Oral Oncology (2007) 43, 523–534

available at www.sciencedirect.com

ScienceDirect

journal homepage: http://intl.elsevierhealth.com/journals/oron/

ORAL ONCOLOGY

REVIEW

Advances in the biology of oral cancer

P.K. Tsantoulis [a], N.G. Kastrinakis [a], A.D. Tourvas [a], G. Laskaris [b], V.G. Gorgoulis [a,*]

[a] *Molecular Carcinogenesis Group, Laboratory of Histology and Embryology, Medical School, University of Athens, Antaiou 53 Str., Lamprini, Ano Patissia, GR-11146 Athens, Greece*
[b] *Department of Dermatology, Medical School, University of Athens, Athens, Greece*

Received 26 September 2006; accepted 2 November 2006
Available online 26 January 2007

KEYWORDS
Oral cancer;
Oncogenes;
Tumor suppressor genes;
HPV;
EBV;
Review

Summary The incidence of oral cancer remains high and is associated with many deaths in both Western and Asian countries. Several risk factors for the development of oral cancer are now well known, including smoking, drinking and consumption of smokeless tobacco products. Genetic predisposition to oral cancer has been found in certain cases but its components are not yet entirely clear.

In accordance with the multi-step theory of carcinogenesis, the natural history of oral cancer seems to gradually evolve through transitional precursor lesions from normal epithelium to a full-blown metastatic phenotype. A number of genomic lesions accompany this transformation and a wealth of related results has appeared in recent literature and is being summarized here. Furthermore, several key genes have been implicated, especially well-known tumor suppressors like the cyclin-dependent kinase inhibitors, *TP53* and *RB1* and oncogenes like the cyclin family, *EGFR* and *ras*. Viral infections, particularly with oncogenic HPV subtypes and EBV, can have a tumorigenic effect on oral epithelia and their role is discussed, along with potential therapeutic interventions. A brief explanatory theoretical model of oral carcinogenesis is provided and potential avenues for further research are highlighted.

Introduction

Oral cancer refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intra-oral locations, according to the International Classification of Diseases (ICD version 9, categories: 140–146, 149). Nevertheless, the term is synonymous to squamous cell carcinoma (SCC) of oral mucosal origin that accounts for more than 90% of all malignant presentations at the aforementioned anatomical sites.[1]

More than 300,000 new cases worldwide are being diagnosed with oral squamous cell carcinoma annually.[2] Approximately 30,000 new cases are recorded annually in the US[3] and 40,000 new cases are recorded in the EU.[4] Oral cancer

* Corresponding author. Tel./fax: +30 210 6535894.
E-mail address: histoclub@ath.forthnet.gr (V.G. Gorgoulis).

1368-8375/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.oraloncology.2006.11.010

is estimated by WHO to be the eighth most common cancer worldwide. However, the incidence of oral cancer has significant local variation and is increasing in some parts of the world. In India and other Asian countries, oral and oropharyngeal carcinomas comprise up to half of all malignancies, with this particularly high prevalence being attributed to the influence of carcinogens and region-specific epidemiological factors, especially tobacco and betel quid chewing.

Risk factors

The most important risk factor for the development of oral cancer in the Western countries is the consumption of tobacco[5] and alcohol.[6] Although drinking and smoking are independent risk factors, they have a synergistic effect and greatly increase risk together. In Asian countries, the use of smokeless tobacco products such as gutkha, masala and betel quid[7,8] is responsible for a considerable percentage of oral cancer cases.

Several studies have reported a significant familial component in the development of oral cancer. The estimates of risk in first degree relatives of oral cancer patients vary widely and have been reported to be 1.1,[9] 2.5,[10] 3.5[11] or 3.8[12] in various studies, although it should be noted that some of these studies refer to head and neck cancer in general. Oral cancer patients whose relatives have upper respiratory and digestive tract tumors are also more likely (odds ratio 3.8) to develop a second primary tumor,[13] an important cause of treatment failure. Familial aggregation of oral cancer, possibly with an autosomal dominant mode of inheritance, was reported in a very small percentage of oral cancer patients[14] but further details are lacking.

The familial risk for oral cancer could be acquired as a result of imitating high risk habits within the family, such as smoking and drinking, or as a genetic trait. Polymorphic variation of genes in the xenobiotic metabolism pathways may be implicated, such as in *CYP1A1* or the genes coding for glutathione S-transferase-M1[15,16] and *N*-acetyltransferase-2.[17] Individuals that carry the fast-metabolizing alcohol dehydrogenase type 3 (*ADH3*) allele[18] may be particularly vulnerable to the effects of chronic alcohol consumption and could be at increased risk to develop oral cancer, although newer evidence does not support this association.[19,20] A recent review[21] has highlighted the necessity for larger and more extensive studies to resolve this issue. Finally, the single nucleotide polymorphism A/G870 in the *CCND1* gene that encodes Cyclin D has been associated with oral cancer susceptibility. The AA genotype may increase risk (odds ratio 1.77) for head and neck cancer[22] or oral cancer (odds ratio 2.38).[23] Intriguingly, in another study, it was the GG wild-type genotype, instead of the AA genotype, that was associated with increased susceptibility to oral cancer (GG genotype, odds ratio 3.37).[24]

Staging and prognosis

Staging of oral cancer is conventionally performed with the use of the ''tumor, node, metastasis'' (TNM) classification system and its variant (pTNM), which are respectively based on clinical and pathological assessment of tumor size and lymph node involvement. However, traditional staging is often inadequate and does not always provide accurate prognostic information. New tumor characteristics, such as locoregional control,[25] extent of recurrence,[26] maximum tumor thickness,[27] differentiation grade and mode of invasion,[28] are being utilized to refine prognosis and allow the selection of appropriate treatment.

