

SYSTEMATIC REVIEW: THE RISK FACTORS OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Abstract: The risk factors of head and neck squamous cell carcinoma. head and neck squamous cell carcinoma (HNSCC) happen to be one of the more common cancers all over the world. Of all head and neck cancers, 90% of them start in squamous cells. It has been researched that there are several risk factors that play a part in developing head and neck squamous cell carcinoma (HNSCC). The purpose of this systematic review is to determine the risk factors of head and neck squamous cell carcinoma. The method of writing this article is systematic review, where the articles were published from 2012 to 2020 that focused on assessing the risk factors of head and neck squamous cell carcinoma. Assessment of the methodological quality of each article was carried out using PRISMA checklist. The results of the analysis of head and neck squamous cell carcinoma risk factors are alcohol (p value = 0.001), HPV in the Oral cavity (p value = 0.0005), HPV in the Hypopharynx (p value = 0.0005), HPV in the Oropharynx (p value = 0.0001), HPV in the Larynx (p value = 0.0001), < 5 missing teeth (p value = 0.001), Annual dentist visit (p value = 0.001), Daily tooth brushing (p value = 0.001), Gum disease (p value = 0.001), Betel nut chewing by people 16–30 years (p value = 0.000), betel nut chewing by people >30 years (p value = 0.000), people 16–30 years (p value = 0.000), Male population who smokes (p value = 0.001), Former smokers (p value = 0.001) and Current smokers (p value = 0.001). To conclude, after reviewing the studies and obtaining the results and discussing and understanding them, in this systematic review it can be said that the risk factors that have a significant association with patients that have head and neck squamous cell carcinoma.

Keywords: Head and Neck Squamous Cell Carcinoma, Risk Factors, HNSCC, Risk Factors.

1. INTRODUCTION

Background

The title of this elective study project is Systematic Review: The Risk Factors of Head and Neck Squamous Cell Carcinoma. Head and Neck Squamous Cell Carcinoma (HNSCC) happens to be one of the more common cancers all over the world. Head and neck cancers represent the sixth most common cancer worldwide with approximately 630,000 new patients diagnosed annually and resulting in over 350,000 deaths every year. There are a variety of head and neck cancers but the most common is head and neck cancer is squamous cell carcinoma. Of all head and neck cancers, 90% of them start in squamous cells. These squamous cells line the mouth, nose and throat hence the cancer would affect the oral cavity, oropharynx and larynx.¹

Head and Neck Squamous Cell Carcinoma (HNSCC) can be curable if it is detected early stages of the disease but can be fatal if detected in the later stages. Survival outcomes for patients with HNSCC diverge by extent of varying factors. Research done by The University of Texas M.D. Anderson Cancer Center (MDACC) during a 9-year period from 2000 to

2009, calculated the survival time from the date of diagnosis to the date of death of any cause or last follow-up. Their researched showed a five-year overall survival was calculated for all the variables assessed.²

Hence, it has been researched that there are several risk factors that play a part in developing Head and Neck Squamous Cell Carcinoma (HNSCC).

Description of HNSCC

Head and neck cancers usually begin in the squamous cells. These epithelial cells line the moist, mucosal surfaces inside the mouth, nose paranasal sinuses and pharynx. These squamous cell cancers are also called squamous cell carcinomas of the head and neck. Cancers of the head and neck are further categorized by the area of the head or neck in which they begin. SCC can occur either in the nasal cavity and paranasal sinuses, the nasopharynx, the hypopharynx, larynx, and trachea, or the oral cavity and oropharynx.³

Following the medical anatomy of the head and neck, we can see that anatomy begins at the Oral Cavity which includes the lips, the front of the tongue, the gums, the lining inside the cheeks and lips, the floor of the mouth under the tongue, the hard palate which is the bony top of the mouth, and the small area of the gum behind the molar. Following after the oral cavity is the Pharynx. The Pharynx or throat consists of a hollow tube about 5 inches long that starts behind the nose and leads to the esophagus. It has three parts: the nasopharynx, the oropharynx and the hypopharynx. Right after the Pharynx, would be the Larynx, also known as the voice box. This part is a short passageway and is formed by cartilage just below the pharynx in the neck. The larynx contains the vocal cords. Next, we would find the paranasal sinuses and nasal cavity.

