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Uniform Risk Profiles in Nasopharyngeal Carcinoma Across Sex and Age: Unmasking Smoking's Pivotal Role

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Abstract

Background

Nasopharyngeal carcinoma (NPC) has a multifactorial aetiology. Although the incidence of NPC varies markedly by sex and age, it remains unclear whether the profile of risk factors differs across these demographic groups. We aimed to compare the sex and age groups.

Methods

A cross-sectional study was conducted on 123 patients with histopathologically confirmed NPC. They completed a structured, questionnaire that had been tested for validity and reliability (Cronbach's alpha: 0.79–0.85). It assessed the family history, lifestyle (smoking and dietary habits), and environmental exposure (passive smoking, household/occupational exposure, and chronic nasopharyngitis). Risk scores were categorised into "no-to-low" and "medium-to-high". Chi-square tests with continuity correction and binary logistic regression were used to compare risk profiles between sexes (male vs. female) and age groups (< 40 vs. ≥40 y).

Results

The male-to-female ratio was 2:1 (82:41). Mean age was 47.6 y (SD ± 14.2), with 34 (27.6%) < 40 y and 89 (72.4%) ≥ 40 y. A family history of cancer was reported in 21 (17.1%) patients. No significant differences were found between the sexes for family history, lifestyle, environmental exposure risks, or combined total risk scores (all $p > 0.05$). However, active smoking was significantly more prevalent among males in both bivariate ($p < 0.001$) and multivariate analysis (AOR = 10.38, 95% CI: 4.52–23.84, $p < 0.001$). Similarly, no significant differences were observed between age groups for most variables, except for passive smoke exposure, which was significantly more prevalent in younger patients (38.2% vs. 18.0%, $p = 0.033$). Multivariate analysis confirmed passive smoke exposure as the only independent predictor of younger age at diagnosis (AOR = 3.06, 95% CI: 1.22–7.68, $p = 0.017$).

Conclusion

The risk factor profile for NPC was similar between sexes and age groups. However, active and passive smoke exposure were independently associated with younger age at diagnosis.

Simple Summary

Nasopharyngeal carcinoma (NPC) shows marked differences in incidence by sex and age, yet risk factor profiles appear similar across groups. This study of 123 Indonesian NPC patients found no significant differences in family history, lifestyle, or environmental exposures between males/females or younger

(<40 years)/older patients. However, active smoking strongly distinguished males (AOR 10.38), while passive smoke exposure independently predicted younger diagnosis (AOR 3.06). These findings urge universal prevention alongside targeted tobacco control

Introduction

Nasopharyngeal carcinoma (NPC) has a complex multifactorial aetiology that is not yet fully understood, and arises from interactions between genetic factors, environmental exposure, and Epstein-Barr virus (EBV) infection [1,2]. Hereditary factors, particularly family history of cancer, interact with various biological, physical, and chemical exposures in NPC pathogenesis. EBV infection and human leukocyte antigen polymorphisms are key genetic risk factors [3].

Significant biological exposure to NPC is characterised by elevated levels of antibodies to the viral capsid antigen and early antigen [4,5]. Lifestyle, home, and work exposures, including smoking, alcohol consumption, smoked/salted foods, and wood dust, are linked to NPC pathogenesis [6,7]. Research on inhalants, herbs, and occupational exposure is inconsistent because of study design flaws, bias, and confounding factors [8,9]. It consistently reports an age-related increase in NPC incidence, with a higher prevalence in males than females, at ratios ranging from 2:1 to 3:1 [10,11].

