REVIEW

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Risk Factors Associated with Nasopharyngeal Cancer Incidences in Indonesia: A Systematic Review and Meta-Analysis

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Abstract

Objective: To determine the risk factors associated the incidence of NPC, particularly in Indonesia. **Methods:** This systematic review and meta-analysis was conducted according to PRISMA statement. Database including PubMed, Scopus, Science Direct, Web of Science, and GARUDA were retrieved. Newcastle-Ottawa scale was used to assess the quality of published study and analyse the risk of bias of included study. Random-effect model and reported pooled Odds Ratio (OR) with 95%CI was carried out in our meta-analysis. **Results:** A pooled of 7 studies were included in our study which included 764 participants. We found that female gender was not associated with the incidences of NPC (OR 1.45, 95% CI: 0.61-3.45, p=0.40), and smoking was highly increased the incidence of NPC (OR 4.39 95% CI (0.79-24.40), but not statistically significant (p=0.09). Furthermore, salted fish consumption and some HLA alleles were associated with increased risk. **Conclusion:** The incidence of NPC is not associated with female gender nor smoking habits. However, the risk of NPC is higher for those who consume salted fish and have some susceptible HLA alleles. Further investigations in larger studies are needed to confirm these findings.

Keywords: Nasopharyngeal cancer- Indonesia- gender- smoking- salted fish

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Introduction

Nasopharyngeal cancer (NPC) has always been one of the global burdens. In 2019, the incidence of NPC reached 176,500 number of cases globally. Indonesia became a country with the third highest mortality rate due to nasopharyngeal cancer, reaching 3,220 deaths in 2019 alone (Yu et al., 2022). Many socioeconomic and demographic factors contributed towards the higher incidence of NPC, starting from diet, lifestyle, to race (Okekpa et al., 2019). These risk factors, however, differ between populations and countries. Being a heterogenous country itself, Indonesia has varieties of ethnicities, culture, and dishes.

As a result, risk factors of NPC among Indonesians become diverse and cannot be generalized with other countries. For such reason, it is necessary to assess these risk factors independently. As no country is not affected by globalization, people in Indonesia have also been experiencing change of dietary habits, gradually changing from consuming the natural local goods to the chemically-preserved foods, such as instant meals and salted fishes in their dishes (Vasan, 2020). The current economic growth and the variety of geographical landscapes may also contribute to the changing flow of lifestyle. For instance, Indonesia has a high rate of tobacco consumption. The trend seems to never stop increasing as cigarette is one of the most substantial contributors towards Indonesia's national economy (Audrine, 2020). Not only that Indonesia provides many foods and culture, it also holds a heterogeneity of ethnicities, creating a special diversity of genetic predispositions toward certain diseases including NPC (Pradana et al., 2020).

As the risk factors of NPC in Indonesia has not yet been established and was found to be inconsistent throughout many studies, therefore, we aimed to conduct a systematic review and meta-analysis of the mentioned scope to assess the possible distinguished risk factor of NPC in Indonesia from pooled case-control studies.

Materials and Methods

Searching Strategy

This is PROSPERO-registered study (CRD42022316497) was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) (Page et al., 2021). A literature search was conducted on 5

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online databases (PubMed, ScienceDirect, Scopus, Web of Science, and Garuda) on March 12th, 2022 using the keywords presented in Supp. 1. As recommended in the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline (Stroup et al., 2000), collected all searches and removed the duplicates using Rayyan. Afterward, the title and abstract were screened independently to exclude articles with irrelevant topics. Finally, all aforementioned authors evaluated the available full texts based on the pre-established eligibility criteria and resolved any disagreement by discussion.

Eligibility Criteria

All case-control studies regarding lifestyle, dietary, and sociodemographic factors in adult patients with nasopharyngeal carcinoma within the past fifteen years were included into the analysis. On the other hand, there were some criteria to exclude the studies: (1) preclinical studies, case reports, case series, review papers, or editorial comments; (2) not published in English nor Indonesia; or (3) no wanted data.

