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Research Article

Role of HPV in Causing Oro-Pharyngeal Squamous Cell Carcinoma (OPSCC) in Indian Perspective-A Systematic Review

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Abstract

Background: Various groups of researchers globally have evaluated the role of HPV (Human papilloma virus) in causing oro-pharyngeal squamous cell carcinoma (OPSCC) and reported its significant role in determining the pathogenesis, development and prognosis in oral cancers. Most of the published data has come from the western countries where the role of HPV is well established in causing OPSCC. However, there is a paucity of data on the role of HPV in causing OPSCC in the Indian perspective.

Aim and Objectives: To investigate the role of HPV in causing OPSCC in Indian Perspective and to further evaluate the utility of cervical cancer screening methods and prophylactic tools in the prevention of OPSCC.

Data: Randomized/Quasi-randomized controlled clinical trials.

Sources: Four electronic databases and grey literature up to July 2023.

Study Selection: Two reviewers independently selected the studies; they extracted the data and assessed the risk of biases using the Cochrane risk of bias tool 2.0. Only 40 studies fulfilled the inclusion criteria.

Participants and Interventions: Indian peer reviewed original studies published in the last 11 years considering patients between the age group 18 - 70 were included. The papers that included confirmatory Biopsy/histopathology reports positive for OPSCC were included. Individuals presented exclusively with OPSCC involving tobacco and non-tobacco consumers were included.

Limitations: No heterogeneity test was evident which may alter the result. Only English language papers were used that might have missed the papers in other languages. Analysis of the impacts of possible confounding factors, such as smoking and tobacco, genetics and heterogeneity of the studies that should be considered has been missed.

Conclusion: In a developing country like India tobacco still remains the primary cause of OSCC. The amount of population presenting non-tobacco causes in the causation of OSCC is very scant. Furthermore, heterogeneity in data was observed which was mainly attributed to a) social and cultural habits of the enrolled cases, b) discrepancies in the nature of samples procured and c) varying sensitivity of the assays employed for detection of HPV. Due to the inconsistency of data pertaining to HPV prevalence in OSCC in different regions of India, it remains inconclusive to draw any correlation between HPV and OPSCC in India. Within the constraints of the current research it can be said that the strategies used for screening and management of cervical cancers can't be applied to the OPSCC carcinomas.

Future Directions: To establish a definitive role of HPV in the prognosis and treatment of OSCC in India, a robust effort is required in terms of the standard operating procedure to be followed for standardization of sample size, sample procuration and testing assays by the practicing oncologists in collaboration with maxillofacial surgeons and researchers in India.

Keywords: *HPV (Human Papilloma Virus); Oro-Pharyngeal Squamous Cell Carcinoma (OPSCC); India; Asian Country; Oral Cancer; Non-tobacco Oral Squamous Cell Carcinoma*

Introduction

HPV is a non-enveloped, double-stranded DNA virus belonging to the Papillomaviridae family, which infects the epithelial cells of mucosa and skin. There are more than 200 genotypes of human papillomavirus (HPV) identified, categorized into high-risk and low-risk types. Low-risk HPV types, such as 6, 11, 42, 43, and 44, generally pose a lower risk for cancer development. On the other hand, high-risk oncogenic HPV types, including 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70, are associated with an increased likelihood of cancer formation. Certain HPV types are commonly found in squamous intraepithelial lesions, denoting an intermediate risk level. Notably, HPV 16 and 18 are frequently linked to head and neck cancers.

In the context of oral carcinogenesis, HPV typically infects basal epithelial cells by entering through micro-abrasions or surface wounds. It then integrates into the host genome, leading to elevated expression of viral oncoproteins E6 and E7. These oncoproteins deactivate tumor suppressor proteins p53 and retinoblastoma pRb, disrupting the cell cycle regulation and resulting in the immortalization of keratinocytes. Although most HPV infections are transient and clear within 12 - 24 months, persistent infection can lead to the development of carcinomas, particularly in immunocompromised individuals with HIV infection [1,41]. The virus is a well-established cause of cervical cancer globally [2-11]. Tobacco and alcohol consumption are major primary risk factors of OPSCC globally, but over the last 15 - 20 years HPV infection has been increasingly recognized as a major etiological factor for a subset of OPSCC [3-5].

