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Association Of Hpv And Oral Cancer

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Abstract

According to the International Research on Cancer (AIRC) oral cancers are a type of cancer that develops in people's lip linings, mouth, and the oropharynx. Studies have shown that the consumption of alcohol and tobacco products are the primary carcinogens that cause oral cancers. However, increasing cases of young individuals with no previous exposure to alcohol or tobacco who are getting oral cancers have prompted studies to look into the role of other carcinogens, especially viruses. Currently, the IARC presents oral cancers as the sixth most common type of cancer in the world. High-risk human papilloma virus (HPV) types are responsible for over 50 percent of cervical cancers worldwide. Also, people also acquire HPV in the mouth, prompting studies to look into the virus's association with oral cancers.

This paper performs a systematic review of studies investigating the association of oral cancers and HPV. The association of HPV and oral cancers began in the 1980s; however, more studies performed in the last decade until now are showing a positive association. From this research, it becomes clear that knowledge about oral HPV and oral cancers is expanding. Emerging research shows that the DNA of the HPV-16 virus are found on oral cancer tumors; hence, a positive causal association. More research is also coming with significant evidence to suggest a causal relationship between HPV and some oral cancers, most notably, those of the tongue and tonsils among people with no previous exposure to the usual carcinogens (Alcohol and tobacco).

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Overview of Oral cancer

Epidemiology:

Oral cancers are cancers that develop in the lining of the lip, the mouth and the oropharynx. They are twice more likely to occur in men than in women in most populations of the world. However, this disparity is fast fading due to more women being exposed to know oral carcinogens such as tobacco and alcohol (Neville et al., 2002). The International agency for research on cancer (IARC) has grouped cancer of the oral cavity and pharynx and presented them as the world's sixth most common cancer. The annual diagnosed cases for oral cancers are over 300,000, and the yearly mortality represents about 145,000 deaths (Bagan et al., 2010). Oral cancer mostly occurs in middle-aged and older individuals. However, a disturbingly high number of cases has been documented in younger individuals (Neville et al., 2002). From the epidemiological perspective, oral cancers can be divided into three categories: those arising from the oropharynx, carcinomas of the lip vermilion, and those of the oral cavity proper (Neville et al, 2002). Pharyngeal cancer is common in African Americans more than in white Americans; however, tumors of the lip vermilion mostly occur in white males (Bagan et al., 2010).

Signs and symptoms:

Oral squamous cell carcinoma(OSCC) is the most common malignancy that is responsible for more than 90 percent of all oral cancers (Bagan et al., 2010). Usually, oral cancer presents itself as pain which occurs in the tongue and the floor of the mouth. OSCC in the initial stages show no symptoms, but as it advances, it appears as ulcers and lumps with irregular margins that are rigid to touch (Bagan et al., 2010). Other symptoms of oral cancer are mucosal lesions, dental occlusions that are altered, red or white spots in the oral mucosa, mucosal alterations, swelling in the oral cavity, loosening of teeth for unknown reasons, persisting foreign body sensations, pain, speech difficulties, neck swelling, and bleeding from unknown causes (Scully & Porter, 2001).

Prognosis:

The prognosis of oral cancer depends on where it is. For instance, in intraoral carcinoma, the five-year survival is lower than 30 percent in posterior lesions that are lately detected. However, the five-year survival for lip carcinoma is more than seventy percent (Wolf et al., 2012). Studies show that essential factors that should be considered in management are the quality of one's life and education. A study found that 47% of patients continued smoking and 36% still drunk alcohol after diagnosis (Wolf et al., 2012). There is a significant disparity between the survival rates in African Americans and White Americans. Between 1985 and 1996, the five-year survival rate among African Americans with carcinoma of the tongue was 27 percent compared to 47 percent in white men. Furthermore, the floor of mouth cancer survival rate was 52 percent in whites and 33 percent among African Americans (Wolf et al., 2012).

Risk factor:

The significant risk factor for oral cancer is tobacco use in its many forms. Evidence shows that smoking tobacco increases the risk of oral cancer by twofold or even tenfold in both men and women. Smokeless tobacco products are attributed to 50 percent of oral cancer in Sudan and India, and four percent of cases in the United States (Neville et al., 2002). Other risk factors are excessive alcohol consumption, and certain types of HPV (Wolf et al., 2012).

Background of HPV

Human Papilloma Viruses (HPVs) are the most common sexually transmitted infections in the United States. Greenblatt (2005) defines HPVs as a family of over 80 serotypes that create pathologies such as genital warts. The IARC associates HPVs to higher vertebrates and mentions that these viruses induce cellular proliferation (IARC, 2007). Moreover, IARC defines HPVs as a small non-enveloped, epitheliotropic, double-stranded DNA viruses that infect the mucosal epithelia in higher vertebrates as mentioned above (IARC, 2007). Currently, more than 100 HPVs have been documented, and more than half of these manifest in the tract of those infected

(IARC, 2019). Munger et al. (2004) mention that HPVs are transmitted either via mucosal or cutaneous means. Within this classification, individual viruses are either low risk or high risk depending on the propensity for malignant progression of the lesions that they cause. Long-term infections of one's larynx, anus, penis, and cervix by high-risk HPV serotypes (HPV-16 and HPV-18) can cause dysplasia that develops into cancer (Greenblatt, 2005).