Therapy

The therapy of oral cancer is not always satisfactory. Early stage (I and II) oral cancer may be curable by surgery or radiation therapy alone but advanced cancers (stage III and IV) are generally treated by surgery followed by radiation therapy.[29] Using multimodal protocols that combine surgery with pre-operative or post-operative radiotherapy and/or adjuvant chemotherapy the 2-year and 5-year survival rates for advanced cancers were as low as 20% and 12%, respectively.[30] In fact, survival of advanced-stage patients rarely exceeds 30 months, even for those that initially achieve complete clinical remission.[31] Furthermore, most oral SCCs exhibit limited responsiveness to common cytotoxic drugs, due to mechanisms that either block the transport of these agents into the cells or interfere with their intracellular molecular targets.[32] Fortunately new sensitive kits for early tumor detection are being developed[33] many of which are based on the molecular analysis of exfoliative cytology[34] or saliva.[35,36] Clearly, a better understanding of the molecular profile of oral cancer should facilitate the development of more efficient targeted therapies.

The genetic evolution of oral cancer

The multi-step model of carcinogenesis is widely accepted[37] and requires the step-wise transition from pre-malignant lesions to the metastatic tumor phenotype. A variety of alterations accumulate to potentiate this transition[38] and gradually increase malignancy. A similar progression has been shown to occur in oral cancer[39] from benign hyperplasia, to dysplasia, to carcinoma in situ and advanced cancer with accompanying genomic alterations.

Several oral lesions are of particular relevance to oral cancer: oral leukoplakia,[40] oral lichen planus[41] and oral erythroplakia.[42] Oral leukoplakia is a clinical diagnosis that describes white patches or plaques that cannot be attributed to any other disease. It is common, especially in older men, and is associated with a variable risk of underlying epithelial alterations depending on its location. Approximately 10–15% of oral leukoplakias will be diagnosed as mild or moderate dysplasia and another 5% may be diagnosed as severe dysplasia or carcinoma in situ.[43] The long term risk of progression to invasive cancer varies between studies from 4% to 18%[44–46] and warrants careful clinical management. Oral lichen planus is also quite common and is estimated to incur a 1–4% risk of subsequent cancer development.[47,48] Oral lichen planus is believed to be an autoimmune disease and the mechanism of its malignant conversion is not yet well understood. Oral erythroplakia is rare but has a very high risk of progression (14–50%) and is frequently diagnosed histologically as carcinoma in situ or severe epithelial dysplasia.

Oral leukoplakia, oral lichen planus and oral erythroplakia can show varying degrees of histological abnormalities, from mild dysplasia to carcinoma in situ. A subset of these lesions will progress to oral cancer and warrant early and aggressive treatment while others may progress slowly, if at all. This progression has been linked to the presence of genomic instability and the appearance of extensive genomic alterations,[49] such as aneuploidy. Indeed, the evaluation of influential genomic alterations may supplant traditional markers that are unable to predict the time course of pre-malignant lesions.

Genomic alterations

Theory of field cancerization

The aggregation of genomic alterations during phenotypic progression is assumed to happen in a wide population of cells, a heterogeneous ''field of genetically altered cells'' that is expected to give rise to precursor lesions. This theory, first proposed by Slaughter et al.,[50] attempts to explain the frequent local recurrence and the emergence of second primary tumors in oral cancer. According to a recent adaptation of this concept,[51,52] the genetically altered cells will gradually proliferate and expand into a non-invasive field that is vulnerable to further genomic damage. This field, despite being macroscopically undetectable, is fertile ground for the evolution of pre-malignant lesions and eventually invasive cancer. Although local excision can completely remove an oral carcinoma, the field may persist and the patient can be at risk for the subsequent appearance of a second tumor from the same field. The exact molecular characteristics of a susceptible genetically altered field are not clearly defined, but key tumor suppressors such as *TP53*,[53] *CDKN2A*[53] and the pRb pathway[54] are likely to be compromised from its early stages.

Common chromosomal aberrations

A large variety of chromosomal aberrations can be found in most cancer types, including oral cancer. A summary of aberrations reported in many published studies in oral cancer or head and neck cancer[55–101] appears in Table 1. The impact of these aberrations varies significantly and their cellular and clinical significance is frequently uncertain. It is generally believed, though, that the number of aberrations increases steadily during cancer progression: oral leukoplakia has fewer chromosomal aberrations than oral cancer[71] and lower tumor stage (T1) is associated with fewer aberrations than higher tumor stage (T2).[72]

Some aberrations have been described as early, or common, and may bear considerable prognostic significance for patients with pre-malignant lesions or early stage oral cancer. Such aberrations may be linked to important target genes like *TP53* in 17p13, *RB1* in 13q14 or the *CDKN2A* gene in 9p21. In particular, several reports indicate the high prevalence of LOH or homozygous deletions in 3p, 9p, 13q and 17p[67,97] in early oral lesions. Chromosome 9 is believed to be one of the earliest targets and allelic losses in the 9p21 region, possibly associated with the genes encoding the p16 and p14 cyclin-dependent-kinase inhibitors, are present in pre-malignant lesions[69] and oral cancer[67,102]. Chromosome 3 frequently hosts allelic imbalance in several regions, especially 3p25, 3p21 and 3p13–14,[103] although the underlying responsible genes are not yet entirely clear. It should be noted that the 3p14 region encompasses the fragile site FRA3B and the *FHIT* gene and is probably one of the most vulnerable areas of the genome in many cancer types. Aberrations that are usually associated with advanced tumor stage or poor differentiation include allelic losses in 5q21–22,[74] 22q13,[100] 4q, 11q, 18q and 21q.[97] Gains in 3q[66] are also a common finding in advanced oral cancer.

