

REVIEW

Role of human papilloma virus infection and oral-genital contact in oral cancer etiopathogenesis

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Abstract: Head and neck squamous cell carcinoma and especially oropharyngeal squamous cell carcinoma is a very significant cause of morbidity and mortality. The major risk factors of these tumors are tobacco smoking, chewing and alcohol consumption. But there is a group, non-drinking and non-smoking, patients with oropharyngeal squamous cell carcinoma. In these patients may be oral-genital contact and human papillomavirus infection the major risk factor for oral carcinogenesis. Aim of this review is to point out this fact in correlation with clinical studies and clinical conclusion for medical practice (Fig. 1, Ref. 32). Full Text in PDF www.elis.sk. Key words: head and neck squamous cell carcinoma, oropharyngeal squamous cell carcinoma, human papilloma virus infection, oral-genital contact, etiopathogenesis.

Head and neck squamous cell carcinoma (HNSCC) is a significant cause of morbidity and mortality around the world with more than 500,000 new cases worldwide and high rates notably in Southeast Asia and eastern Europe (1, 2). While the incidence of HNSCC has remained stable, the incidence of oropharyngeal squamous cell carcinoma (OSCC), a subset of HNSCC has increased 2 % to 3 % annually among American men from 1973 to 2001 (1). The area which is termed the oropharynx includes the soft palate, base of tongue, tonsillar region, and posterior pharynx. Shiboski et al. found an increase in tongue and tonsil carcinoma in young adults (ages 20–39 yrs), five-fold among young men compared with a two-fold increase in older age groups (3). Much is known today about the risk factors which can lead to cancer, as well as its poor prognosis, yet oral cancer still remains an under diagnosed and often fatal disease. Tobacco smoking and chewing and alcohol consumption are the main risk factors for HNSCC and OSCC and have been estimated to account for the vast majority of the disease burden worldwide (4). However, there is a small population of nonsmoking and nondrinking patients with head and neck squamous cell carcinoma, so other risk factors may be important (5). Over the past 15 years, human papillomavirus (HPV), the necessary cause of cancer of the cervix (6), has also been etiologically linked with HNSCCs (2, 7, 8). It is estimated that up to

15–20 % of all head and neck squamous cell carcinomas are associated with high-risk HPV infection 9–13). This prevalence varies broadly, depending on the sublocation of the tumor, the studied population, the detection method, and the type of specimen used (10–13). The highest rates of HPV-DNA (up to 70 %) have been found in oropharynx squamous cell carcinomas (OSCCs), especially the tonsils (7, 12, 14–16). Our review is focused to point on the importance of papilloma virus and oral-genital contact in etiopathogenesis of oral cancer.

Oral carcinogenesis

Oral cancer is characterized in general as a disease attributed to multiple exposures, with tobacco and alcohol abuse considered to be the major risk factors. Other lifestyle and environmental factors have been identified as important contributors in the progression of this disease such as viruses, diet, actinic radiation, and dental factors. Dental factors include poor oral hygiene, and defective dental restorations which repeatedly irritate the oral mucosa. These factors produce an initial insult to the genetic stability of the affected tissue and trigger a cascade of events. Genetic changes have been identified and studied to better identify the pathway to carcinogenesis.

The most frequently mutated gene in human oral cancer is the p53 tumor suppressor gene. P53 is a nuclear phosphoprotein which arrests the cell cycle when DNA damage occurs. The p53 acts as a recessive tumor suppressor gene whereas mutants can behave as dominant oncogenes. The mutagenic effect of smoking and alcohol can be seen in Figure 1.

When a person smokes or drinks for prolonged periods there is continued mucosal damage initially causing an increase in cell number, hyperplasia. Over time, the continued exposure to tobacco or alcohol produces a genetic insult and cells begin to divide at a higher rate, and in unusual patterns changing the maturation of the epithelium which becomes disturbed or dysplastic. Eventually