Epidemiology and method of HPV infection:

It is approximated that about 6.2 million new HPV infections occur in the United States each year and more than 20 million people in the United States are approximated to be currently infected (Ault, 2006). The viruses are spread through skin-to-skin sexual contact and are found in all populations that are sexually active (Ault, 2006). The CDC estimates that at least half of the sexually active people will get HPV at some point in their life. Additionally, at least 80% of women in the US acquire HPV before the age of 50. Furthermore, in the United States, at least 10% of the population have an active HPV infection, 4% have an HPV that has resulted in cytological abnormalities, and 1% have diseases that have developed into genital warts (Ault, 2006). The risk factors for HPV infections are sexual activity, youth, and gender, with the highest number of infections in sexually active women under the age of 25 (Ault, 2006).

Association of HPV and oral cancer:

High-risk HPVs are now categorized as human carcinogens (Chaitanya et al., 2016) with cervical cancer having a strong association with high-risk HPV-16 and HPV-18 infections. Also, strong evidence suggests that DNA viruses such as HPV are involved in oral cancer; however, Chaitanya et al. (2016) reported that the etiopathogenesis of HPV and oral carcinoma is still unclear due to the conflicting evidence regarding the detection of DNA viruses in oral carcinoma. On the other hand, a few studies point to the positive correlation between HPV and oral carcinoma. Although oral cancers have a strong co-relation with tobacco chewing and smoking

and alcoholic beverage drinking, these attribute for about 90% of the causes. However, according to IARC (2007), tumors also occur in subjects not exposed to these risk factor, hence suggesting that other exposures could be involved. Therefore HPV infections which are known to infect the oral cavities of healthy individuals could be one of the possible agents in the development of oral cancer.

This paper aims to evaluate the association between HPV and oral cancer.

Methodology

For the preparation of this paper, a systematic search was conducted using several electronic databases that included PubMed, ClinicalTrials.gov, Google Scholar, Science Direct, ISI-Web of Science, and Pak Medinet. Various combinations of the words “oral cancer,” “oral carcinoma”, “Human Papilloma Virus,” “HPV,” “oral HPV,” “Oral Human Papilloma Virus,” “oral neoplasia,” “throat cancer” “squamous cell carcinoma of the oral cavity,” and “High risk human papilloma virus” were used in the search. Other keywords such as “low-risk human papilloma virus” “risk factors of oral carcinoma,” were also included in the search. Specific searches were done as follows.

Exposure: “Oral Human Papilloma Virus” AND “oropharyngeal cancer.”

“HPV strains” AND “oral cancer.”

“HPV positive throat cancer”

“Epidemiology of HPV positive oral cancer.”

The search results were restricted from 2006 until present. Additionally, filters were avoided during the electronic searches. Articles from the International Agency for Research on Cancer (IARC) were also used to assist with the evidence base. The IARC articles were retrieved from the Agency’s website (https://monographs.iarc.fr).

Having received the selected publications, their respective bibliographies were also analyzed to identify further publications that would assist in the development of this paper. For the sake of the literature search, oral cancer was defined from its epidemiological perspective according to Neville et al (2002). Oral cancer was divided into three categories: those arising from the oropharynx, carcinomas of the lip vermilion, and those of the oral cavity proper (Neville et al, 2002). The literature search was carried out between April 11, 2019 and April 16, 2019.

Inclusion criteria:

Only publications that fulfilled the criteria of being published in the last two decades were considered; although exceptions were made for a select review articles. Furthermore, the search was limited to the aforementioned electronic databases, PubMed, ClinicalTrials.gov, Google Scholar, Science Direct, ISI-Web of Science, and Pak Medinet, which generally restricted the publication material areas of origin to North America and Europe. Only manuscripts that were published as indexed or non-indexed journals were reviewed and the publication dates were restricted not to go back beyond 2006. Additionally, only publications written in English were reviewed. Publications of the reviewed literature had to focus solely on oral cancer, which were those carcinoma arising from the oropharynx, carcinomas of the lip vermilion, and those of the oral cavity proper by definition. Besides review articles, the authors of the reviewed publication had to have affiliations to verifiable and renowned institutions around the world. Finally, the articles of interest had to be within the electronic databases provided above with the exception of IARC articles.