With the advent and popularization of newer, massive methods like comparative genomic hybridization (CGH) and microarray-based CGH a wealth of information regarding the chromosomal aberrations in oral cancer is rapidly becoming available. Nevertheless, due to the variability of the results and their dependence on stage, site and other factors, large studies are required to resolve potential conflicts. Unfortunately, most studies are limited by small sample size and their results cannot be safely generalized. A comprehensive review of chromosomal aberrations in head and neck cancer with a focus on results derived from CGH has been recently published.[104]

Table 1 A survey of common chromosome lesions in oral cancer

Chromosome	Gain or amplification	LOH or deletion
1	–	1p36.3
2	–	2q32–35, 2q35, 2q36
3	3q25-ter	**3p13–14**, **3p21**, **3p25**
4	–	4p14–4p15, **4q25**, **4q31–32**
5	5p	**5q21–22**
6	–	6q13, 6q25
7	7p11	7q31
8	**8q22**, **8q23-ter**	8p21, 8p22, 8p23
9	–	9p21
10	–	10q23,10q26
11	**11q13**	11q22.2–q22.3
12	12p12.2–p13	–
13	–	13q14.3
14	14q31–q32.2	–
15	15q15	–
16	16q23–q24	–
17	**17q24–25**	17p13.1
18	18p	**18q**
19	19q	–
20	**20q**	20p11.2, 20q12–13.1
21	–	**21q11.1**, **21q21**, **21q22.1**
22	–	22q13

Important or common findings are shown in bold type.[55–101]

Oncogenes

Oncogenes are genes that are able to increase malignant potential. Many of the major oncogenes that are implicated in other cancer types also contribute to oral cancer. A large

number of these genes promote unscheduled, aberrant proliferation, override the G—S, G—M and M checkpoints of the cell cycle, prevent apoptosis and enable cellular survival under unfavorable conditions.

Growth receptors are known to induce different cellular responses in response to the binding of specific ligands that represent external stimuli. The ErbB family of receptors and the epidermal growth factor receptor in particular (EGFR, also known as ErbB1 or Her-1) has received attention due to its inherent ability to stimulate the proliferation of epithelial cells.[105] Amplification of *EGFR* is found in a considerable percentage of oral tumors and also in pre-malignant lesions.[106,107] Although several studies demonstrate the association between *EGFR* overexpression and tumor grade or stage there are few studies that determine its practical clinical usefulness. *EGFR* overexpression was reported to be an independent prognostic marker of survival in betel quid chewers[108] and a component of a prognostically significant molecular profile.[109] The usefulness of gefitinib (''Iressa''), a recently developed EGFR inhibitor, has been evaluated in oral cancer cell lines,[110] oral cancer xenografts in mice[111] and patients with advanced head and neck cancer[112,113] with mixed results, but large-scale human studies of its efficiency in oral or head and neck cancer are lacking.

Other members of the ErbB family are also able to exert transforming effects. ErbB2 (also known as Her-2 or Neu) amplification has been found in oral cancer specimens,[114] non-dysplastic oral leukoplakia[115] and patient sera.[77] Notably, ErbB2 over-expression seems to be more frequent in oral cancer than in head and neck cancer. High levels of ErbB2 may be associated with worse prognosis.[114,116] A novel monoclonal antibody against Her-2 (trastuzumab) may serve as targeted adjuvant therapy for a sub-group of patients in the future, but extensive trials are required to justify its use in oral cancer.

Signal transduction from activated transmembrane receptors like EGFR depends on a variety of downstream mediators that are frequently altered in various cancer types. A nodal example is the *ras* gene family that includes the *H-*, *K-* and *N-ras* oncogenes. Indeed, constitutive activation of the K-ras protein in a mouse model is sufficient to induce oral tumor formation.[117] Nevertheless, the frequency of *ras* gene mutations is estimated to be approximately 0—10% in the USA,[118] Europe[119] and Japan.[120,121] Very different results have been reported in India, where *H-ras* and *K-ras* mutations may be present in 28—35% of tumors.[122,123] Interestingly, a recent study has shown significant risk (odds ratio 1.6) associated with an *H-ras* gene polymorphism in the Indian population.[124] Downstream components of the signal transduction cascade, like Raf and ERK and other MAP kinases, have received relatively less attention and are less well studied.

The cyclin family of proteins is tightly coupled with cell cycle progression and its various members are expressed in sequence to enable cycle phase transitions. The D-type cyclins are able to initiate the G—S transition by phosphorylating the retinoblastoma protein in response to mitogenic signals.[125] Abundant expression of cyclin D is a common (36—66%) feature of oral cancer[126,127] and pre-malignant lesions.[128] Cyclin D overexpression or, more specifically, *CCND1* gene amplification may predict worse prognosis[127] and a greater risk of occult cervical lymph node metastasis in low stage tumors.[129] Furthermore, as discussed above, a cyclin D single nucleotide polymorphism has been be associated with susceptibility to oral cancer. Cyclin A overexpression, which is closely associated with the presence of S-phase cells, has also been observed immunohistochemically[130,131] and was most prevalent in advanced tumors. Similarly, Cyclin B, was overexpressed in 37% of tongue tumors[132] and in oral cancer in general.[130]

Angiogenesis, the formation of new vessels from pre-existing ones, is a crucial step in tumor growth, progression and metastasis. Regulation of angiogenesis in vivo is complex and is controlled by a variety of factors. Among them VEGF (vascular endothelial growth factor) is considered to play a dominant role. It has been well established that VEGF promotes the progression of OSCC by up-regulating MVD (microvessel density).[133,134] Its enhanced expression in oral malignant tumors may be triggered by a hypoxic stimulus.[133] Furthermore, VEGF-C expression has been reported to be a reliable predictor of regional lymph node metastasis in early OSCC.[135,136] The expression of Flt-4, a member of the family of VEGF receptors, has also been reported to correlate with lymph node metastasis, which agrees with its preferential expression in lymphatic endothelium.[137]

Matrix metalloproteinases are zinc metalloenzymes with the ability to degrade the components of the ECM (extracellular matrix). Their action is crucial during the progression of cancer since they allow the remodeling of the surrounding healthy tissues and enable local invasion. It has been demonstrated that gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11), collagenases (MMP-1 and -13) and membrane-bound MMPs (MT1-MMP) are expressed in OSCC and may play a role in its progression.[138] MMP-3, 9, -10 and -13 and possibly MT1-MMP are expressed by the malignant cells, while MMP-2 and -11 are probably produced by the stromal cells.[138] The immunohistochemical expression of gelatinases MMP-2 and -9 is related to the invasive potential of OSCC.[139] However, MMP-2 expression seems to be more prominent than MMP-9 in OSCC samples and correlates with lymph node metastasis.[140] Another interesting finding is the association between the overexpression of MMP-2 and MMP-9 and alcohol consumption., which led the researchers to hypothesize that the contribution of alcohol in the carcinogenetic process of oscc may be attributed to the overexpression of these two enzymes.[139]

