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This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management , and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in Oral Oncology 2010; ***46****; 485–570.*

Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

3. Other Risk Factors

Among young people (under the age of 45 years) with oral cancer there is a sub-group of patients (about 25%) who appear not to have been exposed to the major risk factors such as tobacco, alcohol or betel (Article 2).

Other factors may be involved in oral cancer. These include solar irradiation in lip cancers, and human papillomavirus (HPV) infection in oropharyngeal cancer in young people. Immunodeficient patients may also develop oral potentially malignant and malignant neoplasms, including oral cancer.

Infections in the oral cavity, such as HPV, herpesviruses, chronic candidiasis (candidosis), syphilis and poor oral hygiene, and periodontal disease, link statistically with cancer.

Bacteria

Poor oral hygiene may be an independent risk factor for oral cancer. Many patients with oral cancer present with poor oral health, ie they have carious teeth and periodontitis. The number of teeth lost has been associated with cancer but oral health-related variables also link with use of tobacco and alcohol. This confounding factor is difficult to control in epidemiological studies. Nevertheless, periodontal disease has been shown to increase the statistical risk for head and neck cancer and the association persisted in subjects who never used alcohol or tobacco. Interestingly, practising no regular oral hygiene also conferred a risk for oesophageal cancer compared with those who brushed daily.

Specific oral bacteria have been suggested to play a role in carcinogenesis. Clear differences have been observed when comparing microbial populations on mouth mucosa between healthy and malignant sites. For example, *Streptococcus anginosus* and *Treponema denticola* have been linked with various upper gastrointestinal tract carcinomas. Infections may trigger cell proliferation, activate oncogenes, inhibit apoptosis, and interfere with cellular signalling. In addition, several oral micro-organisms metabolize alcohol to carcinogenic acetaldehyde thus possibly explaining any association between poor oral hygiene, alcohol and carcinogenesis. Table 1 summarizes some of the carcinogenic mechanisms possibly involved.

The capacity of oral micro-organisms to convert alcohol to acetaldehyde might explain why poor oral hygiene is often associated with oral cancer in heavy drinkers and smokers; namely their salivary acetaldehyde concentrations are significantly increased, along with their poor oral hygiene.

Fungi

Yeasts may invade oral epithelium and be causally involved in oral leukoplakia and dysplastic changes.

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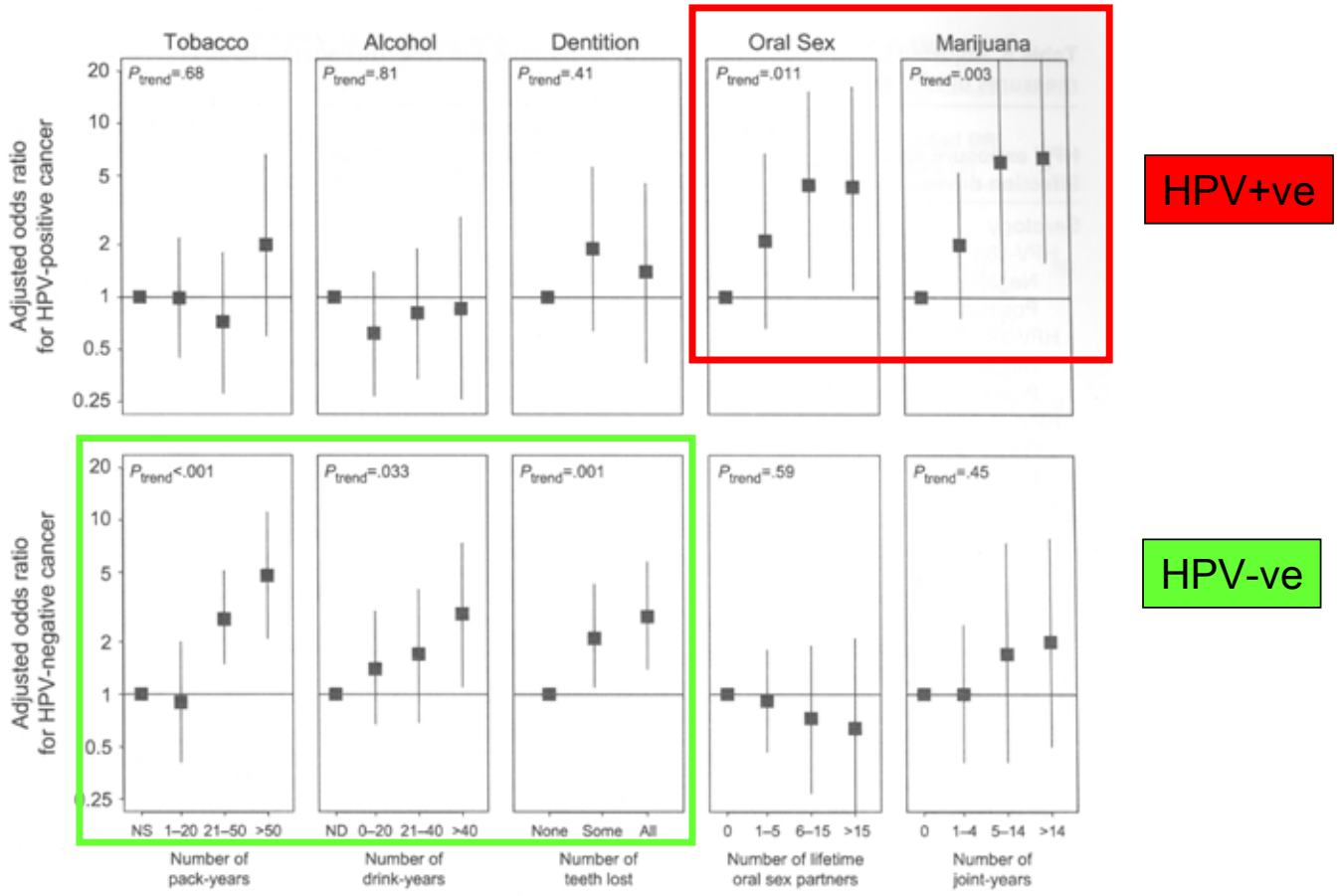
Putative risk factor	Potential carcinogenic mechanisms
Candida albicans	Dysplastic changes Converts alcohol to acetaldehyde
Herpes simplex virus	Activates oncogenes, inactivates p53 tumour suppressor gene
Human papilloma viruses	Epithelial cell immortalization Interferes with tumour suppressor genes
Oral biofilm (dental plaque) bacteria	Induce cell proliferation, inhibit apoptosis, interfere with cellular signalling Mutagenic interaction with saliva
Periodontal disease	Acts on inflammatory reactions and oncogenes
Viridans streptococci	Interfere with cellular signalling mechanisms Convert alcohol to acetaldehyde

Table 1. Examples of infectious agents and potential mechanisms in carcinogenesis.



From Gillison 2008 JNCI 100; 407

Figure 1. HPV-positive oropharyngeal cancers are associated with oral sex and marijuana use; HPV-negative tumours are associated with tobacco use, alcohol use and poor dental status.

Candida albicans is the common oral yeast but increasing numbers of *non-albicans Candida albicans* (NACA) are seen, particularly among medically compromised patients. These strains are often resistant to antifungal agents such as fluconazole. NACA strains have emerged increasingly in oral cancer patients. *Candida* in general is more prevalent on carcinoma lesions than on healthy mouth mucosa.

Candidal leukoplakias have been estimated to develop into carcinomas in up to 40% of cases. Patients with congenitally determined chronic candidosis may be predisposed to carcinoma but their immunocompromised state may play a role. Animal studies confirm the potential of *Candida* to induce malignant transformation in oral mucosa. However, the carcinogenic mechanisms involved are unknown. Nitrosamine compounds produced by *Candida* may activate specific proto-oncogenes. Candidosis may have a synergistic effect with lifestyle factors in oral carcinogenesis. *Candida* also efficiently converts alcohol into carcinogenic acetaldehyde.

Viruses

Viral infections may disturb gene regulation (Table 1). HPV is the most common sexually transmitted infection (STI). Most adults are infected with high-risk (cancer-promoting) types such as HPV-16 and HPV-18 at some stage but most (90%) patients usually clear HPV infection within 2 years.

Risk factors for HPV infections include:

- Early onset of sexual activity;
- Lack of condom use;
- Multiple sexual partners;
- Unknown partners.

HPVs play a role in some anogenital cancers, including cancers of the:

- Cervix;
- Anus;
- Vulva;
- Vagina;
- Penis.

Persistent infection, which affects around 10%, can cause cancer; thus few people infected with HPV actually develop cancer. HPVs can be transmitted by close contact between skin and/or mucosae. HPV-6, -11, -16, -18, -31, -33 and -42 have been isolated from the mouth, and

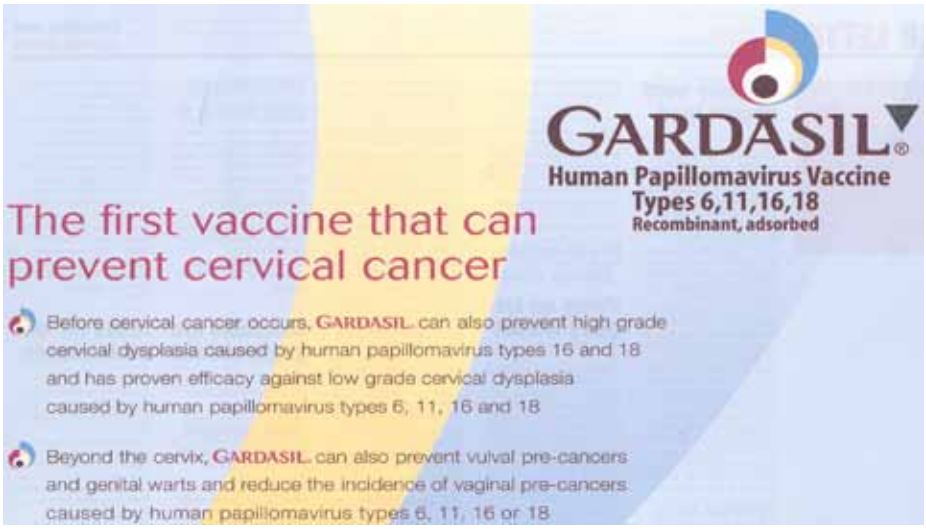


Figure 2. HPV vaccines.

Figure 3. Fruit and vegetables may confer some cancer protection

infection may be latent in 12% of subjects with clinically healthy oral mucosa. HPV-16, regarded as oncogenic, is increased in oral cancer, mainly in oropharyngeal cancer (tongue base: fauces). HPV-associated cancers are:

- Often basaloid carcinoma;
- Associated with HPV-16 (90%): also types 18, 31, 33;
- Reduced tumour suppressor gene expression (p53 and Rb genes);
- Not linked to alcohol or tobacco use or poor oral status (Figure 1);
- Possibly associated with a genetic element;
- Associated with a better prognosis than other cancers.

HPV can be transmitted between the mouth and ano-genital region, and there are associations demonstrated between oral and ano-genital cancers. It seems irrefutable therefore, that at least some forms of oral cancer can be sexually transmitted.

A vaccine against HPV is now administered to young people (Figure 2) in an effort to prevent cervical cancer, however, the evidence as to any protective effect against oral cancer is not yet available.

Herpes simplex viruses (HSV) have also been associated with carcinogenesis on the lip. In general, however, there are no studies showing that controlling any viral infections would affect the incidence of oral cancer.

Dietary factors

The consumption of adequate portions of fruit and vegetables (5 a day) is associated with a reduced risk of oral cancer (Figure 3). This suggests a diet deficient in antioxidants is a further factor predisposing towards oral precancer and cancer. The Mediterranean diet has been shown to be particularly associated with a reduced oral and pharyngeal cancer risk. One US study showed an inverse association between total fruit and vegetable intake and incidence of head and neck cancer (Figure 3).

No single dietary factor alone appears responsible: antioxidants may be anti-carcinogenic eg in green tea, but a Cochrane review concluded that the evidence is insufficient and conflicting. Similarly, any role of polyphenols abundant in vegetarian diets, and the recent report of a protective effect of coffee, call for more investigation.

In contrast, social deprivation is associated with an increased risk for oral cancer.