RELATIONSHIP BETWEEN CIGARETTE SMOKING AND NASOPHARYNGEAL CARCINOMA

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Abstract

Introduction: In recent years many environmental and biological factors have shown a risky relationship to the occurrence of NPC and the latest research results indicate the role of genetic and viral factors in the development of this disease

Objectives: Etiology of nasopharyngeal cancer (NPC) is multifactorial, and many of these factors overlap where one factor may occur together with other elements as a cause. Cigarette smoking is thought to also play a role in the development of NPC.

Methods: The study design was in case of control with an analytical approach during February-October 2007. Samples are 96 patients with NPC as case and 96 people as a control. Case group and control samples were taken from RSUP H. Adam Malik Medan and RSU Dr. Pirngadi Medan.

Results: The majority of NPC patients are: Men (74%), 50-59 years (29.2%), Batak ethnic (56.3%), and farming (32.3%), WHO type 3 (38.6%), and stage III (58.4%). There were significant relationship between smokers and NPC with consumption of cigarettes 11-20 cigarettes per day ($p=0.021$; OR=2.53). In the multivariate logistic regression analysis, the number of cigarettes per day did not show a significant relationship ($p=0.587$). NPC were significantly associated with people who had started smoking before the age of 20 years ($p=0.000$; OR 5.35), consuming habits of salted fish before 10 years of age with sometimes frequency consumption of salted fish ($p=0.000$; OR 7.766), often ($p=0.000$; OR 16.515) and the habit of using firewood ($p=0.014$; OR 3.147). There was no significant relationship between the duration of cigarette smoking ($p=0.293$), a number of cigarettes ($p=0.021$) and the types of cigarettes smoked ($p=0.081$) with the incidence of NPC.

Conclusion: Cigarette smoking as a risk factor for NPC cannot act stand-alone, but there is a role for other factors that also influence as a risk factor.

Article Info

Keywords:

NPC, smoking, relationship, multifactorial risk

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1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a multifactorial disease. The incidence and geographic distribution depend on several factors, such as genetic susceptibility, environmental factors, diet, and personal habits [1].

Many theories of etiological factors have been put forward, but there is still nothing certain [2]. At present, a number of studies have shown that the etiology of NPC is multifactorial, including genetic, environmental and viral [3]. These etiological factors will be highly dependent on an individual basis, but it must be remembered that many of these factors overlap and one factor may coincide with other factors as the cause of NPC [4].

Speculation and hypotheses about the etiology of the NPC began in the early 20th century, first put forward by Jackson in 1901, who proposed the hypothesis that dust irritation in cork workers would damage the airway epithelium. He concluded that the irritation could not cause NPC, as was the case with laryngeal cancer. Since then the pathogenesis of NPC has been intensively studied, specifically aimed at geography and racial variation. In recent years many environmental and biological factors have shown a risky relationship to the occurrence of NPC and the latest research results indicate the role of genetic and viral factors in the development of this disease [4].

During the 1950s, it began to prove quite clearly that tobacco smoke was a carcinogen. Carcinogens have been identified in tobacco smoke, and condensation of cigarette smoke can cause tumors when applied to the skin of experimental mice. At the end of the 1950s, convincing evidence of the relationship between smoking and lung cancer and other cancers was obtained from case-control and cohort studies [5].

In the previous decade, the number of deaths from smoking increased sharply, with this picture occurring in heavy smokers. In 1986, the International Agency for Research on Cancer (IARC) Working Group found enough evidence that smoking can cause cancer in humans, and concluded that smoking can cause not only lung cancer but also can occur in the urinary tract, including the kidneys

and bladder, the upper respiratory tract includes the oral cavity, pharynx, larynx, esophagus, and pancreas. In 2002, Vineis et al. Also members of the IARC Working Group found an increased risk of sinonasal cancer and nasopharyngeal cancer among smokers, which were consistently reported in several case-control studies, with positive dose-response trends associated with the number and duration of smoking [5].

Cigarette smoke contains more than 4000 mixed ingredients and in the chemical analysis, it is known to have identified at least 50 types of carcinogens. From existing studies, carcinogens that have been identified include polycyclic aromatic hydrocarbons (PAHs), nitrosamines, aromatic amines, aza-arenes, aldehydes, various organic compounds, inorganic compounds; such as hydrazine and some metals, and some free radicals [6, 7].

In addition to the gas component, in cigarette smoke, there are solid components or particles consisting of nicotine and tar. Tar contains carcinogens, while nicotine is an addictive ingredient that causes dependence or addiction [8].

The location of the nasopharynx in the upper airway where the flow of air pollution and cigarette smoke is a location that can adversely affect the mucosa of the site, where carcinogens carried by air can induce cancer [9]. The nasopharyngeal mucosa can be directly exposed to smoked cigarette smoke, and cancer can be induced in contact areas with carcinogens [10].

Enzyme Cytochrome P450 2E1 (CYP2E1) is known to be an activation enzyme in nitrosamines and other carcinogens that may be involved in the development of NPC. Hildesheim et al., In a case-control study, suggested that cigarette smoke is an important source of nitrosamine exposure thereby modulating CYP2E1 activity, and he sees its effect as a risk factor in NPC, where smoking is positively associated with the risk of NPC [11].