Exclusion criteria:

Publications outside the electronic databases above were excluded from the study because it was hard verifying their authenticity. Research publications published before 2006

were left out of the review because of the constantly evolving nature of research. Since the study focused on oral cancer and HPV, publications focusing on cancers that did not originate in the oropharynx, lip vermilion, and those of the oral cavity proper were excluded. Furthermore, publications that included HPV in other areas of the body but not found in the mouth were excluded. Several researches found in other medical research databases focusing on the relationship between HPV and oral cancer and not written in English were all excluded from the review. Other studies that were excluded were those that reported relationship between HPV and other cancer other than oral cancer as the end point. Case reports, editors, and commentaries were all excluded. Clinical trials that were not yet formally published were also excluded. Publications that did not relate HPV's connection to oral cancer were excluded. HPV is a common virus that affects most higher vertebrates, and as a result, studies focusing on animals were excluded from this research.

Selection of publication:

The selection of publications reviewed in the article was done in three stages; the first stage involved screening the titles of the identified publications of interest through an electronic search on the electronic databases via the above-mentioned platforms. The second step involved scrutiny of the abstracts of the publications of interest, after which the full texts were retrieved if they fulfilled the search criterion. Finally, the publications were then selected to be included as a part of the evidence base for this paper depending on the entire scrutiny of the text.

Keeping track of publication and references:

Data was abstracted from the selected publications of interest mentioned above on to a spreadsheet (Microsoft Excel was used). The spreadsheet was divided into the first author's name, the year that the publication was published, focus or type of study of the publication, database hosting the publication, and the link leading to the publication. The data was further

compared and any discrepancies were dealt with. To keep track of my references, I used the Zetoro software to capture, import, and archive item information and files.

Results

The search in PubMed, ClinicalTrials.gov, Google Scholar, and Science Direct returned 100 publications, duplications included. After excluding publications based on duplication, 70 papers remained. Moreover, after an application of the selection criteria, 40 publications remained. Twenty-five publications were further removed for not including the inclusion criteria, which were publications published before 2006 and publications that did not focus on oral cancer or oral HPV. Besides the selected databases mentioned above, five more papers that are eligible were identified through a superficial google search. Three other publications were identified by going through the bibliographies of the eligible publications. In total, the final review consisted of twenty-three publications (figure 1). Full texts of a further six papers that had been selected could not be retrieved though they were suggestive of the relationship between HPV infection and oral cancer and, thus, could not be included in the final review.

