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Identification of Risk Factors Associated with Nasopharyngeal Carcinoma (NPC) in the Pahang State of Malaysia Hospitals

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is the fifth most common cancer reported in Malaysia. Although several studies on NPC have been carried out, the risk factors associated with NPC in Malaysia are unknown. Therefore, this study was designed to investigate the risk factors associated with NPC cases in Pahang state.

Methods: NPC cases that were diagnosed between 2012 and 2017 were recruited from two referral hospitals in Pahang. An interview was conducted using adapted questionnaires, which included demographic data, family history of cancer, and lifestyle. The data were analyzed statistically to identify the associations between the selected variables and NPC.

Results: A total of 71 NPC cases and 81 control subjects were recruited from the hospitals. Multivariate analysis showed that a family history of NPC and current smoking were significantly associated with the risk of NPC ($p < 0.05$). Further analysis revealed a significant association between the risk of NPC in smokers with no family history of NPC ($p < 0.05$).

Conclusions: This study suggests that family history and smoking are factors associated with the development of NPC in Pahang, which was consistent with previous studies.

Keywords: Malaysia, nasopharyngeal carcinoma, risk factors, smoking

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor that arises from the nasopharyngeal epithelial cells, usually at the pharyngeal recess. The World Health Organization has classified NPC into the keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, and non-keratinizing undifferentiated or poorly differentiated carcinoma subtypes.[1,2]

The interplay between genetic susceptibility factors and Epstein-Barr virus (EBV) infection are crucial drivers in the etiology and pathogenesis of NPC. Particular environmental agents have also been implicated in the multistep tumorigenic process of NPC, albeit more evidence is required for a better understanding.[1] A hypothetical model proposed by Wong *et al.*[1] suggests that genetically susceptible nasopharyngeal cells may undergo malignant transformation upon acquisition of a persistent latent EBV infection and expression of various viral oncogenic proteins and non-coding RNAs, which enable cellular transformation and clonal expansion.

Patients with NPC commonly present with nasal symptoms, such as nasal obstruction and a blood-tinged nasal discharge. These symptoms may be accompanied by otological symptoms, such as conductive hearing loss and tinnitus; neurological symptoms, such as intracranial extension; and nodal involvement, including the presence of a neck mass due to enlargement of the neck nodes.[2] Histopathological

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analysis using nasopharyngoscopy and biopsy sampling are commonly used procedures to diagnose NPC. The diagnosis is further refined using an imaging technique, such as computed tomography, magnetic resonance imaging, or positron emission tomography.[2]

NPC is relatively rare in most parts of the world but it has a distinct geographical and racial distribution worldwide and is more common in Asian countries.[3,4] Malaysia is among the countries in Southeast Asia reporting a high incidence of NPC.[3] The 2012–2016 Malaysian National Cancer Registry Report stated that NPC was the fifth most common cancer among Malaysians, particularly men.[5] The high incidence and prevalence of NPC are particularly apparent in the Malaysian-Chinese ethnicity.[5] The Bidayuh, which are native to the Sarawak state of East Malaysia, had the highest prevalence of NPC in any population-based registry in the world between 1996 and 1998.[6] Additionally, the age-standardized rate (ASR) of NPC among Bidayuh between 2007 and 2011 was almost as high as the ASR of a population in China.[7] Although NPC is among the most common cancers in Malaysia, updated studies on the risk factors for NPC are scarce and most of the available data are obsolete.[8]

NPC is a multifactorial disease in which the interaction between EBV infection and genetic and environmental factors, including diet, cigarette smoking, and occupational exposure has been speculated to contribute to the incidence.[4,7] Several studies have reported on the risk factors associated with NPC in the Malaysian population, including occupational inhalants, such as wood dust and industrial heat as well as salt-preserved foods, such as salted fish and eggs, although these reports are obsolete.[9,10] A recent review by Linton *et al*.[7] explained hypothetically that the genetic predisposition and consumption of salt-preserved foods are associated with the incidence of NPC in the Bidayuh. The presence of N-nitrosamines, a known carcinogen in most salt-preserved food has been postulated to be the chemical involved in the development of NPC.[11] Due to the scarcity and obsolete information available on the risk factors of NPC in Malaysia, studies are warranted to obtain a better understanding of the carcinogenesis of NPC. Furthermore, identifying the environmental risk factors for NPC is important to reduce the probability of development. Thus, this study was conducted to identify the risk factors associated with NPC in the Pahang state of Malaysia.

METHODS

This study protocol was reviewed and approved by the Medical Research Ethics Committee (NMRR-15-1976-27156) and International Islamic University Malaysia Research Ethics Committee (IREC 457) before commencing the study. This study was a cross-sectional case-control study. The sample size was calculated using the PS: Power and Sample Size Program version 3.1.2. This study planned to match one case with at least one control subject. The probability of exposure among controls was 0.3.[12] The true odds ratio (OR) for disease in exposed subjects relative to unexposed subjects was set to 2.[12] The calculated sample size was 65 subjects per group using 0.8 power and a type I error rate of 0.05. Considering that non-responses will be excluded from the study, a 10% sampling error was added, resulting in 72 subjects per group.

Seventy-one patients were recruited from two Pahang state referral hospitals, such as Hospital Tengku Ampuan Afzan (HTAA) in the Kuantan district and Hospital Sultan Haji Ahmad Shah (HOSHAS) in the Temerloh district. NPC patients who were newly diagnosed with NPC from January 01, 2012 to December 31, 2017 and had no history of other cancers were traced from the cancer registry of the respected hospital and invited to participate in this study. Eighty-one participants were recruited as a control group and were matched with the case group according to age, gender, and ethnicity. The NPC patients were recruited during their appointments at the respected hospitals. The control subjects were recruited during a blood drive donation at the respected hospitals. The NPC patients and control subjects were physically approached face-to-face and invited to participate in the study voluntarily. They were briefed about the study, including information on confidentiality of their personal information and the right to withdraw from the study. Consent forms were given to the subjects who agreed to participate voluntarily in the study and share their information with the research team. Written informed consent was obtained from the subjects before the study was initiated.

A face-to-face interview was conducted with the eligible subjects to collect data using a standard questionnaire developed by the International Agency for Research on Cancer for NPC study that was adapted to suit the practices and customs of the local population.[12] The questionnaire consisted of sociodemographic characteristics, histopathological status (for NPC cases only), family history of NPC and/or other cancers, and lifestyle, including smoking status, alcohol drinking status, and consumption of preserved foods. The sociodemographic characteristics included age, gender, ethnicity, residence (current, 5 years ago, during childhood, and birth), educational level, and marital status.

The histopathological data included the date of diagnosis, the type of NPC according to the World Health Organization Classification of Nasopharyngeal Carcinoma,[13] and the stage of NPC according to the

American Joint Committee on Cancer Staging for Nasopharyngeal Carcinoma.[14] The cancers were traced among first-degree and second-degree relatives (grandparents, parents, siblings, children, or relatives, such as uncles, aunts, cousins, nieces, and nephews) to determine the family history. The lifestyles included cigarette smoking status (never/current/former), alcohol drinking status (never/current/former), and frequency of consuming preserved foods. Current smokers and drinkers were defined as those who had smoked tobacco or drank alcohol continuously for at least 1 year, and former smokers and drinkers were those who had quit tobacco smoking or alcohol drinking for 2 years or more before the interview.

Moreover, additional information on smoking, such as the number of cigarettes smoked per day and the duration of smoking (age at initiation and cessation) was also included. The consumption of preserved foods was based on a previous study that reported a list of Malaysian foods associated with NPC.[10] The types of preserved foods included salted fish, *pekasam* (traditional Malay fermented fish with rice), salted meat, salted vegetables, and preserved fruit (pickles). The subjects were asked about the consumption frequency of those foods, including never or rarely (less than once a month), less than weekly (1–3 times/month), and weekly or more (1–7 times/week).

Statistical analyses were conducted using SPSS software version 21 (IBM, Armonk, NY, USA). Descriptive statistics were used to explore the distribution of sociodemographic characteristics of the NPC patients in Pahang. Multiple logistic regression (MLR) analysis was performed to determine the risk factors for NPC. The models were compared by the forward likelihood ratio (LR) and backward LR methods to determine the final model. A P-value < 0.05 was considered significant.

RESULTS

Table 1 illustrates the sociodemographic characteristics of the NPC and control subjects. The majority of the NPC subjects were male (74.6%), Malay (60.6%), had secondary education (52.1%), and were married (80.3%).

Table 2 shows the associations between the sociodemographic characteristics of the subjects and NPC. No significant associations were observed between age, gender, ethnicity, educational level, or marital status, and NPC.

Table 3 illustrates the associations between a family history of NPC, other cancers, smoking and alcohol drinking status, and NPC. The simple linear regression (SLR) analysis revealed a significant association between a family history of NPC and NPC ($p < 0.05$) in which the subjects with a family history of NPC had a seven times higher risk of developing NPC than those who did not have a family history of NPC (OR = 6.96, 95% CI = 1.92–25.21). On the other hand, no significant association was detected between a family history of other cancers and NPC. The SLR analysis of smoking status revealed a significant association between current smoking and NPC ($p < 0.05$), where the risk of developing NPC was more than two-fold among current smokers than non-smokers (OR = 2.62; 95% CI = 1.24–5.54). The analysis also showed a dose-dependent trend in the association between the number of cigarettes smoked per day, the duration of smoking, and the risk of NPC, where risk increased as the frequency of these variables increased, albeit the results were not significant. No significant association was observed between alcohol drinking status and NPC.

Table 4 shows the association between the frequency of consuming preserved foods and NPC. The SLR analysis detected no significant association between the consumption of preserved foods and NPC.

TABLE 1. Sociodemographic characteristics of the subjects

Variables	NPC (n=71)	Control (n=81)
Age (year)		
Mean (SD)	51.2 (12.8)	50.5 (14.9)
Range	15–73	17–79
Gender		
Male (%)	53 (74.6)	58 (71.6)
Female (%)	18 (25.4)	23 (28.4)
Ethnicity		
Malay (%)	43 (60.6)	54 (66.7)
Chinese (%)	26 (36.6)	25 (30.9)
Indigenous (%)	2 (2.8)	2 (2.5)
Educational Level		
No formal (%)	6 (8.5)	2 (2.5)
Primary (%)	19 (26.8)	18 (22.2)
Secondary (%)	37 (52.1)	47 (58.0)
Tertiary (%)	9 (12.7)	14 (17.3)
Marital Status		
Single (%)	9 (12.7)	13 (16.0)
Divorced (%)	3 (4.2)	0 (0)
Widowed (%)	2 (2.8)	5 (6.2)
Married (%)	57 (80.3)	63 (77.8)

SD = Standard deviation, NPC = Nasopharyngeal carcinoma

TABLE 2. Crude analysis between the sociodemographic characteristics and nasopharyngeal carcinoma

Factors	NPC (n=71)	Controls (n=81)	Crude odds ratio (95% CI)	*p**
Age	71	81	1.004 (0.98, 1.03)	0.751
Gender				
Female	18	23	1 (reference)	
Male	53	58	1.17 (0.57, 2.40)	0.673
Ethnicity				
Indigenous	2	2	1 (reference)	
Malay	43	54	0.80 (0.11, 5.89)	0.823
Chinese	26	25	1.04 (0.14, 7.96)	0.970
Educational Level				
No formal	6	2	1 (reference)	
Primary	19	18	0.35 (0.06, 1.98)	0.235
Secondary	37	47	0.26 (0.05, 1.38)	0.114
Tertiary	9	14	0.21 (0.04, 1.30)	0.095
Marital Status				
Single	9	13	1 (reference)	
Divorced	3	0	NA	0.999
Widowed	2	5	0.58 (0.09, 3.66)	0.560
Married	57	63	1.31 (0.52, 3.29)	0.570

*Based on the Simple Linear Regression analysis. NA = Not available, NPC = Nasopharyngeal carcinoma, CI = Confidence interval

TABLE 3. Associations between a family history of nasopharyngeal carcinoma, other cancers, smoking and alcohol drinking status, and nasopharyngeal carcinoma

Factors	Cases	Controls	Crude odds ratio (95% CI)	*p**
Family history of NPC				
No	56	78	1 (reference)	
Yes	15	3	6.96 (1.92, 25.21)	0.003
Family history of other cancers				
No	45	54	1 (reference)	
Yes	26	27	1.16 (0.59, 2.25)	0.672
Smoking status				
Never	31	46	1 (reference)	
Current	30	17	2.62 (1.24, 5.54)	0.012
Former	10	18	0.82 (0.34, 2.02)	0.673
Cigarettes smoked/day				
Never	31	46	1 (reference)	
≤ 5	7	10	0.70 (0.22, 2.23)	0.543
6 to 10	6	7	1.20 (0.37, 3.88)	0.767
>10	23	15	2.14 (0.97, 4.71)	0.059
Duration of smoking (years)				
None	31	46	1 (reference)	
1 to 20	8	9	1.32 (0.46, 3.79)	0.607
21 to 40	17	13	1.94 (0.83, 4.56)	0.128
>40	10	6	2.47 (0.82, 7.50)	0.110
Alcohol drinking status				
Never	55	61	1 (reference)	
Current	10	19	0.59 (0.25, 1.36)	0.213
Former	6	1	6.66 (0.78, 57.02)	0.084

*Based on the Simple Linear Regression analysis. NPC = Nasopharyngeal carcinoma, CI = Confidence interval

Two variables with $p < 0.05$ from a previous SLR analysis, such as the family history of NPC and smoking status were selected for the MLR analysis. Forward LR and backward LR steps were applied. No multicollinearity or interaction terms were found. The three goodness-of-fit assessment methods showed that the p for the Hosmer–Lemeshow test was 0.957, the overall correctly classified percentage of the classification table was 66.4%, and the area under the receiver operating characteristic curve was 68.1%, indicating that all the assumptions for model fit were met.

The MLR analysis showed that subjects with a family history of NPC and who were current smokers were independently associated with NPC (Table 5). Subjects who had a family history of NPC had a more than a seven-fold increased risk of developing NPC compared to those who did not have a history of NPC (adjusted OR = 7.90, 95% CI = 2.12–29.38). Current smokers had a three-fold increased risk for developing NPC compared to non-smokers (adjusted OR = 3.01, 95% CI = 1.38–6.59). Furthermore, the MLR analysis also showed that both factors were significantly associated with NPC.

The significant independent associations of both factors with NPC aroused our interest to understand the joint effect of family history and a smoking habit with NPC. Further analysis showed that subjects who were current smokers with no family history of NPC had a significantly increased risk of NPC ($p < 0.05$) (adjusted OR = 3.19, 95% CI = 1.19–8.56), as illustrated in Table 6. Unfortunately, we could not analyze the subjects who were current smokers with a family history of NPC due to the limited sample size.

TABLE 4. Crude analysis between the frequency of consuming preserved foods and nasopharyngeal carcinoma

Factors	Cases	Controls	Crude odds ratio (95% CI)	*p**
Salted fish				
Never or rarely	28	36	1 (reference)	
Less than weekly	32	39	1.06 (0.53, 2.08)	0.877
Weekly or more	11	6	2.36 (0.78, 7.16)	0.130
Pekasam				
Never or rarely	58	69	1 (reference)	
Less than weekly	12	11	1.30 (0.53, 3.16)	0.566
Weekly or more	1	1	1.19 (0.07, 19.44)	0.903
Salted meat				
Never or rarely	66	77	1 (reference)	
Less than weekly	4	4	1.17 (0.28, 4.85)	0.832
Weekly or more	1	0	NA	1.000
Salted vegetables				
Never or rarely	57	68	1 (reference)	
Less than weekly	13	13	1.19 (0.51, 2.78)	0.683
Weekly or more	1	0	NA	1.000
Preserved fruits				
Never or rarely	52	61	1 (reference)	
Less than weekly	19	19	1.17 (0.56, 2.45)	0.671
Weekly or more	0	1	NA	1.000

*Based on the Simple Linear Regression analysis. NA = Not available, CI = Confidence interval

TABLE 5. Factors associated with nasopharyngeal carcinoma in Pahang

Factors	Regression coefficient (b)	Adjusted odds ratio[a] (95% CI)	Wald statistic	*p**
Family history of NPC				
No	0	1		
Yes	2.07	7.90 (2.12, 29.38)	9.51	0.002
Smoking status				
Never	0	1		
Current	1.10	3.01 (1.38, 6.59)	7.65	0.006

*****Based on the Multiple Logistic Regression analysis.
[a]Adjusted for age, sex, ethnicity, educational level, and family with other cancer history,
NPC = Nasopharyngeal carcinoma, CI = Confidence interval

TABLE 6. The joint effect of cigarette smoking and no family history of nasopharyngeal carcinoma

Smoking status	No family history of NPC		Adjusted odds ratio (95% CI) [a]
	Case	Control	
Never	23 (34.3%)	44 (65.7%)	1 (reference)
Current	25 (59.5%)	17 (40.5%)	**3.19* (1.19, 8.56)**
Former	8 (30.8%)	18 (69.2%)	1.12 (0.35, 3.56)

*****$p < 0.05$. [a]Adjusted for age, sex, ethnicity, educational level, and family with other cancer history,
NPC = Nasopharyngeal carcinoma, CI = Confidence interval.

DISCUSSION

The current study found that the risk of developing NPC was significantly higher among those with a family history of malignancy, even though the percentage was much lower than patients without a family history of NPC. This trend was consistent with previous studies. Earlier reports showed that NPC patients with a family history of NPC had a higher risk of developing NPC compared to NPC patients without such a family history, and the percentage was less than one-fifth compared to patients without a family history of NPC.[15–17]

Xie *et al*.[18] and Liu *et al*.[15] reported an increased risk for NPC among individuals with a first-degree family history of NPC and the risk was higher in siblings with a history of NPC compared to parental history of NPC. Shared genetic and environmental risk factors could be the reason for the increased risk of NPC among subjects with a first-degree family history.[19] Nevertheless, the current study was unable to stratify the family history variables into first- and second-degree family members due to the small sample size of the subjects with a family history of NPC (N = 15), as illustrated in Table 3. Our findings provide support to the contribution of a family history of NPC to the increased risk of the disease.[15,18]

Our data also show that current cigarette smokers had a significant three-fold increased risk of developing NPC compared to those who never smoked cigarettes. This finding was consistent with previous studies conducted in Hong Kong,[18] China,[17] Indonesia,[20] and Taiwan[21] which also reported an increased risk of NPC among cigarette smokers. Furthermore, the NPC patients who were current smokers without a family history of NPC had a significantly increased risk of NPC. Although the current study was unable to show the risk of the joint effect between NPC patients who were current smokers and a family history of NPC, the result suggests that current smoking is a stronger independent risk factor of NPC than a family history of the malignancy. We also discovered a dose-dependent smoking trend in which risk increased as the number of cigarettes smoked per day increased, albeit it was not statistically significant. This finding supports previous studies showing the same trend of the risk for NPC.

The current analysis showed no association between alcohol drinking and NPC. This is in line with previous reports whereby they also reported no significant association was observed between these two variables.[22,23] A meta-analysis by Du *et al*.[22] reported that some studies showed a similar trend as the present study in terms of the risk for NPC among current and former drinkers, where a reduced risk for NPC was observed among current drinkers and an increased risk for NPC was observed among former drinkers. However, the results were not significant and they did not specify the details in those studies. In contrast, the overall risk analysis by Du *et al*.[22] showed that most studies reported an increased risk for NPC in alcohol drinkers, although it was not significant. The same result was obtained by Feng *et al*.[23] who found a tendency for an increased risk of NPC among alcohol drinkers. Our result was likely due to a small sample size compared to the study by Feng *et al*.[23] Furthermore, the majority of the subjects in this study were Malays with Islam as their religion (60.6%) in which alcohol drinking is prohibited.[24]

An earlier review by Putera *et al*.[25] found that the association between consuming salted fish and NPC was inconsistent across studies in different regions. This association was only apparent in Southern China due to the extremely high incidence of NPC and the consumption of Chinese-style salted fish, while other regions had different incidence rates of NPC and styles of preparing salted fish. The current study found a dose-dependent trend between salted fish consumption and NPC but it was not significant. Although this association was weak, Barret *et al*.[26] reported a weak association between consuming salted fish and NPC in adults in Southern China. An earlier study by Lau *et al*.[27] found no correlation between reduced consumption of salted fish and a decrease in the incidence of NPC in Hong Kong, which is located in Southern China. Furthermore, the current study determined that most of the subjects consumed other preserved foods less than weekly and rarely or never consumed salted fish. Since economic development began in 1987, there has been a gradual change in eating habits and lifestyle in Malaysia.[10] Food variety, processing, packaging, marketing, handling, and pricing are undergoing rapid changes and modernization. Fresh foods are increasingly preferred compared to salted and preserved foods with the increased manufacture of home refrigerators. Therefore, the change in diet may explain the low consumption of salted fish and other preserved foods among subjects in this study and indirectly decrease the risk factors contributing to the incidence of NPC.

Some limitations of this study should be discussed. This study used a non-probability sampling method for the case and control groups called convenience sampling. The use of non-probability sampling poses certain drawbacks such as bias and the presence of outliers and allows for the statistical assessment of sampling error or statistical validity, so, eventually, the results do not represent the target population.[28–30] However, convenience sampling was seen as the best method for this study to obtain the sample size required. The subjects recruited in this study came from various regions of Pahang state. The HTAA and HOSHAS hospitals are NPC referral hospitals in Pahang state, where suspected cases of NPC from clinics around

Pahang state are referred to for further diagnosis. Although our statistical findings did not exactly represent the studied population, the results were generated based on data from subjects who came from different regions of Pahang state.

The sample size was smaller than the calculated sample size required for the study due to the inaccessibility and ineligibility of patients. The small sample size prevented sub-analyses, such as the degree of relative that contributed to NPC and the joint effect between the NPC patients who were current smokers and a family history of NPC. The lower sample size also produced poor statistical power. Previous studies with different study designs addressed the same concerns of insufficient sample size with poor statistical power to obtain a significant and reliable result.[31,32] For example, we detected a significant association in smoking only where previous studies with larger sample sizes showed significant associations with status, intensity, and duration of smoking.[21,33] Nevertheless the current results can be used to develop hypotheses and objectives for future studies with better designs.

CONCLUSIONS

The current study identified two significant risk factors associated with an increased risk of NPC in Pahang, such as family history and smoking. The results of this study are important for developing hypotheses and objectives for future studies. Identifying significant risk factors for NPC is an important public health action to improve the management of risk for NPC in Malaysia, such as the no-smoking campaign and screening programs among high-risk populations.

CONFLICT OF INTEREST

None declared.

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