The relationship between smoking and NPC has been investigated in geographic areas with high and moderate incidents, such as in South China and parts of Southeast Asia. The results of these studies varied, from positive relationships to having any relationship [12].

Today 80% of smokers live in developing countries. In 1997 there were 5.7 trillion cigarettes consumed in the world. The top five cigarette consumers in the world are China with 1.679 billion cigarettes a year, the United States 480 billion cigarettes, Japan 316 billion cigarettes, Russia 230 billion cigarettes and Indonesia ranked fifth which consumes 188 billion cigarettes a year [13].

Research conducted by the Institute for Addressing Smoking Problems (LM3) in 14 provinces in Indonesia received 59.04% of male smokers aged 10 years and over, while for women smokers aged 10 years and above only 4.83%. Meanwhile, the data of the Household Health Survey (SKRT) of the Indonesian Ministry of Health in 2001 showed that overall (male and female) 31.5% of the Indonesian population smoked (Aditama, 2004). In Indonesia, the most consumed types of cigarettes are clove cigarettes (81.34%), which are cigarettes containing a mixture of tobacco and cloves [14].

In addition to the gas component, there are solid components or particles consisting of nicotine and tar. Tar contains carcinogens, while nicotine is not a carcinogen, [15] but is an addictive ingredient that causes dependence or addiction [8].

The relationship between cigarette smoking and NPC has been investigated in geographic areas with high and moderate incidents, such as in South China and parts of Southeast Asia. The results of these studies varied, from positive relationships to not having any relationship [12].

During the 1950s, it began to prove quite clearly that smoking tobacco was a carcinogen. At the end of the 1950s, convincing evidence of the relationship between smoking and lung cancer and other cancers has been obtained from case-control studies and cohorts, carcinogens have been identified in tobacco smoke, and cigarette smoke can cause tumors when the plates are smeared on rat skin. In the previous decade, the number of deaths from smoking increased sharply, with this picture occurring in heavy smokers [5, 16].

Carcinogenesis is a study of the origin of cancer. Research on biological systems can be done to produce an observation that can find out about the stages that occur in changes from normal cells to cancer cells. Allegations of the relationship between tobacco use and cancer have been suggested by Hill [17]. The potential for carcinogens in cigarette smoke and their relationship to cancer can be evaluated in various ways, but it is important to consider the components present in cigarette smoke and their ability to induce tumors in animal experiments [15]. Current evidence shows that tobacco smoke is a mixture of multipotent carcinogens. With advances in biochemistry and molecular biology research has been carried out to measure cigarette metabolites in different bodily fluids and organs, to measure carcinogens and carcinogens, and to identify related genetic damage (mutations or chromosomal irregularities) with smoking [5]. Doctor A.C Ivy of the University of Illinois United States who has been investigating cigarettes for years, found that people who smoked a pack per day for 10 years inhaled about 7 liters of tar in that period [14].

Then the statement was reviewed by Dr. Graham and Dr. Wynder. They painted the backs of the mice with tobacco tar. This experiment has actually been carried out by other researchers but did not produce convincing conclusions. According to these two doctors, the cause was that the previous study had not been carried out for a long time, so before the results were seen the research had been stopped. This time Dr.Graham and Dr.Wynder will perfect the research, namely by using a more concentrated tar solution and a longer trial period. The tar they use is taken from cigarette smoke produced by a machine that can suck 60 cigarettes at once. The tar that has been collected is dissolved by a solvent, then applied to the back of the shaved mouse three times a week. During the first two months, they gradually increase the tar solution level by three times the previous level. On week 42, a mouse showed early symptoms of cancer. Entering the 72nd week, on average each mouse has been attacked by cancer [14].

Brennan et al., In their study of the relationship between smoking and the p53 gene mutation in squamous cell carcinoma in the head and neck, stated that from 129 tumor specimens of squamous cell carcinoma in the head and neck, p53 gene mutations were found which had a strong association with smoking [17].

In the analysis of other studies found that smokers are a major risk factor for the occurrence of cancer in the head and neck. This study shows significant results comparing smokers with nonsmokers, where the likelihood of smokers suffering from head and neck cancer is very large. There was also a relationship between the duration of smoking and the number of cigarettes consumed with the trend of positive dose-response relationships [16, 18, 19]. In the results of other studies it was found that the risk of cancer in the pharynx was greater when associated with smoking, compared to the risk relationship with the number of cigarettes consumed [20]. The following shows a scheme about the relationship between nicotine

addiction and lung cancer associated with carcinogenic substances in cigarette smoke. Where a similar scheme can be considered for other cancers that have a relationship with smoking [21].