Data Extraction

Data regarding authors, publication year, location, study design, sample size, and primary outcomes (NPC) were extracted by the four aforementioned authors and checked by other authors. The data were compiled into an online spreadsheet. The primary outcomes were the number of populations with risk factors of NPC (i.e., lifestyle, dietary, or sociodemographic factors) in the NPC patients versus the control subjects.

Quality Assessment

The risk of bias in all case-control studies were appraised using the Newscale-Ottawa Scale (NOS) tool. The reported outcome would be in numeric scale and classified according to the number of stars attributed for each item into high (seven to eight), medium (five to six), and low (less than five). Four prementioned authors contributed and resolved any disagreements over the risk of bias.

Data Analysis

Dichotomous data (with versus without risk factors) were presented as odds ratio (OR) and 95% confidence interval (95%CI). Heterogeneity analysis were conducted using the I^2 test. Subsequently, if the I^2 test were $\leq 50\%$, the analysis is considered to be homogenous and a Mantel–Haenszel (M-H) fixed-effect is applied. However, if the data were considered to be heterogenous, a M-H random-effect is applied. These statistical analyses are performed in Review Manager 5.4.

Results

Study selection

The overall study selection process is illustrated in Figure 1. The initial electronic database searches yielded 572 records. After deduplication process, the total studies were 436. Then 339 records were excluded based on the titles and abstracts. Total of 12 reports were excluded because of full-text not retrieved, 13 reports were excluded because of irrelevant study design, 19 reports were excluded because of unsuitable outcome, 14 reports were excluded because of wrong population and 7 reports were excluded because of inapt publication type. Finally, there were 7 studies included for qualitative analysis and 4 studies for quantitative analysis. All these