Tissue inhibitors of metalloproteinases (TIMPs) bind to the MMPs and inhibit their action. However TIMP-1 and -2 are homologues of erythroid potentiating activity (EPA) factors, which promote the growth of erythroid precursor cells. In this context, TIMP-2 expression correlates with local recurrence and poor prognosis.[141]

Tumor suppressors

Tumor suppressors are genes that prevent cells from acquiring malignant characteristics. Tumor suppressor genes are usually entrusted with the regulation of discrete checkpoints during cell cycle progression and with the monitoring of DNA replication and mitosis. Cellular stress and a variety of insults can activate tumor suppressor pathways to arrest the cell cycle.

The retinoblastoma protein and its associated molecular network are frequent and early targets in many tumor

types. When in a hypo-phosphorylated state, the retinoblastoma protein and the other pocket protein family members p107 and p130 bind and inactivate the E2F transcription factors which are essential for cell cycle progression from G to S. Lack of immunohistochemical pRb expression was found in approximately 70% of oral tumors[142,126] and 64% of pre-malignant lesions[142]. Similarly, in a later study, about half of oral cancer specimens did not express pRb and 20% of those that did express pRb only contained the inactive, phosphorylated form[143]. Most importantly, 84% of pre-malignant lesions and 90% of oral squamous cell carcinomas show altered expression of at least one of the components of the pRb network.[54] The cyclin dependent kinase inhibitors (CDKIs), in particular, are known targets in oral cancer, most likely due to their ability to prevent pRb phosphorylation. The *CDKN2A* locus that encodes $p16^{INK4A}$ is located in 9p21, one of the most vulnerable areas of the genome in oral cancer, as discussed above. Indeed, lack of immunohistochemical p16 expression can be found in up to 83% of oral tumors[144,142,145] and up to 60% of pre-malignant lesions.[142] The predominant mode of inactivation is allelic imbalance, but point mutations and promoter methylation also occur with lower frequency.[145] The alternative *CDKN2A* transcript, $p14^{ARF}$, is also commonly suppressed,[146] but down-regulation of other INK4 family members, like $p15^{INK4B}$, is less frequent. The prognostic significance of $p16^{INK4A}$ levels is uncertain, although a study has reported favorable prognosis for patients overexpressing $p16^{INK4A}$.[147]

The deregulation of the p53 tumor suppression network is observed in many tumor types, including oral cancer. In fact, the activation of the DNA damage response is one of the earliest findings in the natural history of cancer.[148,149] The p53 protein is able to enforce cell cycle arrest or apoptosis under replication stress, thus halting the proliferation of potentially malignant cells. As mentioned above, loss-of-heterozygosity in the 17p13 region that hosts the *TP53* gene is very common in oral cancer.[94,95] Immunohistochemical evaluation for p53 is positive in up to 57% of oral tumors[150,151] but is also positive in distant, macroscopically normal areas,[152,153] in accordance with the theory of ''field cancerization''. Immunohistochemical p53 overexpression in the normal mucosa is associated with an increased incidence of second primary carcinoma in some studies,[154] but not in others.[153] The prognostic value of the p53 status in oral cancer is uncertain and many studies have not found any impact on patient survival.[155,156] Nevertheless, p53 expression may predict poor prognosis in the subset of patients with low stage, node-negative disease[151] or in those carrying specific *TP53* mutations.[157] Interestingly, tumors with *TP53* mutations seem to be more resistant to radiotherapy[158–160] and this information could be vital for the selection of an appropriate treatment.

Figure 1 offers a simplified model of oral carcinogenesis. The initial alterations seem to occur at the basal cell layer under the influence of smoke, alcohol and/or other carcinogens and may involve deactivation of TP53 and other key tumor suppressors. The transition of normal epithelium to invasive cancer is—more often than not—progressive and is accompanied by ''multiple hits'' which promote proliferation, angiogenesis, local invasion and, eventually, distant metastatic spread.