This simple scheme illustrates the main role of DNA changes in the process of carcinogenesis. In this scheme, nicotine causes addiction to continue smoking and causes chronic exposure to carcinogens. Metabolic carcinogens can be activated to react with DNA, forming combined covalent products called altered DNA (DNA adducts). Competing with this metabolic process, the detoxification process of carcinogenic products fails to be excreted. If the changed DNA can be repaired (repair) by cellular repair enzymes, DNA will return to its normal shape. But if changes continue during DNA replication, DNA coding failures can occur, which tend to become permanent mutations in the DNA sequence. Cells with damaged or mutated DNA can be excreted by the apoptosis process. If the mutation occurs in the main part of the crucial genes, such as in RAS or MYC oncogenes or TP53 or CDKN2A tumor suppressor genes, the result can be a loss of control of regulation of normal cell growth and tumor growth. Nicotine and carcinogens can also bind directly to several cell receptors, then activate protein kinase B (AKT), protein kinase A (PKA) and other factors. This can cause a decrease in the process of apoptosis, increased angiogenesis and increased cell transformation. Tobacco contents also contain tumor promoters and cocarcinogens, which can activate protein kinase C (PKC), activator protein 1 (AP1) or other factors, which further increases the carcinogenesis process [21].

Smoking has given a picture as a significant risk factor for the occurrence of cancer in various organs and components of the contents of cigarettes, including nitrosamine and formaldehyde, also shows that cigarettes have carcinogenic potential. Cigarette smoking will expose carcinogenic substances that are present in cigarettes directly to the nasopharynx, thus the relationship between smoking and NPC is biologically quite acceptable. Some results from studies that examined the relationship between smoking and NPC showed unequal results. However, Lin et al in 1971, in a study in Taiwan, reported a significantly increased risk of NPC with an increase in the duration of smoking. The results of this study are supported by several subsequent studies, but several other studies show the opposite results about the relationship between smoking and NPC [22].

Vaughn et al. Found evidence about the relationship between the risk of NPC and the potential for stronger exposure to formaldehyde in smokers. Among smokers and ex-smokers, the odds ratio was associated with those who had worked in jobs exposed to formaldehyde (OR 2.3), compared to people who had never smoked (OR 0.5) [23].

The amount of exposure to cigarette smoke is complex and is influenced by the number of cigarettes smoked and the smoking sucking pattern. Other factors that influence the exposure to cigarette smoke include the age of smoking, the length of smoking, the depth of suction, etc [7]. Based on the duration of smoking can be grouped as follows; smoking for less than 10 years, between 10-20 years, and more than 20 years [23, 24].

The number of cigarettes smoked can be expressed in pack-years, equivalent to how many packets of cigarettes smoked in one day (1 pack=20 cigarettes) multiplied by the length of smoking in a year [7]. Classification according to the number of cigarettes consumed per day can be grouped as follows; mild (1-10 sticks per day), moderate (11-20 cigarettes per day) and heavy (more than 20 cigarettes per day) [23, 24].

Mobuchi et al., In a case-control study, investigated possible etiological factors in NPC. His results showed an increase in the odds ratio with the number of cigarettes smoked, which illustrates the existence of a positive dose-response relationship [3, 10, 25, 26]. Meanwhile, Zhu et al. Obtained the same results regarding the relationship of an increased risk of NPC with smoking status, the longer smoking and the number of cigarettes smoked [12, 27]. Men who routinely smoke will have a 2 times greater risk of developing NPC compared to non-smoker [12].

Chow et al., In a cohort study examined the relationship of smoking with NPC to approximately 250.000 United States veterans. During the 26 years of research found 48 sufferers of NPC. Smokers are four times more likely to develop NPC compared to nonsmokers, and the risk will increase again to 6.4 times in people who smoke more than 2 packs per day [28].

Picture 1. Scheme about the relationship between nicotine addiction and lung cancer associated with carcinogenic substances in cigarette smoke [21]

2. MATERIAL AND METHODS

This Research conducted in case of control with an analytical approach. The study was carried out at the Department of THTKL SMF FK-USU/H. Adam Malik General Hospital Medan. The sampling site was carried out at the Department of THTKL SMF FK-USU/H. Adam Malik General Hospital Medan and RSU Dr. Pimgadi Medan was conducted from February-October 2007. The samples are all patients with nasopharyngeal carcinoma and as controls are people who do not suffer from malignancy. Criteria of the samples are NPC patients diagnosed based on histopathological biopsy results, both men and women in all age groups and willing to be included in the study and as control samples are people who are not sufferers malignancies. Smoking status, salted fish consumption, existence of families suffering cancer, the use of oil lamps, firewood and mosquito repellent were measured using questionnaire.

3. RESULT

The study was conducted in the Department of ENT-KL FKUSU/H. Adam Malik General Hospital Medan from March 2007 to November 2007 with a sample of 192 people consisting of 96 people with nasopharyngeal carcinoma (NPC) and 96 non-malignant people who fit the criteria of the research subject. Sampling was carried out at H. Adam Malik Hospital Medan and Dr. Pirngadi Hospital Medan. Results of Univariate Logistic Regression Analysis (Descriptive-Analytical Statistics)

