer among whites in Europe and North America. In contrast, NPC is common in certain areas of southern China, particularly in the Cantonese population of the central Guangdong province. The age-specific mortality rate of NPC is very high in the Guangdong, Guangxi and Fujian provinces in the coastal region of southern China (2). In a report from the city of Guangzhou, southern China, NPC constituted 32% of all cancers and 78% of all cancers in the head and neck area (3).

Epstein-Barr virus (EBV) is believed to be closely associated with NPC since the viral genomes are regularly found in NPC biopsies by DNA hybridization (1, 4) and EBV-related antigens have been demonstrated in the tumor cells of NPC (5), suggesting that EBV infection in nasopharyngeal epithelium may be a prerequisite for the development of NPC. Moreover, sera from patients with NPC contain high titers of antibodies to EBV-related antigens (1, 4). In a population screening of 42 048 subjects in southern China, 2 823 persons were found to be seropositive for IgA/VCA. During the 2-year follow-up, 41 cases of NPC were found among the seropositive persons (6). This finding suggests that IgA/VCA, which may be produced by the nasopharyngeal lymphoid tissue against EBV infection in the nasopharynx (1, 4, 7), is a biomarker associated with risk of NPC development.

Genetic factors have also been implicated in the etiology of NPC, a disease that occurs relatively more often in the Chinese population even after emigration from China. Offsprings of marriages between southern Chinese and non-Chinese groups show an intermediate incidence (8), and families with multiple cases of NPC have been reported (9, 10). Moreover, certain HLA profile has been found to be associated with increased risk of NPC (11).

In the early 1970s, Ho (12) suggested that the consumption of salted fish, a traditional southern Chinese food speciality favored by the Cantonese, might be a risk factor

Received 7 February 1994.
Accepted 10 May 1994.
From the Departments of Otolaryngology (X. Zheng, B. Drettner), Huddinge University Hospital, Karolinska Institute, 141 86 Huddinge, Sweden, Cancer Epidemiology (B. Nilsson, G. Eklund), Karolinska Hospital, Stockholm, Sweden and Otolaryngology (Y. Luo), Guangdong Provincial People's Hospital, Guangzhou, People's Republic of China.
Correspondence to: Professor Börje Drettner, Department of Otolaryngology, Huddinge University Hospital, Karolinska Institute, S-141 86 Huddinge, Sweden.

 ISSN 0284-186X

for NPC. Several case–control studies have since then been performed among Chinese populations originating particularly from southern China. In Malaysia, Hong Kong and the Guangxi province of China, consumption of salted fish has been found to have a significant association with NPC (13–15). More recently, a case–control study from Guangzhou, southern China, showed that exposure to salted fish was significantly associated with an increased risk of NPC, but the relative risk (RR) was lower than that reported in the authors' previous study in Hong Kong (16). However, as pointed out by the IARC working group, none of these early case–control studies on NPC and consumption of salted fish examined the concomitant role of EBV infection (17). Thus, an epidemiological study covering the main suspected risk factors and performed in the area with the highest incidence of NPC is highly relevant.

The present epidemiological study was performed in the city of Guangzhou and seven surrounding counties, situated in that province of China which has the highest NPC mortality rate. The aim of the study was to compare several possible risk factors, isolated and simultaneously, in order to determine which of them were the most important for the development of NPC in a high risk area and, furthermore, to analyse the correlation and possible synergetic effect between EBV and salted fish.

Material and Methods

We studied histologically confirmed cases of NPC among the residents of the city of Guangzhou and seven surrounding counties covering a total population of 7 million people. The cases were identified from the files of the Guangdong Provincial People's Hospital, Guangzhou, China. The patients were aged 55 years or below at the time of diagnosis. We attempted to contact all eligible patients diagnosed between November 1, 1985 and November 1, 1988. Of 232 eligible cases identified, 26 had died and one could not be located. We interviewed the remaining 205 cases.

For each case a control was selected. This control was usually a friend of the case living in the same area, and of the same sex and age (± 5 years) as the case. If no such friend could be recommended or in the uncommon situation when the friend refused to participate, we selected as control a person who lived in the same area, and had the same sex and age as the case. This was done with the help of Street Committees, Factory Health Stations and Village Authorities. We also interviewed the surviving mothers of each case and control. Twenty-three case mothers had died and 5 did not reside in the Guangzhou area any more. Five control mothers had died and 3 did not reside in the Guangzhou area. All interviews were conducted between September 1987 and January 1989 in the homes of the participants.