As evident in western literature the HPV-positive patients tend to be younger with a median age of 54 years, less exposure to tobacco and alcohol, and belong to higher socioeconomic status and education [4,5]. The recent increased incidence of this disease in the western world is reflected in societal changes in sexual behavior that have occurred over time [3]. Lastly, other risk factors or cofactors such as genetic susceptibility or nutritional factors, or tobacco and alcohol interaction with HPV cannot be ignored in this aspect [3]. HPV positivity is less frequent in blacks than in Caucasians (4% of OPSCC in blacks vs. 34% in whites) [5]. Indian culture, genetics and socioeconomic status is very different from western culture. The popular western studies conducted by Millers., *et al*. cannot be applied to the Indian scenarios due to the lack of standardization and above mentioned racial and cultural differences. Hence it is necessary to investigate the association of HPV with OPSCC in the Indian perspective.

There has been an abnormal increase in the global incidence of OPSCC in developed countries from 16.3% - 72.7% during the last 2 decades, despite the reduction in tobacco users in the western countries [12]. The consistent increase in the occurrence of OPSCC has prompted the investigators to look for an alternate cause of carcinogenesis in these countries. In this process a lot many pathological agents were investigated but HPV infection was credited the most in the causation of cancer of the oropharynx [12].

There exists a tremendous heterogeneity in the HPV prevalence association in OPSCC worldwide which fluctuates somewhere in the range of 0 - 100% [2,3]. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States which also has a paucity of the database in relation to the current association between HPV and OPSCC. The strains of HPV most commonly detected in OPSCC are HPV-16, 18 in association with HPV-6, whereas, HPV strains common to oral benign lesions and papilloma were majorly HPV-6 and 11 [3,4].

In India, OPSCC is the most well-known type of oral cancer that accounts for 90 - 95% of all oral cancers. Tobacco remains the primary cause of OPSCC in India [1]. Furthermore, there are inconsistent reports regarding the role of HPV in the origin and progression of oral squamous cell carcinoma (OSCC) in Asian nations like India [4]. The objective of this paper is to throw light on the supportive evidence of existing Indian data on the role of HPV in the causation of OPSCC.

A significant rise in the prevalence of HPV-related oropharyngeal squamous cell carcinoma (HPV-OPSCC) and oral squamous cell carcinoma (HPV-OSCC) would have significant implications for patients, healthcare professionals, and healthcare systems. Patients would face substantial treatment challenges and would require increased support from healthcare systems. Healthcare professionals would be tasked with managing a higher volume of cases and providing appropriate care and resources. Furthermore, healthcare commissioners would need to allocate resources efficiently to meet the growing demand for treatment and support services. The rapid increase in

HPV-OPSCC and HPV-OSCC prevalence underscores the need for proactive measures, including prevention strategies, early detection programs, and sufficient healthcare infrastructure, to effectively address the rising burden on patients and healthcare systems.

The Indian researchers have been working for many years on defining the role of HPV in causing OPSCC, but inconclusive results were found due to heterogeneity in data collection due to various reasons. Keeping in view the increasing role of HPV as a potential risk factor for OPSCC in India, an attempt has been made in this report to gather the information from all available authentic databases and derive a conclusion on the role of HPV in OPSCC in India. A solution has been proposed to overcome the deficiencies and lacunae in the literature.

Methodology

This review followed the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines and the Cochrane handbook.

Inclusion and exclusion criteria

Studies included were controlled clinical trials performed within the last 15 years with any duration of follow-up.

Participants: Indian peer reviewed original studies published in last 15 years considering patients between the age group 18 - 70 were included. The papers that included confirmatory Biopsy/histopathology reports positive for OPSCC were included. Individuals with exclusive OPSCC including both tobacco and non-tobacco consumers were included in the study. Studies that included patient's malignancy other than OPSCC were excluded. Studies where, OPSCC is not the primary malignancy, were also excluded. Studies included age group below 18 and above 70 are excluded. An insignificant sample size and non RCT's were also excluded.