Increasing NPC incidence among young people presents a significant challenge, likely driven by unhealthy, carcinogenic childhood lifestyles (e.g., smoking and processed food). A 2002–2011 Semarang study showed improving trends alongside an increase in cases under 20 years of age [12]. This finding is consistent with those of recent systematic reviews highlighting the persistent burden of NPC in Indonesia [13]. Despite the declining mortality over the past three decades in China, rising NPC incidence rates indicate the need for stronger prevention efforts [14]. Although male-dominant, age-related NPC trends are known, Indonesian studies lack comprehensive data on multifactorial risks such as diet and environment across different demographics; therefore, this study aimed to compare the risk factor profiles of patients with NPC by sex and age groups

Materials and Methods

A descriptive-analytical design with a cross-sectional approach was used to investigate the risk factor profiles of patients with NPC. This research was part of an umbrella study conducted from 2022 to 2024 at the Dr. Kariadi Hospital in Semarang, Indonesia. The primary objective of this study was to compare the distribution of family history of cancer, lifestyle, and environmental exposure between sexes and across age groups among patients with histopathologically confirmed NPC.

Study Population and Participants

Consecutive patients with NPC with confirmed World Health Organization-classified histopathology was recruited from Dr. Kariadi Hospital. Inclusion required a definitive diagnosis and interview completion,

whereas incomplete records or different diagnoses were excluded. The final study included 123 patients, which is consistent with the typical sample size for NPC risk factor studies [13,15,16].

Research Instrument

Trained personnel conducted structured face-to-face interviews to collect the data. The questionnaire was based on an extensive literature review covering all the major domains of NPC aetiology [1–9,11]. The first section captured sociodemographic characteristics, including age at diagnosis, sex, marital status, occupation, monthly household income, highest educational level attained, and source of medical funding. The second section assessed family history of cancer, which has been consistently identified as a significant risk factor for NPC in both endemic and non-endemic populations [2,3]. The third section evaluates the lifestyle risk factors in detail [6,7,16]. The fourth section focused on environmental exposure [8,9]. A self-reported history of chronic nasopharyngitis has also been documented, and chronic inflammation of the nasopharyngeal epithelium has been proposed as a potential contributor to malignant transformation [3,4].

Ethic: This study was approved by the Research Ethics Committee of dr. Kariadi Hospital (No. 16206/EC/KEPK-RSDK/2024, dated 9 July 2024) and was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines and its subsequent amendments. Informed consent to participate was obtained from all participants in the study prior to enrolment.

Results

A total of 123 patients with NPC, with males outnumbering females 2:1, from 9–82 years ($\bar{x}$ = 47.6 ± 14.2). The 40–49 y age group was most common (33.3%), while only 5 people (4.1%) were under 20. (Table 1).

Table 1
Sociodemographic characteristics of the subjects (n = 123)

Variable	**Frequency (%)**
Sex	
Male	82 (66.7%)
Female	41 (33.3%)
Ages	
Mean	47.6
Median	48.0
Std. Deviation	14.15
Skewness	-0.123
Kurtosis	0.091
Minimum	9
Maximum	82
Group Ages	
< 20 y	5 (4.1%)
20–29 y	6 (4.9%)
30–39 y	23 (18.7%)
40–49 y	41 (33.3%)
50–59 y	26 (21.1%)
≥ 60 y	22 (17.9%)
Marital Status	
Not yet married	11 (8.9%)
Married	100 (81.3%)
Widow/widower	12 (9.8%)
Job	
Government Officer/BUMN	12 (9.8%)
Private Sector	25 (20.3%)
Farmer/fisherman	22 (17.9%)
Labor	32 (26.0%)

Variable	Frequency (%)
Household	18 (14.6%)
Retirement	7 (5.7%)
Unemployed/student/college student	7 (5.7%)
Head of Family Income per month (Rp)	
< 1 million	58 (47.2%)
1–2 million	36 (29.3%)
2.1-3 million	18 (14.6%)
> 3 million	11 (8.9%)
Last Education	
Elementary	68 (55.3%)
Junior High	12 (9.8%)
High School/Vocational High School	33 (26.8%)
University	10 (8.1%)
Medical Funds Source	
BPJS (Govermental-coverage insurance)	84 (68.3%)
Insurance	25 (20.3%)
Private Funding	14 (11.4%)

Cross-tabulation of the cancer family history scores showed that men (68.6%) were slightly more likely to be at risk than women (31.4%). However, the chi-square test with continuity correction (n = 123) showed no significant difference between the sexes (p = 0.581).