One questionnaire was used for cases and controls and another for the corresponding mothers. The questionnaire given to cases and controls concerned occupation, date of birth, ethnic origin, relatives with cancer, food and drinking habits, living conditions, smoking and alcohol habits, types of cooking fuel, occupational and environmental exposure to smoke, dust, fumes or other chemical products, and diseases during childhood. For all cases and controls the questions concerned two periods of life: the last 7 years and the age of 10. The questions to the mothers covered the first 3 years of life and the age of 10, and they concerned ethnic origin, smoking, drug intake and diseases of the mothers during pregnancy, breast feeding and remedies for weaning, diseases in childhood, and food and drinking habits of the cases and controls. Five frequency categories (never: fewer than five times in lifetime; yearly: once a year to less than once a month; monthly: once a month to less than once a week; weekly: once a week to less than daily; daily: every day) were used to describe the consumption frequency of 37 food items. The subjects were asked to choose the category that best described their food consumption.

The cases were subjected to serological IgA/VCA test and the controls were also asked to undergo this test. In all, 203 cases and 163 controls were tested while 42 controls refused to be tested. IgA/VCA was measured by the immunoperoxidase method (18). In brief, cell smears were prepared from B95-8 (VCA expressing B cell line immortalized by EBV) cultures and fixed in acetone. Sera diluted to 1:5 were added to separate wells of slides. The slides were incubated at 37°C for 30 min, then incubated with peroxidase-conjugated rabbit anti-human IgA antibody in an appropriate dilution for 30 min and developed in a substrate solution containing DAB (3,3′-diaminobenzidine tetrahydrochloride) and H_2O_2 for 10 min. Between each step, slides were washed 3 times with phosphate-buffered saline (PBS). A serum was considered positive if the cells in the well that contained the 1:5 dilution showed the brown colour characteristic of this test. If the sera diluted 1:5 showed a positive reaction they were tested in further dilution. The highest dilution of serum still positive for IgA antibody to VCA was considered as the antibody titer of that serum.

Binomial sign test (two-sided) and t-test (comparisons between cases and controls regarding variables not presented in the tables) were performed (19). Confidence intervals for OR-values according to Thomas (20) were estimated. Multivariate analyses were performed by conditional logistic regression on the matched pairs (21). For each studied variable, odds ratios (estimates of OR) and their corresponding p-values were calculated. In order to compare the impact of salted fish consumption and of IgA/VCA (EBV indicator) on the development of NPC and the possible synergetic effect between these two factors, a representative parameter of the highest intake of salted fish was produced. The five salted fish consumption variables in the three time periods investigated were taken together and the highest frequency was identified and referred to as Maximum Salted Fish (MAXSF).

Results

Of 205 cases and 205 controls interviewed, 141 (69%) were males and 64 (31%) were females. The mean age at diagnosis of cases was 40.2 years (SD = 7.8) and that of controls at the time of interview was 40.0 (SD = 7.8).

Table 1 shows that for 191 of 203 cases IgA/VCA was positive, and that 11 of 163 IgA/VCA tested controls were positive. The difference is strongly significant ($p < 0.001$) and the OR value is estimated at 220 (95% CI: 94–516). Among the IgA/VCA positive subjects the titer of the antibody ranged between 1:5 and 1:1 280 with a geometric mean titer value of 43.2. The IgA/VCA titer in the controls ranged from 1:5 to 1:20 with a geometric mean of 6.4. The difference in the geometric mean of IgA/VCA between cases and controls was strongly significant ($p < 0.001$). No less than 131 titer values from the 203 cases were found in the interval 1:40 to 1:1 280, but none among the 163 controls.

Table 2 shows a significant difference in the intake of salted fish between cases and controls during the last 7 years as well as at the age of 10. The consumption frequency of salted fish, both tough and soft meat, in the first 3 years of life as reported by mothers was significantly higher among cases compared to controls ($p < 0.001$). The OR values indicate that a high intake of salted fish was associated with an excess risk of NPC. As expected, a significant difference was obtained in MAXSF between cases and controls ($p < 0.001$). We questioned both the mothers and the subjects about consumption of salted fish at the age of 10 and the results were very similar. The attributable fraction (21) was considerable. If the distribution of salted fish consumption for the controls was regarded as being valid for the entire population this fraction for MAXSF was estimated to be 73%. However, the corresponding fraction for IgA/VCA was 94%.