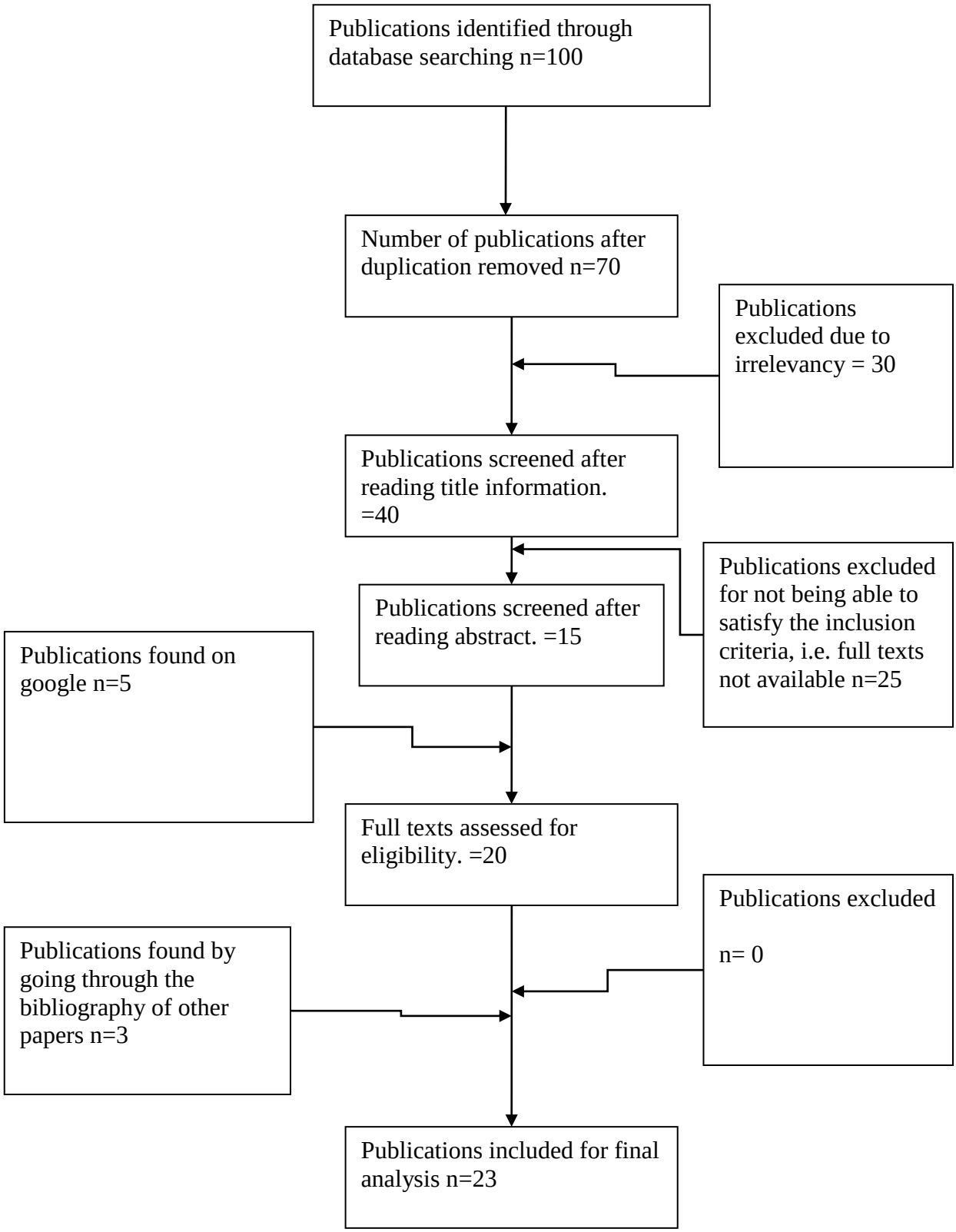

Figure 1. Flow Chat detailing the publication selection process.

Characteristics of the selected studies:

The first publication selected for the study was published in 1985 by Scully et al, with the title, “Papillomaviruses: Their possible role in oral disease.” Though the article did not provide conclusive evidence to support HPV's correlation to oral cancers, the study believed that oral papillomaviruses were responsible for some premalignant and malignant oral lesions. The latest study selected for this paper was the "Systematic meta-analysis on the association of human papillomavirus and oral cancer" by Chaitanya et al (2016) which had strong evidence indicating that DNA viruses could have a role in oral cancers.

Chaitanya et al. termed HPV a ‘human carcinogen’ but mentioned that besides the positive associations indicating that HPVs were involved in oral cancers, there were still conflicting evidence. The publication results retrieved for this study shows that the cumulative research on the involvement of DNA viruses on the development of oral cancer has been steadily rising over time. Out of the studies that I reviewed that investigated the relationship between oral carcinoma and HPV, 30% (n=30) were published before 2006, and 70 percent of the publications were published after 2006. The most productive year in cancer research and HPV research based on the selection of my literature was in 2013.

Thirty-six of the total articles that I selected in my initial search were case series studies. Additionally, 21 of my initial study selections were cross-sectional surveys. Case-control studies were 18, of which some were about how individuals could modify their lifestyle to lower the risks with the rest being genetic, viral, and chemical epidemiology studies. Study reviews constituted eleven of the documents selected, and six were laboratory research studies. Among the total studies, two were clinical trials.

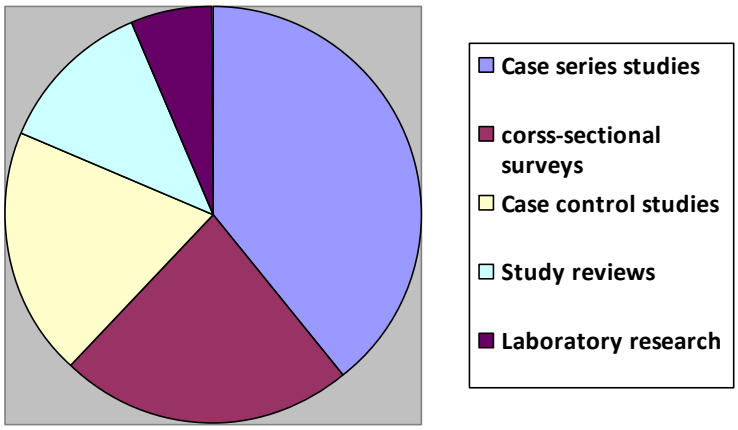

Figure 2: Pie Chart showing the type of research.

Seven of the studies for my final review focused on the risk factors that caused oral carcinoma, most of which were case-control studies and a few comparative designs. Most of the studies that suggested a positive association between human papillomaviruses and oral cancers were published after 2006, while most studies that were inconclusive about the association were published before 2006. Some of the risk factors mentioned in all seven reviews were genetic, viral, lifestyle, and molecular or chemical risk factors. The publications that associated the genetic predisposition for oral cancer were those published after 2008. Twenty of my initially selected studies were about the frequency of oral cancer in the clinic or hospital distribution, while 15 reviews were about the treatment modalities for oral carcinoma. Some studies were about the procedures for diagnosing HPV and oral cancers while some were about the attitudes that different populations had regarding oral cancer of HPVs. A few studies also focused on cancer care, the follow up of oral HPV patients, and the quality of life of both HPV patients and those with oral cancer.