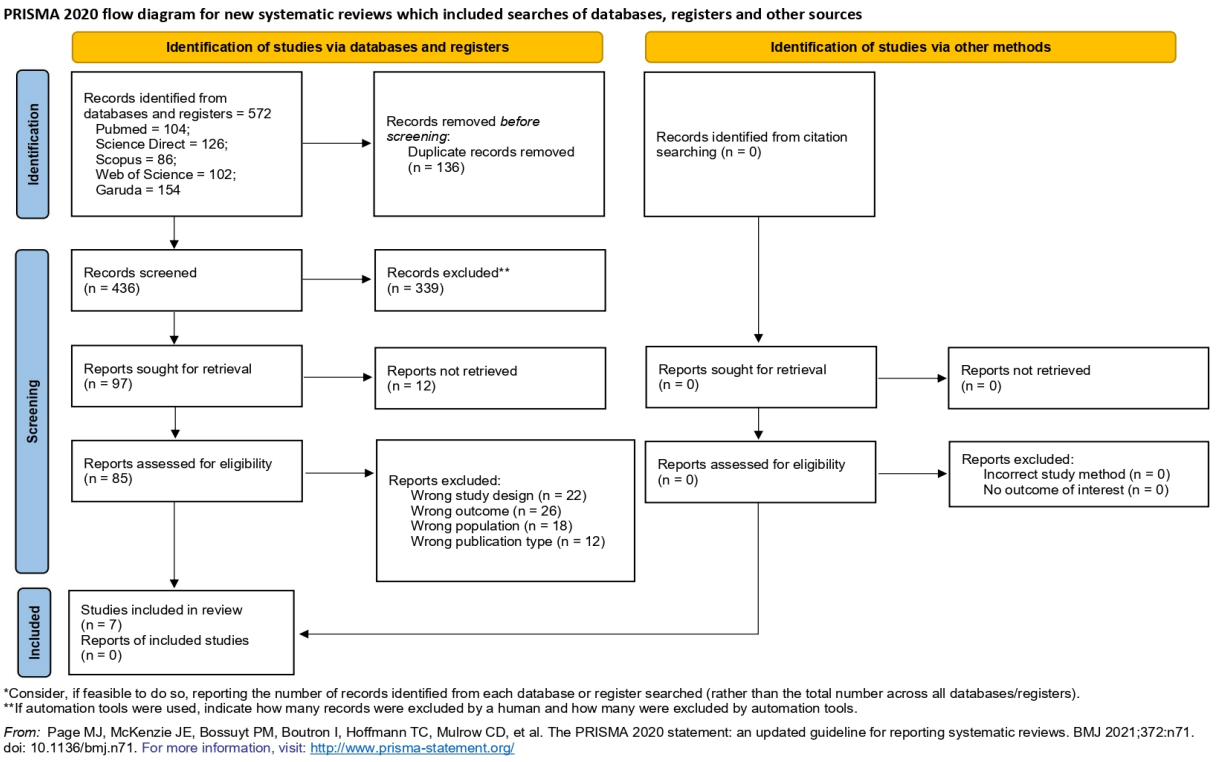

Figure 1. PRISMA Flowchart

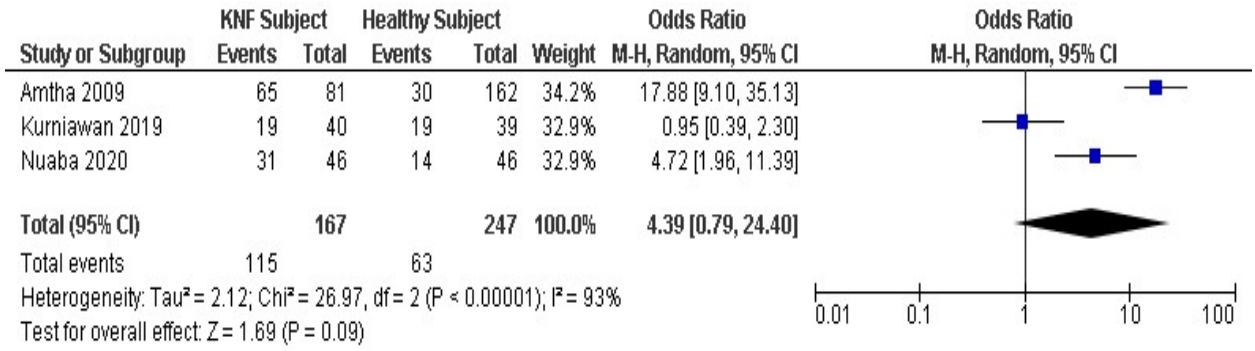

Figure 2. Forest Plot for Smoking Status as a Risk Factor for Nasopharyngeal Cancer

variables were reviewed for qualitative analysis of NPC risk factor in Indonesia.

Study characteristic

The characteristics of the included studies are summarized in Table 1. A total of 764 participants were included with a total of 368 were NPC subjects and 396 were healthy controls. The males dominated with percentages ranging from 47.8% to 70.1%. There were only three studies which reported smoking status as a result. One study disclosed about alcohol consumption, one study reported about salted fish consumption, and two studies described the distribution of HLA allele (Amtha et al., 2009; Arania R, Puji S, 2014; Judajana, 2018; Kurniawan et al., 2019; Nuaba et al., 2020; Purwanto, 2015; Tao Li et al., 1995).

Quality assessment of the studies

According to the Newcastle Ottawa Scale score for case-control studies, 4 studies have 7 scores, 1 study has 6 scores, 2 studies have 4 scores, given a satisfactory quality of bias among all studies. The item-specific quality assessment of the studies was showed in the Table 2.

Risk factor for NPC in Indonesia

Out of four studies, there were three reported higher incidences of NPC in male gender compared to woman (Amtha et al., 2009; Arania R, Puji S, 2014; Purwanto, 2015). The pooled analysis revealed that gender was not a significant risk factor of NPC in Indonesian population (OR 1.45, 95% CI: 0.61-3.45, p=0.40). However, a high level of heterogeneity was observed (I^2 = 72%). Smoking status analysis included three studies for meta-analysis (Amtha et al., 2009; Kurniawan et al., 2019; Nuaba et al., 2020) (Figure 2). The overall pooled analysis revelaed that smoking increased the odds of NPC, although no statistical emerge as risk factor (OR 4.39, 95% CI: 0.79-24.40) the risk of NPC; however, it was not statistically significant (p=0.09). The random effect model was used since the result showed a high level of heterogeneity (I^2 = 93%).