NPC was significantly related to consumption of a number of other food items, drinking of polluted water and chemical exposure (data not shown). The association was weaker than for salted fish. Besides, fresh fruit consumption was significantly more common in controls than in cases during the past 7 years ($p < 0.05$) but not in other time periods. Pharyngitis at the age of 10 showed a weak case-positive relation to NPC ($p < 0.05$). Other food items which were reported by cases, controls and their mothers did not show any significant difference in consumption

Table 1

Comparison of EBV indicator (IgA/VCA) in cases and controls

IgA/VCA titer values	No. of cases	No. of controls	OR	95% CI
Negative	12	152	1.00	
1:5	13	8		
1:10	19	2		
1:20	28	1		
1:40	51	0		
1:80	54	0	220*	(94–516)
1:160	11	0		
1:320	12	0		
1:640	1	0		
1:1 280	2	0		
Missing	2	42		
Total	205	205		

* IgA/VCA positive subjects with different titers were taken together for calculating the OR value.

Table 2

Comparison of salted fish consumption and MAXSF between cases and controls

	No. of cases	No. of controls	OR	95% CI
SFTM[1] the last 7 years				
Never and yearly	104	160	1.0	
Monthly	57	39	2.2	(1.4–3.6)
Weekly and daily	44	6	11.2	(4.6–32)
SFTM at the age of 10				
Never and yearly	38	95	1.0	
Monthly	62	81	1.9	(1.1–3.3)
Weekly and daily	105	29	9.1	(5.1–16.4)
SFSM[2] the last 7 years				
Never and yearly	126	181	1.0	
Monthly	55	22	3.6	(2.0–6.5)
Weekly and daily	24	2	17.2	(4.1–152.1)
SFSM at the age of 10				
Never and yearly	71	146	1.0	
Monthly	65	45	3.0	(1.8–4.0)
Weekly and daily	69	14	10.1	(5.2–20.7)
SF at first 3 years[3]				
Never and yearly	35	102	1.0	
Monthly	49	74	1.9	(1.1–3.4)
Weekly and daily	67	19	12.9	(5.2–20.6)
MAXSF[4]				
Never and yearly	19	70	1.0	
Monthly	53	97	2.0	(1.1–3.8)
Weekly and daily	133	38	12.9	(6.9–24.0)

[1] The salted fish tough meat (SFTM) is prepared by salting raw marine fish in covered wooden vat for about one week and then drying under sunlight for another week depending on the size of the fish and the weather.

[2] The salted fish soft meat (SFSM) is prepared by decompositing the fish so that it becomes soft before the salting procedure. Afterwards, the fish undergo the salting and drying procedure.

[3] Salted fish (SF) both tough meat and soft meat consumption reported by case-mothers and control-mothers.

[4] The five salted fish consumption variables in the three time periods investigated were taken together and the highest frequency was identified and referred to as MAXSF.

Table 3

Reported history of relatives with tumor among cases and controls

	No. of cases	No. of controls	OR	95% CI
No recording of tumor among relatives	133	197	1.0	
Relatives with tumor[1]	72	8	13.3	6.1–32.9
Relatives with NPC[2]	49	4	15.8	5.6–61.2
First degree relatives with NPC[3]	29	2	16.7	4.1–145.2
Father/mother with NPC	12	1	12.7	1.8–544.8
Brother/sister with NPC	16	1	17.3	2.6–727.7

[1] Including NPC and other types of tumors. Tumors other than NPC is recorded in 23 cases and in 4 controls, OR = 8.5.
[2] Including first degree of relatives and other relatives with NPC.
[3] Including parents, siblings and children.

frequency for any of the time periods investigated. Other living conditions were quite similar between cases and controls. Neither was there any difference between cases and controls in exposure to environmental air pollution, kind of cooking fuel, smoking habits (including smoking time and quantity) and alcohol habits nor in occupational exposure (dust and smoke). A history of NPC among first degree relatives (parents and siblings) was also a significant risk factor for NPC (Table 3). Twenty-nine cases as compared with 2 controls reported such a history ($p < 0.001$). However, none of these factors had a significant association with NPC after adjusting for IgA/VCA and salted fish intake (model 4 in Table 4).