Results of the studies:

The focus of the earliest study analyzed in this paper –Scully et al. (1985) suggests that the suspicion of the involvement of DNA viruses on oral carcinoma started as early as the 1980s. The studies also showed that oral squamous cell carcinoma was made up the bulk of oral cancers, accounting for 90 percent of oral carcinoma cases (IARC, 2007; Began et al., 2010; Greenblatt, 2005). Concerning the symptoms associated with Oral carcinoma, Pain was the obvious symptom. Oral carcinoma was more common in men than it was in women (IARC, 2007; Scully et al., 1985; Neville et al., 2002) and this might be because more men are exposed to more risk factors such as tobacco smoking and alcohol drinking than women are. According to the IARC, oral cancer included cancers of the oral cavity, the pharynx, and it was the sixth most common cancer in the world. Began et al. (2010) mentioned that oral cancer was diagnosed in more than 300,000 individuals worldwide each year and that it resulted in 145,000 deaths annually.

Wolf et al. (2012) mentioned that the prognosis of cancer depended on where it occurred. For example, the five-year-survival for intraoral carcinoma was lower than the five-year survival for lip carcinoma. When it came to the relationship between oral carcinoma and pre-existing oral HPV, most studies suggested a causal association. Syrjänen et al. (2011) aimed at calculating risk estimates that associated HPV malignant disorders and healthy oral mucosa were the control experiment; the study found a definite causal association. Another survey by Campisi & Giovannelli (2009) mentions that no precise results linking HPV to oral cancers have emerged so far. However, some studies report the association between HPV-16 with oral squamous cell carcinoma. Studies that show a less definitive association between HPV and oral cancers are Eversole et al. (2006), Scully et al. (1986), Miller et al. (2007), and Sugarman et al. (2007). The studies that provide a positive association between HPV-16 and oral cancers are Syrjänen et al. (2011), Andrews et al. (2009), and Giovonelli et al. (2002), among other studies.

Possible risk of bias in studies used:

Evidence-based medicine (EBM) has been called one of the most critical milestones in modern medicine. Since the last half of the twentieth century, clinical practice has become more literature based and data-driven than before. Bias in research results from the introduction of systematic error in sampling and testing, when one outcome is encouraged over the others. A lot of evidence already associate human papillomaviruses as the major risk factor for cervical cancer, and it would only be natural to find other carcinogenic associations between the virus and other places it occurs such as the lips and oral cavity. Possible risk of bias in the studies analyzed by this paper could have occurred at the study design stages, data collection stages, and when analysis was done. Pre-trial preferences for the study of HPV and oral cancer association could have resulted from flawed study designs, the subject selection criteria, and the channeling process. Bias during trials of the study might have come from exposure misclassification, outcome misclassification, and performance bias. The preference after tests for the studies could have come from confounding and citation biases. Different types of studies are prone to different biases. For example, non-blinded studies are prone to information bias due to assessor bias because the assessors are aware of the study they can have a bias towards a favourable outcome. For studies like case control studies it is difficult to ensure temporality – hence making it prone to information bias.

Discussion

The main findings of all the evidence

Epidemiology of oral cancer:

Oral cancer is the sixth most common forms of cancer in the world (Neville & Day, 2002). IARC (2007) defines oral cancers of the oral cavity and pharynx. Annually, oral cancer is diagnosed in more than 300,000 individuals worldwide, and fatalities related to oral cancer were 0ver 145,000 with five-year prevalence cases of 702,000 (Neville & Day, 2002). When the

cancers of the oral cavity and pharynx are broken down further, oral cancers include cancers of the mucosal lip, mouth palate, floor of the mouth, tongue, and gum (Began et al., 2010). Close to two-thirds of diagnosed oral cancers globally are found in low to middle-income countries, with South Asia contributing to half of the two thirds (IARC, 2007). As of 2013, one-fifth of oral cancer cases came from India (Chaitanya et al., 2016). In the United States, oral cancer (cancers of the pharynx and oral cavity) constitute three percent of all the cancers in the country, and over 90% of all oral cancers originate from squamous cells (Began et al, 2010).

Geographically, between 1987 and 1991 in the United States, regions that had the most deaths associated to oral cancers were Alaska, Delaware, South Carolina, and Louisiana respectively (Campisi & Giovannelli, 2009). The states with the lowest mortality rates were Arkansas, Wyoming, Idaho, and South Dakota. Different subgroups within America have separate oral cancer incidences. Between 1973 and 1991, incidence rates of oral cancer in black men rose from 16.8 to 20.7 per 100,000 people (Began et al., 2010). For the same period (1973-1991) white men saw a decline in oral cancer from 17.5 percent to 15.3 per 100,000 people. Several primary lesions occur as a result of oral cancer which increases an individuals chance of having a second oral cancer by 20 percent (IARC, 2007). What's more, people with tumors in the pharynx and oral cavity have an increased chance of developing other cancers such as those of the esophagus, stomach, lung, and larynx (Scully et al., 1985).