Nuaba et al. (2020) reported a significant result (p=0.036) regarding salted fish consumption, with OR 2.438 (1.051-5.654), meaning an increased risk to develop into NPC8. Meanwhile, Amtha et al., 2009 was the only study which compared the consumption of alcohol in NPC patients (1.2%) to healthy subjects (0.6%)(Amtha et al., 2009) (Figure 3). Two studies reported the association between HLA-antigen types with NPC. Judajana et al. (2009) disclosed a significant association between HLA–A24 (RR 2.25; p<0.001), HLA A2 (RR 1.635; p<0.001) and HLA A11 (RR 1.065; p<0.05), while study by Delfitri et al. (2011) revealed no association between HLA-DQB1 genotypes with NPC (Judajana, 2018; Tao Li et al., 1995).

Discussion

The results of our meta-analysis showed that male gender and smoking habits increased the risk of developing NPC in adult patients in Indonesia, though not statistically significant.

Smoking habit was identified as a risk factor for NPC development in various regions(Long et al., 2017; Okekpa et al., 2019). Our study revealed that smoking habit increases NPC risk with the OR 1.45; however,

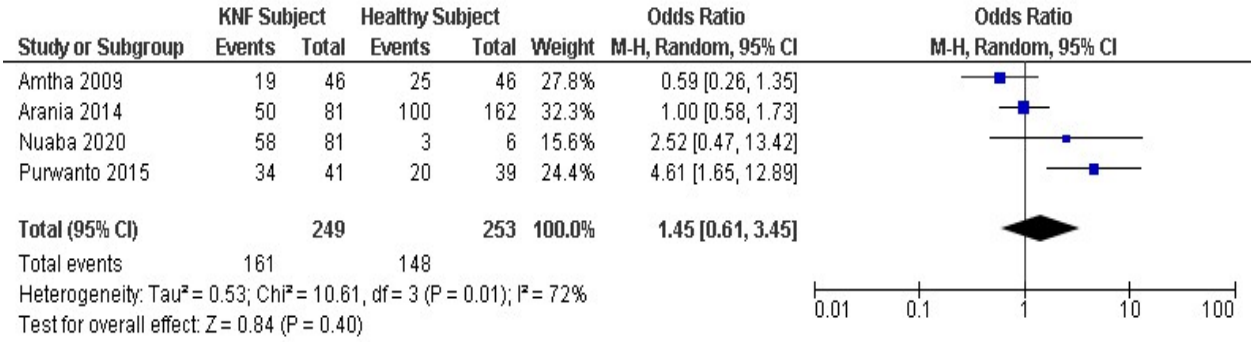

Figure 3. Forest Plot for Female Gender as a Risk Factor for Nasopharyngeal Cancer