The paranasal sinuses are small hollow spaces in the bones of the head surrounding the nose and the nasal cavity is the hollow space inside the nose. Lastly, we have the Salivary glands which produce Saliva. The major salivary glands are found on the floor of the mouth and near the jawbone.³

Head and neck squamous cell carcinoma (HNSCC) remain a significant disease, making up a larger proportion of cancers worldwide. A study done in the Netherlands between 1989 and 2011, produced results that showed that there was a 4.9% total cancer incidence worldwide in the year 2012. The data also showed a cancer mortality of 4.6% worldwide in 2012.⁴

Study Theory

Based on a brief study of Head and Neck Squamous Cell Carcinoma has produced information on certain risk factors that may or may not play a factor in its development. The risk factors are alcohol, developing Human Papilloma Virus, oral hygiene, smokeless tobacco, smoking, inherited conditions, and immunodeficiency.

Alcohol

Alcohol is a major independent risk factor in developing head and neck cancer. Patients who continue to drink heavily after treatment for head and neck cancer have shown a significant drop in quality of life and continued drinking has a negative impact on survival rate. The beneficial effects of quitting alcohol, on the risk of developing head and neck cancer, are only observed after more than 20 years, when the level of risk reaches that of non-drinkers. Cessation of alcohol on admission for surgery can present a significant problem in heavy drinkers. Although alcohol is not considered to be a carcinogen, excessive alcohol intake increases the risk of HNSCC most often acting synergistically with tobacco.⁵

Human Papilloma Virus (HPV)

Patients that have Human Papilloma Virus (HPV), a very common sexually transmitted infection, tend to develop HNSCC. The overall prevalence of HPV in HNSCC is around 50%, with the highest prevalence in cancers of the tonsil and base of tongue. The rise in HPV-related cancers has been mainly attributed to the change in sexual practices in the Western world. These patients are younger, have bulky nodes, predominantly oropharynx involvement, equal gender distribution, and have better survival. HPV associated SCC showed an 82% three-year survival compared to 57% survival for smokers with head and neck cancer squamous cell carcinoma.⁵

Oral Hygiene

Indicators of poor oral health is associated with increased risk of head and neck squamous cell carcinoma, especially oropharyngeal carcinoma (OPSCC). Oral health indicators including poor dental health, tooth loss, lack of routine dental care by a dentist and a diagnosis of periodontitis have been associated with HNSCC. It has been said that the association

between poor oral health and cancer risk may be driven by a chronic inflammatory state that alters the natural course of HPV infection but findings suggest poor oral hygiene affects HPV positive patients just the same as HPV negative patients. It is also said that the frequent use mouthwash use seems to elevate the risk of tumor-specific death in HNSCC patients.⁶

Tobacco Chewing

Chewing tobacco seems to be the most common cause in Southeast Asia. Chewing tobacco are for example betel quid, khaini, mava, and many others. Tobacco and areca nut are the two important carcinogens that are linked to the development of head and neck cancers. Betel quid chewing is the most common form of tobacco chewing in the Asia-Pacific region. Betel quid consists of areca nut, betel leaf, catechu, and slaked lime. It has been reported from many countries like India, Pakistan, Bangladesh, Sri Lanka, Thailand, Cambodia, Malaysia, Indonesia, China, Philippines, Taiwan, Vietnam, and migrant populations in Europe, Africa, North America, and Australia. About 10% of the world's population chew betel quid regularly. Areca nut alone is a confirmed carcinogen and causally associated with a premalignant condition called oral sub mucous fibrosis (OSMF) and oral cancer.⁵