Comparison between different randomized Indian studies was based on the sample collection, method of procuration and diagnostic assays used.

Outcome was an observed heterogeneity due to the social and cultural habits of the enrolled cases, varying sensitivity of the assays used for HPV detection, and the discrepancies in nature of the procured samples.

Search, sources, and strategy

English language peer reviewed literature, published in the last 15 years, was identified. Two independent reviewers used four databases, namely MEDLINE, PubMed, Cochrane Library, and Google Scholar up to July 2023. A blend of the key terms like India, oral squamous cell carcinoma, cervical cancer, screening, early detection, HPV, HPV vaccination, HPV role in causing OPSCC (squamous cell carcinoma) in Asian nations, were used for searching relevant publications. The literature was identified, reviewed and the key information regarding methods and findings was abstracted and organized. An aggregate of 249 articles were selected for review from the database. The full search strategy is presented in appendix 1. A manual search was performed on the reference lists of previous studies to look for potential papers for inclusion in this review. Then the two reviewers extracted the data and assessed the risk of biases using the Cochrane risk of bias tool 2.0. Only 40 studies fulfilled the inclusion criteria.

Study selection

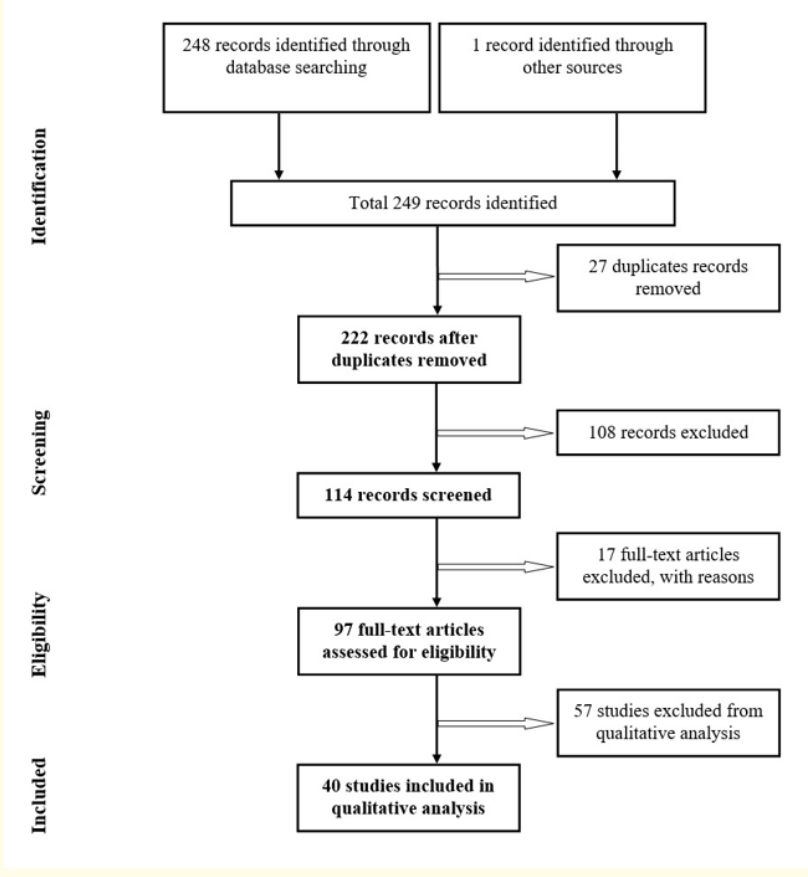
In the first round of selection, after the removal of duplicate records, abstracts were screened based on the defined inclusion/exclusion criteria by the two independent reviewers. Inter-rater agreement was measured by Cohen's kappa. In case of disparity between the two, a third reviewer was allotted to screen out the cases. Only 97 papers that fulfilled the criteria were selected into the full-text reading stage. During the second round of selection on full article screening, only 40 articles were selected that met the inclusion criteria to finally compose this paper. The remaining articles were excluded from the study either due to the low quality of Randomized Clinical Trial (RCT) or due to the difference in design protocol from the traditional ones, repetitions, or publications of low significance due to small sample size.