Table 1. Pooled Data of Included Studies

Study; Country	Population, n (case vs control)	Study design	Age (Mean±SD/ n (%))		Gender, male n (%)	Outcome
			NPC	Control		
Nuaba, 2020; Indonesia	NPC (46) vs non-NPC (46)	Retrospective study	47.35±11.89	38.04±10.58	44 (47.8%)	Salted fish consumption, OR 2.438 95%CI (1.051-5.654), p=0.036 Smoking, OR 4.7 95%CI (1.959-11.389), p<0.001
Amtha et al., 2009; Indonesia	NPC (81) vs non-NPC (162)	Retrospective study	> 49 years, 35 (43.2%)	> 49 years, 69 (42.6%)	150 (61.7%)	Alcohol consumption, OR 2.012 95%CI (0.123-32.977), p=0.616 Smoking, OR 17.875 95%CI (9.096-35.126), p=0.000
Purwanto, 2015; Indonesia	NPC (81) vs non-NPC (6)	Retrospective study	≥ 40 years, 65 (80.3%)	≥ 40 years, 5 (83.3%)	61 (70.1%)	N/A
Arania et al., 2014; Indonesia	NPC (41) vs non-NPC (39)	Retrospective study	> 40 years, 34 (82.9%)	> 40 years, 7 (17.95%)	54 (67.5%)	N/A
Kurniawan, 2019; Indonesia	NPC (40) vs healthy controls (39)	Retrospective study	49.58 ± 2.56	50.58 ± 2.38	N/A	Smoking, OR 0.975 95%CI (0.420-2.262), p=0.91 Smoking duration, mean ± SD 28.89 ± 13.07 vs 33.21 ± 2.99, p=0.47 Cigarette/day, mean ± SD 8.95 ± 1.30 vs 12.89 ± 1.93, p=0.21
Judajana et al., 2009; Indonesia	NPC (24) vs non-NPC (N/A)	Retrospective study	N/A	N/A	N/A	HLA-A2, RR 1.635, p<0.001 HLA-A11, RR 1.065, p<0.05 HLA-A24, RR 2.25, p<0.001 HLA-B16, RR 1.632, p<0.05
Delfitri, 2011; Indonesia	Bataknese NPC patients (55) vs bataknese non-NPC patients (104)	Retrospective study	N/A	N/A	N/A	HLA-DQB1 *02, OR 1.65 95% CI (0.64-4.27), p=0.3 HLA-DQB1 *0301, OR 0.77 95% CI (0.37-1.7), p=0.49 HLA-DQB1 *0302, OR 0.62 95% CI (0.12-3.14), p=0.56 HLA-DQB1 *0303, OR 0.62 95% CI (0.06-6.14), p=0.68 HLA-DQB1 *0501, OR 0.67 95% CI (0.3-1.51), p=0.33 HLA-DQB1 *0502, OR 2.11 95% CI (0.85-5.25), p=0.1 HLA-DQB1 *0503, OR 1.02 95% CI (0.38-2.73), p=0.97 HLA-DQB1 *0601, OR 1.19 95% CI (0.52-2.75), p=0.68 HLA-DQB1 *0603, OR 1.93 95% CI (0.26-14.05), p=0.51 HLA-DQB1 *0609, OR 1.92 95% CI (0.12-31.1), p=0.65

NPC, nasopharyngeal cancer; N/A, not available; SD, standard deviation; CI, confidence interval; OR, odds ratio; RR, relative risk; HLA, human leukocyte antigen

the result was not statistically significant. In contrary to a meta-analysis conducted by Okekpa et al., (2019), the study showed similar but significant risk of smoking habit among people from Asia (OR 1.41, 95% CI: 1.27-1.57). Previous studies in several regions have shown a significant association of tobacco consumption, including in Indonesia (Amtha et al., 2009; Chang et al., 2017; Nuaba et al., 2020), although some were insignificant(Adoga et al., 2018; Kurniawan et al., 2019). Given a larger population in genetic diversity will present more representative results; however, limited studies and high heterogeneity might explain the difference in the current pooled analysis. We speculate that different susceptibility to smoking-related-DNA methylation among ethnicity could be one of the reasons. Even so, further studies are still needed to confirm such hypothesis (Elliott et al., 2014; Huang et al., 2015; Risanti et al., 2018).

The contact between smoke and nasopharynx has a direct chemical effect that irritates the epithelium. Moreover, nicotine present in tobacco contains nitrosamine-derived carcinogenic agents which promote carcinogenesis (Mydin and Okekpa, 2019).The regulation between cell-stimulating and cell-inhibitory factors played by α4β2 nicotinic-acetylcholine receptors (nAChRs) and α7nAChRs, respectively, were impaired. The level of nAChR which contributes to the regulation of various cellular activities was upregulated in smokers. Altered cellular signalling pathways will then result in disrupted microenvironment balance. Hence, enhanced tumor cell activities leading to carcinogenesis were seen(Mydin and Okekpa, 2019).

Lifestyle has been linked to correlate with NPC development, especially in maritime countries such as Indonesia where fish commodities were common(Mydin and Okekpa, 2019). Studies in Indonesia showed that salted fish consumption increased the risk of NPC significantly (OR 2.438; 95% CI: 1.051-5.654). This finding was correlated with nitrosamine, which could lead to carcinogenesis as discussed before(Mydin and Okekpa, 2019). Another lifestyle identified as a risk factor was alcohol consumption. Studies in various regions showed that heavy alcohol consumption significantly increases the risk of getting NPC (Chen et al., 2009; Du et al., 2019; Polesel et al., 2011), contrasting to a study in Indonesia that showed insignificant results (Amtha 2019). Increase in reactive oxygen species (ROS), lipid peroxidation, and acetaldehyde as alcohol by-products exert immune reactions, mutation, and DNA lesions (Mydin and Okekpa, 2019). However, Indonesia is a country with a majority of the citizens who are Muslims. It was found that alcohol had a dose-response relationship, hence, the risk was more extrusive in heavy compared to low alcohol consumption. This statement also explains the lack of data between alcohol consumption and NPC development in Indonesia, thus, pooling analysis was not possible for us to conduct (Chen et al., 2009; Polesel et al., 2011).

As our strength, this is the first systematic review and meta-analysis that identified the risk factors of NPC patients by evaluating case controls studies in Indonesia. However, we acknowledge several limitations in our

Table 2. Risk of Bias Analysis Using Newcastle-Ottawa Scale (NOS) for Case-Control

Newcastle-Ottawa Scale	Nuaba, 2020	Amtha,2009	Purwanto, 2015	Arania et al, 2014	Kurniawan, 2019	Delfitri, 2019	Judajana et al, 2019
Study Design	Case-Control	Case-Control	Case-Control	Case-Control	Case-Control	Case-Control	Case-Control
Selection							
Is the case definition adequate	1	1	0	0	1	1	1
Representativeness of the cases	1	1	1	1	0	0	1
Selection of Controls	1	1	0	0	0	1	0
Definition of Controls	0	0	0	0	1	1	1
Comparability							
Comparability of cases and controls on the basis of the design or analysis	1	1	1	1	1	1	1
Exposure							
Ascertainment of exposure	1	1	0	0	1	1	1
Same method of ascertainment for cases and controls	1	1	1	1	1	1	1
Non-Response Rate	1	1	1	1	1	1	1
Total Score	7	7	4	4	6	7	7

study. First, given the small number of studies, we cannot provide the pooled estimated effect of alcohol and salted fish consumption on the risk of NPC. Second, there was a high level of heterogeneity in both gender and smoking habits risk, so the random-effects model has been employed to minimize the variability effects.

In conclusion, the incidence of NPC is not associated with female gender nor smoking habits. However, the risk of NPC is higher for those who consummate salted fish and have some HLA alleles susceptibility. Further investigated in larger study are needed to confirm these findings.

Abbreviations

NPC: Nasopharyngeal Cancer, PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis, GARUDA: Garba Rujukan Digital, OR: Odds Ratio, CI: Confidence Interval, HLA: Human Leucocyte Antigen, NOS: Newscale-Ottawa Scale, M-H: Mantel–Haenszel, nAChRs : Nicotinic-Acetylcholine Receptors, DNA: Deoxyribo Nucleic Acid, ROS: Reactive Oxygen Species, MOOSE: Meta-Analysis of Observational Studies in Epidemiology.

Author Contribution Statement

ACR, PSR, and HRG conceptualizing and finding ideas; checking and revising the manuscript. CM and RRM screening, extracting, investigating, writing, editing, checking, and revising the manuscript. V and DN screening, extracting, analyzing, and writing the manuscript. All the authors have read and approved the final manuscript.

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Data Availability Statement

This manuscript use data previously published by other authors and all data are presented into results section.

Conflict of Interest

All authors declared no conflict of interest.

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