Smoking

Smoking is an independent risk factor for head and neck cancer. Smoking is the main reason for HNSCC in western populations. Continued smoking through radiotherapy was thought to have an adverse effect on local control and survival, but more recent evidence, according to the specialty associations involved in the care of head and neck cancer patients in the UK, would suggest baseline smoking status is more important. Smoking cessation before surgery is desirable to reduce the risk of anaesthetic related complications and improve wound healing, particularly after reconstructive surgery. Quitting tobacco smoking for a short period of time, even for a one to four years' period, results in a head and neck cancer risk reduction of about 30 per cent compared with current smoking.⁵

Inherited Conditions

Cancers that occur in families more often than would be expected by chance are known as Familial Cancer Syndromes (FCS). They occur due to an inherited genetic mutation and account for 5%-10% of all cancers. Patients predisposed to FCS inherit one mutant allele of genes, either maternal or paternal, and neoplasia develops only when additional mutation of remaining allele occurs. In contrast, sporadic tumours develop in individuals who do not have a germline mutation but who acquire, over a period of time, somatic mutations of both alleles. Some inherited conditions have shown to have increased risk of HNSCC. This includes Fanconi anaemia (FA), ataxia telangiectasia, Bloom's syndrome and Li-Fraumeni syndrome. Fanconi anaemia has a very high risk of developing HNSCC (particularly oropharyngeal squamous cell carcinoma), noticed mostly after haematopoietic stem cell transplantation has been done. Fanconi anaemia patients do not tolerate cisplatin and have severe toxicity with radiotherapy. Life expectancy has improved so that the population at risk for HNSCC is greater. Head and neck squamous cell carcinoma can occur early in patients as young as 11 years old.⁵

Immunosuppression

There are patients who are immunosuppressed. This is due to poor nutrition, advanced age, immunosuppressive therapy after a transplant or acquired immunodeficiency syndrome (AIDS) are at greater risk of developing malignancy. The most frequently reported AIDS-related neoplasms of the head and neck region include Kaposi's sarcoma and non-Hodgkin's lymphoma. There is also a bigger risk of oropharyngeal squamous cell carcinoma. Although HPV-related HNSCC has been seen in immunosuppressed patients, further clinical studies are needed to determine the safety and efficiency of HPV vaccines in this setting.⁵

2. MATERIALS AND METHODS

Protocol

This is a comprehensive summary in the form of a systematic review entitled the risk Factors of head and neck squamous cell carcinoma. The protocol in this study shall use The Center for Review and Dissemination and as well as The Joanna Briggs Institute Guideline, that will act as a guide to assess the quality of the studies that will be summarized. To evaluate the systematic review, the PRISMA checklist will be used to determine the study completion that has been found and will be adjusted for the purpose of the systematic review.

Table 1. PICO framework systematic review format: The Risk Factors of Head and Neck Squamous Cell Carcinoma

P	The population of patients who have been diagnosed with Head and Neck Squamous Cell Carcinoma
I	Risk Factors related to Head and Neck Squamous Cell Carcinoma
C	Is not applicable to this study
O	Studies that have evidence indicating the risk factors of head and neck squamous cell carcinoma

Information Source

A Systematic Review is a comprehensive summary of several research studies that are determined based on a specific theme. The literature search was carried out in October – January 2021. The data used in this study are secondary data which was not obtained from observations.

Literature Strategy

The search for articles or journals will use keywords and the boolean operators (AND, OR NOT, or AND NOT) which are used to expand or specify a search. This makes it easier to find the articles or journals used. The keywords used for this systematic review are adjusted to the Medical Subject Heading (MeSH) and consist of the following:

Table 2. Keywords: Systematic Review: The risk factors of head and neck squamous cell carcinoma

Head and Neck Squamous Cell Carcinoma		Risk Factors
OR	AND	OR
HNSCC		Etiology

Study Selection

A literature search was conducted through three databases, Google Scholar, PubMed and Science Direct using the keywords, ‘Head and Neck Squamous Cell Carcinoma’, ‘Epidemiology’ and ‘Risk Factors’. Based on the results of literature search through publications in all three databases and using keywords, there were 1,187 articles that matched these keywords. A screening was then carried out based on the title adjusted to the theme of systematic review, as many as 1,142 articles were excluded because they were not suitable or had to be paid for to be accessed and the remaining 45 articles were excluded. After that, the selection is done by studying the abstract of the remaining articles. A feasibility study on the 27 articles chosen based on abstract and overall text and compliance with the eligibility criteria found 9 articles that can be used in a systematic review.