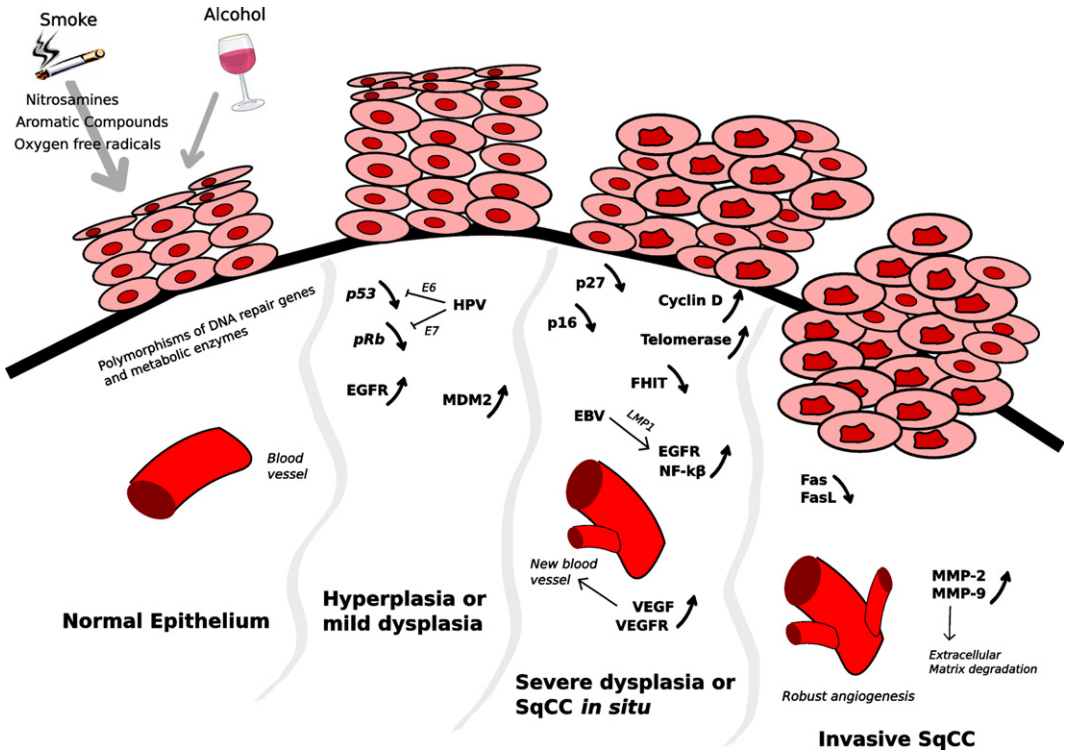

Figure 1 Theoretical model of carcinogenesis in the oral cavity based on the ''multiple hit'' hypothesis. The majority of the molecular/genetic lesions that accompany the histological transition from normal to cancerous epithelium persist during later stages, but they are presented in the stage of their appearance.

Viral infections

Human Papillomavirus (HPV)

A plethora of viral agents have been linked to human tumors. Among these, human papillomavirus (HPV) holds a prominent position. To date, more than one hundred HPV types have been identified, and are referred to as ''low'' or ''high risk'' according to their oncogenic potential.[161] Two products, in particular, of the early genomic region of high-risk HPVs are capable of forming specific complexes with vital cell-cycle regulators: E6, which binds to p53 and induces its degradation, and E7, which interacts with pRb and blocks its downstream activity. Functional deregulation of these key oncosuppressors results in uncontrolled DNA replication and apoptotic impairment, and explains the increased tumorigenic ability of high-risk types.[162]

Research on the participation of HPV in oral carcinogenesis has generated varied results, with the reported infection percentages in potentially malignant and cancerous lesions ranging from 0 to 90%. Controversial reports are mainly attributable to the varying sensitivity of HPV detection techniques that have been applied, such as immunohistochemistry,[163] in situ hybridization,[164,165] and polymerase chain reaction (PCR) variants,[166–168] sometimes followed by Southern[169–171] or dot blotting.[172,173] Research groups that employed a combination of two or more of the aforementioned assays tended to obtain higher infection rates.[174]

In a recent study, we investigated the presence of HPV genomic sequences in a series of oral leukoplakias, with histological features of hyperplasia and/or dysplasia, and SCCs, with the use of a highly sensitive nested PCR-based approach.[175] Viral DNA was detected in 91% of oral lesions, which still represents the highest infection percentage ever reported. The vast majority of specimens harbored high-risk viral sequences, with HPV 16 being the prevailing type. The fact that HPV positivity and genotyping patterns were independent of histology urged us to propose an early involvement of high-risk types in oral carcinogenesis. Several groups have supported the implication of HPV during the early stages of oral neoplasia,[168] with some assigning the virus a role in malignant progression[176] and others suggesting a ''hit and run'' action.[177] Most study groups have observed no correlation between viral presence and age, gender or cancer differentiation,[172,178] although sporadic reports of such associations do exist.[174,170]

Immortalization of human oral keratinocytes has been achieved through transfection with the early region of HPV 16,[179,180] and has provided a useful in vitro system for assessing the involvement of the virus in oral neoplasia. Infected cultured cells accumulate progressive chromosomal aberrations through passages,[181] express high levels of dedifferentiation markers, such as the nerve growth factor (NGF),[182] and reach a growth-independent state, possibly due to autocrine interleukin (IL)-6 production.[183] However, despite repeated attempts, HPV 16-immortalized keratinocytes have demonstrated no tumorigenic activity in nude mice,[181,184] unless subjected to chronic exposure to the tobacco carcinogen benzo(*a*)pyrene or other chemicals.[184,185] Following carcinogenic treatment, these cells secreted increased levels of VEGF(vascular endothelial growth factor), contained a higher number of integrated viral copies, and exhibited a malignant phenotype in organotypic ''raft'' culture.[185] Furthermore, both benzo(*a*)pyrene stimulation and HPV 16 infection of cultured oral epithelial cells have been shown to confer anti-apoptotic characteristics, such as downregulation of Fas and Bax, as well as overexpression of Bcl2 via p53 deregulation.[186]

Taken together, these observations suggest that HPV alone is incapable of inducing malignant transformation. Instead, the tumorigenic action of high-risk HPV probably becomes significant in synergy with chemical carcinogens and other risk factors. Epidemiological data seem to confirm this hypothesis: while the role of HPV in cervical carcinoma is crucial, its contribution to oral cancer is much less spectacular, with an odds ratio reported to range between 1.5 and 4.3.[187,188] Furthermore, there seems to be a difference between anatomic locations, with oral cancer being generally less affected by the presence of HPV,[188] compared to oropharyngeal cancer and tonsillar cancer in particular. The clinical implications are yet unclear, but HPV positive patients have been reported to be younger, consume less alcohol and tend to have a better prognosis.[189]

Recent trials have shown that an HPV vaccine can provide effective protection against high risk types 16 and 18[190] and the development of associated cervical lesions for up to 4.5 years. There are no data that demonstrate its efficacy in the prevention of oral lesions, but a preliminary study of an HPV DNA vaccine against HPV-associated oral carcinogenesis in mice has produced promising results.[191] Clearly, large, prospective randomized trials are needed to document the clinical usefulness of HPV vaccines against oral cancer.