Table 1. Distribution of characteristics of research subjects

Variable	Case		Control		p*
	Total	%	Total	%	
Gender					
Male	71	74.0	70	72.9	0.870
Female	25	26.0	26	27.1	
Age					
<10 years	1	1.0	1	1.0	0.998
10-19 years	7	7.3	6	6.3	
20-29 years	5	5.2	5	5.2	
30-39 years	19	19.8	16	16.7	
40-49 years	23	24.0	24	25.0	
50-59 years	28	29.2	29	30.2	
>60 years	13	13.5	15	15.6	
Ethnicity					
Batak	54	56.3	49	51.0	0.722
Java	28	29.2	28	29.2	
Aceh	6	6.3	11	11.5	
Melayu	4	4.2	4	4.2	
Mining	3	3.1	4	4.2	
China	1	1.0	0	0.0	
Occupation					
Farmers	31	32.3	35	36.5	0.441
Labor	4	4.2	5	5.2	
Household	17	17.7	13	13.5	
Trader	5	5.2	9	9.0	
Self Employed	19	19.8	17	17.7	
Teacher	1	1.0	2	2.1	
Civil	2	2.1	5	5.2	
Servants	8	8.3	7	7.3	
Student	3	3.1	0	0.0	
Mechanic	3	3.1	2	2.1	
Driver	3	3.1	0	0.0	
Fisherman	3	3.1	0	0.0	
Security	0	0.0	1	1.0	

* p-value with chi-square

From table 1, the data shows that based on sex, in the case group there were more men (74%) than women (26%) with a ratio of 2.84:1, as well as more control groups in men (72.9%) than women (27.1%) with a ratio of 2.69:1. Statistically, it can be stated that there is no difference in the proportion of NPC events by sex ($p=0.87$).

The age group with the highest number of NPC patients is between the ages of 50 and 59, which is 28 people. Of the 96 patients with NPC, there is the youngest age of 9 years, and the oldest is 74 years. Statistically, it can be stated that there is no difference in the proportion of NPC incidence according to age group ($p=0.998$).

The Batak ethnicity is the largest ethnicity in the case group (56.3%) and controls (51%), where the statistical test found no difference in the proportion of NFP events by ethnicity ($p=0.722$).

Based on the type of work obtained the most jobs were farming, both the case group (32.3%) and the control group (36.5%). With statistical tests, there were no differences in the proportion of NPC events according to the type of work ($p=0.411$).

Table 2. Distribution of NPC patients based on histopathology type and tumor stage

Variable	Case	
	Total	%
Types of histopathology		
Squamous cell carcinoma with keratinization (WHO type 1)	27	28.1
Squamous cell carcinoma without keratinization (WHO type 2)	32	33.3
Cell carcinoma undifferentiation (WHO type 3)	37	38.6
NPC Staging		
Stage I	0	0.0
Stage II	1	1.0
Stage III	56	58.4
Stage IV	39	40.6

From table 2, the results of this study it was found that NPC patients with the most tumor cell types were 37 differentiated cell carcinomas (38.6%), followed by 32 keratinized squamous cell carcinomas (33.3%), and squamous cell carcinoma with keratinization 27 people (28.1%).

Table 3. Relationship between smoking and NPC based on the age of smoking, duration of smoking, cigarette consumption per day and type of cigarette

Variable	Case		Control		P*	OR	CI (95%)
	Total	%	Total	%			
Smoking status							
Smokers	67	69.8	55	57.3	0.072	1.722	0.950-3.121
Age starts smoking							
10-19 years	49	51.0	16	16.7	0.000	4.330	2.070-9.057
>20 years	18	18.8	39	40.6		0.653	0.313-1.35
Smoking time							
1-10 years	6	6.3	7	7.3	0.293	1.212	0.369-3.982
11-20 years	13	13.3	11	11.5		1.671	0.657-4.248
>20 years	48	50.0	37	38.5		1.834	0.967-3.476
Cigarettes per day							
1-10 sticks	12	12.5	21	21.9	0.021	0.808	0.344-1.898
11-20 sticks	34	35.4	19	19.8		2.530	1.212-5.280
>20 sticks	21	21.9	15	15.6		1.979	0.876-4.474
Cigarette types							
White	11	16.4	10	18.2	0.081	1.555	0.584-4.142
Kretek	35	52.2	21	38.2		2.356	1.147-4.842
Linting	1	1.5	5	9.1		0.283	0.031-2.550
Mix	20	29.9	19	34.5		1.488	0.677-3.271

* p-value with chi-square

In table 3 it can be seen that in the case group, NPC patients who smoked were 67 people (69.8%) compared to smokers in the control group as many as 55 people (57.3%), where statistically there were no significant differences between both groups ($p=0.072$).

Based on the age of starting smoking, as many as 49 people (51%) from the case group had started smoking since they were less than 20 years old, while from the control group only 16 people (16.7%). From the statistical test, there were significant differences in the age of starting smoking ($p=0.000$). From the table above we can determine the odds ratio (OR) 4.330 (95% confidence interval (CI), 2.070-9.057) which means the risk of developing NPC is 4.330 times in people who start smoking before the age of 20 compared to nonsmokers.

Based on the duration of smoking, it was found that the case group that smoked for more than 20 years was 48 people (50%) and smoking less than 10 years as many as 6 people (6.3%), while in the control group who smoked for more than 20 years as many as 37 people (38.5%) and smoking less than 10 years were 7 people (7.3%). In statistical tests, there were no significant differences between the two groups ($p=0.293$).