The total risk factor scores for NPC, including family history, lifestyle, and environment, did not differ significantly between the sexes (p = 1.00), indicating similar risks for men and women (Table 2). No significant difference in NPC risk (p = 0.518) was found between sexes, suggesting similar exposure levels. NPC risk is categorised by age: under 40 (young) and ≥ 40 (old). There were 27 young (26.5%) and 75 old (73.5%) patients in the low-risk group; this difference was not significant (p = 0.710). Analysis of the combined genetic, lifestyle, and environmental risks showed no significant NPC risk differences between young and old patients (chi-square, p = 0.102) (Table 2).

Table 2
The differences in the family history and combination of risk factors between gender and ages (n = 123)

Sex†	**Score of Family History with cancer[1]**		**Total**
	No (N) to Low-risk (L) (Score 1–6)	**Medium (M) to High (H) (Score 7–13)**	
Men	70 (68.6%)	12 (57.1%)	82 (66.7%)
Women	32 (31.4%)	9 (42.9%)	41 (33.3%)
Total	102 (100.0%)	21 (100.0%)	123 (100.0%)
	Total score of the combination of risk factors[2]		Total
	No (N) to Low-risk (L) (Score 1-150)	Medium to High (Score 151–253)	
Men	71 (67.0%)	11 (64.7%)	82 (66.7%)
Women	35 (33.0%)	6 (35.3%)	41 (33.3%)
Total	106 (100.0%)	17 (100.0%)	123 (100.0%)
Group of ages†	Score of Family History with Cancer[3]		Total
	N to L (Score 1–6)	M to (Score 7–13)	
< 40 y	27 (26.5%)	7 (33.3%)	34 (27.6%)
≥ 40 y	75 (73.5%)	14 (66.7%)	89 (72.4%)
Total	102 (100.0%)	21 (100.0%)	123 (100.0%)
	Total score of the combination of risk factors[4]		Total
	No to Low-risk (Score 1-150)	Medium to High (Score 151–253)	
< 40 y	26 (24.5%)	8 (47.1%)	34 (27.6%)

[1]Continuity correction chi-square (X^2) = 0.581, p = 0.446 (not significant)

[2]Continuity correction chi-square (X^2) = 0.0, p = 1.00 (not significant)

[3]Continuity correction chi-square (X^2) = 0.139, p = 0.710 (not significant)

[4]Continuity correction chi-square (X^2) = 2.677, p = 0.102 (not significant)

† M=medium; H=high; N = no; L = low

Sex†	Score of Family History with cancer[1]		Total
	No (N) to Low-risk (L) (Score 1–6)	Medium (M) to High (H) (Score 7–13)	
≥ 40 y	80 (75.5%)	9 (52.9%)	89 (72.4%)
Total	106 (100.0%)	17 (100.0%)	123 (100.0%)
[1]Continuity correction chi-square (X^2) = 0.581, p = 0.446 (not significant)			
[2]Continuity correction chi-square (X^2) = 0.0, p = 1.00 (not significant)			
[3]Continuity correction chi-square (X^2) = 0.139, p = 0.710 (not significant)			
[4]Continuity correction chi-square (X^2) = 2.677, p = 0.102 (not significant)			
† M=medium; H=high; N = no; L = low			

The total risk scores indicated that 66 men (66.0%) were in the no-to-low risk category compared to women (34), and fewer men (16) were at mid-high risk than women (7). Chi-squared tests showed no significant sex differences in the lifestyle risk of NPC (p = 0.935). The environmental exposure risk was not statistically significant (p > 0.05) (Table 3). Smoking history varied significantly by sex (45.5% overall), but only by 10.7% in females. Conversely, the consumption of salted fish, pickled foods, and instant noodles did not differ significantly by sex (Table 3).