Conditional logistic regression analysis was used to examine the effects of a number of factors on NPC including IgA/VCA, individual food factors, drinking of polluted water, chemical exposure and history of relatives with NPC (Table 4). In model 1 only MAXSF was studied. A high excess risk was found for weekly and daily intake of salted fish. After MAXSF was included in the analysis none of the other indicators of salted fish reached significance level. Even in models 2–4, in which an EBV indicator was included, MAXSF was found to have almost the same OR-estimates as in model 1. In models 2 and 3, where a dichotomous and a continuous IgA/VCA predictor was added respectively to MAXSF, the high OR-values for IgA/VCA were striking but not of the same magnitude as in Table 1. In model 4 the predictor 'relatives with NPC' was added. It was non-significant with an OR value of 9.3 and a broad confidence interval. In addition, drinking of polluted water and other food and environment predictors were given a chance to be included in the model if in the stepwise analysis they had reached significance at the level of $p < 0.15$. None of them, however, reached this modest significance level. The estimates of OR for IgA/VCA in its dichotomous form are vulnerable. In Table 1, OR is 220, but in Table 4 below 60 in models 2 and 4. This reduction in the multivariate analyses could be caused by the inclusion of MAXSF, but further analysis (Table 5)

Table 4

Multiple logistic regression analyses based on matched pairs of cases and controls

	Model 1 (205 pairs)			Model 2 (162 pairs)			Model 3 (162 pairs)			Model 4 (162 pairs)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
MAXSF												
Never + yearly	1.0			1.0			1.0			1.0		
Monthly	1.9	(0.9–3.7)		1.9	(0.2–17)		2.2	(0.2–29)		2.1	(0.2–21)	
Weekly	20	(7.5–52)		17	(1.2–261)		19	(0.6–641)		17	(1.1–260)	
Daily	296	(33–2 700)	<0.001	267	(3.1–22 900)	<0.01	2 630	(0.0–∞)	NS[1]	203	(2.0–20 500)	<0.05
IgA/VCA												
Negative				1.0						1.0		
Positive				59	(12–295)	<0.001			NS	55	(11–276)	<0.001
IgA/VCA titer step[2]							6.7	(2.1–21.3)	<0.01			
First degree of relatives with NPC												
No										1.0		
Yes										9.3	(0.2–475)	NS
SF in Table 2[3]			NS			NS						
Other factors[4]												NS

[1] NS = non-significant
[2] IgA/VCA titer values in Table 1 treated as equidistant with one unit between succesive steps.
[3] SF, salted fish consumption frequencies except for MAXSF as shown in Table 2.
[4] Other factors: individual food factors, drinking of polluted water and chemical exposure.

Table 5

Distribution of IgA/VCA and MAXSF among cases and controls

IgA/VCA MAXSF	No. of cases	No. of controls	OR[1]	OR[2]	95%CI[1]	95%CI[2]
Negative, never + yearly	2	49	1.0	1.0		
Negative, monthly	1			11		
Negative, weekly + daily	6	26	5.6	5.6	(1.1–42.2)	(1.1–42.2)
Positive, never + yearly	14	5	1.0	69		(12.0–489)
Positive, monthly	39	4	3.5	239	(0.8–16.1)	(41.8–1647)
Positive, weekly + daily	100	2	18	1 225	(3.1–138)	(166–9508)

[1] In the IgA/VCA negative group, 'never + yearly' served as reference; in the IgA/VCA positive group, 'never + yearly' served as reference.
[2] 'Never + yearly' in IgA/VCA negative group served as reference.

showed that MAXSF and IgA/VCA were weakly negatively correlated. Furthermore, it is evident that the confidence interval for the OR values became broader after inclusion of more than one of the three factors: IgA/VCA, MAXSF, and relatives with NPC.

In Table 5 the 162 matched pairs included in models 2–4 in Table 4 were separated. From Table 5 it is evident that only 3 cases had negative IgA/VCA values combined with low consumption frequency of salted fish (never, yearly or monthly), whilst no less than 125 controls showed such a relation. Furthermore, Table 5 shows that only 2 positive IgA/VCA controls had weekly or daily intake of salted fish against 100 cases. Positive IgA/VCA combined with at least monthly intake of salted fish was associated with a considerable excess risk of contracting NPC (139 of 162 cases in Table 5 belonged to this group). Further analysis showed that in model 2 the logistic-linear analysis led to sufficient goodness of fit, and from Table 5 it is evident that an additive model is not in agreement with the observations. A synergetic effect on NPC from positive IgA/VCA and high intake of salted fish is thus corroborated.