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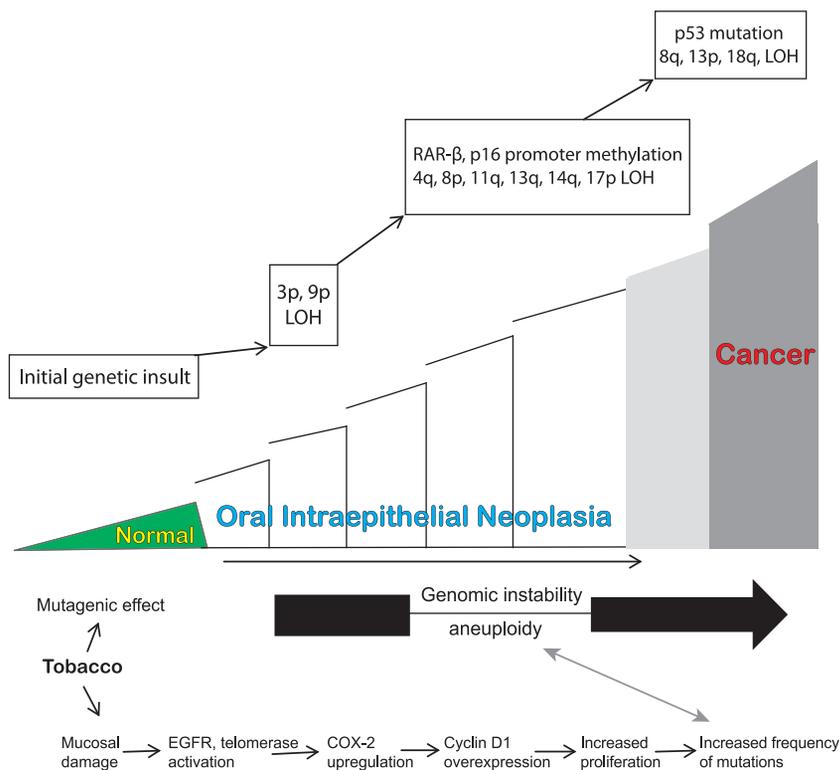


Fig. 1. Journal of Clinical Oncology, 2005.

the damaged mucosa cannot recover as p53 is mutated allowing unchecked cell division and the affected area progresses to cancer. It has also been shown that smokers and alcohol abusers who have had an oral cancer are at a higher risk of either a recurrence of the original cancer or having a new cancer in the field which was subjected to the offending carcinogen (17, 18). Approximately 75 % of oral cancers can be attributed to smoking and/or alcohol abuse (18), but we know that not all smokers get cancer. It is not known why some smokers and drinkers are affected by their habit and others are not. Interestingly, approximately 25 % of cancers occur in people with no known risks suggesting cofactors, such as viruses, as a possible etiology (19).

Viruses associated with cancer

The link between viruses and cancer was one of the pivotal discoveries in cancer research. Today, it is generally agreed that viruses are involved in 10–20 % of all cancers (20). Many viruses target the p53 and pRb tumor suppressor pathways, altering the cell cycle. Hepatitis B infection, for example, is associated with an increased risk of hepatocellular carcinoma development. Hepatitis B proteins, such as the Hepatitis Bx protein, regulate transcription of many candidate genes for liver carcinogenesis by trans-mechanisms. They also alter mechanisms of apoptosis and interfere with nucleotide excision repair of damaged DNA (21). This mechanism is similar to the pathogenesis of high-risk types

of the human papillomavirus (HPV). HPV has been found to be associated with multiple types of epithelial cancers.

Human papillomavirus and cancerogenesis

HPV is a small DNA virus that infects the squamous epithelium of the skin or mucosa. It causes both asymptomatic infections and various benign or malignant lesions. Its structure consists of a non- enveloped, circular, double stranded DNA of about 8000 base pairs. The HPV genome consists of 9 open-reading frame sequences, located on only one of the strands of DNA, and is divided into seven early-phase genes (E) and two late-phase genes (L). About 10 % of the genome is contained in the long control region (LCR) and functions in the regulation of viral gene expression. The remainder of the genome is organized into early (E) or late (L) genes, encoded by 50 % and 40 % of the genome, respectively.

There are approximately 100 types of HPV. The type is determined by a greater than 10 % sequence difference in the E6, E7, and L1 regions. The L-late genes encode for proteins involved in viral spread, such as capsid proteins. The L1 and L2 genes encode the major and minor capsid proteins which are only expressed in terminally differentiated squamous epithelial cells. The E-early genes encode nonstructural proteins that regulate virus transcription and replication and are expressed in nonproductively infected cells and in transformed cells (22–24). HPV’s have evolved proteins, specifically E6 and E7, to control the growth of the epithelial

cells they infect. This was a necessity since these viruses require a metabolically active, dividing cell in order to complete their life cycle. The viral oncoproteins E6 and E7 from high-risk HPV types prevent cells from differentiating and

withdrawing from the cell cycle as they move outward through the cell layers, while those from low risk types do not (23). The E1 and E2 genes are responsible for initiation of DNA replication. E2 also regulates transcription through a feedback mechanism. When there are high levels of E6 and E7 the E2 gene will shut down viral transcription. The E2 gene normally binds to a sequence in the upstream regulatory region and monitors viral transcription by shutting down E6 and E7. In order for malignancy to occur after infection, the virus must become integrated in the host genome. When the virus integrates there is a break in the E2 region and the normal repressor activity of the virus is rendered ineffective and E6 and E7 are highly expressed. The E5 gene from high-risk viruses destabilizes the cell membranes and changes the cellular responses to programmed cell death or apoptosis and the E4 gene binds the cytoskeleton proteins and prevents a proper cellular differentiation. E6 binds to the tumor suppressor protein, p53 marking it for degradation, while E7 binds and inactivates retinoblastoma protein (pRB) (25).

Oral-genital contact as a risk factor in oral cancer

Oral-genital contact has been found epidemiologically to result in oral and cervical cancers within couples (26, 27). An analysis of the Swedish cancer registry data (1958–1996) showed that husbands of women with cervical cancer had a significantly increased risk of developing either tongue or tonsil cancer. Husbands of cervical cancer patients developed an excess (SIR over 2.00) of both tonsillar cancer (SIR 2.39 when wife with in-situ cancer and SIR 2.72 when wife with invasive cervical cancer) and cancer of the tongue. Also, women diagnosed with cervical carcinoma in-situ after the age of 50 were 2.58 times more likely to develop tonsillar cancer (26).

In a study by Herrero et al 1670 patients with oral cancer found that HPV16 was detected in most of the oropharyngeal cancers and the patients with tumors containing the HPV16 strain were three times more likely to report a history of oral sex than those with tumors that did not contain the virus (7). Specific sexual behaviors have been more strongly associated with risk of an HPV-positive tumor, including a history of performing oral sex and oral-anal contact according to Gillison (24).

Human papilloma virus and oral carcinoma

The first reports of HPV in oral cancers came in the early 1980's. Since then many studies have looked at HPV and its possible connection to the development of oral cancer and more specifically oropharyngeal cancer (OSCC). The role that HPV may play in OSCC has been controversial. The controversy relates mainly to the variable detection rate of HPV in these tumors, but this is due to the different sensitivities of various detection techniques, the type of specimen taken and its handling, as well as the population examined as many tumors are unquestionably tobacco-related. Also important was the sub-site examined. There appears

to be different etiologies depending on the oral sites; for example lip cancer is undoubtedly related mainly to sun exposure (28). The human papillomavirus (HPV) DNA has been consistently detected in 20 % of HNSCCs overall and in 50 % of OSCCs. The following studies confirm this finding and support the hypothesis of HPV as an etiology in oral cancers.

An important pathway in many cancers is the methylation of regions of DNA important in the progression of the cell cycle and this is a marker that is being looked at in cancers studies. The term DNA methylation refers to the transfer of a methyl group to cytosine residues, which are stably maintained at CpG dinucleotides (meCpGs). Methylated CpGs lead to the binding of transcriptional repressors, part of a network of epigenetic regulatory pathways. Balderas-Loeza et al reports hypermethylation of the L1 gene and part of the long control region, a diagnostically important segment of the viral DNA, in 10 out of 12 HPV-16 positive oral carcinomas from Mexican patients. These data indicate epigenetic changes of HPV-16 in oral carcinomas similar to those in anogenital carcinomas suggesting carcinogenic processes under the influence of HPV-16 in most if not all of these oral malignant lesions (29).

Study by Pintos et al matched on age and gender, examined oral exfoliated cells from the buccal mucosa utilizing consensus PCR as well as serum based ELISA. 30 % of their cases were non-smokers and 11 % were non-drinkers. HPV DNA was detected in 19 % of cases (14 out of 72), and 5 % of controls (six out of 129). Among tonsil-related cancers (palatine tonsil and base of tongue) viral DNA was detected in 43 % of cases (30). Smith et al utilized oral exfoliated cells to look for HPV. They found that 22.9 % (201 cases) and 10 % (333 controls) of controls were HPV positive. They concluded that oral exfoliated cells were predictive of HPV types in tumor tissue (31). Dahlstrom et al designed the only study which compared smokers to non-smokers. They looked for the presence of HPV-16 antibodies in ever-smoker and never smoker patients matched on age (± 5 years), sex, and tumor site. Serum was assayed for HPV-16 L1 virus-like particles by using an ELISA. They found HPV-16 antibodies in 40.8 % cases and 9.2 % controls. Subjects with HPV-16 seropositivity was more common in never-smokers with HNSCC than in ever-smokers (43.3 % vs 38.3 %, respectively), this difference was not statistically significant. They only used subject's serum which has not been found to be as reliable a marker of HPV infection as the examination of tumor DNA and they did not look at alcohol as a confounding factor (32).

Conclusion

Specific sexual behaviors (oral sex, oral-anal contact) are frequently associated with high risk of human papilloma virus-positive oropharyngeal squamous cell carcinoma. Though clinical conclusion for the medical practise should be early detection of the HPV infection in these groups of population. Simultaneously the screening also rises public awareness. Preventive HPV vaccines may be effective in preventing cervical infection in women and may likewise prevent oral infection with subsequent oropharyngeal cancer. But modification of the sexual behavior, especially heterosexual or homosexual promiscuity, has been strongly recommended.

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