Prognosis of oral cancer:

Based on the 1983-1990 data, the five-year survival rate for oral cancer in the United States was 52.5. Females had better survival rats than men, and Black men had lower survival rates compared to their white counterparts (34 percent of black men survived compared to 55 percent of White males for five years). Also, the five-year survival rate for cancer from the point of diagnosis had not changed since the 1974-1976 period (Wolf et al, 2012). Prognosis of oral

cancer depends on where it is. For instance, in intraoral carcinoma, the five-year survival is low than 30 percent in posterior lesions that are lately detected (Began et al, 2012). However, five-year survival for lip carcinoma is more than seventy percent. Studies show that essential factors that should be considered in management are quality of one's life and education; for instance, a study found that 47% of patients continued smoking and 36% still drunk alcohol after diagnosis (Wolf et al., 2012). Between 1985 and 1996, the five-year survival rate among African Americans with carcinoma of the tongue was 27 percent compared to 47 percent in white men. What's more, the floor of mouth cancer survival rate was 52 percent in whites and 33 percent among African Americans (Wolf et al., 2012).

Oral cancer risk factors:

The use of Tobacco and many of its products and the massive consumption of alcohol remain as the most significant risk factors of oral cancers worldwide (Andrews' et al, 2009). Socio-economic factors also play a role, as oral cancers remain predominantly widespread in poor societies (Herrero et al,2003). Smokeless and smoking tobacco use increases the risk of oral precancerous lesions by 2-fold to 15-fold (Andrews et al, 2009). Over 50 percent of oral cancer cases in the United States, Sudan, and India are associated with tobacco use (Began et al, 2012). Evidence from most studies also shows that tobacco use increases the risk of developing oral cancer by two-fold to ten-fold (Began et al., 2012). The biological evidence of tobacco association with oral cancer are the several carcinogens found in tobacco such as N-nitrosonornicotine (Herrero et al, 2003).

Alcohol is an independent risk factor for oral cancer and it increases its risk by two-fold and six-fold and risks increase with heavy alcohol use (Ault, 2006) For combined alcohol and tobacco use, the risk for oral cancer is multiplicative (Gupta & Gupta, 2015). Poor nutrition also

accounts as a risk factor high consumption of vegetables and fruits significantly reducing the risks. Genetics also play a role in oral cancer (Gupta & Gupta, 2015). A system in the liver known as the cytochrome p450 metabolizes carcinogens and sometimes it might be faulty under inheritance; hence, increasing an individual's predisposition to oral cancer (Prabhu & Wilson, 2013). Recent studies show an association between HPV and oral cancer. Other studies also suggest that HPV modulates the carcinogenesis process in cancers induced by alcohol and tobacco and induces carcinogenesis among non-smokers (Prabhu & Wilson, 2013)

Human Papilloma Virus:

Human Papilloma Viruses (HPVs) are the most common sexually transmitted infections in the United States. Greenblatt (2005) defines HPVs as a family of over 80 serotypes that create pathologies such as genital warts. The International Agency for Research on Cancer (IARC) associates HPVs to higher vertebrates and mentions that these viruses induce cellular proliferation (IARC, 2007).

Moreover, IARC defines HPVs as a small non enveloped, epitheliotropic, double-stranded DNA viruses that infect the mucosal epithelia in higher vertebrates as mentioned above (IARC, 2007). Currently, more than 100 HPVs have been documented, and more than half of these manifest in the tract of those infected (IARC, 2019). Munger et al. (2004) mention that HPVs are either mucosal and cutaneous and within this classification, individual viruses are either low risk or high risk depending on the propensity for malignant progression of the lesions that they cause. Long-term infections of one's larynx, anus, penis, and cervix by high-risk HPV serotypes (HPV-16 and HPV-18) cause dysplasia that develop into cancer (Greenblatt, 2005).

Epidemiology and method of HPV infection:

It is approximated that about 6.2 million new HPV infections occur in the United States each year and more than 20 million people in the United States are approximated to be currently

infected (Ault, 2006). The viruses are spread through skin-to-skin sexual contact and are found in all populations that are sexually active (Ault, 2006). The CDC estimates that at least half of the sexually active people will get HPV at some point in their life. What's more, at least 80% of women in the US acquire HPV before the age of 50. Still, in the United States, at least 10% of the population have an active HPV infection, 4% have an HPV that has resulted in cytological abnormalities, and 1% have diseases that have developed into genital warts (Ault, 2006). The risk factors for HPV infections are sexual activity, youth, and gender, with the highest number of diseases in sexually active women under the age of 25 (Ault, 2006).

HPV association with oral cancer:

HPV apart from affecting the genital area, it also contaminates a person's oral cavity (Badarraco et al., 1998). A healthy oral mucosa sometimes becomes a reservoir for HPV infections and the manifestation points of HPV related lesions (D'Souza et al., 2009). Several pathways for HPV infection in the oral cavity exist with the most common ones being genital infections, oral sex, and a neonate infection while passing through the mother's birth canal (De Villiers, 2004). Acquisition of new oral HPV is associated with the frequency of open mouth kissing and oral sex than the rate of vaginal sex (D'Souza et al., 2009). Other reports suggest that men who have sex with other men have an increased chance of developing oral HPV (D'Souza et al., 2009). No evidence suggests the transmission of HPV by human saliva (Gillison, 2008).