Epstein-Barr virus (EBV)

The Epstein-Barr virus (EBV) is a member of the herpesvirus family. Even though its contribution to the malignant transformation of B lymphocytes has been well established, the influence of EBV in the pathogenesis of oral squamous cell carcinoma remains elusive. It has been reported that EBV is more frequently detected in oral lesions such as oral lichen planus and oral squamous cell carcinoma in comparison with healthy oral epithelium.[192,193] In another study, LMP-1, the principal oncoprotein of the virus, has been found in many EBV-positive OSCCs, which means that this latent infection may play a role in the malignant transformation of oral mucosa.[194] However, these findings are not universal and several studies[195–197] have reported the lack of a conclusive relation between EBV and oral cancer or premalignant lesions. Considerable skepticism is justified, in view of the variability between studies that employ different detection methods and refer to different patient populations.

Hepatitis C virus (HCV)

Oral verrucous and squamous cell carcinomas have been reported in HCV-infected patients[198,199] while HCV infection has been found to be more prevalent in patients with oral lichen planus.[200,201] However, 1–2% of the patients with oral lichen planus develop squamous cell carcinoma of the

oral cavity, which implies the existence of common pathogenic mechanisms among them.[47] Finally HCV-RNA strands were detected in OLP tissues[202] and there is evidence to indicate that HCV may occasionally replicate in oral lichen tissue[203] and contribute to mucosal damage.

Conclusion

The study of oral cancer is particularly challenging. Oral cancer is an important cause of morbidity and mortality, especially in developing countries, and its prevalence may rise in the foreseeable future. Advances in diagnosis and treatment have slowly accumulated, but a sound understanding of underlying cell biology is likely to enable further, much-needed progress.

Conflict of interest

We wish to declare that the submitted work is original and has not been submitted or published elsewhere. Also, all authors have read and approved the manuscript and agree with the current submission. Finally, there are no potential conflicts of interest.

Acknowledgement

This work was co-financed within Op. Education by the ESF (European Social Fund) and National Resources.

References

1. Shah JP, Johnson NW, Batsakis JG. Oral cancer. Taylor & Francis; 2003.
2. Parkin DM, Läärä E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer 1988;41 (2):184—97.
3. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55 (1):10—30.
4. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33 (7):1075—107.
5. Warnakulasuriya S, Sutherland G, Scully C. Tobacco, oral cancer, and treatment of dependence. Oral Oncol 2005;41 (3):244—60.
6. Ogden GR. Alcohol and oral cancer. Alcohol 2005;35 (3):169—73.
7. Nair U, Bartsch H, Nair J. Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. Mutagenesis 2004;19 (4):251—62.
8. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. Respirology 2003;8 (4):419—31.
9. Goldstein AM, Blot WJ, Greenberg RS, Schoenberg JB, Austin DF, Preston-Martin S, et al. Familial risk in oral and pharyngeal cancer. Eur J Cancer B Oral Oncol 1994;30B (5):319—22.
10. Brown LM, Gridley G, Diehl SR, Winn DM, Harty LC, Otero EB, et al. Family cancer history and susceptibility to oral carcinoma in Puerto Rico. Cancer 2001;92 (8):2102—8.
11. Copper MP, Jovanovic A, Nauta JJ, Braakhuis BJ, de Vries N, van der Waal I, et al. Role of genetic factors in the etiology of squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1995;121 (2):157—60.
12. Foulkes WD, Brunet JS, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study. BMJ 1996;313 (7059):716—21.
13. Bongers V, Braakhuis BJ, Tobi H, Lubsen H, Snow GB. The relation between cancer incidence among relatives and the occurrence of multiple primary carcinomas following head and neck cancer. Cancer Epidemiol Biomarkers Prev 1996;5 (8):595—8.
14. Ankathil R, Mathew A, Joseph F, Nair MK. Is oral cancer susceptibility inherited? Report of five oral cancer families. Eur J Cancer B Oral Oncol 1996;32B (1):63—7.
15. Sato M, Sato T, Izumo T, Amagasa T. Genetic polymorphism of drug-metabolizing enzymes and susceptibility to oral cancer. Carcinogenesis 1999;20 (10):1927—31.
16. Sreelekha TT, Ramadas K, Pandey M, Thomas G, Nalinakumari KR, Pillai MR. Genetic polymorphism of CYP1A1, GSTM1 and GSTT1 genes in Indian oral cancer. Oral Oncol 2001;37 (7):593—8.
17. González MV, Alvarez V, Pello MF, Menéndez MJ, Suárez C, Coto E. Genetic polymorphism of *N*-acetyltransferase-2, glutathione *S*-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. J Clin Pathol 1998;51 (4):294—8.
18. Harty LC, Caporaso NE, Hayes RB, Winn DM, Bravo-Otero E, Blot WJ, et al. Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers. J Natl Cancer Inst 1997;89 (22):1698—705.
19. Sturgis EM, Dahlstrom KR, Guan Y, Eicher SA, Strom SS, Spitz MR, et al. Alcohol dehydrogenase 3 genotype is not associated with risk of squamous cell carcinoma of the oral cavity and pharynx. Cancer Epidemiol Biomarkers Prev 2001;10 (3):273—5.
20. Wang D, Ritchie JM, Smith EM, Zhang Z, Turek LP, Haugen TH. Alcohol dehydrogenase 3 and risk of squamous cell carcinomas of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14 (3):626—32.
21. Brennan P, Lewis S, Hashibe M, Bell DA, Boetta P, Bouchardy C, et al. Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. Am J Epidemiol 2004;159 (1):1—16.
22. Zheng Y, Shen H, Sturgis EM, Wang LE, Eicher SA, Strom SS, et al. Cyclin D1 polymorphism and risk for squamous cell carcinoma of the head and neck: a case-control study. Carcinogenesis 2001;22 (8):1195—9.
23. Huang M, Spitz MR, Gu J, Lee JJ, Lin J, Lippman SM, et al. Cyclin D1 gene polymorphism as a risk factor for oral premalignant lesions. Carcinogenesis 2006.
24. Holley SL, Matthias C, Jahnke V, Fryer AA, Strange RC, Hoban PR. Association of cyclin D1 polymorphism with increased susceptibility to oral squamous cell carcinoma. Oral Oncol 2005;41 (2):156—60.
25. Beer KT, Greiner RH, Aebersold DM, Zbären P. Carcinoma of the oropharynx: local failure as the decisive parameter for distant metastases and survival. Strahlenther Onkol 2000;176 (1):16—21.
26. Lacy PD, Spitznagel EL, Piccirillo JF. Development of a new staging system for recurrent oral cavity and oropharyngeal squamous cell carcinoma. Cancer 1999;86 (8):1387—95.
27. Matsuura K, Hirokawa Y, Fujita M, Akagi Y, Ito K. Treatment results of stage I and II oral tongue cancer with interstitial brachytherapy: maximum tumor thickness is prognostic of nodal metastasis. Int J Radiat Oncol Biol Phys 1998;40 (3):535—9.
28. Bundgaard T, Bentzen SM, Wildt J, Sørensen FB, Søgaard H, Nielsen JE. Histopathologic, stereologic, epidemiologic, and clinical parameters in the prognostic evaluation of squamous