Data Collection Process

The data collection process will follow a checklist sheet obtained from the PRISMA template to randomly check the selected articles and make adjustments to the guidelines. The data extracted from articles will be that of which is met with the inclusion criteria. The data collection process on this systematic review goes through the following stages:

1. Preparation of a systematic review proposal according to the summary topic that will be carried out.
2. To state and organize the registration protocol used based on The Centre for Review and Dissemination and the Joanna Briggs Institute and the PRISMA Checklist.
3. Determine the keywords that will be used based on MeSH, using phrase searching and Boolean operators to find articles.
4. Determine which database to use, in this study using Google Scholar, PubMed, and Medscape.
5. Determine eligibility criteria with an article search strategy using the PICOS framework that is tailored to finding of the inclusion and exclusion criteria.
6. Describe the source of the information in the search for articles in the predetermined database until the final article is found for a comprehensive summary.

7. The study selection process is done by reading the entire article and selecting the non-conforming articles will be discarded and recorded in the selection strategy using the PRISMA flow chart.
8. Attention is need to determine the risk of bias. This is assessed by using the JBI Critical appraisal and a checklist and the results meet the cut-off while the selected articles can be included in the study.
9. Articles that have been found based during the protocol and eligibility criteria are then analysed one by one to determine the results and discussion in the study.

Types of Data and Variables

Based on the theme chosen in the systematic review of the risk factors of head and neck squamous cell carcinoma, the data collected in each article should have the following information:

1. The characteristics of the study shoinclude data on the type of design, the variables used, the management used, the data analysis, the location of the intervention application, and the results of the application of the intervention.
2. Risk Factors related to Head and Neck Squamous Cell Carcinoma
3. Research done to prove the relation of the risk factors to the Head and Neck Squamous Cell Carcinoma
4. Limitations faced by researchers in conducting data analysis and research processes.

Assessment of Risk of Bias in Individual Studies

The Joanna Briggs Institute (JBI) Critical Appraisal is used for several types of Quasi-experimental studies, randomized control and trial studies, systematic reviews, qualitative research to analyse the quality of the methodology in each study (n = 9). The JBI Critical Appraisal assessment checklist provided several questions to assess the quality of the study. The scoring criteria are given a score of 'yes', 'no', 'unclear', or 'not valid', and each criterion with a score of 'yes' is assigned one point and the other is zero, each score is then counted and added up. Critical appraisal for assessing eligible studies by the researchers themselves. If the study score reached at least 50% fulfilling the critical appraisal criteria with the cut-off point agreed upon by the researcher, the study was included in the inclusion criteria. We excluded low-quality studies to avoid bias in the validity of the results and the review recommendations. In the final screening, 9 studies achieved scores higher than 50%. So that a systematic review can be done.

The risk of bias in this systematic review uses an assessment research method of each study, which consists of:

1. Theory: Incorrect, outdated theory and lacking credibility
2. Design: The design is not in accordance with the research objectives
3. Sample: There are 4 things that must be considered, namely population, sample, sampling, and sample size that are not in accordance with the sampling rules
4. Variable: The variable that is determined is not appropriate in terms of quantity, control of confounding variables, and other variables
5. Instrument: The instrument used does not have sensitivity, specificity and validity-reliability
6. Data Analysis: Data analysis is not in accordance with the principles of analysis in accordance with standards

Summary Measures

The identification of risk factors in relation with Head and Neck Squamous Cell Carcinoma. The results of searching for article data based on protocol and registration have obtained the appropriate articles and are used in making the summary of this study. The data that will be presented in this systematic review are the characteristics of the study based on the articles found, which summarizes 9 articles from the references of this study. The research characteristics include the risk factors that has been proven to aid the development of Head and Neck Squamous Cell Carcinoma.

