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Oropharyngeal carcinomas related to human papillomavirus - A systematic review

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Abstract

Instruction: Head and neck squamous cell carcinoma (HNSCC) represent the sixth most common cancer worldwide, affecting the oropharynx comprising tonsils, soft palate, the base of the tongue and lateral/posterior pharyngeal walls.

One of the leading causes of HNSCC is tobacco use in both smoking and smokeless forms, along with alcohol abuse, which has synergistic effects. Recently, there has been an increase in oropharyngeal squamous cell carcinoma despite the decline in tobacco and alcohol usage.

With the emergence of this data, efforts are being made to understand the trend of increasing oropharyngeal squamous cell carcinoma (OPSCC) while other head and neck cancers are decreasing.

Since human papillomavirus (HPV) is a causal factor in a subset of OPSCCs, it has been proposed that a steadily rising rate of HPV-associated cancers has led to changes in OPSCC incidence. [1,3,22,24]

Objective: This article aims to discuss the etiopathology, course of the disease, treatment modalities and prognosis of the oropharyngeal carcinomas related to human papillomavirus.

Keywords: Human papillomavirus, Oropharyngeal carcinoma, Squamous cell carcinoma, Cancer etiopathology, HPV vaccines, Radiotherapy, Immunotherapy, Chemoradiation therapy, CtDNA, Biomarkers, Prognostic biomarkers.

Introduction

Head and neck cancer is the sixth most common cancer, with about 640,000 new cases each year worldwide. Human papillomavirus has been associated with head and neck cancer, especially with the oropharynx, with the highest distribution in the tonsils and is emerging as a different subtype of head and neck cancer.[3]

The increase in oropharyngeal squamous cell carcinoma seems to be accounted for by a rise in human papillomavirus (HPV) related to oropharyngeal carcinoma.

Despite the decline in tobacco and alcohol usage worldwide, the increase in cases is due to sexual practices involving multiple partners, oral sex practises, early age of sexual encounter, and prior history of sexually transmitted diseases. [4,5,16]

All these may have led to higher rates of oral HPV infection and ultimately HPV positive OPSCCs.

The statistics collected from various researches show evidence for the same.

The relative contribution of HPV 16/18 and HPV 6/11/16/18/31/33/45/52/58 was estimated.

4.5% of all cancers worldwide (640,000 new cancer cases per year) are attributable to HPV: 8.6% in women and 0.8% in men. Attributable fractions (AF) in women ranges from <3% in Australia/New Zealand and the USA to >20% in India and sub-Saharan Africa. Cervix accounts for 83% of HPV-attributable cancer, two-thirds of which occur in less developed countries.

In the head and neck, HPV-attributable cancers represent 38,000 cases, of which 21,000 are oropharyngeal cancers occurring in more developed countries. The relative contributions of HPV16/18 and HPV 6/11/16/18/31/33/45/52/58 are 73% and 90%, respectively. Universal access to vaccination is the key to avoiding most HPV-attributable cancer cases. [1,5,6,24,29]

In the United States, the incidence of oropharyngeal squamous cell carcinoma increased by 22% from 1.53 per 100,000 to 1.87 per 100,000 between 1999 and 2006, after showing no change between 1975 and 1999. [1,27]

The United Kingdom has seen a 51% increase in oral and oropharyngeal squamous cell carcinoma in men from 7 per 100,000 to 11 per 100,000 between 1989 and 2006. [1,27]

The prevalence in India was 36.6%, slightly higher than the global prevalence.

- About 1.8 women and 9.4 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer among white people.
- Among black people, about 1.4 women and 6.6 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer.
- Among American Indian and Alaska Native people, about 1.0 women and 5.3 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer.
- Among Hispanic people, about 0.9 women and 4.4 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer.
- Among Asian and Pacific Islander people, about 0.6 women and 2.2 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer.
- Among non-Hispanic people, about 1.8 women and 9.3 men per 100,000 were diagnosed with HPV-associated oropharyngeal cancer. [1,2,13,19,20,21,25,27]
- Infection with sexually transmitted human papillomavirus (HPV) is a cause of virtually all cervical cancers. Molecular evidence also supports a role for HPV, particularly HPV-16, in the pathogenesis of a subgroup of squamous-cell carcinomas of the head and neck.