The number of smokers in the case group who smoked between 11-20 cigarettes was 34 people (35.4%) and more than 20 cigarettes per day were 21 people (21.9%), while in the control group that sucked between 11-20 cigarettes were 15 people (15.6%) and more than 20 cigarettes per day were 21 people (21.9%) From the statistical test there were significant differences ($p=0.021$) between the two groups. From the table above we can determine the odds ratio (OR) 2.530 (95% confidence interval (CI), 1.212-5.280) in the

group of people who smoke 11-20 cigarettes per day. Although the relationship of the effect of increasing the number of cigarettes smoked per day with an increased risk of developing NPC is less consistent, but people who smoke more than 11 cigarettes per day, still have a high risk of suffering from NPC.

Regarding the types of smokers, it is categorized as non-smokers, white smokers, kretek smokers, rolling smokers, and mixed smokers. Found in the case group, the highest number of clove cigarette smokers was 35 people (52.2%) while in the control group it was found that the most were non-smokers followed by 21 clove cigarettes (38.2%). In the statistical test, there were no significant differences according to the type of smoker ($p=0.081$).

Table 4. Relationship between the consumption of salted fish and NPC

Variable	Case		Control		P*	OR	CI (95%)
	Total	%	Total	%			
Eat salted fish when <10 years old							
Never	20	20.8	44	45.8	0.000		
Rarely	16	16.7	28	29.2		1.257	0.559-2.827
Sometimes	30	31.3	17	17.7		3.882	1.752-8.605
Often	30	31.3	7	7.3		9.429	3.546-25.068

* p-value with chi-square

Table 4 shows the relationship between the history of consuming salted fish when NPC patients are still less than 10 years old. History of consuming this is categorized as never, rarely, sometimes and often. In the case group, the number of sufferers who consumed salted fish with occasional and frequent categories was the highest, namely 30 people (31.3%), while in the control group the most was in the never category, followed by the category rarely as many as 20 people (29.2%). In the statistical test, there were significant differences in the relationship between the consumption of salted fish and NPC ($p=0.000$). From the table above can be determined each of the odds ratio (OR) 1.257; 3.882; 9.429 in people who rarely, sometimes and often consume salted fish when they are less than 10 years old, which means that the risk of developing NPC will increase if the frequency of eating salted fish is higher at that age range.

Table 5. Relationship between the existence of families suffering from cancer, the use of oil lamps, firewood and mosquito repellent with the NPC

Variable	Case		Control		P*
	Total	%	Total	%	
Families with cancer					
No	93	96.9	94	97.9	0.650
Yes	3	3.1	2	2.1	
Use of oil lamps					
No	21	21.9	16	16.7	0.360
Yes	75	78.1	80	83.3	
Use of firewood					
No	25	26.0	16	16.7	0.113
Yes	71	74.0	80	83.3	
Use of mosquito repellent					
No	25	26.0	31	32.3	0.341
Yes	71	74.0	65	67.7	

* p-value with chi-square

In table 5 is data about the relationship between the existence of families suffering from cancer, the use of oil lamps, the use of fuelwood and mosquito repellent drugs with the risk of the possibility of the occurrence of NPC, and statistical tests found no significant differences regarding the relationship between the four variables with NPC ($p=0.650$, $p=0.360$, $p=0.113$ and $p=0.341$).

Table 6. Results of Multivariate Logistics Analysis of the relationship between the age of starting smoking, use of firewood and consumption of salted fish at the age of 10 years.

Variable	P*	OR	CI (95%)
Age starts smoking			
10-19 years	0.000	5.350	2.290-12.499
>20 years	0.253	0.609	0.261-1.426
The use of firewood	0.014	3.147	1.260-7.860
Eat salted fish when <10 years old			
Rarely	0.082	2.367	0.896-6.255
Sometimes	0.000	7.766	2.937-20.538
Often	0.000	16.515	5.300-51.463

* p value with chi-square

Table 6 is the result of multivariate logistic regression analysis, which found that the age variables start smoking between 10-19 years, use of

firewood and consumption of salted fish when they are less than 10 years old with frequency and often have significant associations with the incidence of NPC, each with OR=5.350 ($p=0.000$), OR=3.147 ($p=0.014$), OR=7.766 ($p=0.000$) and OR=16.515 ($p=0.000$).

Furthermore, the above variables are confounders, with statistical tests attempted to be excluded, and it was found that the factor of fuelwood consumption and consumption of salted fish before the age of 10 years is still an influential factor as a risk factor, so it cannot be excluded from its role as risk factors for the occurrence of NPC.

4. DISCUSSION

This study was conducted to determine the relationship between cigarette smoking and nasopharyngeal carcinoma (NPC). Based on the calculation of the minimum sample size, this study used a sample of 192 people consisting of 96 people with nasopharyngeal carcinoma (NPC) as a case and 96 non-malignant people as controls that matched the criteria of the research subject. This study is a case-control study comparing smoking exposure and several confounding factors in NPC patients and not those with malignancy. The significance of the difference between smoking and several confounding factors in cases and controls was determined by the chi-square test. The risk of developing the disease is determined by the relative risk of the Odds Ratio. Odds ratio (OR) equal to 1 means, not a risk factor, if OR is less than 1 means a protective factor, and if OR is more than 1 means a risk factor.