Collectively, head and neck cancer are the sixth most common types of cancer in the world; these consists of cancers of the oral cavity, the pharynx, and the sinusoidal tract (Campisi & Giovannelli, 2009). Also, over 90 percent of oral cancers are the squamous cell cancers that occur at the oropharynx, mouth, and mucous membranes (Eversole & Laipis, 2006). Evidence suggests that cancers associated with tobacco and alcohol consumption are declining worldwide, but incidences of cancers of the tonsils and the base of the tongue (oropharyngeal) cancers are

increasing; these results have prompted studies to investigate alternative risk factors other than tobacco and alcohol (Miller & Johnstone, 2001). When the use of tobacco and alcohol is adjusted, high-risk HPV (HPV-16 and HPV-18) infections are significantly associated with an increased risk in developing oral cancer (Giovannelli et al., 2002). Studies that suggest the role of oral HPV infections in increased incidences of oral cancer indicate the presence of the papillomavirus in tissues found in tumors (Chaitanya et al, 2016). To further buttress this point, when the polymerase chain reaction method was used, HPV was detected 34.5 percent of the time in tumor tissues through the application of the in situ hybridization method and the southern blot method revealed HPV in 24.5 percent of the cases (Eversole & Laipis, 2006). The reviewed case-control study that involved several countries (Sudan, Australia, Canada, Cuba, India, Northern Ireland, Spain, and Italy) suggested an aetiological relationship between HPV and oropharynx and oral cavity cancers, with HPV-16 being the most mentioned virus type (Prabhu & Wilson, 2013).

Other studies that suggest the relationship between HPV and oral cancers assert that the HPV oncogenes have a synergistic contact with the carcinogens found in alcohol and tobacco; hence, leading to a malignant transformation of oral keratinocytes (Gupta & Gupta, 2015). Under the situations where chemical carcinogens are not present, oral cancers associated with HPV infections may arise from the HPV types E6 and E7 (Pintos et al., 2008). In vitro studies that detected the DNA sequence of an HPV-16 pile further evidence towards HPV's role in oral carcinogenesis (Giovannelli et al., 2002) Some reviews link the development of oral cancer with the number of oral and sex partners one has in a lifetime (D'Souza et al., 2009). Other evidence suggests a poor differentiation between tongue-tonsillar squamous cells cancers and HPV association (Ostwald e al, 2003) Other studies also indicate that real risk in oral cancer increased

with a history of genital warts, a younger age of first sexual intercourse, and increased marijuana use (Ragin et al., 2011).

The relevance of the research to healthcare:

The findings from this study regarding the association between HPV and the development of oral cancer has several benefits to healthcare. First, the findings provide new insight into oral carcinomas, their trends, and possible risk factors. The results mentioned above suggest growing evidence towards the association of HPV and oral carcinomas. Meanwhile, other studies indicate that cancers associated with alcohol and tobacco use are declining, yet oral cancers of the squamous cells are increasing. Therefore, it is evident that other risk factors have a more substantial hand in oral carcinomas than previously believed; hence, the relevance of research looking for other risk factors, with HPV topping the list. The above finding suggests significant evidence on the association between oral carcinomas and HPV; therefore, it is relevant to healthcare since it influences public health interventions, outcomes of treatment, patterns of care, costs, and functional abilities.

Findings that suggest an association between HPV and oral cancers is relevant because it gives reasons for the comparing and improved use of drugs, HPV vaccines, and diagnostics (Nass, 2009). The findings are also crucial in the development of new therapies, which would significantly improve health care and public health since HPV is one of the most common sexually transmitted infections. These findings could eventually have an impact on human health and longevity once they start screening for cancer the moment one has oral HPV. The findings could also reduce medical errors that go into detecting oral carcinomas and induce preventive methods that would eventually and substantially reduce morbidity and mortality that result from oral carcinomas. These finding could also have an impact governmental level by informing and

influencing national policies, and also emphasizing the importance of HPV vaccines to people of all sexes.

The potential benefits that patients would get from these findings include a better estimation of risk among people with HPV for developing oral carcinoma, better drug response prediction, better patient prognosis, earlier initiation of treatments, and enhanced knowledge and experience among people with increased risk of oral carcinoma.