Genomic DNA of oncogenic HPV is detected in approximately 26% of all squamous-cell carcinomas of the head and neck worldwide. Still, the molecular evidence is most rigorous and consistent for oropharyngeal squamous cell carcinoma, in which viral integration and the expression of viral oncogenes (E6 and E7) have been shown.[4]

Multiple original studies have been conducted to study the association between human papillomavirus and the increased incidence of oropharyngeal carcinomas.

The incidence of HPV-related OSCC increases in North America and Western Europe, with up to 70% of new

oropharyngeal cancer causes being attributed to HPV, whereas data from the developing world remain lacking. [6,11,17,21,24,29]

It is of paramount importance to understand that the etiopathology of OPSCC in non-smokers and non-drinkers is different from those with a history of tobacco and alcohol abuse.

HPV-related OPSCC is associated with improved prognosis both at the time of primary diagnosis and disease progression. [18,3]

Materials and methods

This systematic review was carried after referring to the guidelines for preferred reporting items for systematic reviews. The literature for this paper was identified and selected by performing a thorough search in the electronic databases like PubMed, Medline, Embase, Google Scholar, Scopus, Web of Science, published over the past two decades. by using keywords such as human papillomavirus, oropharyngeal carcinoma, squamous cell carcinoma, cancer cytopathology, HPV vaccines, radiotherapy, immunotherapy, chemoradiation therapy, CtDNA, biomarkers, prognostic biomarkers.

Resources selection

Full-length articles were retrieved. Electronic searching was performed to go through the journals. The required data for this review was selected in two stages. In the first stage, the articles were selected based on the title and abstracts related to our research topic. The preliminary search resulted in 53 articles that were appropriate enough to address the paper's aim. 30 articles were retrieved for the second stage of selection. Next, the following criterion was applied.

Criteria for considering studies for this review

Inclusion criteria

1. The article must be focused on oropharyngeal carcinomas related to HPV
2. There must be some predictive or measurable outcomes so they can be quantified.
3. There has to be a proper mention of datasets that are used to assess a model.

Exclusion criteria

1. The articles that are related to other carcinomas associated with HPV
2. Articles that were unpublished.
3. Articles that were not written in English.

Result

The systematic review was conducted on 53 articles, out of which 30 were selected based on the inclusion and exclusion criteria.

30 articles indicated the causal role of HPV in oropharyngeal carcinomas.

- 8 articles showed statistical evidence for an increase in the number of HPV related OPSCC.
- 17 articles were studied to understand the etiology, course and implications of the disease.
- 7 articles explained the improved prognosis of HPV related OPSCC when compared to HPV negative OPSCC.

Discussion

In 2007, human papillomavirus (HPV) type 16 was defined, in addition to smoking and alcohol, as a risk factor for oropharyngeal squamous cell carcinoma (OPSCC) by the International Agency for Research on Cancer. Among OPSCC sites, HPV is primarily found in SCCs of the tonsils and the base of the tongue (TSCC and BOTSCC, respectively), which differ from the corresponding HPV-negative Tumors.

Many epidemiological studies have been conducted to provide support in proving the association between HPV and the subgroup of oropharyngeal cancers. The strength of the evidence is underscored by the associations of high-risk sexual behaviours, oral HPV infection, and

HPV-16 exposure with oropharyngeal cancer. Furthermore, it was found that HPV-16 DNA was localized explicitly to tumor-cell nuclei in 72% of specimens of oropharyngeal cancers, a finding corroborated by the high prevalence of antibodies for HPV-16 oncoprotein E6, E7, or both (64%) in the patients with oropharyngeal cancer according to a case-control study conducted. [4,6,11,17,19,20,22,24,29]

The global increase in HPV driven OPSCC is seen due to multiple risk factors. In Australia and New Zealand, it is elucidated that males of the white race with age bracket 40 to 59 years with various sexual partners have a higher risk of contracting the HPV infection and thereby OPCC.[14]

A review of an article revealed a total of 9,943 HNSCC patients with known HPV status from the SEER database were enrolled, with 6,829 (68.7%) HPV-positive patients. HPV-positive and HPV-negative HNSCC were distinct and had different clinical and socioeconomic features. Primary sites, socio-economical factors (age, sex, marital status, and race), and pathological features (TNM stage and grade) were closely related to HPV status. HPV-positive status was a favourable prognostic marker in HNSCC patients with cancers of the oropharynx and hypopharynx but was not in nasopharyngeal carcinoma patients.