Discussion

EBV and salted fish consumption have been found separately to be associated with NPC, but no previous epidemiological studies have combined these two factors into a simultaneous analysis. As a first approach to compare these two suspected risk factors and study their possible synergetic effect, we included IgA/VCA, salted fish consumption and reports of relatives with NPC in a multivariate analysis.

Prospective seroepidemiological studies have demonstrated that IgA/VCA is associated with a risk of developing NPC (22–24). The presence of a close association between IgA/VCA and NPC was also found in the present case–control study. Since IgA/VCA in NPC patients was tested at the time of diagnosis, we had access only to the later values but not to the values at the time before clinical onset of NPC. IgA/VCA can rise from 9 months to 9 years prior to the clinical onset of NPC and a variation of antibody titers have been reported (24). Therefore, a dichotomous form of IgA/VCA (positive versus negative status of IgA/VCA) seems to better reflect the early presence of local immune reaction to activated viral infection in the nasopharynx prior to the clinical onset of NPC.

In the present study, we also found a significant association between salted fish and NPC, and the association persisted when the dichotomous form of IgA/VCA was included in the multivariate analysis. Furthermore, if a genetic factor (indicated as a history of first degree relatives with NPC) was included in the multivariate analysis, the significance level was less evident. This finding suggests that the association between salted fish intake and NPC might have been overestimated in previous studies because EBV and the genetic factor were not taken into consideration. EBV infection exists worldwide, and IgA/VCA is also found in other EBV related diseases, but NPC has one of the most marked geographical and racial distributions of all cancers, indicating that some other cofactors must be present. Extract of salted fish has been shown to activate EBV in Raji cells (latent EBV infected cell line) (25) suggesting that salted fish might be such a cofactor. The results from Tables 4 and 5 suggest a synergetic effect between salted fish and EBV. This may support the hypothesis of a biological interaction between salted fish and EBV, presuming a causal relationship and the fact that IgA/VCA in a dichotomous form is an indicator of earlier presence of positive EBV.

A history of NPC cases among first degree relatives has previously been found to be a risk factor for NPC. Yu et al. found that 5.9%–7.2% of NPC cases compared with 1%–1.6% of controls had such reports (10, 14). Our data, including about 14% of cases and 1% of controls with such reports, are similar to the previous findings that a history of NPC among first-degree relatives is a risk factor for NPC at least if the IgA/VCA is not taken into consideration. It is evident that genetic factors might be of importance for the etiology of NPC. Thus, it is shown in Table 3 that almost 24% of the NPC cases reported that they had at least one relative with NPC, against only 2% of the controls. However, the small number of controls with NPC-relatives makes the coefficients of salted fish, IgA/VCA and the genetic factor uncertain. It is possible that the cases are more anxious and better informed about NPC among relatives than controls. Moreover, ignorance may in fact hamper the reporting of NPC among relatives. Other genetic markers such as HLA type (11) need to be further investigated in multivariate analysis to study their correlation to EBV and salted fish.

In the present study, many suspected confounders were collected and they have been allowed for in the logistic regression analysis. The inclusion of candidate confounders, such as water pollution, other salted foods, etc. has followed the stepwise regression analysis (significance $p < 0.05$ required). Almost 25 variables were included in the multivariate analyses and the MAXSF still reached the same OR value. An important objection remains: hidden confounders might be present.

The hypothesis that salted fish is of etiological relevance for NPC has received new, additional support in the present study under the presumption that IgA/VCA is a causal factor of NPC. If this presumption is abandoned and IgA/VCA is instead regarded as an effect of NPC and thus not of etiological relevance, the indisputable correlation between salted fish and NPC can be given contradictive interpretations. One interpretation is that salted fish is a genuine causal factor, another that there is no such factor at all. Thus, by rather simple assumptions it can be claimed that the genetic factor can replace salted fish as an etiological factor and that the attributability of the genetic factor to NPC could reach a level higher than 80%. The difficulty of separating genetic and environmental factors is a well known problem in epidemiological studies. It is surprising that earlier case–control studies have failed to observe that the genetic factor might be such a dominating confounder that the correlation between salted fish and NPC might be interpreted as a spurious correlation. In order to clear up the central question of causality between IgA/VCA and NPC, a study comprising siblings to randomly chosen cases would provide valuable information.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Swedish Agency for Research Cooperation with Developing Countries (SAREC) and the Wennergren Center Foundation.