Table 3
The differences in lifestyle and environmental exposure risks between gender (n = 123)

Lifestyle risk variable†	Sex		Total	Value *p*
	Men	Women		
Active smoking				*p* = 0.00*
N to L (score 1–20)	32 (47.8%)	35 (52.2%)	67 (100%)	
M to H (score 21–40)	50 (89.3%)	6 (10.7%)	56 (100%)	
Eating salted fish				*p* = 0.280**
N to L (score 1–8)	63 (70.0%)	27 (30.0%)	90 (100%)	
M to H (score 9–14)	19 (57.6%)	14 (42.4%)	33 (100%)	
Eating smoked/roasted fish/meat				*p* = 0.390**
N to L (score 1–8)	67 (69.1%)	30 (30.9%)	97 (100%)	
M to H (score 9–14)	15 (57.7%)	11 (42.3%)	26 (100%)	
Eating Pickles				*p* = 0.178**
N to L (score 1–8)	76 (69.1%)	34 (30.9%)	110 (100%)	
M to H (score 9–14)	6 (46.2%)	7 (53.8%)	13 (100%)	
Drinking liquor				*p* = 0.366**
N to L (score 1–8)	75 (65.2%)	40 (34.8%)	115 (100%)	
M to H (score 9–14)	7 (87.5%)	1 (12.5%)	8 (100%)	
Chewing betel habit				[a]
N to L (score 1–6)	82 (65.2%)	41 (33.3%)	123 (100%)	
M to H (score 7–11)	0 (0%)	0 (0%)	0 (0%)	
Eating instant noodles				*p* = 0.829**
N to L (score 1–10)	61 (67.8%)	29 (32.2%)	90 (100%)	
M to H (score 11–20)	21 (63.6%)	12 (36.4%)	33 (100%)	

* Continuity correction chi-square (X^2), $p < 0.05$ (significant)

** Continuity correction chi-square (X^2), $p > 0.05$ (not significant)

[a] No statistics are computed because 'Total conversion score of chewing betel risk' is a constant.

† M=medium; H=high; N = no; L = low

Lifestyle risk variable[†]	Sex		Total	Value *p*
	Men	Women		
Eating canned/preserved food				*p* = 1.00**
N to L (score 1–16)	75 (67.0%)	37 (33.0%)	112 (100%)	
M to H (score 17–28)	7 (63.6%)	4 (36.4%)	11 (100%)	
Eating MSG contained food				*p* = 0.073**
N to L (score 1–10)	69 (71.1%)	28 (28,9%)	97 (100%)	
M to H (score 11–18)	13 (50.0%)	13 (50.0%)	26 (100%)	
Total				*p* = 0.935**
N to L (score 1–86)	66 (66,0%)	34 (34,0%)	100 (100%)	
M to H (score 87–159)	16 (69,6%)	7 (30,4%)	23 (100%)	
Environmental risk[†]				
Passive smoker				*p* = 0.202**
N to L (score 1–12)	66 (70.2%)	28 (29.8%)	94 (100%)	
M to H (score 13–20)	16 (55.2%)	13 (44.8%)	29 (100%)	
Household exposure				*p* = 0.219**
N to L (score 1–12)	77 (68.8%)	35 (31.3%)	112 (100%)	
M to H (score 13–17)	5 (45.5%)	6 (54.5%)	11 (100%)	
Work-related exposure				p = 0.857**
N to L risk (score 1–28)	80 (67.2%)	39 (32.8%)	119 (100%)	
M to H (score 29–47)	2 (50.0%)	2 (50.0%)	4 (100%)	
Chronic nasopharyngitis				*p* = 0.131**
N to L (score 1–6)	64 (71.1%)	26 (28.9%)	90 (100%)	
M to H (score 7–10)	18 (54.5%)	15 (45.5%)	31 (100%)	

* Continuity correction chi-square (X^2), p < 0.05 (significant)

** Continuity correction chi-square (X^2), p > 0.05 (not significant)

[a] No statistics are computed because 'Total conversion score of chewing betel risk' is a constant.

[†] M=medium; H=high; N = no; L = low

Lifestyle risk variable[†]	Sex		Total	Value *p*
	Men	Women		
Total				*p* = 0.518**
N to L (score 1–58)	78 (67.8%)	37 (32.2%)	115 (100%)	
M to H (score 59–94)	4 (50.0%)	4 (50.0%)	8 (100%)	
* Continuity correction chi-square (X^2), p < 0.05 (significant)				
** Continuity correction chi-square (X^2), p > 0.05 (not significant)				
[a] No statistics are computed because 'Total conversion score of chewing betel risk' is a constant.				
[†] M=medium; H=high; N = no; L = low				

The analysis of lifestyle risks (Table 4) revealed no significant differences (p > 0.05) across all variables. Active smoking, consumption of salted/smoked/roasted food, pickles, liquor, instant noodles, canned food, and MSG posed similar NPC risks for both age groups (< 40 and ≥ 40 y). The chi-square test confirmed no total risk difference between the age groups (p = 0.555). Passive smoke risk was significantly higher for those < 40 years (38.2%) than ≥ 40 (18.0%, p = 0.033), indicating younger age increases NPC risk. Conversely, home, occupational, and chronic nasopharyngitis exposures showed no significant differences between the age groups (p > 0.05). Home, work, and chronic nasopharyngitis exposures pose equal NPC risks across all ages, with no significant difference between young and old individuals (chi-square, p = 0.863).

Table 4
The differences in lifestyle risk, household exposure between ages (n = 123)

Lifestyle risk variable[†]	**Group of Ages (years)**		**Total**	**Value *p***
	< 40	**≥ 40**		
Active smoking				*p* = 1.00**
N to L (score 1–20)	19 (28.4%)	48 (71.6%)	67 (100.0%)	
M to H (score 21–40)	15 (26.8%)	41 (73.2%)	56 (100.0%)	
Eating salted fish				*p* = 0.279**
N to L (score 1–8)	22 (24.4%)	68 (75.6%)	90 (100.0%)	
M to H (score 9–14)	12 (36.4%)	21 (63.6%)	33 (100.0%)	
Eating smoked/roasted fish/meat				*p* = 0.253**
N to L (score 1–8)	24 (24.7%)	73 (75.3%)	97 (100,0%)	
M to H (score 9–14)	10 (38.5%)	16 (61.5%)	26 (100,0%)	
Eating Pickles				*p* = 0.552**
N to L (score 1–8)	29 (26.4%)	81 (73.6%)	110 (100.0%)	
M to H (score 9–14)	5 (38.5%)	8 (61.5%)	13 (100.0%)	
Drinking liquor				*p* = 1.00**
N to L (score 1–8)	32 (27.8%)	83 (72.2%)	115 (100.0%)	
M to H (score 9–14)	2 (25.0%)	6 (75.0%)	8 (100.0%)	
Chewing betel habit				[a]
N to L (score 1–6)	34 (27.6%)	89 (72.4%)	123 (100%)	
M to H (score 7–11)	0 (0%)	0 (0%)	0 (0%)	
Eating instant noodles				*p* = 0.863**
N to L (score 1–10)	24 (26.7%)	66 (73.3%)	90 (100%)	
M to H (score 11–20)	10 (30.3%)	23 (69.7%)	33 (100%)	

* *Continuity correction chi-square* (X^2), $p < 0.05$ (significant)

** *Continuity correction chi-square* (X^2), $p > 0.05$ (not significant)

[a] *No statistics are computed because* the total conversion score of chewing betel risk' *is a constant.*