In this study case subjects and controls with male sex more than women, in the case subject compared 2.84:1, and in control subjects 2.69:1. Statistically, there were no significant differences according to sex between case subjects and controls (similar age between cases and controls). In this research, the results are more or less the same as the study of Douglas et al. (1996) in RSUP Dr.Kariadi Semarang, which obtained a comparison between men and women who suffered NPC 1.87:1. Magdalena et al. (1996) in Dr. Sardjito General Hospital Yogyakarta reported a correlation of men and women 2.47:1. Vaughan et al (1996) in the United States declared a ratio of 1.88:1, while Armstrong (2000) in Malaysia 2.24:1, and Sun (2005) in America 2.25:1 [6, 24].

In this study, the youngest subjects with NPC were nine years old and 74 years old at the most. Roezin (1995) in Jakarta reported that in Indonesia the youngest age range of NPC sufferers was four years and the oldest 84 years, while McDermott (2001) in the UK received the youngest 2 years and the oldest 91 years. From the distribution of age grouping data of NPC patients with statistical tests, there was no significant difference between the case and control groups, and the highest number of patients was obtained in the 40-49 year age group and 50-59 years old, 23 people (24%) and 28 people respectively (29.2). This is almost the same as that reported by Roezin (1995) who got the age group of 40-49 years 25.92% and 50-59 years 19.75% and Douglas et al (1996) in RSUP Dr.Kariadi Semarang who got age 40-49 years 22.2% and 50-59 years 27.8%. Magdalena (1996) in Yogyakarta who received the highest incidence of NPC in the age group of 40-49 years as much as 42.4%, Lutan (2003) in Medan received the highest incidence in the 41-50 year age group of 40%, Abdi (2005) in Medan get the highest incidence in the age group 40-49 as many as 37 cases (35.1%). Whereas McDermott (2001) wrote that NPC patients in Arab Maghreb North Africa and in Tunisia, obtained an age distribution in the form of a bimodal curve, where the first increase was in the 10-20 year age group and the second increase was 55-65 years. Almost the same bimodal curve also occurs in several places in India [4].

The Batak ethnicity is the largest ethnic group, both in the NPC case group 54 people (56.3%) and the control group 49 people (51%), followed in the second place the most are Javanese. According to the ethnicity, between cases and controls, there was comparability (statistical tests had no significant difference). This might be correlated with the proportion of the population of Medan city, which indeed the majority of the population is Batak and Javanese. Zhu (1995) in the United States obtained the distribution of NPC patients according to ethnicity (ethnicity) most were White (non-Hispanic) 56.6%, followed by successively Blacks, Asians and Hispanics, while Vaughan (2000) in the United States also got almost the same results namely the most ethnicity were white people (White) 76%, followed by Asian ethnicity, Blacks, and Americans-Indians/Eskimos. Meanwhile, Cheng (1999) in Taiwan got the most ethnicity were Fukienese 308 people (82.1%), followed by Hakka, Han, and Guangdong ethnicity [12, 23, 24].

A total of 31 people (32.3%) NPC sufferers worked as farmers, followed by entrepreneurs 19 people (19.8%) and domestic work 17 people (17.7%). Looking at the picture of distribution according to the type of work in table 4.1.1, it can be said that the majority of NPC patients (the case group) and the control group who went to RSUP H. Adam Malik Medan and Dr. Pirngadi General Hospital Medan had a lower middle socioeconomic level. In the statistical test, there were no significant differences between the two groups. Douglas et al. (1996) in Dr. Kariadi General Hospital, Semarang, got a more or less the same picture about the distribution of the NPC patients according to the type of work, i.e. 38.54% farmers followed by 18.57% of entrepreneurs, 14.93% of laborers, and 12.85% of civil servants. In this study most NPC patients had WHO type 3 histopathologic type, cell carcinoma undifferentiated 37 people (38.6%), WHO type 2 (cell carcinoma without keratinization) 32 people (33.3%) and WHO type 1 (cell carcinoma with keratinization) 27 people (28.1%). Some studies have found that WHO type 3 is the most common type, as Magdalena (1996) in Yogyakarta gets type 3 (88.98%), type 1 (7.26%), and type 2 (3.74%), Sudyartono (1996) in Semarang received type 3 (60.9%), type 2 (29.7%) and type 1 (9.4%), Erkal (2001) in Turkey getting type 3 (60.8%), type 1 (34.7%), and type 2 (4.5%). Unlike what was reported by Vaughan (1996) in the United States where type 1 was the most (61%), followed by type 3 (26%) and type 2 (13%), as well as Sun (2005) in America getting type 1 (40.8%), type 3 (36.9%), and type 2 (22.3%). From the description of the distribution of histopathology, there appears to be the most different type of type in NPC patients, in Asia the most common type is undifferentiated cell carcinoma, whereas in the United States the most is the type of carcinoma with keratinization.

Tumor degree (T), gland status (N), metastasis (M), and nasopharyngeal carcinoma stage based on 1992 UICC classification (TNM). Based on the clinical stage can be categorized as stage I and II is the early stage, and stage III and IV are advanced stages. The results of the study found that most subjects with NPC cases were stage III (58.4%), followed by stage IV (40.6%), stage II (1%), and no patients with stage I. The study was the same as that Armiyanto (1993) found in Jakarta as many as 93.34% of 30 cases were stadium III-IV, Magdalena (1996) in Yogyakarta had an advanced stage 91.26% of 454 cases of NPC, Sudyartono (1996) in Semarang had an advanced stage of 50% of 64 cases, Erkal (2001) in Turkey received 93% of advanced stages from 447 cases, and Krishna (2004) in India received an advanced stage of 58.6% of 29 cases.