Limitations of this paper

Primary research studies which were included in this study, such as Herrero et al (2003) and Ault (2006), carried out matching of the samples and covariate and stratification adjustment in order to reduce bias in observational studies. However, the methods employed although in favour of reducing bias, reduced the potential sample size of the studies. Although Herrero et al. (2003) sampled subjects from nine countries, most of the primary research in other study articles were obtained from the United States; hence, the studies had a strong regional focus and results do not have a worldwide inclusive approach hence reducing the overall generalisability of the results. Another limitation is that this research relied heavily on a limited number of databases. These were PubMed, Clinicaltrials.gov, Science Direct and Google Scholar. Both science direct and google scholar, during the literature search, led to some publications, that could not be fully accessed. Only the studies' abstracts of these were accessible. As a result of this, it is worth noting that the studies reviewed to generate this paper do not represent the total research on this subject area as some papers could not be retrieved from the database; hence, the accuracy of the findings might be biased due to the selection criteria.

A limitation in this study also comes from the heterogeneity of the published studies. Different results from various studies on the same topic were combined, despite the different methods, different number of subjects and different conditions which were employed.

An additional limitation also comes from the systematic review studies which formed part of the body of evidence: Gupta & Gupta (2015) and Chaitanya et al (2016). These did not provide the search strategies that were used; rather, they resorted to providing statistical information with conclusions. Without mentioning the search strategy, it is difficult to determine whether the researchers came about their conclusion through rational and search procedure techniques.

Selection of studies to be included in a meta-analysis should be based on quality criteria. However, for the studies analyzed such as D'sSouza et al (2009), Andrews et al (2009) and Chaitanya et al. (2016), it wasn't mentioned whether their reviews had been done in a review protocol. As a result of this, the quality criteria was unknown. Most of the reviews selected for this study did include adequate summaries of those studies of the primary studies that they used. These summaries include: the test settings, the aim of the tests, study design characteristics, or the demographics of those who participated.

In respect to the quality of the publications used, the assessment of the quality of the publications that I included in my research was limited. Studies were from many sources and geographical regions and it was unclear whether validated checklists such as QUADAS were used. Also, the studies included did not completely report the assessment of the statistical heterogeneity. My research also does not use the random effects meta-analysis model; therefore, estimates of the summary are not generalizable for studies in the future.

Finally, some of the data from the studies might have been subject to bias due to the type of studies used and their methodology. Besides, interestingly, most studies published before 2008 showed no association between oral cancer and HPV infections; however, newer studies found a positive association. A possible explanation for this could be due to better methods of

virus detection. Nevertheless, some of the data used for this study might have been old and out of date.

Conclusion

It is clear that knowledge about the association between the oral HPV family and oral cancers is expanding. Most importantly, emerging significant evidence suggests a causal relationship between HPV and some oral cancers; most notably those of the tongue and tonsils, especially among younger people with no previous exposure to alcohol or tobacco. From the results of this paper, one key recommendation would be to focus on population education on HPV and its role in oral carcinoma. This can serve as one of the key preventive strategies. Further research should focus on more risk factors for oral HPV and the role of other HPV types in the development of oral carcinoma.

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Appendix 1.

Firtst Author	Year	Focus of publication	Database	
Began, J.	2010	Oral cancer: clinical features. Oral oncology,	PubMed	https:
Neville, B. W	2002	Oral cancer and precancerous lesions.	Wiley Online Lib	https:
Scully, C.,	2001	Oral Cancer	ncbi	https:
Wolff, K.	2012	The diagnosis and treatment of oral cavity cancer.	ncbi	https:
Greenblatt, RJ	2005	HPVs: diseases, diagnosis and possiblevaccine	Science Direct	https:
IARC	2007	HPV	Monographs.IARC	https:
Munger, K,	2004	Mechanisms of human papillomavirus-induced oncogenesis.	PubMed	https:
Ault K.	2006	Systematic meta-analysis on association of human papilloma	PubMed	https:
Herrero R,	2003	HPV and Oral Cancer	PubMed	https:
Lee SY,	2010	Relevance of human papilloma virus (HPV) infection to carcin	ncbi	https:
Nallan C.	2016	https://www.ncbi.nlm.nih.gov/pubmed/27461683	PubMed	https:
Sugerman, PB,	2007	relationship: The high risk human papillomavirus and oral can	PubMed	https:
Ostwald, C,	2003	oral carcinomas and benign lesions	PubMed	https:
Miller, CS,	2007	HPV as a risk factor for oral squamous cell carcinoma	PubMed	https:
Panici, PB,	2006	Oral condyloma lesions in patients with extensive genital hun	PubMed	https:
Eversole, LR,	2006	Oral squamous papillomas: detection of HPV DNA by in situh	PubMed	https:
Scully, C,	1985	Papillomaviruses: their role in oral disease	Science Direct	https:
D'Souza, G,	2009	Oral sexual behaviours associated with prevalent oral human	PubMed	https:
Ragin, C	2011	Oral HPV infection and sexuality	PubMed	https:
Campis, G	2009	Controversies: HPV and Oral cancer	PubMed	https:
Villiers, EM,	2004	Classification of papillomaviruses.	PubMed	https:
Syrjänen,	2011	Human papillomavirus in oral carcinoma and oral potentially	PubMed	https: