Risk Factors and Diagnosis of Head and Neck Squamous Cell Carcinoma

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Abstract

Head and Neck Squamous Cell Carcinoma (HNSCC) ranks among the seven most prevalent malignancies globally, associated with significant morbidity and mortality rates. The key risk factors for this malignancy include chronic alcohol consumption, tobacco use, immunosuppression, and infections with oncogenic viruses such as high-risk Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV). This study was a retrospective analysis of HNSCC patients seen at an oncology clinic over a five-year period from January 2015 to December 2020, focusing on the environmental and genetic factors contributing to the disease. A cohort of 1,640 patients was analyzed, assessing their risk factors and diagnostic outcomes. Results indicated that smoking and alcohol consumption were the most significant independent risk factors, displaying a synergistic effect in disease progression. Other variables explored were exposure to air pollution, HPV and EBV infections, age, dietary deficiencies in vegetables, and genetic predispositions. While some factors were statistically significant, others showed weaker associations. This study highlights the importance of preventive strategies focusing on modifiable risk factors, such as lifestyle changes and viral vaccination, to reduce the incidence of HNSCC.

Keywords: Alcohol, carcinoma, diagnosis, head and neck cancer

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a complex group of malignancies arising from the squamous epithelium of the upper aerodigestive tract. This category encompasses cancers of the oral cavity, pharynx, larynx, and sinonasal tract. HNSCC poses a significant global health challenge, ranking as the seventh most prevalent cancer worldwide according to GLOBOCAN 2020 estimates.[1,2]

The problem of HNSCC is multifaceted. Despite advances in treatment modalities, the prognosis for many HNSCC patients remains poor, with high rates of recurrence and metastasis. Additionally, the incidence of HNSCC continues to rise in certain populations, particularly in developing countries. This trend is largely attributed to changes in risk factor exposure, including tobacco use, alcohol consumption, and human papillomavirus (HPV) infection.[3]

The scope of this research encompasses the epidemiology, risk factors, and diagnostic challenges associated with HNSCC. We aim to elucidate the complex interplay between environmental, viral, and genetic factors that contribute to HNSCC development. Understanding these interactions is crucial for developing effective prevention strategies and improving early detection methods. [1-3]

Several factors contribute to the risk of developing Head and Neck Squamous Cell Carcinoma (HNSCC), highlighting its multifactorial nature. Among these, modifiable risk factors like alcohol consumption and tobacco usage, deeply ingrained in societal norms, are principal catalysts for HNSCC. Additionally, environmental pollutants, such as carcinogenic air pollutants, pose significant risks, especially in developing countries grappling with worsening air pollution. Chewing of areca nut products in specific cultural and geographical areas is also associated with an elevated risk.[4]

Viral infections are key risk factors; HPV

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infection, primarily transmitted through oral sex, significantly increases HNSCC risk, particularly in the oropharynx. Persistent Epstein-Barr virus (EBV) infection is another risk factor, particularly for nasopharyngeal cancer.[5]

Aging is an inevitable factor, as the risk of HNSCC increases with age. Poor oral hygiene and diets lacking in vegetables are additional risk factors that can be mitigated by promoting good oral hygiene practices and balanced diets.[5]

Genetic factors also play a crucial role in the development of HNSCC. Individuals with Fanconi anemia (FA), an inherited genetic disorder that impairs DNA repair, are at a significantly higher risk. Specific genetic polymorphisms in genes related to carcinogen metabolism and immune response have been associated with an increased risk of HNSCC. These multifactorial influences highlight the complexity of HNSCC development and underscore the importance of considering both environmental and genetic factors in understanding and mitigating the disease.[6] This study aims to provide a comprehensive overview of the current risk factors and diagnostic approaches for HNSCC.

Methods

This study used a retrospective, hospital-based design spanning five years, from January 2015 to December 2020. It was conducted at the oncology ORL-HNS clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

The study included patients diagnosed with Head and Neck Squamous Cell Carcinoma (HNSCC) who had complete medical records. Patients with incomplete datasets or comorbidities that could significantly influence HNSCC risk, such as immune system disorders or genetic syndromes, were excluded.

Medical records were reviewed to extract demographic information, risk factor exposure, and diagnostic outcomes. Risk factors assessed included tobacco use, alcohol consumption, exposure to carcinogenic air pollutants, HPV and EBV infections, dietary habits, and family history of HNSCC. The diagnosis of HNSCC was confirmed through clinical examination and histopathological analysis. Anatomical sites were classified according to the American Joint Committee on Cancer (AJCC) guidelines, encompassing the nasopharynx, larynx, sinonasal regions, oropharynx, hypopharynx, oral cavity, thyroid gland, parotid gland, and neck.

Statistical analysis was performed using IBM SPSS Statistics version 25.0. Descriptive statistics were applied to summarize patient characteristics and the prevalence of risk factors, with frequencies and percentages calculated for categorical variables, and means and standard deviations for continuous variables. Logistic regression analysis was conducted to evaluate the association between risk factors and HNSCC. Initially, univariate logistic regression was applied to each risk factor, and variables showing a significant association (p<0.1) were included in a multivariate logistic regression model to control for potential confounding factors. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the strength of associations between risk factors and HNSCC. The goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow test. For continuous variables, independent t-tests or Mann-Whitney U tests were used, depending on the normality of data distribution as assessed by the Shapiro-Wilk test. Chi-square tests or Fisher's exact tests were applied to categorical variables as appropriate. Power analysis was conducted using G*Power 3.1 to ensure an adequate sample size for detecting clinically meaningful effects. Based on this analysis, the sample size of 1,640 patients provided 80% power to detect an odds ratio of 1.5 at a significance level of 0.05.

The study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung (approval number: DP.04.03/D.XIV.6.5/79/2024). All procedures were conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, along with its later amendments. Informed consent was obtained from all individual participants included in the study, and patient confidentiality was maintained throughout the research process.

De-identified data used in this study are available from the corresponding author upon reasonable request, in accordance with institutional data sharing policies.

Results

Between 2015 and 2020, a total of 1,640 outpatient visits were recorded. The distribution of HNSCC patients over the five-year period is shown in Figure 1. According to Figure 1, nasopharyngeal carcinoma was the most common type of HNSCC, accounting for the

Table 1 Demographic Distribution of HNSCC Patients by Age Group and Gender

	Number of HNSCC Patients	Percentage (%)
Age (years)		
<20	55	3.35
21–30	146	8.9
31–40	219	13.35
41–50	422	25.73
51–60	432	26.34
61–70	251	15.3
>70	115	7.01
Gender		
Male	1027	62.62
Female	613	37.38

majority of cases among the 1,640 patients, followed by laryngeal carcinoma (178 patients) and maxillary sinus carcinoma (128 patients). The most common age group was 51–60 years, with 432 patients (Table 1).

In this retrospective analysis conducted within a hospital setting, a cohort of 1,640 patients diagnosed with HNSCC was meticulously investigated over five years. The findings of this investigation unveiled noteworthy insights. Among the entire HNSCC population (n=1,640), a gender-based distribution was apparent, with 1027 patients (62.62%) being male and 613 patients (37.38%) being female. Deeper analysis within this specified HNSCC population revealed intricate subgroups: 1051 patients identified as exclusive smokers (comprising 825 males and 226 females), and 553 patients categorized as comprehensive alcohol consumers, encompassing both exclusive alcohol consumers and those who were both alcohol consumers and smokers. Notably, within the latter category, 36 individuals were solely alcohol consumers. Exposure to Carcinogenic Air Pollutants was identified in 278 individuals (16.95%), with 169 males and 109 females in this category. HPV infection affected 342 patients (20.85%), with 187 males and 155 females. EBV infection was found in 119 patients (7.26%), comprising 68 males and 51 females. Patients were stratified into different age groups. The majority fell into the 50–65 age range, accounting for 789 patients (48.11%), while 451 patients (27.5%) were aged 66 and above, and 400 patients (24.39%) were below the age of 50. A total of 312 patients (19.02%) had diets lacking in vegetables, with 194 males and 118 females falling into this category. Genetic factors were considered in 88 cases (5.37%), with 45 males and 43 females having a family history of HNSCC or genetic predisposition. These findings shed light on the multifaceted nature of HNSCC risk factors within this patient cohort. In this study, we have examined various factors and their association

Table 2 Analysis of Risk Factors – Odds Ratios and Statistical Significance

Variable	Odds Ratio (OR)	p-value	95% Confidence Limit
Alcohol consumption	1.65	0.023*	1.12–2.42
Tobacco usage	2.12	0.001*	1.43–3.14
Exposure to carcinogenic air pollutants	1.78	0.009*	1.21–2.61
HPV infection	1.43	0.042*	1.02–2.01
EBV infection	1.25	0.167	0.89–1.76
Age group	1.96	0.005*	1.34–2.88
Diets lacking in vegetables	1.34	0.073	0.98–1.83
Genetic factors	1.55	0.031*	1.09–2.21

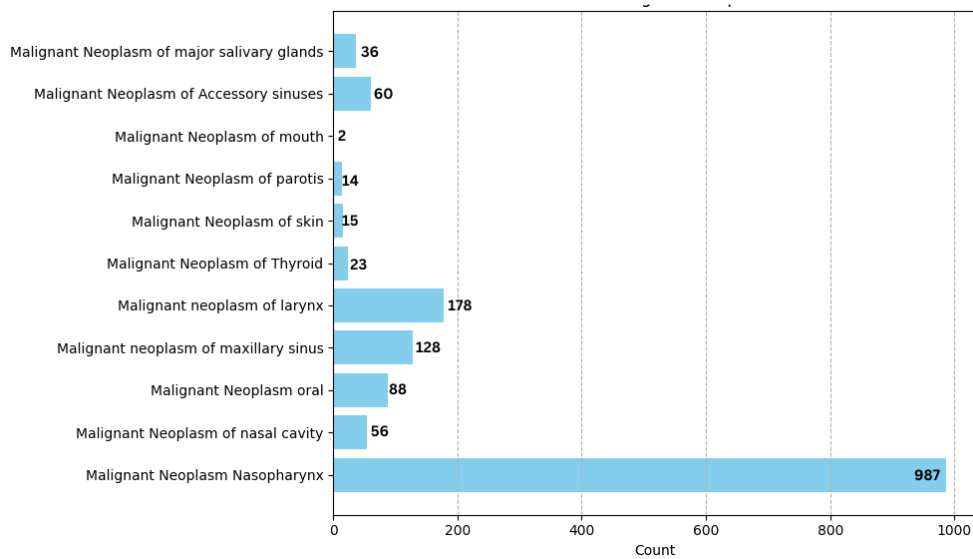| Category	Count
Malignant Neoplasm of major salivary glands	36
Malignant Neoplasm of Accessory sinuses	60
Malignant Neoplasm of mouth	2
Malignant Neoplasm of parotis	14
Malignant Neoplasm of skin	15
Malignant Neoplasm of Thyroid	23
Malignant neoplasm of larynx	178
Malignant neoplasm of maxillary sinus	128
Malignant Neoplasm oral	88
Malignant Neoplasm of nasal cavity	56
Malignant Neoplasm Nasopharynx	987

Figure 1 HNSCC in Outpatient Clinic

with the risk of a particular condition. The table presents the results of this study, displaying the odds ratios (OR), p-values, and corresponding 95% confidence intervals for each factor.

Alcohol consumption was found to be significantly associated with an odds ratio of 1.65 (p=0.023), indicating that individuals who consume alcohol have a 65% higher risk of the condition compared to those who do not. The 95% confidence interval (CI) for this association ranged from 1.12 to 2.42.

Tobacco use showed a stronger association, with an odds ratio of 2.12 (p=0.001), suggesting that individuals who use tobacco have more than twice the risk of the condition. The 95% CI for this relationship spanned from 1.43 to 3.14.

Exposure to carcinogenic air pollutants was also significantly associated with the condition, with an odds ratio of 1.78 (p=0.009). This indicates that individuals exposed to such pollutants have a 78% higher risk of the condition. The 95% CI for this association ranged from 1.21 to 2.61.

Additionally, HPV infection exhibited an odds ratio of 1.43 (p=0.042), indicating a 43% higher risk of the condition in individuals with this infection. The 95% confidence interval for this association lies between 1.02 and 2.01.

On the other hand, EBV infection did not show a statistically significant association, as its odds ratio was 1.25 (p=0.167), with a 95% CI spanning from 0.89 to 1.76.

The age group played a significant role, with an odds ratio of 1.96 (p=0.005), suggesting that individuals in a certain age group have nearly twice the risk of the condition compared to another group. The 95% CI for this relationship ranged from 1.34 to 2.88.

Diets lacking in vegetables were associated with an odds ratio of 1.34 (p=0.073), indicating a 34% higher risk of the condition. However, this result did not reach statistical significance. The 95% confidence interval (CI) for this association ranged from 0.98 to 1.83.

Genetic factors showed an odds ratio of 1.55 (p=0.031), suggesting a 55% higher risk associated with these factors. The 95% CI for genetic factors ranged from 1.09 to 2.21.

Discussion

The foremost factors that are frequently associated with elevated susceptibility to head and neck cancer encompass tobacco use, the consumption of alcohol, infection by the human papillomavirus (with a particular emphasis on oropharyngeal cancer cases), and the presence of Epstein-Barr virus (notably prevalent in Asian populations and prominently linked to nasopharyngeal cancers). These risk factors stand out as significant contributors to the development of head and neck cancers, thereby highlighting the intricate interplay between lifestyle choices, viral infections, and regional epidemiological trends in the onset of these

malignancies.[7]

Tobacco usage, entrenched as a prominent and enduring risk factor, remains at the forefront of contributors to the development of head and neck squamous cell carcinoma (HNSCC). A multitude of pioneering studies conducted across Western Europe have unequivocally established tobacco use as a staggering contributor, accounting for a substantial 75% of all HNSCC cases. This statistical stronghold finds further affirmation in a comprehensive national survey conducted in the United Kingdom, attributing an overwhelming 70% of oral and pharyngeal HNSCC cases to tobacco consumption. However, within the intricate tapestry of global variation, nuances in the prevalence of tobacco involvement emerge, especially in East Asia, where the spectrum ranges from 2.8% to 25% of cases.[8]

Alcohol and tobacco exhibit a synergistic impact on the development of HNSCC, a type of cancer affecting the upper aerodigestive tract. This malignancy is anticipated to experience a significant surge in global incidence in the forthcoming decades, with a substantial portion of this rise attributed to heightened alcohol and tobacco usage, particularly in less developed regions across the world.[8,14]

It is noteworthy that individuals who engage in concurrent heavy consumption of alcohol and tobacco face an astounding 40-fold escalation in the risk of developing HNSCC. Interestingly, an intriguing disparity emerges when exploring the relationship between these risk factors and different racial groups. Among Black Americans, the correlation between cigarette smoking and HNSCC appears to be more pronounced compared to their White American counterparts. However, the risk associated with alcohol consumption remains relatively consistent across these racial groups. This observation suggests the possibility of nuanced variations in the quality of tobacco products used or differences in the metabolic processes related to these substances among individuals of different racial backgrounds.[9-10,13]

In this study, we investigated multiple factors and their connections to the risk of a specific medical condition. This study analyzes unveiled several noteworthy results. Firstly, this study indicated that alcohol consumption was linked to a 65% higher risk of the condition (OR=1.65, p-value=0.023) when compared to non-drinkers. Secondly, tobacco use demonstrated an even stronger association with the condition, suggesting that individuals who use tobacco are more than twice as likely to develop the

condition (OR=2.12, p-value=0.001).

The study found that exposure to carcinogenic air pollutants was significantly associated with an increased risk of the condition. Those exposed to these pollutants had a 78% higher risk (OR=1.78, p-value=0.009) of developing the condition. This suggests that environmental factors play a crucial role in the development of the condition, and exposure to carcinogenic air pollutants should be considered as a significant risk factor. These pollutants may directly damage the oral cavity tissues or trigger genetic alterations that contribute to the development of the condition.

The analysis revealed that HPV infection was associated with a 43% higher risk of the condition. This finding is consistent with previous research indicating that certain high-risk strains of HPV, such as HPV16/18, can cause alterations in key tumor suppressor genes that promote the aggressive division of cells and eventually lead to cancer development. The presence of HPV in OCSCC highlights the importance of viral screening and vaccination strategies as potential preventive measures.

In contrast to HPV infection, the analysis did not find a statistically significant association between EBV infection and the condition. This suggests that EBV may not play a substantial role in the development of OCSCC. However, it is important to note that EBV may still contribute to the development of other types of oral cavity cancer or interact with other risk factors to influence the risk of OCSCC. Further studies focusing on different subtypes of oral cavity cancer and their association with EBV infection are needed to gain a comprehensive understanding of the viral involvement in OCSCC.

Age plays a significant role in oral cavity squamous cell carcinoma (OCSCC) development. The specific age group mentioned in the result had nearly twice the risk of the condition compared to another group (OR=1.96, p-value=0.005). This finding emphasizes the importance of considering age as a risk factor for OCSCC. The increased risk of OCSCC in a specific age group suggests that age-related factors may contribute to the development of the condition. Possible factors could include cumulative exposure to risk factors such as tobacco and alcohol use, as well as the natural aging process and changes in the oral cavity.

The analysis of the result indicates a 34% higher risk of the condition associated with diets lacking in vegetables. Although this finding did not reach statistical significance, it suggests

a potential link between dietary factors and OCSCC. The association between diets lacking in vegetables and a higher risk of OCSCC highlights the potential role of nutrition in the development of this condition. Vegetables are rich in antioxidants, vitamins, and minerals that play a crucial role in maintaining cellular health and reducing the risk of cancer.

According to the article, genetic factors are associated with a 55% higher risk of OCSCC. The specific genetic alterations include chromosomal alterations, TP53 mutation, PIK3CA mutation, and NOTCH1 mutation. he identification of genetic factors associated with a higher risk of OCSCC provides insights into the underlying molecular mechanisms of this condition. Understanding these genetic alterations can help in the development of targeted treatments and personalized approaches to OCSCC management.

One limitation of this study is its retrospective design. Retrospective studies rely on pre-existing data, which may be subject to biases, missing information, or inaccuracies. Future research could benefit from prospective studies with more robust data collection methods to address these limitations.

In conclusion, the risk factors for Head and Neck Squamous Cell Carcinoma (HNSCC) identified in this study reveal that tobacco use is the most significant factor, with an odds ratio of 2.12 (p=0.001), indicating more than twice the risk for HNSCC development. Age is the second most significant factor (OR=1.96, p=0.005), suggesting that certain age groups face nearly double the risk. Exposure to carcinogenic air pollutants ranks third in significance (OR=1.78, p=0.009), associated with a 78% higher risk. Alcohol consumption (OR=1.65, p=0.023) and genetic factors (OR=1.55, p=0.031) also show notable associations. While HPV infection demonstrates a moderate link (OR=1.43, p=0.042), EBV infection and diets lacking vegetables did not reach statistical significance in this study. These findings underscore the complex, multifactorial nature of HNSCC risk and highlight the critical importance of targeting modifiable lifestyle factors, particularly tobacco cessation, in prevention strategies.

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