The frequency of the most common NFP is at the age of 40 to 59 years and smoking habits generally begin between the ages of 10 and 30 years. Based on multivariate logistic regression analysis, it can be seen from the age of smoking, the number of stems per day, the type of cigarette smoked, and the influence of other factors, namely the use of firewood and the consumption of salted fish when it is not yet 10 years old. (odds ratio) for smokers, users of firewood and consuming salted fish before the age of 10, as can be seen in table 4.2.1. The results of multivariate logistic regression, the variables of age starting smoking between 10-19 years, use of fuelwood and consumption of salted fish when they are less than 10 years with frequency of consumption sometimes and often have a significant association with the incidence of NPC, respectively with $OR=5.350$ ($p=0.000$), $OR=3.147$ ($p=0.014$), $OR=7.766$ ($p=0.000$) and $OR=16.515$ ($p=0.000$).

When viewed based on age, starting smoking, there is a difference in the younger group of cases when they start smoking compared to the control group. From the results of univariate logistic regression analysis, there were significant differences with $OR=4.330$ ($p=0.000$). The age of starting smoking is also the primary variable in this study, so from the results of the multivariate logistic regression analysis, there were significant differences with $OR=5.350$ ($p=0.000$). In other words, if someone's smoking is delayed by 10 years from their present age, then he will get a risk of NPC more than one fifth of the time, or it can be said that the age of smoking 10 years earlier than now will have a risk of NPC as much as five times. Pelucchi (2006) in Italy found that people who started smoking before the age of 17 had a high risk ($OR=13.6$) for the occurrence of NPC. Chow (2006) in the United States reported a 26-year cohort study on US war veterans with the result that people who started smoking before the age of 15 had a very high risk of developing NPC. Meanwhile, Friborg (2007) in Singapore found different results where the age of smoking began to have no association with the occurrence of NPC but got a relationship between the age of starting smoking and the incidence of oropharyngeal carcinoma [21, 29].

When viewed from the duration of smoking, the case group was relatively longer than the control group. The results of univariate logistic regression analysis showed no significant difference with $p\text{-value}=0.293$. Keep in mind that smoking is related to the age at which you start smoking, the younger you start smoking the longer the patient smokes. Chow (2006) in the United States reported a cohort study with the results that there was no clear relationship between the duration of smoking and the incidence of NPC. In contrast to Chen (1990) in Taipei who got an increase in the risk of smoking in the incidence of NPC will increase if the longer consuming cigarettes, Nam (1992) in the United States get an increased risk of developing NPC in people who consume cigarettes more and more, Zhu (1995) in the United States in a case-control study with a whole sample of men found that men who smoked for 25 years or more had a high risk of developing NPC (without getting rid of confounding factors) [12, 27, 29]. Meanwhile, Hildesheim (1997) in Taiwan found that people who smoked more than 30 years had 2.1 times the risk of developing NPC compared to non-smokers with 95% $CI=1.2\text{-}3.7$ [11]. Cheng (1999) in Taiwan found an increased risk according to smoking time, where people who smoked for less than 25 years $OR=1.1$ and who smoked for more than 25 years $OR=1.7$ ($p=0.03$), and Friborg (2007) in Singapore getting in people who smoke for more than 40 years has a double risk of developing NPC ($OR=2.0$; 95% $CI=1.2\text{-}3.3$) [23].

When viewed from the number of cigarettes consumed every day, in the case group more cigarettes were smoked per day compared to the control group. The results of univariate logistic regression analysis showed significant differences with $OR=2.530$ ($p=0.021$) in smokers with the consumption of cigarettes 11-20 cigarettes per day. In multivariate logistic regression analysis, the number of cigarettes per day showed no significant difference with a value of $p=0.587$. More or less the same results were reported by Friborg (2007) in Singapore who found no relationship between the number of cigarettes consumed with the incidence of NPC, Cheng (1999) in Taiwan found that the number of cigarettes consumed did not have a significant effect on the occurrence of NPC [23]. In contrast to Zhu (1995) in the United States who found that the more cigarettes consumed, the level of estimation of relative risk increased for the occurrence of NPC. Chow (2006) in the United States has increased the risk of developing NPC as much as 6.4 times in people who consume more than 2 packs of cigarettes per day [12, 29].

Judging from the type of cigarette found smokers with the type of kretek were more in the case group than the control group. The results of the univariate logistic regression analysis showed no significant differences with $p=0.081$. In multivariate logistic regression analysis, the type of cigarette consumed did not show a significant difference with a value of $p>0.05$. In comparison to others, Pelucchi (2006) in Italy found an increase in the incidence of pharyngeal and oral cancers in smokers with filtered cigarettes compared to those who did not filter [21].

When viewed from variables outside the influence of smoking (confounding factors), people who consume salted fish before 10 years of age are more likely and the frequency of consumption is more frequent in the case group than in the control group. The results of univariate logistic regression analysis showed a very significant difference $p=0.000$ with each OR according to the frequency of consumption; rarely $OR=1.257$, sometimes $OR=3.882$, and often $OR=9.429$. In the multivariate logistic regression analysis, consuming salted fish before the age of 10 years showed a significant difference with the value of $p=0.000$ at the level of consumption frequency sometimes and rarely, with each OR according to the frequency of consumption; sometimes $OR=7.766$, and often $OR=16.515$. In this study, it means that every increase in the frequency of eating salted fish when before 10 years of age, the risk of getting the NPC will be greater. Ho (1985) in Hong Kong in a case-control study with 250 cases of NPC patients found that people who consumed salted fish at an early age with a frequency of at least one meal a week had a relative risk of 37.7 compared to those who consumed only 1 time per month, meanwhile in his research in Malaysia with 100 cases, it was found that people who consumed foreign fish at an early age had a relative risk of 17.4 compared to people who did not consume it. Yu (1989) in Guangzhou-China and found that consuming salted fish both in childhood and adulthood had a significant relationship with an increased risk of developing NPC [30]. Ning (1990) in Tianjin-China found that consuming salted fish at an early age with long consumption and increasing frequency levels would also have a high risk of the occurrence of NPC [31]. Zheng (1994) in Guangxi-China found that

people who consumed salted fish before 2 years of age had a risk of developing NPC with OR=3.8. Whereas Zou (1994) in Beijing-China obtained results that supported the conclusion of the risk of high occurrence of NPC in southern China as a result of consumption of salted fish in which there was a high level of N-nitrosamines [32, 33]. Armstrong (1998) in Malaysia found that there was a very clear relationship between the occurrence of NPC and the consumption of salted fish [6]. Yang (2005) in Taiwan found that there was a correlation between the incidence of NPC at an early age in people who consumed salted fish before the age of 10 years with OR=3.94 (95% CI=1.47-10.55) [3].

When viewed from fuelwood use, it was found that firewood users were more in the case group than in the control group. The results of the univariate logistic regression analysis showed no significant difference with $p=0.113$. In multivariate logistic regression analysis, firewood users showed significant differences with $p=0.014$ with OR=3.147. More or less the same results were reported by Zheng (1994) in Guangxi-China, where those who were exposed to smoke from household fires had a risk of developing NPC with OR=5.4. Armstrong (2000) in Malaysia found an association between firewood smoke exposure and NPC with OR=1.65 (95% CI=0.69-3.92) [3, 32]. Meanwhile McDermott (2004) in The Journal on the etiology of the NPC wrote that the population in Kenya exposed to firewood smoke has a relationship with NPC, where in the smoke analysis the firewood found high levels of carcinogenic hydrocarbons, namely benzpyrene and benzanthenicityne, other similar and consistent results were obtained in the population Alaska and Indonesia in people who often use firewood [4].

After testing multivariate logistic regression analysis in stages, it was found that only the age factor began smoking, consuming salted fish before the age of 10 years and the use of firewood alone can be tested statistically as risk factors for NPC. Then two confounding factors, namely the consumption of salted fish before the age of 10 years and the use of fuelwood with statistical tests were tried to be excluded, and the results showed that the use of fuelwood and consumption of salted fish before the age of 10 years is still a confounding factor that influences risk factors, so cannot be excluded as risk factors for NPC.

From the overall results, it can be said that there is a relationship between cigarettes and NPC, where smoking can be a risk factor for NPC if it has been smoked when it is less than 20 years old. But from statistical tests, it turns out that factors other than smoking (confounding factors), namely the factor of consumption of salted fish before the age of 10 years and the use of fuelwood also has a relationship with the NPC as a risk factor. So the cigarette factor as a risk factor for NPC cannot act as a stand-alone risk factor, but the consumption factor of salted fish before the age of 10 years and the use of fuelwood are also factors that will influence each other as risk factors for NPC. This is in accordance with what is reported in many studies in the literature that the etiology of NPC is multifactorial, and many of these factors overlap where one factor may occur together with other factors as a cause.

5. CONCLUSION

In this study, there is no relationship between the status of smoking and not smoking with nasopharyngeal carcinoma. However, the relationship between cigarette smoking and NPC, could be seen from the relationship between people who started smoking before the age of 20 years with the incidence of NPC there was a very significant difference ($p=0.000$) between NPC patients and non-NPC patients with an odds ratio of 5.350 (95% CI=2.290-12.499)

There were no significant differences in the duration of smoking, the number of cigarettes and the type of cigarettes smoked by the incidence of NPC, among NPC patients with non-NPC patients.

Risk factors other than smoking were also found to be significantly different, among NPC patients with non-NPC patients in people who consumed salted fish before 10 years of age, with the frequency of salted fish consumption sometimes ($p=0.000$), OR=7.766 (95% CI=2.937-20.538), often ($p=0.000$), OR=16.515 (95% CI=5.300-51.463), and firewood users ($p=0.014$), OR=3.147 (95% CI=1.260-7.860).

Cigarette smoking as a risk factor for NPC cannot act stand-alone as a risk factor but is also influenced by other factors, namely the consumption of salted fish before the age of 10 years and the use of fuelwood, where these factors will influence each other as risk factors the occurrence of NPC.

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