A case-control study showed that substantial molecular evidence suggested a role for HPV in the pathogenesis of OPSCC, but epidemiologic evidence has been inconsistent. The association between the virus and OPSCC increased among subjects regardless of their tobacco and alcohol use. [7,23,28]

The epidemiologic evidence of a causal role for HPV in a subgroup of SCC of the head and neck is less rigorous than the molecular evidence.

The example of the relationship between HPV and cervical cancer indicates that high-risk sexual behaviour and exposure to infection with HPV will increase the risk of other cancers caused by HPV.[1,3,5,22,24,27]

Oropharyngeal cancer was also strongly associated with serologic measures of exposure to HPV-16 and with the presence of oral HPV infection.

OPC was significantly associated with seropositivity for the HPV-16 LI capsid protein, a validated measure of the lifetime of HPV-16 exposure.

Cervista HPV assays for fine-needle aspiration specimens are a valid option for human papillomavirus testing in patients of OPSCC.[31]

The measure of both lifetime and prevalent oral HPV-16 infection was associated with an increased risk of oropharyngeal cancer, whether or not there was a history of tobacco, alcohol, or both. [6,20,22]

As for the treatment modalities, a retrospective analysis was conducted of the association between the tumor and HPV status and survival among patients with stage 3 and 4 OPSCC who were enrolled in a randomized trial comparing accelerated fractional radiotherapy with standard fractional radiotherapy, each combined with cisplatin therapy, in patients with SCC of the HN. Although the response to induction chemotherapy rates is higher among patients with HPV-positive Tumors than those with HPV-negative Tumors, four single-agent cisplatin therapy did not appear to affect the elimination of distant occult metastases differentially. Second primary Tumors, which are primarily related to smoking, were less frequent among patients with HPV-positive Tumors, a finding that is consistent with the lower exposure to tobacco in this subgroup. However, the death rates from second primary Tumors were similar in the HPV-positive and HPV-negative subgroups and do not account for the overall survival rates. [12,26]

Prognostic implications of HPV in oropharyngeal carcinomas.

HPV status is a strong and independent prognostic factor for survival among patients with OPSCC, which is consistent with the hypothesis that HPV-positive and HPV-negative OPSCC carcinomas are distinct and have different causes, risk factors, prognosis and survival outcomes.

The superior prognosis for HPV-positive OPSCC, compared with that of the HPV-negative cancer, appears to have multifactorial underpinning. Known favourable prognostic factors associated with HPV-positive subgroups account for approximately 10% of the detected difference in the outcome. The higher survival rate among patients with HPV-positive cancer is due to greater local-regional control, reflecting higher intrinsic sensitivity to radiation or better radio sensitization with the use of cisplatin.

The data collected from the study mentioned above clearly indicate that HPV status and status concerning tobacco-smoking are major independent prognostic factors for patients with OPSCC, probably because they determine the molecular profile of cancer concerning patterns of loss of heterozygosity, chromosomal abnormalities, and gene expression profiles and inversely correlated with biomarkers for a poor prognosis in SCC of the Head and Neck. No specific mechanism is shown to explain the higher rates of response to radiation therapy and chemotherapy among patients with HPV-positive cancer. [3,4,8,9,10,14,15,26]

Conclusion

A systematic review was conducted in detail to reflect upon the oropharyngeal carcinomas related to human papillomavirus. The global increase in the percentage of oropharyngeal squamous cell carcinoma despite the decrease in tobacco and alcohol usage is seen due to the rise in human papillomavirus cases, which subsequently leads to the development of OPSCC. [1,3,5,30]

Various causal factors contribute to carcinoma. This review emphasizes the role of HPV in it.

The etiology, course, treatment modalities and prognosis differ from HPV-negative OPSCC. HPV-positive OPSCC has an improved prognosis and lower rates of adverse events compared with HPV-negative OPSCC. HPV-negative OPSCC have significantly worse outcomes when treated with primary radiation than primary surgery.[12]

Although multiple studies have been done in the western developed countries to understand this trend, there is scope in developing Asian countries to reflect upon the same as there is lack of evidence.

The role of vaccination against HPV in preventing OPSCC has not gathered enough evidence and information. Studies are being conducted on the same. Newer research coming up can help us better understand this disease

The incidence of HPV associated with OPSCC is expected to continue to rise over the coming decades until the gender-neutral prophylactic HPV vaccination begins to manifest.[29]

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