Results Synthesis

The result synthesis used in this systematic review is to use a descriptive method based on the themes that have been determined in the systematic review. The study uses a descriptive analysis that describes and explains through narrative research results described in the literature. Relevant data reviewed by the review question, including: author, country,

year, background, theoretical framework, research objectives, research content, study design, sample size, sampling method, participant description, reliability and validity, measurement instruments, analysis and statistical techniques, and analysis of results. A narrative approach with the main objective of gathering evidence on the effectiveness of interventions and developing a coherent textual narrative about the similarities and differences between studies, was used to synthesize the data in this systematic review.

3. RESULTS

Study Selection

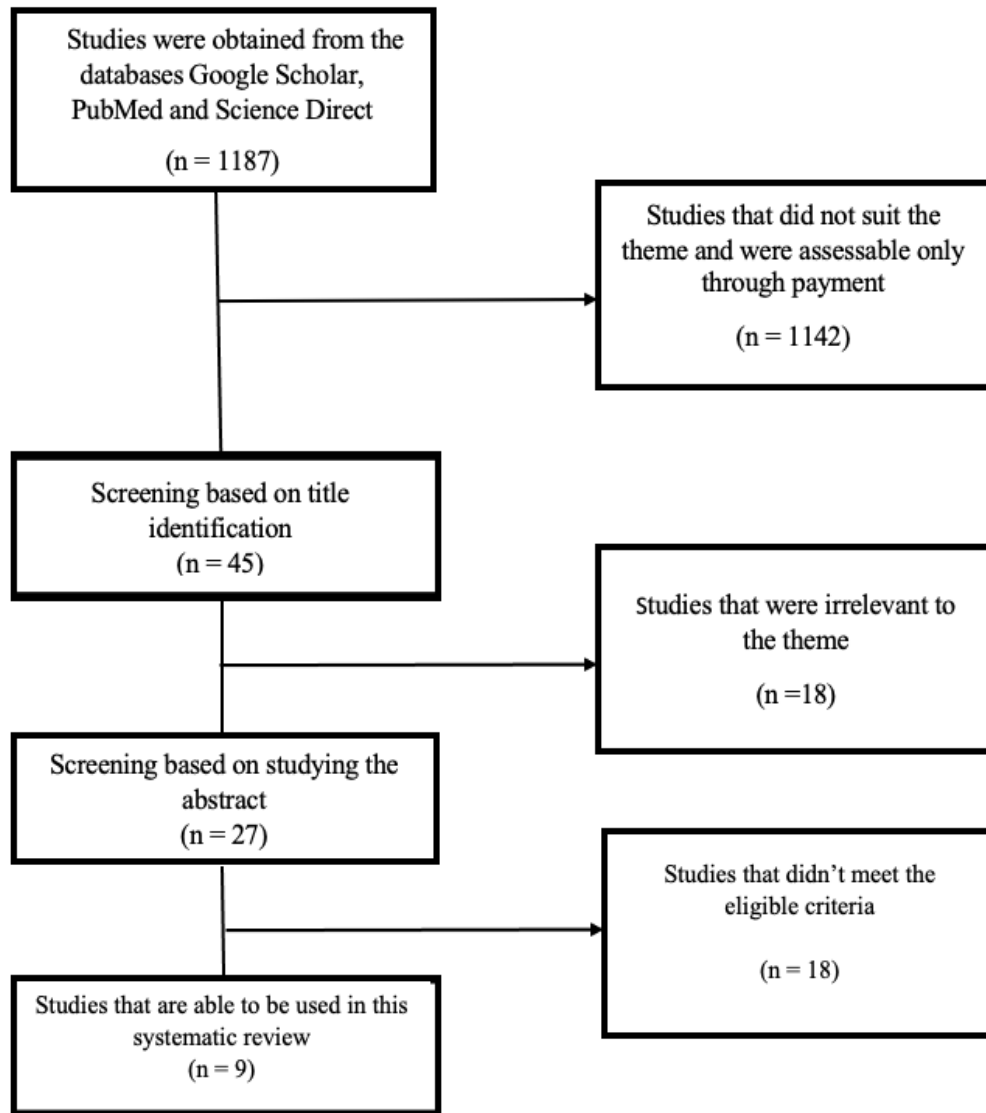


Figure 1. Flow Chart of Literature Search for The Risk Factors of Head and Neck Squamous Cell Carcinoma

Study Characteristic

Out of 9 included studies, 8 studies were case-control studies and 1 was a meta-analysis study. The studies were carried out from the period of 2012 to 2020. The population of the case control studies were carried out in 7 countries across the 9 articles reviewed in this systematic review. The countries involved are Japan, Greece, Iran, France, Taiwan, India and 2 studies done in the United States. As for the meta-analysis study, the population was from multiple countries. A number of data collection techniques were used such as interviews, questionnaires and clinical examinations. The study characteristics of the articles reviewed in this study shown in Table 3.

Table 3. Characteristics of studies reviewed

Author, Year	Region	Type of Study	Risk Factors	Number of cases	Sample control
Daisuke K & Keitaro M, (2017)	Japan	Case-control	Alcohol	-	43
Melina T et al (2018)	Greece	Case-control	Human Papilloma Virus	90	206
Asvadi et al (2012)	Iran	Case-control	Human Papilloma Virus	-	94
Hashim D et al (2016)	United States	Case-control	Poor Oral Hygiene	8,925	12,527
Chan C et al (2019)	Taiwan	Case-control	Poor Oral Hygiene	740	296
Bhupendra N et al (2015)	India	Case-control	Betel Nut Chewing	87	46
Aviane A et al (2020)	France	Case-control	Smoking	170	450
Zhang Y et al (2015)	Multiple	Meta-Analysis	Smoking	13830	-
Gaelen S et al (2018)	United States	Case-control	Smoking	1389	57

Individual-related Risk Factors

About 5 risk factors involving head and neck squamous cell carcinoma have been identified after reviewing the studies chosen. These includes Alcohol consumption, Human Papilloma Virus (HPV), poor oral hygiene, betel nut chewing, and Smoking. After studying all the articles it is deduced that of all the studied variables, alcohol (p value = 0.001), HPV in the Oral cavity (OR: 6.8, p value = 0.0005), HPV in the Hypopharynx (OR: 6.8, p value = 0.0005), HPV in the Oropharynx (OR: 19.55 p value = 0.0001), HPV in the Larynx (OR: 19.55 p value = 0.0001), < 5 missing teeth (OR: 0.78, p value = 0.001), Annual dentist visit (OR: 0.82, p value = 0.001), Daily tooth brushing (OR: 0.83, p value = 0.001), Gum disease (OR: 0.94, p value = 0.001), Betel nut chewing by people 16–30 years (OR: 8.28, p value = 0.000), betel nut chewing by people >30 years (OR: 33.19, p value = 0.000), people 16–30 years (OR: 8.28, p value = 0.000), Male population who smokes (OR: 1.68, p value = 0.001), Former smokers (OR: 1.01, p value = 0.001) and Current smokers (OR: 4.16, p value = 0.001) show significance. The table below shows the odds ratio between the risk factors and head and neck squamous cell carcinoma.