[†] M=medium; H=high; N = no; L = low

Lifestyle risk variable†	Group of Ages (years)		Total	Value *p*
	< 40	≥ 40		
Eating canned/preserved food				*p* = 0.303**
N to L (score 1–16)	29 (25.9%)	83 (74.1%)	112 (100%)	
M to H (score 17–28)	5 (45.5%)	6 (54.5%)	11 (100%)	
Eating MSG contained food				
N to L (score 1–10)	23 (23.7%)	74 (76.3%)	97 (100%)	
M to H (score 11–18)	11 (42.3%)	15 (57.7%)	26 (100%)	
Total				*p* = 0.555**
N to L (score 1–86)	26 (26.0%)	74 (74.0%)	100 (100%)	
M to H (score 87–159)	8 (34.8%)	15 (65.2%)	23 (100%)	
Environmental risk†				
Passive smoker				*p* = 0.033*
N to L (score 1–12)	21 (22.3%)	73 (77.7%)	94 (100.0%)	
M to H (score 13–20)	13 (38.2%)	16 (18.0%)	29 (100.0%)	
Household exposure				*p* = 1.00**
N to L (score 1–12)	31 (27.7%)	81 (72.3%)	112 (100.0%)	
M to H (score 13–17)	3 (27.3%)	8 (72.7%)	11 (100.0%)	
Work-related exposure				*p* = 1.00**
N to L risk (score 1–28)	33 (27.7%)	86 (72.3%)	119 (100.0%)	
M to H (score 29–47)	1 (25.0%)	3 (75.0%)	4 (100.0%)	
Chronic nasopharyngitis				*p* = 0.124**
N to L (score 1–6)	21 (23.3%)	69 (76.7%)	90 (100.0%)	
M to H (score 7–10)	13 (39.4%)	20 (60.6%)	33 (100.0%)	

* *Continuity correction chi-square* (X^2), $p < 0.05$ (significant)

** *Continuity correction chi-square* (X^2), $p > 0.05$ (not significant)

[a] *No statistics are computed because* the total conversion score of chewing betel risk' *is a constant.*

† M=medium; H=high; N = no; L = low

Lifestyle risk variable[†]	Group of Ages (years)		Total	Value *p*
	< 40	≥ 40		
Total				*p* = 1.00**
N to L (score 1–58)	32 (27.8%)	83 (72.2%)	115 (100.0%)	
M to H (score 59–94)	2 (25.0%)	6 (75.0%)	8 (100.0%)	
* *Continuity correction chi-square* (X^2), $p < 0.05$ (significant)				
** *Continuity correction chi-square* (X^2), $p > 0.05$ (not significant)				
[a] *No statistics are computed because* the total conversion score of chewing betel risk' *is a constant.*				
[†] M=medium; H=high; N = no; L = low				

To identify the dominant risk factors and control for confounders, binary logistic regression was performed for two outcomes: sex and age (< 40 vs. ≥40 years). Variables associated with outcomes at p < 0.25 in the bivariate analysis were included in multivariate models [25]. Table 5 presents the full results.

Table 5
The binary logistic regression analysis of factors associated with sex and age group (n = 123)

Variable	Category†	B	Wald	p-value	AOR	95% CI
Sex (Male vs. Female)						
Active smoking	M/H vs. N/L	2.34	18.45	< 0.001	10.38	4.52–23.84
Pickled foods	M/H vs. N/L	-0.42	0.89	0.345	0.66	0.28–1.56
MSG-containing foods	M/H vs. N/L	0.51	1.23	0.267	1.67	0.67–4.16
Passive smoke exposure	M/H vs. N/L	0.38	0.76	0.383	1.46	0.62–3.44
Household exposure	M/H vs. N/L	0.67	1.02	0.313	1.95	0.53–7.19
Chronic nasopharyngitis	M/H vs. N/L	0.59	1.87	0.172	1.80	0.77–4.21
Constant		-1.23	8.91	0.003	0.29	—
Age Group (< 40 y vs. ≥40 y)						
Salted fish	M/H vs. N/L	0.52	1.45	0.229	1.68	0.72–3.92
Smoked/roasted fish/meat	M/H vs. N/L	0.44	0.98	0.322	1.55	0.65–3.70
Canned/preserved foods	M/H vs. N/L	0.71	1.34	0.247	2.03	0.61–6.76
MSG-containing foods	M/H vs. N/L	0.63	2.12	0.145	1.88	0.80–4.42
Passive smoke exposure	M/H vs. N/L	1.12	5.67	0.017	3.06	1.22–7.68
Chronic nasopharyngitis	M/H vs. N/L	0.76	3.12	0.077	2.14	0.92–4.98
Constant		-1.56	12.34	< 0.001	0.21	—
† M=medium; H=high; N = no; L = low						
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Based on the bivariate analysis (Table 3), variables with $p < 0.25$ entered into the sex logistic regression model included: active smoking, pickled foods, MSG consumption, passive smoking, household exposure, and chronic nasopharyngitis. After adjusting for all variables, only active smoking remained a statistically significant factor for distinguishing male from female NPC.

In Table 5, male had approximately 10 times higher odds of being in the medium-to-high risk category for active smoking compared to female (AOR = 10.38, 95% CI: 4.52–23.84, $p < 0.001$). The Hosmer-Lemeshow test indicated a good model fit ($\chi^2 = 6.78$, $p = 0.56$). Logistic regression for age comparisons included bivariate variables ($p < 0.25$; Table 4). After adjustments, high passive smoke exposure significantly predicted earlier NPC diagnosis. Those in medium-to-high risk groups showed 3 times

higher odds of diagnosis before age 40 than low-risk individuals (AOR = 3.06, 95% CI: 1.22–7.68, p = 0.017).

Discussion

Although NPC risk profiles are similar across demographics, passive smoke exposure is a major independent risk factor for diagnosis in patients aged < 40 years. Although the causes of the disease are generally consistent, this finding suggests that the timing and type of exposure differ among younger patients, and require targeted prevention.

The 2:1 male: female ratio aligns with the well-documented global sex disparity in the incidence of NPC. Similar ratios in Indonesian, Middle Eastern, and North African populations reinforce this consistent and diverse epidemiological pattern [13,15,18]. A recent Asian cohort analysis linked reproductive factors to NPC risk, suggesting hormonal influences [19], consistent findings suggest that NPC susceptibility drivers are not geographically unique. However, similar risk profiles across sexes indicate that the higher incidence in males is not fully explained by the traditional risk factors we examined. This paradox suggests that differing incidence rates, despite similar risk profiles, may stem from unmeasured factors, such as genetics, EBV subtypes, or hormonal influences [3,4,19,24].

Significant sex differences in smoking were expected owing to its high prevalence among Indonesian men [20]. The World Health Organization reported that Indonesia has one of the world's highest male smoking rates, with over 60% of men being current smokers [17]. In the bivariate analysis, active smoking was substantially more prevalent among males, with 89.3% of male patients in the medium-to-high-risk category compared to only 10.7% of females). Multivariate analysis confirmed that active smoking was a single independent factor separating the sexes in terms of NPC risk. Males had 10 times higher odds of medium-to-high risk than females (AOR = 10.38, p < 0.001). Defined as daily/occasional tobacco use, this study's definition of active smoking aligns with the standard epidemiological criteria [17,21]. At 89.3%, smoking in our Indonesian male cohort was nearly four times the 25% global average, emphasising the need for tobacco control for NPC prevention [17]. Despite this, the overall lifestyle risk score did not differ significantly between the sexes (p = 0.935), suggesting comparable lifestyle habits, such as diet, in this population. An Indonesian meta-analysis confirmed that while smoking is a risk factor, sex-specific incidence is also influenced by genetics and EBV infection [13]. The carcinogenic load of smoking, including nitrosamines, likely interacts with genetic or viral factors to disproportionately amplify cancer risk in males, even at similar exposure levels [21,22].

Younger patients with NPC (< 40 years) had a significantly higher passive smoke exposure risk than older ones, with 38.2% classified as medium-to-high risk compared to 18.0% (p = 0.033). Multivariate analysis showed passive smoke as the only independent predictor of younger diagnosis. Medium-to-high risk patients had triple the odds of being diagnosed before age 40 (AOR = 3.06, 95% CI: 1.22–7.68, p = 0.017). This study reveals a novel age-related link in the NPC literature: early life passive smoking exposure may be a critical driver in initiating nasopharyngeal carcinogenesis at a younger age. The

nasopharyngeal epithelium in children and adolescents has higher cell proliferation, and an immature immune system may increase carcinogen vulnerability, potentially leading to malignant transformation after exposure [22,23], 40% of young patients in our study faced medium-to-high second-hand smoke exposure, a major concern.

Unlike passive smoking, similar consumption of salted fish, pickled foods, and instant noodles across all age groups suggests consistent exposure to dietary carcinogens. Salted fish, rich in N-nitrosamines, is a key Asian dietary risk factor for NPC, often introduced in early life [6,13]. The absence of age-related differences may reflect that dietary habits are established in childhood and persist into adulthood, making it difficult to detect temporal differences in cross-sectional studies. This finding highlights the importance of prospective cohort studies to better understand the timing and duration of exposure required for carcinogenesis.

A trend was observed for chronic nasopharyngitis, which approached, but did not reach statistical significance. The higher proportion of younger patients in the medium-to-high-risk category for chronic nasopharyngitis (39.4% vs. 23.3% in the low-risk category) is noteworthy and may suggest a trend worthy of further investigation. Chronic childhood nasopharyngeal inflammation may contribute to early malignant transformations, particularly when combined with other risk factors [3,4]. The small sample size and limited power likely hindered the identification of significant effects. This study had two key implications. First, uniform risk across age groups and sex necessitates universal prevention measures. Strategic efforts should include reducing tobacco exposure, improving diet (less salted fish/preserved foods), and increasing NPC awareness for the entire population, not just high-risk groups. Second, the specific findings regarding passive smoke exposure in younger patients call for targeted interventions to protect children and adolescents. These findings provide a strong rationale for prioritising policies that create smoke-free environments in households, schools, and public spaces frequented by children and adolescents.

The present findings highlight the persistent complexity of nasopharyngeal carcinoma (NPC) pathogenesis, where Epstein–Barr virus (EBV) infection alone is insufficient for malignant transformation, requiring co-factors such as environmental carcinogens and host susceptibility [26, 27]. The similarity of risk profiles across sex and age groups is consistent with large epidemiological studies indicating that endemic populations share relatively homogeneous exposure patterns, particularly dietary nitrosamines and environmental risks [28,29]. Importantly, the association between tobacco exposure and earlier onset supports mechanistic evidence that smoking promotes EBV lytic activation, oxidative stress, and genomic instability in nasopharyngeal epithelium [30,31]. These findings reinforce the importance of integrating tobacco control with EBV-based screening and early detection strategies to effectively reduce NPC burden in high-risk regions [32].

Conclusion

The overall risk factor profile for NPC is largely similar between the sexes and across age groups; therefore, universal prevention strategies targeting smoking cessation and healthy dietary habits remain essential for the general population. Future prospective studies are warranted to further elucidate the aetiology of early onset NPC and to develop more precise prevention strategies.

Declarations

Conflict of Interest:

None.

Funding Statement:

None

Author Contribution

AP, US, RA contributed to the study conception and design, as well as the final data analysis, interpretation and manuscript drafting. DS was responsible to ensuring data accuracy and integrity. DR, BS, EAP, YWP, CHWP, AP contributed to finalization of the manuscript report. All authors have read and approved the final version of the manuscript

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Data Availability

The data used to support the findings of this study are restricted by the Ethics Committee of the Faculty of Medicine, Diponegoro University, and Dr. Kariadi Hospital and available on request from the corresponding author, (AP). The data are not publicly available due to the information that could compromise the privacy of the research participant.

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