VERIFIABLE CPD PAPER

IN BRIEF

- Oral cancer appears to be increasing in young people.
- Most oral cancer is causally related to tobacco and alcohol, but remains unexplained in other cases.
- Infective agents such as papillomaviruses may be indicated, particularly in oropharyngeal tumours.
- These viruses can also cause ano-genital lesions.

Oral cancer; the evidence for sexual transmission

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The incidence of oral cancer amongst young adults is increasing in many European and high incidence countries. Most oral cancer is aetiologically linked to the use of tobacco and/or alcohol but nearly two decades ago, we produced the first evidence for the presence of viral nucleic acids in oral squamous cell carcinoma (OSCC) tissues, hypothesising that there may be a viral involvement in at least some OSCC. Subsequently, human papillomaviruses (HPV) in particular have been implicated in OSCC. Antibody responses to HPV are seen and HPV-DNA detected in tumours by us and many others, the virus being mainly HPV-16, the genotype associated with ano-genital cancer. Recent studies have indicated that HPV may be aetiologically important particularly in some types of oropharyngeal cancer, at least in tonsillar carcinogenesis, and may represent an alternative pathway in carcinogenesis to the established factors of tobacco and alcohol. Studies of patients with OSCC have suggested possible sexual transmission of HPV.

What is cancer?

Malignant neoplasms are disorders characterised by autonomous cell proliferation, usually triggered by DNA mutation. Such mutation can be spontaneous, or precipitated by exposure to mutagens such as ionising radiation, or chemicals (carcinogens) found in tobacco, alcohol and in the environment. Thus it is evident that cancer does not necessarily have a single cause.

Risk factors for mouth cancer

The most common oral malignant neoplasm is oral squamous cell carcinoma (OSCC), a disease mainly affecting people after middle age and, when intra-oral, usually aetiologically linked with lifestyle risk factors, particularly with tobacco and/or alcohol use in the developed world, and with tobacco and betel in the developing world.[1] The majority of patients with OSCC report lifestyle risks of tobacco and alcohol use even at younger ages, but other factors also seem to be involved.[2]

In contrast, some lifestyle factors such as diets high in fruits and vegetables appear to confer some protection against OSCC.[1]

Cancer also occurs in the absence of known risk factors

However, there are clearly many people who pursue these lifestyle risk habits and yet develop no cancer, and other unfortunate individuals who develop OSCC in the absence of either exposure to these factors, or any obvious predisposing genetic defect.[3-5] Indeed, a recent study of young patients with OSCC found that 26% of the group showed little, if any, exposure to the recognised major risk factors.[1]

It is possible that microbial agents could be alternative aetiological agents at play in these patients.[6]

Viruses are implicated in many cancers

More than two decades ago, we produced the first evidence for the implication of viruses in OSCC, by demonstrating viral nucleic acids,[7-9] and this has subsequently been the subject of intense interest.[7,9-15,6,16-22]

Viruses are especially associated with cancers in immunocompromised persons

Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human papillomaviruses (HPV) can be found in normal oral mucosa of immunocompromised patients.[23] Immunocompromised persons, such as transplant recipients and persons with HIV/AIDS suffer a range of virally-related cancers: Kaposi's sarcoma, and non-melanoma skin cancer, non-Hodgkin's lymphoma, and anogenital cancers show the most impressive increases (10 to 20-fold higher)[24] as does lip cancer, and there is also an increase in oral potentially malignant lesions.[25-26]

Herpes simplex viruses and mucosal carcinomas and potentially malignant lesions in the head and neck region

The first study in the field examined OSCC for herpes simplex virus (HSV) and suggested an association with HSV.[7-8] Others have since demonstrated HSV-1 DNA in OSCC.[27] A number of studies have shown changes in levels of serum antibodies to HSV.[27-31] There is a higher reactivity to the HSV immediate early protein ICP4 in patients with OSCC, suggesting a different course of an earlier herpetic infection, with a prolonged exposure to early immediate proteins of HSV as a consequence of smoking.[28] Evidence of HSV viral

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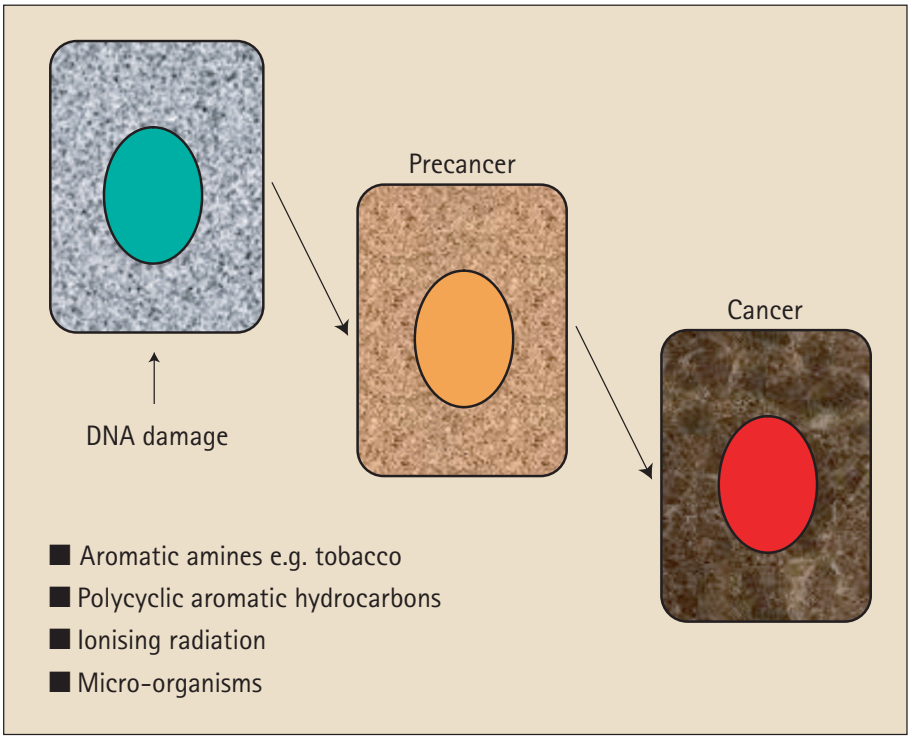

Fig. 1 Aetiopathogenesis of cancer

'footprints' has thus given interesting results, though this is not *proof* of a causal relationship. In one US epidemiological study, the relative risks for OSCC associated with serologically detected HSV-1 and HSV-2 infections were 0.8 (95% CI 0.3-1.7) and 1.8 (CI 0.7-4.6) respectively[32] but, although those infected with the mainly genital virus HSV-2 were at increased risk, such associations may have been due to chance. Genital HSV-2 infection is typically sexually transmitted.

Substantial evidence suggests that HSV might, under particular circumstances, be oncogenic[33,9,11,34,35,28] but further studies are needed to clarify any causal role of HSV in oral carcinogenesis.

Human papillomaviruses

HPV are small DNA viruses that can induce hyperplastic, papillomatous, and verrucous lesions in skin and mucosae, including the oral mucosa, and they are thus termed 'epitheliotropic'.[36,14,10,37,11,38,13,19] Well over 100 HPV genotypes have been identified, and the numbers seem to increase almost monthly. Some genotypes such as HPV-6 and HPV-11 are typically associated with benign lesions such as warts and papillomas and are thus termed *benign*, while others such as HPV-16 and HPV-18 are strongly associated with malignancy and thus termed *malignant* or *oncogenic* or *high-risk* genotypes.

HPV — a sexually transmitted disease

HPV is probably the most common sexually transmitted disease (STD),[39] with estimates that each year over 5 million people in USA acquire HPV infection. Overall, 50%-75% of sexually active men and women acquire genital HPV infection at some point in their lives (http://www.cdc.gov/nchstp/od/program_brief_2001/Genital%20HPV%20Infection.htm) and some studies estimate that the majority of the sexually active population is exposed to at least one or more types of HPV — although most do not develop symptoms (http://www.cdc.gov/nchstp/od/news/RevBrochure1pdfhpv.htm). Infection in female virgins is rare, but any type of sexual contact is associated with an increased risk, and the incidence of HPV associated with acquisition of a new sex partner is high.[40] For example, prevalence among women in Argentina reporting no previous sexual activity is 3%, and among sexually active young women it is 17.7%.[41] Infection is most likely where there is an early age of first intercourse, multiple sex partners, and low use of barrier protection such as condoms. HPV is not *highly* transmissible but can be spread sexually, and commercial sex workers can be reservoirs of oncogenic HPV.[42]

It should, however, be borne in mind that HPV can also occasionally be transmitted by other routes; for example, HPV lesions are sometimes detected in virgins, who have never had sexual intercourse,[43] possibly due to vertical transmission, fomites or skin-to-skin contact.

HPV and non-oral mucosal carcinomas

The high risk or oncogenic genotypes, such as HPV-16, HPV-18, HPV-31, HPV-35 and others, are associated with ano-genital carcinomas.[44] Cervical cancer for example, appears to have a strong relationship with oncogenic HPV.[45] The risks of cervical carcinoma in monogamous women and of oncogenic HPV in their husbands can be associated with the men having had unprotected intercourse with prostitutes.[42]

HPV in the mouth and oral fluids

HPV is present in the oral cavity in around 5% of adolescents[46] and from 1% to 60% of healthy adults[21] and may be a common oral commensal. HPV-DNA has been demonstrated in *normal* tissues adjacent to HPV-related lesions in the genital tract, in normal tonsils[47] and in normal oral mucosa.[48] By Southern blot hybridisation, HPV-DNA has been detected in from 15%[49] to over 40%[48,50] of biopsies from clinically normal buccal mucosa from adults, and the PCR technique increased the detection to 21.8%.[49] HPV may also be associated with a range of oral lesions, mainly warts or papillomas.[13]

Antibodies to HPV appear in the saliva.[51] However, though HPV-DNA can be detected in exfoliated oral squames from clinically healthy individuals[50,52] there are no data to indicate the transmissibility of HPV in saliva. The finding of anogenital HPV infections in the absence of anal sexual intercourse, such as recorded in non-abused pre-school children[53] and in homosexual adults who deny anal sexual intercourse[54] could however, possibly be via this route.

Human papillomavirus transmission to the mouth

HPV-DNA was demonstrated in oral mucosa of 41.6% of infants born to mothers with HPV-positive cervical smears.[55] A study on oral HPV infection in women with past or present genital HPV infection[56,49] using dot-blot hybridisation on exfoliated oral squames showed only a 3.8% HPV-DNA prevalence, almost certainly an underestimation of the true HPV prevalence because basal layer cells cannot be readily collected in this way. The prevalence of oral HPV-16 infection is greater in HIV-seropositive than non-infected individuals.[57] In view of the high infectivity of genital warts, it is interesting to note a low prevalence of oropharyngeal warts in adults indulging in orogenital contact in one UK study[58] but the lesions can be very small or inaccessible to non-specialist examination.

HPV and mucosal carcinomas and potentially malignant lesions in the head and neck region

HPV have been implicated in oral and

head and neck squamous carcinoma (HNSCC)[14-15,20-22,19] but the role HPV may play has been controversial. The controversy relates mainly to the variable detection rate of HPV in these tumours but this is because of the different sensitivities of various detection techniques, the type of specimen taken and its handling, the population examined (many tumours are unquestionably tobacco-related), and the subsite examined (it may be that there are different aetiologies at different oral sites; eg lip cancer is undoubtedly related mainly to sun exposure).

Evidence of HPV infection, together with a clonal relationship between HPV and the tumour, as shown by virus integration into the host cell genome, would argue against HPV being merely a secondary invader, and would strongly suggest a causal role in carcinogenesis. The identification of HPV transforming genes such as E6 and E7 in OSCC further substantiates an oncogenic role for HPV.

Human papillomavirus nucleic acid studies in head and neck cancers and potentially malignant lesions

The rate of HPV detection in OSCC has varied from 0 to 94%.[59-64] HPV detection is higher when analysed by *in situ* hybridisation and polymerase chain reaction (PCR), and studies with these techniques have disclosed HPV 11, 16 or 18 DNA sequences in up to 60% of OSCC[65-68,61,64,63,69] and in up to 28% of oral potentially malignant lesions.[69-70] HPV is identified in oral squames in significantly more patients with OSCC than controls.[71] A particularly high prevalence of HPV has been found in betel-quid-associated OSCC in India.[72]

A higher incidence of HPV 16 and 18 infections is revealed by combining the findings of a consensus PCR, restriction fragment length polymorphism by using the restriction enzyme digestion of the PCR products and Southern blot hybridisation.[73] Nested PCR studies have found HPV in even more lesions – in one Greek study in up to 86% of hyperplasias, 100% of dysplastic lesions and 95% OSCC.[74] The polymerase chain reaction (PCR) has shown HPV in over one quarter (25-35%) of HNSCC, and most HPV-positive tumours contained 'high risk' HPV genotypes 16 and 18.[21,75]

When data from 94 reports that analysed 4680 OSCC samples were included in a meta-analysis,[76] HPV was found to be between two and three times more likely to be detected in precancerous and 4.7 times more likely to be detected in oral carcinoma than in normal mucosa. The probability of detecting high-risk HPVs in OSCC was 2.8 times greater than that of low-risk HPVs, providing further quantitative evidence that oral infection with HPV, particularly with oncogenic genotypes, is a significant independent risk factor for OSCC.[76]

Human papillomavirus studies in cancers at different sites

Recent studies have implicated HPV particularly in a sub-type of poorly differentiated tumour with basaloid histological features arising in the posterior tongue and fauces.[75] One quarter of HNSCC contained HPV, and of these, 90% were HPV-16. Around 57% of tonsillar tumours were HPV-positive compared with 12% of intraoral tumours.[75] An Italian study confirmed a more frequent association of HPV with tonsillar carcinomas (50%) compared with carcinomas of the tongue (38%) or buccal mucosa (12%).[77] HPV-16 DNA was also found by PCR in 50% of oropharyngeal and 14% of tongue cancers in a Scandinavian study.[78]

Human papillomavirus genotypes in head and neck cancers and potentially malignant lesions

DNA technology has shown HPV sequences, often of the 'high risk' genotypes (mainly HPV-16 and HPV-18), in a substantial portion of OSCC and premalignant lesions and that HPV may be involved in the early stages of the development of some OSCC.[79] Others have found other oncogenic HPV.[80,69,74] OSCC thus may contain especially the oncogenic genotypes HPV-16 or HPV-18[75,74,77] or HPV-31, 45, 56, and 57.[77] A novel HPV 16-related virus was found by us in a UK study in about 40% OSCC[48] and, interestingly, HPV-16 subtypes associated with HNSCC have changes in the promoter-enhancer region that make them especially active in oral keratinocytes.[81]

Human papillomavirus antibody responses in head and neck cancers and potentially malignant lesions

Antibodies to HPV capsid antigens are reliable markers of past or present HPV infection, and serological studies have confirmed HPV-16 to be a risk factor in OSCC, since HPV-16 E6 and E7 antibodies (considered indicative of invasive HPV-16-transformed tumours) have been demonstrated especially in oropharyngeal cancers,[41] and in about 12% of patients with HNSCC, mainly in tonsillar carcinoma.[82]

Human papillomavirus role in head and neck carcinogenesis

Interactions of HPV with various genes provide at least a theoretical model as to how HPV might be involved in carcinogenesis. The hypothesis is that the inactivation of normal function of the tumour suppressor genes p53[83] or pRB (or the related p107) is a critical step in squamous cell carcinogenesis.

Human papillomavirus: an agent in the sexual transmission of oral cancer?

The chances of oral HPV infection increase with age, male sex, and HSV-2 seropositivity.[57] Epidemiologic studies have shown that exposure to HPV increases the risk of HNSCC[32,84] suggesting it may be sexually transferred, and that HPV infection may interact with alcohol and tobacco exposure in tumour promotion.[85-86] HPV association with OSCC was greatest in males with a young age of first intercourse, those with multiple sexual partners, and those with genital warts.[84] This study found that the associations with a higher lifetime number of sexual partners and with a total of more than four partners with whom the subject had engaged in oral sex, was stronger for patients with HPV-16-positive tumours than those that were HPV-16-negative.[84] In contrast, a US study found that HPV-related genital lesions, oro-genital sexual behaviour, and number of sexual partners, did not differ between patients with OSCC and controls[71] and similar findings were reported from Italy.[87] However, a recent study by one of the same groups, set up to explore any significantly different risk factors between HPV-positive and HPV-negative OSCC cases, showed the prevalence of oncogenic mucosal HPV to be higher in younger-age oral cavity/oropharynx cancer cases whose sexual practices are typically associated with sexual transmission of HPV.[88] This study evaluated HPV in cancer tissue and exfoliated oral cells of OSCC patients using PCR and direct DNA sequencing and showed high-risk HPV in 20% of OSCC cases (HPV-16 [87%], HPV-18 [3%] and HPV-33 [11%]). (Fig. 1)

The Swedish Family Cancer Database was used to analyse second cancers in women first diagnosed with cervical cancer.[89] Tonsillar cancers were increased among women with cervical cancer aged 50 years or more at diagnosis of *in-situ* cervical cancer, and this was ascribed to the effects of HPV, smoking, alcohol or their interaction. Interestingly, the husbands of patients with cervical cancer developed an excess of cancer both of tonsils and tongue.[89] Cancers in the upper aerodigestive tract also appeared increased in people who had had children with more than a single partner.[90-91] Furthermore, in a separate study, patients with anogenital cancer also had an increased risk of tonsillar carcinoma.[92]

Summary

Though not in any way *proof* of a relationship of OSCC with HPV and sexual activity, all this suggests a possible transmission or other environmental factor. In any event, we have come a very long way in the two decades since our first suggestion of a viral aetiopathogenesis was greeted with incredulity. Who knows, but HPV-based therapeutic vaccines currently being developed for cervical cancer may thus also eventually prove of benefit in the management of some patients with OSCC.

Since this paper was submitted for publication in 2004, a systematic review has shown HPV in 26% of HNSCC; in 36% of oropharyngeal SCC and 24% of OSCC.[93]

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