Table 4. Odds ratios for association between risk factors and head and neck squamous cell carcinoma

Risk Factor	OR	P-Value	Sample Size		Study	Design
			Cases	Control		
Alcohol						
≤ 1 drink/day		0.001	43	2	Daisuke et al	Case-control
≥ 4 drinks/day			38	2	Daisuke et al	
Human Papilloma Virus						
Oral cavity	6.8	0.0005	20	206	Melina et al	Case-control
Hypopharynx	6.8	0.0005	38	206	Melina et al	Case-control
Oropharynx	19.55	0.0001	2	100	Asvadi K et al	Case-control
Larynx	19.55	0.0001	4	100	Asvadi K et al	Case-control
Oral Hygiene						
< 5 missing teeth	0.78	0.001	2065	15,955	Hashim et al	Case-control
≥ Annual dentist visit	0.82	0.001	3,368	6891	Hashim et al	
≥ Daily tooth brushing	0.83	0.001	13,286	12,527	Hashim et al	

Gum disease	0.94	0.001	12,109	33,127	Hashim et al	
Dental floss		0.57	317	296	Chan et al	Case-control
Betel Nut Chewing						
0–15 years duration	1.13	0.816	7	28	Bhupendra et al	Case-control
16–30 years duration	8.28	0.000	20	11		Case-control
>30 years duration	33.19	0.000	51	7		Case-control
Tobacco/Smoking						
Male	1.68	0.001	13830	-	Zhang et al	Meta-Analysis
Female	1.62	0.267	13830	-	Zhang et al	Meta-Analysis
Never smoker	1.00		145	405	Aviane et al	Case-control
Former smoker	1.01	0.001	26	18	Aviane et al	Case-control
Current smoker	4.16	0.001	737	57	Gaelen et al	Case-control

Risk of Study Bias

Based on the quality analysis of the JBI Critical Appraisal Tools, the study quality of each article has been determined as the source of the systematic review. There were 9 articles that were compatible with the theme of this systematic review. The findings of the literature which were reviewed and determined for this systematic review are as follows:

Table 5. Result of study assessment for systematic review using the JBI Critical Appraisal Tools

Citation	Criteria											Results	
	1	2	3	4	5	6	7	8	9	10	11		
Daisuke K & Keitaro M (2017)	✓	✓	✓	✓	✓	✓	✓	✓	✓				9/10
Melina T et al (2018)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			10/10
Asvadi K et al (2012)	✓	✓	✓	✓	✓	✓	✓	✓	✓				9/10
Hashim D et al (2016)	✓	✓	✓	✓	✓	✓	✓	✓					8/10
Chan C et al (2019)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			10/10
Bhupendra N et al (2015)	✓	✓	✓	✓	✓			✓	✓	✓			8/10
Aviane A et al (2020)	✓	✓	✓	✓	✓	✓		✓	✓	✓			9/10
Zhang Y et al (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		11/11
Gaelen S et al (2018)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			10/10

The findings of the 9 studies meet the criteria for this systematic review shown in (Table 5). There are 8 case-control studies and 1 meta-analysis study. Based on the findings, the case control studies were scored over ten to determine total quality based on the JBI critical appraisal method for case control. As for the meta-analysis, the quality score was based out of 11 following the score JBI critical appraisal method for meta-analysis. Based on the overall researched reviewed using these methods, all chosen research fulfilled at least 50% of the critical appraisal criteria and has showed important data analysis and assessment findings on the risk factors relating to head and neck squamous cell carcinoma. The high

risk of bias is a factor that may have an effect that may lead to issues in determining head and neck squamous cell carcinoma risk factors, thereby being a confounding factor in the research.

4. DISCUSSION

Summary of Evidence

A risk factor is a factor that may aid in a person eventually developing a certain disease. Based on the study done it has been deduced that certain risk factors do in fact play a role in the development of head and neck squamous cell carcinoma in people. The first risk factor found was alcohol assumption. Based on the study done by Daisuke K and Keitaro M alcohol assumption ($p < 0.001$) is an established risk factor in head and neck squamous cell carcinoma.⁷ The researches have stated that patients that have had ≤ 1 drink/day and ≤ 4 drinks/day show an increasing risk of developing head and neck squamous cell carcinoma. It has also shown that a higher alcohol consumption that is done over a shorter period tends to do more harm rather than alcohol consumption over a longer period.

The Human Papilloma Virus (HPV) is a major risk factor for head and neck squamous cell carcinoma. The study by Melina T et al, shows that patients who are HPV positive are also patients who have head and neck cancer squamous cell carcinoma in the oral cavity and the hypopharynx ($p < 0.0005$).⁸ The research of Asvadi K et al, instead has associated HPV positive patients with have head and neck cancer squamous cell carcinoma in the oropharynx and larynx.⁹ This states that HPV indeed has role in the formation in all types of head and neck cancer squamous cell carcinoma. Across both these studies it also states that majority of the head and neck squamous cell carcinoma patients affected by HPV, we're mostly impacted by the stronger HPV 16.

Hashim et al study correlates Oral Hygiene ($p < 0.001$) as a risk factor.¹⁰ The researchers found that patients with gum disease, < 5 missing teeth, a lack of annual dentist visits and less than daily tooth brushing showed great magnitude of association with head and neck squamous cell carcinoma patients. It was said from the research that the mechanisms that comes from poor oral hygiene and are associated with head and neck squamous cell carcinoma patients fall into the categories of trauma and inflammation. The research done by Chan et al, have similar findings as well except on where its proven that dental flossing ($P < 0.57$) has no association to head and neck squamous cell carcinoma patients.¹¹

The research done by Bhupendra N et al, betel nut chewing is indeed a risk factor ($p < 0.000$). The researches states that with a history of tobacco chewing or chewing betel nut both in the past and at present with a duration of chewing tobacco for 15 to 30 years, with the tobacco quid retention in mouth for 1 to 10 minutes were found to be significant in being related to head and neck squamous cell carcinoma.¹²

Aviane et al and Gaelen et al both researched topics concerning smoking and its correlation to head and neck squamous cell carcinoma. Both studies showed a relation to risks of smoking to head and neck squamous cell carcinoma. The studies state that more head and neck squamous cell carcinoma patients that smoke are of the male population ($p < 0.001$), as well most patients are either former or current smokers. The study also found that the risk of head and neck squamous cell carcinoma increased with the duration and intensity of smoking. The greater duration would be affected on the average number of cigarettes per day.^{13,14}

Based on the research done in this study, the risk factors identified as relatable to head and neck squamous cell carcinoma are alcohol consumption, Human Papilloma Virus development, oral hygiene, smokeless tobacco and smoking. Comparing to the study theory it is indeed proven that five out of the seven intended risk factors do have an effect on head and neck squamous cell carcinoma. As for the other two identified risk factors, which are inherited conditions and immunodeficiency, while may not have been proven to be relatable in this study, has also not been proven to be unrelatable to head and neck squamous cell carcinoma development.

Limitation

During the preparation of this systematic review, there were possibilities of errors occurring when determining the risk of bias from various studies. Some of the limitations were such as small sample size and absence of case and control selection can impact the interpretation of the final findings. Even though the findings cannot be generalized; we could still use the results to determine that certain risk factors for head and neck squamous cell carcinoma can vary in their relations. To add on, the risk of bias is also present in the literature search due to the limited number of studies that assessable on the risk factors of head and neck squamous cell carcinoma.

5. CONCLUSION

To conclude, after reviewing the studies and obtaining the results and discussing and understanding them, in this systematic review it can be said that the risk factors that have a significant association with patients that have head and neck squamous cell carcinoma are alcohol consumption, patients who are HPV positive, bad oral hygiene, betel nut chewing and smoking. It is also said that a joint affect of any of these risk factors could have an even bigger impact on head and neck squamous cell carcinoma.

6. RECOMMENDATION

The hopes for these cases are that there would be more health programs advising and educating against the risk factors that can be avoidable like smoking, betel chewing, developing HPV and alcohol consumption, as well as providing funding for people that cannot afford basic oral care. In addition to that, people should be educated on head and neck squamous cell carcinoma.

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