REFERENCES

1. De-Thé G, Ho JHC, Muir CS. Nasopharyngeal carcinoma. In: Evans AS, ed. Viral infection of humans, epidemiology and control. New York: Plenum Publishing Corporation, 1989: 737–67.
2. Sham JST, Poon YF, Wei WI. Nasopharyngeal carcinoma in young patients. Cancer 1990; 1: 2606–10.
3. Li CC, Yu MC, Henderson BE. Some epidemiologic observations of nasopharyngeal carcinoma in Guangdong People's Republic of China. Natl Cancer Inst Monogr 1985; 69: 49–52.
4. Klein G. The relationship of the virus to nasopharyngeal carcinoma. Progr Exp Tumor Res 1978; 21: 340–50.
5. Lung ML, Chan KH, Lam WP, et al. In situ detection of Epstein-Barr virus markers in nasopharyngeal carcinoma patients. Oncology 1989; 46: 310–7.
6. Zong YS, Jonathan STS, Ou XT, et al. Immunoglobulin A against viral capsid antigen of Epstein-Barr virus and indirect mirror examination of the nasopharynx in the detection of asymptomatic nasopharyngeal carcinoma. Cancer 1992; 69: 3–7.
7. Miller G. Epstein-Barr virus: biology, pathogenesis, and medical aspects. In: Fields BN, Knipe DN, eds. Virology. Second edition. New York: Raven Press, 1990: 1921–58.
8. Andersson-Anvret M, Forsby N, Klein G. Nasopharyngeal carcinoma. Progr Exp Tumor Res 1978; 21: 100–16.
9. De-Thé G. The Chinese epidemiological approach of nasopharyngeal carcinoma research and control. Yale J Biol Med 1981; 54: 33–9.
10. Yu MC, Garabrant DH, Huang TB, et al. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. Int J Cancer 1990; 45: 1033–9.
11. Lu SJ, Day NE, Degos L, et al. Linkage of a nasopharyngeal carcinoma susceptibility locus to the HLA region. Nature 1990; 346: 470–1.
12. Ho JHC. Nasopharyngeal carcinoma (NPC). Adv Cancer Res 1972; 15: 57–92.
13. Armstrong RW, Armstrong MJ, Yu MC, et al. Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. Cancer Res 1983; 43: 2967–70.
14. Yu MC, Ho JHC, Lai SH, et al. Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: Report of a case–control study in Hong Kong. Cancer Res 1986; 46: 956–61.
15. Yu MC, Mo CC, Chong WX, et al. Preserved foods and nasopharyngeal carcinoma: A case–control study in Guangxi, China. Cancer Res 1988; 48: 1954–9.
16. Yu CC, Huang TB, Henderson BE. Diet and nasopharyngeal carcinoma: a case-control study in Guangzhou, China. Int J Cancer 1989; 43: 1077–82.
17. IARC. Salted fish. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals of humans. Vol. 56, Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. Lyon: IARC, 1993: 41–82.
18. Zeng Y, Liu Y, Liu C, et al. Application of an immunoenzymatic method and an immunoautoradiographic method for a mass survey of nasopharyngeal carcinoma. Intervirology 1980; 13: 162–8.
19. Siegel N. Nonparametric statistics. London: McGraw-Hill, 1956: 63–7.
20. Thomas DG. Exact and asymptotic method of the combination of 2 × 2 tables. Comput Biomed Res 1975; 8: 423–46.
21. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. IARC Sci Publ 32, Lyon: IARC, 1980.
22. Zeng Y, Zhang LG, Wu YC, et al. Prospective studies on nasopharyngeal carcinoma in Epstein-Barr virus IgA/VCA antibody-positive persons in Wuzhou city, China. Int J Cancer 1985; 36: 545–7.
23. Chan CK, Mueller N, Evans A, et al. Epstein-Barr virus antibody patterns preceding the diagnosis of nasopharyngeal carcinoma. Cancer Causes Control 1991; 2: 125–31.
24. De-Thé G, Desgranges C, Zeng Y, et al. Search for pre-cancerous lesions and EBV markers in the nasopharynx of IgA positive individuals. In: Grundmann E, Krueger GRF, Ablashi DV, eds. Nasopharyngeal carcinoma. New York: Gustav Fischer Verlag Stuttgart, 1981: 111–7.
25. Shao YM, Poirier S, Ohshima H, et al. Epstein-Barr virus activation in Raji cells by extracts of preserved food from high risk areas for nasopharyngeal carcinoma. Carcinogenesis 1988; 9:455–7.