cell carcinoma of the oral cavity. Head Neck 1996;18 (2):142–52.
29. Harris L, Sessions R, Hong W. Head and neck cancer: a multidisciplinary approach. Philadelphia: Lippincott-Raven; 1998.
30. Reichard KW, Joseph KT, Cohen M, Greager JA. Squamous cell carcinoma of the tongue: experience with 86 consecutive cases. J Surg Oncol 1993;54 (4):239–42.
31. Hill BT, Price LA. Lack of survival advantage in patients with advanced squamous cell carcinomas of the oral cavity receiving neoadjuvant chemotherapy prior to local therapy, despite achieving an initial high clinical complete remission rate. Am J Clin Oncol 1994;17 (1):1–5.
32. Hanson WG, Ferguson PJ. Dierential methotrexate toxicity between two human oral squamous carcinoma cell lines. J Otolaryngol 1993;22 (3):143–7.
33. Warnakulasuriya KA, Johnson NW. Sensitivity and specificity of OraScan (R) toluidine blue mouthrinse in the detection of oral cancer and precancer. J Oral Pathol Med 1996;25 (3):97–103.
34. Diniz-Freitas M, García-García A, Crespo-Abelleira A, Martins-Carneiro JL, Gándara-Rey JM. Applications of exfoliative cytology in the diagnosis of oral cancer. Med Oral 2004;9 (4):355–61.
35. Li Y, John MARS, Zhou X, Kim Y, Sinha U, Jordan RCK, et al. Salivary transcriptome diagnostics for oral cancer detection. Clin Cancer Res 2004;10 (24):8442–50.
36. Westra WH, Califano J. Toward early oral cancer detection using gene expression profiling of saliva: a thoroughfare or dead end? Clin Cancer Res 2004;10 (24):8130–1.
37. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61 (5):759–67.
38. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100 (1):57–70.
39. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, et al. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res 1996;56 (11):2488–92.
40. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52 (4):195–215.
41. Dissemond J. Oral lichen planus: an overview. J Dermatolog Treat 2004;15 (3):136–40.
42. Reichart PA, Philipsen HP. Oral erythroplakia—a review. Oral Oncol 2005;41 (6):551–61.
43. Waldron CA, Shafer WG. Leukoplakia revisited. A clinicopathologic study 3256 oral leukoplakias. Cancer 1975;36 (4):1386–92.
44. Einhorn J, Wersall J. Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. Cancer 1967;20 (12):2189–93.
45. Bánóczy J. Follow-up studies in oral leukoplakia. J Maxillofac Surg 1977;5 (1):69–75.
46. Silverman S, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer 1984;53 (3):563–8.
47. Lozada-Nur F, Miranda C. Oral lichen planus: epidemiology, clinical characteristics, and associated diseases. Semin Cutan Med Surg 1997;16 (4):273–7.
48. Mignogna MD, Muzio LL, Russo LL, Fedele S, Ruoppo E, Bucci E. Clinical guidelines in early detection of oral squamous cell carcinoma arising in oral lichen planus: a 5-year experience. Oral Oncol 2001;37 (3):262–7.
49. Sudbø J. Novel management of oral cancer: a paradigm of predictive oncology. Clin Med Res 2004;2 (4):233–42.
50. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6 (5):963–8.
51. Braakhuis BJM, Tabor MP, Kummer JA, Leemans CR, Brakenho RH. A genetic explanation of slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003;63 (8):1727–30.
52. Braakhuis BJM, Leemans CR, Brakenho RH. A genetic progression model of oral cancer: current evidence and clinical implications. J Oral Pathol Med 2004;33 (6):317–22.
53. Tabor MP, Brakenho RH, Ruijter-Schippers HJ, Wal JEVD, Snow GB, Leemans CR, et al. Multiple head and neck tumors frequently originate from a single preneoplastic lesion. Am J Pathol 2002;161 (3):1051–60.
54. Soni S, Kaur J, Kumar A, Chakravarti N, Mathur M, Bahadur S, et al. Alterations of rb pathway components are frequent events in patients with oral epithelial dysplasia and predict clinical outcome in patients with squamous cell carcinoma. Oncology 2005;68 (4–6):314–25.
55. Araki D, Uzawa K, Watanabe T, Shiiba M, Miyakawa A, Yokoe H, et al. Frequent allelic losses on the short arm of chromosome 1 and decreased expression of the p73 gene at 1p36.3 in squamous cell carcinoma of the oral cavity. Int J Oncol 2002;20 (2):355–60.
56. Rupa DS, Eastmond DA. Chromosomal alterations aecting the 1cen-1q12 region in buccal mucosal cells of betel quid chewers detected using multicolor fluorescence in situ hybridization. Carcinogenesis 1997;18 (12):2347–51.
57. Yamamoto N, Mizoe etsu J, Numasawa H, Tsujii H, Shibahara T, Noma H. Allelic loss on chromosomes 2q, 3p and 21q: possibly a poor prognostic factor in oral squamous cell carcinoma. Oral Oncol 2003;39 (8):796–805.
58. Yamamoto N, Mizoe etsu J, Numasawa H, Yokoe H, Uzawa K, Shibahara T, et al. Allelic loss of chromosome 2 in human oral squamous cell carcinoma: correlation with lymph node metastasis. Oral Oncol 2003;39 (1):64–8.
59. Numasawa H, Yamamoto N, Katakura A, Shibahara T. Loss of heterozygosity and microsatellite instability on chromosome 2q in human oral squamous cell carcinoma. Bull Tokyo Dent Coll 2005;46 (1–2):17–25.
60. Wu CL, Sloan P, Read AP, Harris R, Thakker N. Deletion mapping on the short arm of chromosome 3 in squamous cell carcinoma of the oral cavity. Cancer Res 1994;54 (24): 6484–8.
61. Ishwad CS, Ferrell RE, Rossie KN, Appel BN, Johnson JT, Myers EN, et al. Loss of heterozygosity of the short arm of chromosomes 3 and 9 in oral cancer. Int J Cancer 1996;69 (1):1–4.
62. Partridge M, Kiguwa S, Langdon JD. Frequent deletion of chromosome 3p in oral squamous cell carcinoma. Eur J Cancer B Oral Oncol 1994;30B (4):248–51.
63. Partridge M, Emilion G, Langdon JD. LOH at 3p correlates with a poor survival in oral squamous cell carcinoma. Br J Cancer 1996;73 (3):366–71.
64. Wol E, Girod S, Liehr T, Vorderwülbecke U, Ries J, Steininger H, et al. Oral squamous cell carcinomas are characterized by a rather uniform pattern of genomic imbalances detected by comparative genomic hybridisation. Oral Oncol 1998;34 (3):186–90.
65. Okafuji M, Ita M, Hayatsu Y, Shinozaki F, Oga A, Sasaki K. Identification of genetic aberrations in cell lines from oral squamous cell carcinomas by comparative genomic hybridization. J Oral Pathol Med 1999;28 (6):241–5.
66. Oga A, Kong G, Tae K, Lee Y, Sasaki K. Comparative genomic hybridization analysis reveals 3q gain resulting in genetic alteration in 3q in advanced oral squamous cell carcinoma. Cancer Genet Cytogenet 2001;127 (1):24–9.
67. Rosin MP, Cheng X, Poh C, Lam WL, Huang Y, Lovas J, et al. Use of allelic loss to predict malignant risk for low-grade oral epithelial dysplasia. Clin Cancer Res 2000;6 (2):357–62.