Data extraction

The 2 reviewers used a previously designed form to extract the data independently based on sample size, age of participants, and type of research study, level of significance and credibility.

Risk of bias in individual studies

Cochrane risk of bias tool 2.0 was used to evaluate the included clinical trials. The following domains were assessed: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported results. One of the 3 levels of bias, namely low risk, some concerns, and high risk, were allocated to each domain. The highest level in these domains was assigned as the overall risk of bias.



Results and Discussion

Cause of inconsistent Indian data

The observed heterogeneity was mainly attributed to the social and cultural habits of the enrolled cases and also due to discrepancies in the nature of samples procured and varying the sensitivity of the assays employed for detection of HPV [5]. Various studies have been performed in different parts of India where various methods for HPV sample collection from within the mouth and oropharynx were used for example the collection of cells with a cotton swab, cytobrush, or a mouth rinse [3].

A study was conducted in Southwest India where 50 histologically confirmed OSCC biopsies were tested negative for HPV DNA by conventional nested PCR and TaqMan based real-time Multiplex PCR. The investigations preclude the role of HPV subtype HPV-16, 18, 31, and 45 in the etiology of OSCC [6].

While another study conducted in Indore (Madhya Pradesh) claimed out of 100 patients of OSCC, 6 patients indicated positive results for the presence of p16 or HPV, which was found to be statistically significant and as per the study despite the absence of any other risk factors [7]. However, the study results were unreliable because they tested HPV by a single method only that is HPV PCR. In the light of the fact that HPV PCR testing can suffer from false positives, it is greatly preferred to have p16 immunohistochemistry testing or *in situ* hybridization testing as a more complete and powerful approach to classify tumors as HPV positive or negative [8]. But in the last few years PCR sensitivity and specificity has been improved as compared to ISH. HPV PCR has a sensitivity of 97 - 98% and a specificity of 84 - 87%, whilst HPV ISH has sensitivity of 85 - 88% and a specificity of 83 - 88% [42]. Based on recent meta-analyses, the prevalence of HPV-related oropharyngeal squamous cell carcinoma (HPV-OPSCC) in Asian regions differs based on the diagnostic method employed. The use of HPV PCR testing reveals a higher prevalence, consistent with a previous meta-analysis [43].

One of the studies conducted in north India demonstrated the HPV detection rate of 22.8% in 105 patients with OPSCC. The most frequent genotype found in the study was HPV 16 followed by HPV 18. The results of this study were consistent with previous studies that patients with HPV-positive OPSCC in India. In contrast to other studies, they did not discover any impact of smoking and alcohol consumption on HPV status in their population [8].

Due to the observed discrepancies in data between western countries and Asian counterparts, it is deduced that Human HPV associated head and neck squamous cell cancers (HNSCC) have become progressively common in the West, however the same cannot be said about India. To remove the confusion a combined oncology meet was conducted in the year 2016. Below are the detailed structure and minutes of the meeting.

The key points concluded by combined oncology meet: At the 35th Indian Cooperative Oncology Network meeting held in September 2016 where a board of radiation, surgical, medical oncologists, pathologists, and essential researchers from across the country having experience in clinical research with respect to HPV were made to sit across the table to discuss the role of HPV in causing OPSCC in India [7].

The meeting agenda was to clear the various subjects of controversy in managing the diagnosis and management of HPV-associated OPSCC. Many valid points were highlighted in that report. Keeping all the pieces of evidence in hand present at that time ranging from the prevalence of HPV and its association with tobacco and high-risk sexual behavior and inconsistencies were deeply analyzed. Lastly, a set of recommendations has been proposed by the panel to guide the practicing oncologists of the country. The key points of the meeting were as follows:

- Increasing incidence of HPV-related OPSCC was mostly attributed to HPV-16. HPV-related OSCCs was considered to be associated with a more youthful age at presentation. General oral-sexual practices, oral HPV contamination, immunodeficiency, male gender and higher socioeconomic status were also mentioned as the contributing factors of high significance.
- It was reported that distinct molecular genetic alterations intervened by E6, E7 oncoproteins and downstream pathways affect HPV and non-HPV related OPSCC.
- Controversy over the use of p16 as a surrogate biomarker findings in many of the studies on biomarkers was again found to be conflicting or contradictory.
- It was made clear that HPV-related OPSCC represent a different clinical element with potential for de-escalation of therapy and quick healing like it is there in western countries.
- It was also made clear that the information supporting the predominance of HPV related OPSCC in India is scanty, No SOP (standard operating procedure) for the management of OPSCC will be introduced until proved otherwise.
- The impacts of prophylactic HPV vaccination on or pharyngeal SCC remains indistinct [8]. Hence it was made clear that prophylactic immunization will not be established in India in context to OPSCC.

The primary cause of OPSCC in India till date

Tobacco and alcohol consumption are well-established primary risk factors for HNSCC worldwide and the same is valid for Asian nations [9]. The risk of HNSCC in a smoker is up to 10 times as compared with never smokers worldwide [10]. In India, tobacco users use

60% more smokeless tobacco [11,12], which increases the relative risk of oral cancers to as high as 15%, in contrast, to never smokers [9,10]. Insufficient availability of healthcare facilities, inadequate hygiene practices, subpar nutrition, unfavorable work settings, and generally unfavorable living conditions all contribute to the overall risk of developing oral cancer. In recent years, the evidence linking Epstein-Barr virus (EBV) to oral squamous cell carcinoma (OSCC) has strengthened, indicating an increased understanding of the strength of this association [44].

In India and other developing nations, consumption of tobacco has been relatively steady for many years and tobacco and alcohol consumption still remains the primary risk factors for causing OPSCC [13,14].

The sexual behavior in India

Western literature showed an association between high-risk oro-sexual behavior and HNSCC [15]. Indian data are inadequate in this regard as eliciting detailed sexual history is usually awkward for the patients as well as for the clinicians. Furthermore, the Indian literature on HPV infection of the oral cavity, in general, is not exceptionally noticeable. Again the same discrepancy is taking stake everywhere. One study revealed only 2.75% positive patients for HPV16 and 22% positive for HPV18 (samples were taken from oro-pharyngeal tract) among all the subjects suffering either from oral SCC or pharyngeal SCC [16]. In another study, oral mucosal smears were set up from 60 sound individuals, and their genotyping was done, the study has reported 65% of individuals to be certainly positive for HPV16/18 [17]. The existing literature indicates a clear pattern wherein HPV-negative patients with oropharyngeal squamous cell carcinoma (OPSCC) and oral squamous cell carcinoma (OSCC) tend to be older with a history of alcohol consumption and smoking. Conversely, HPV-positive patients are typically younger, male, and sexually active. Additionally, a direct correlation has been observed between high-risk HPV 16 infection and frequent sexual activity, while oral sexual behavior might account for some of the epidemiological variations in HPV-OPSCC and HPV-OSCC across different ethnic groups and genders [43,45], it is important to note that generalizing such assumptions to Asian countries may not be appropriate. This is due to the challenges of obtaining comprehensive sexual behavior histories, which can make patients and researchers uncomfortable and limit the availability of relevant data. Therefore the results are inconsistent and contradictory.

Current status of OSCC classification in India

According to the National Comprehensive Cancer network (NCCN) there are certain guidelines and classification of HPV related OPSCC that is followed in western nations [18]. HPV testing is recommended for every oropharyngeal tumours in the United States of America. In addition, according to the US National Cancer institute and Cancer Therapy Evaluation Programme HPV status has to be incorporated as a stratification factor for preliminaries including oropharynx cancer patients [18]. However, as Indian scenarios are unclear on the role of HPV in causation, development, prognosis and pathogenesis of OSCC, therefore; no classification, vaccination, screening and treatment guidelines are followed in India towards HPV testing.

The prognosis of HPV related OSCC in western countries

Data has been analyzed in terms of prognosis for HPV positive OPSCC in western countries. HPV-positive OPSCC conveyed a favorable prognosis compared to HPV-negative tumors. Five-year survival rates for patients with advanced-stage HPV+ OPSCC ranges between 75 - 80%, whereas survival rates of less than 50% are found among patients with similarly staged HPV tumours [19]. HPV (+) tumours are profoundly treatment sensitive tumours have been shown to respond favorably to chemotherapy and radiation than HPV (−) tumours [20]. Data is scanty on the prognosis of HPV in Indian scenarios, but whatever available data is there it can be interpreted that prognosis is inconsistent with western countries. These cancers in the west have different biology and confer a better prognosis than the kind of OSCC happens in India [8].

HPV cervical cancer in contrast to HPV OPSCC

In comparison with cervical cancer, the establishment of a strong link between high-risk persistent human papillomavirus (HPV) infections and OPSCC has not been found [21]. The solid connection of HPV with cervical cancer has resulted in the recent development of HPV related prevention strategies for cervical cancer [22,23]. The prophylaxis incorporates interventions like HPV vaccines [24] and various

screening approaches such as visual inspection with acetic acid or Lugol's iodine (VIA/VILI), Papanicolaou test (Pap test or Pap smear) and HPV DNA testing [25].

Experience from developed nations shows that screening for cancer cervix either with Pap smear or HPV DNA is viable and cost-effective. It is known for reducing more than half of the cervical cancer incidence and mortality [26]. It is suggested that adolescent girls 9 - 13 years should be vaccinated with two doses of the HPV vaccine. Vaccine coverage should be monitored within the programmed framework and cervical cancer trends need to be monitored through the network of cancer registries [27,28].

There is another variation in the presentation of cervical cancer and OPSCC. In cervical lesions, there is no correlation between viral load and progression of tumour whereas in OPSCC high viral load predicts active HPV infection [29]. The proportion of HPV-positive OPSCCs with high viral load varies between studies from 33% - 77.5% [30]. It is possible that in cases of low viral load that HPV presence is the coincidental and alternative cause of carcinogenesis is implicated [24].

It can be concluded that the strategies used for screening and management of Cervical cancers can't be applied to the OPSCC carcinomas.

Role of genetic susceptibility of host for HPV infection and progression of OPSCC

There is paucity of literature in relation to the genetic susceptibility of the host for HPV in the causation of OPSCC. Whereas similar data on genetic host susceptibility in Cervical cancer for HPV is strongly supported by epidemiological studies [31-36]. A hereditary component of cervical tumors is well known which precisely is 26% and also there are 2 fold more chances of cervical cancer development in biological first degree relatives of the women who have developed a cervical tumor [37-40]. No such genetic correlation has been found for the occurrence of OPSCC.

Limitations of the Study

A small number of studies were included, and heterogeneity was evident and no heterogeneity test was used. This affects the strength of the conclusion that can be drawn from this review. All of the included studies were published in English, as language restriction was set when searching the selected databases. Relevant reports written in other languages in other databases may be missed, but this risk is likely to be small. Analysis of the impacts of possible confounding factors, such as smoking and tobacco, genetics and heterogeneity of the studies that should be considered has been missed. This should also be investigated in future studies. Other than the limitations of the study there were observed lacunae in the literature as well. Only few studies listed in the literature has used standardized guidelines for assessing the role of HPV in OPSCC. The utility of data on HVP as a causation factor of OPSCC has not been explored in Indian scenarios. The data on the association between HPV and tobacco consumption is also sparse. The Host genetic susceptibility of HPV in the causation of OPSCC is also not established.

Strength of the Study

This is the first systematic review of to investigate the role of HPV in OPSCC in Indian perspective. The information summarized in the paper overview can help researchers to design future clinical trials. Meanwhile, this review provides with valuable clinical information on the current Indian scenario and future directions in HPV related OPSCC. Results of this review clearly point to the need for more high-quality clinical trials on HPV related OPSCC. Although clinical trials are time- and resource-demanding, more trials should be conducted to generate stronger evidence to guide good clinical practice. In addition, there is room for improving the reporting of studies as well. Moreover, despite the high reliability and specificity of HPV diagnostic methods, the absence of false-positive results may introduce a certain level of bias to the current data. The presence of significant data heterogeneity, diverse study designs, and the extensive pooling of primary data from different Asian countries with varying inclusion and exclusion criteria for patients make it difficult to draw definitive conclusions from the current meta-analysis. Despite efforts to mitigate heterogeneity through stratification based on diagnostic tools and sub-regions in Asia, data heterogeneity persists in the current review. Additional measures such as subgroup analysis, meta-regression, and study exclusion have been employed to address this heterogeneity.

Conclusion

In a developing country like India, there Tobacco still remains the primary cause of OSCC. The amount of population presenting non – tobacco causes in the causation of OSCC is very scant. Furthermore, due to the inconsistency of data pertaining to HPV prevalence in OSCC in different regions, for example, 33.6% in the Eastern region [31]. 48% in South India [32], 15% in West India [33], 27.5% in Central India [34]. And 28% in Northeast India [35]. Another study with a larger sample size detected HR-HPV subtypes in only 6% of patients with OPSCC (28%) that has further added to the controversial role of HPV in the causation of OSCC. Similarly, for oropharyngeal carcinoma studies have reported 22.8% HPV positivity in 105 oropharyngeal cancer patients [36]. There is a wide range of discrepancies in data in defining the role of HPV in OPSCC in India. The observed heterogeneity was mainly attributed to the 1) Social and cultural habits of the enrolled cases, 2) Discrepancies in the nature of samples procured, 3) Varying sensitivity of the assays employed for detection of HPV [5]. Various techniques are utilized in the diagnosis of HPV-associated OPSCC. Many of the methods utilized for testing HPV in OSCC were not even reliable, for e.g. HPV PCR testing can suffer from false positives, it is much preferred to have p16 immunohistochemistry testing or *in situ* hybridization testing as a more complete and robust approaches to classify tumors as HPV positive or negative [6]. Due to the lack of "valid data" on the strong association between HPV and OPSCC in comparison to cervical cancer, the strategies used for screening and management of Cervical cancers can't be applied to the OPSCC carcinomas. The results obtained are significantly impacted by the choice of diagnostic methods and the geographical regions involved. It is crucial to account for additional factors that may affect the outcomes, including age, gender, race, and the specific locations within the oropharyngeal and oral cavities. Nonetheless, there is a need for further research focusing on standardizing diagnostic approaches and implementing cancer prevention and treatment initiatives, with a particular emphasis on promoting HPV vaccination.

Future Directions

To establish a definitive role of HPV in the prognosis and treatment of OSCC in India, a robust effort is required by the practicing oncologists, maxillofacial surgeons and researchers in the country.

1. There are various areas that need attention in this matter: The standard operating procedures should be created for the management of OPSCC.
    1. There should be standardization of testing and reporting of p16 IHC for HPV detection. In the light of the fact that HPV PCR testing can suffer from false positives, it is greatly preferred to have p16 immunohistochemistry testing or *in situ* hybridization testing as a more complete and powerful approach to classify tumours as HPV positive or negative. The Pan India campaign should work on finding the exact etiology of HPV-related head and neck carcinomas in India.
    2. After detection Quantitative analysis has to be performed to ascertain the viral load.
    3. Standardization of sample size from various Indian states in high volume centers.
    4. Standardization of sample procuration to avoid to reduce false negative results.
2. Research is needed to establish definite risk factors for HPV-related OPSCC including correlation between:
    1. Sexual practices and primary risk factors of OPSCC in India.
    2. The relationship between HPV and Tobacco consumption has to be studied in detail.
    3. Role of genetics can be studied in pathogenesis of HPV related OPSCC.
3. The formulation of a national team may be considered that might include oral surgeons, oncologists, and specialists dealing with cervical cancers to have an overall view of the situation.
    1. The knowledge related to the preventive role of vaccine in cervical cancer, if can be applied in the management of OPSCC.
    2. Knowledge related to the methods of cervical cancer screening if can be utilized in the oral cavity.

Targeting individuals with low socioeconomic status, efforts should be directed towards enhancing health literacy regarding the risk factors associated with oral cancer, as well as promoting early detection through screening programs.

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