68. Pershouse MA, El-Naggar AK, Hurr K, Lin H, Yung WK, Steck PA. Deletion mapping of chromosome 4 in head and neck squamous cell carcinoma. Oncogene 1997;14 (3):369—73.
69. Jiang WW, Fujii H, Shirai T, Mega H, Takagi M. Accumulative increase of loss of heterozygosity from leukoplakia to foci of early cancerization in leukoplakia of the oral cavity. Cancer 2001;92 (9):2349—56.
70. Wang XL, Uzawa K, Imai FL, Tanzawa H. Localization of a novel tumor suppressor gene associated with human oral cancer on chromosome 4q25. Oncogene 1999;18 (3):823—5.
71. Weber RG, Scheer M, Born IA, Joos S, Cobbers JM, Hofele C, et al. Recurrent chromosomal imbalances detected in biopsy material from oral premalignant and malignant lesions by combined tissue microdissection, universal DNA amplification, and comparative genomic hybridization. Am J Pathol 1998;153 (1):295—303.
72. Okafuji M, Ita M, Oga A, Hayatsu Y, Matsuo A, Shinzato Y, et al. The relationship of genetic aberrations detected by comparative genomic hybridization to DNA ploidy and tumor size in human oral squamous cell carcinomas. J Oral Pathol Med 2000;29 (5):226—31.
73. Mancini UM, Estécio MRH, Góis JFF, Fukuyama EE, Valentim PJ, Cury PM, et al. The chromosome 5q21 band minisatellite and head and neck cancer. Cancer Genet Cytogenet 2003;147 (1):87—8.
74. Mao EJ, Schwartz SM, Daling JR, Beckmann AM. Loss of heterozygosity at 5q21—22 (adenomatous polyposis coli gene region) in oral squamous cell carcinoma is common and correlated with advanced disease. J Oral Pathol Med 1998;27 (7):297—302.
75. Queimado L, Reis A, Fonseca I, Martins C, Lovett M, Soares J, et al. A refined localization of two deleted regions in chromosome 6q associated with salivary gland carcinomas. Oncogene 1998;16 (1):83—8.
76. Garnis C, Campbell J, Zhang L, Rosin MP, Lam WL. OCGR array: an oral cancer genomic regional array for comparative genomic hybridization analysis. Oral Oncol 2004;40 (5):511—9.
77. Chen YJ, Lin SC, Kao T, Chang CS, Hong PS, Shieh TM, et al. Genome-wide profiling of oral squamous cell carcinoma. J Pathol 2004;204 (3):326—32.
78. Steinhart H, Bohlender J, Iro H, Jung V, Constantinidis J, Gebhart E, et al. DNA amplification on chromosome 7q in squamous cell carcinoma of the tongue. Int J Oncol 2001;19 (4):851—5.
79. Zenklusen JC, Thompson JC, Klein-Szanto AJ, Conti CJ. Frequent loss of heterozygosity in human primary squamous cell and colon carcinomas at 7q31.1: evidence for a broad range tumor suppressor gene. Cancer Res 1995;55 (6):1347—50.
80. Wang XL, Uzawa K, Miyakawa A, Shiiba M, Watanabe T, Sato T, et al. Localization of a tumour-suppressor gene associated with human oral cancer on 7q31.1. Int J Cancer 1998;75 (5):671—4.
81. Sunwoo JB, Holt MS, Radford DM, Deeker C, Scholnick SB. Evidence for multiple tumor suppressor genes on chromosome arm 8p in supraglottic laryngeal cancer. Genes Chromosomes Cancer 1996;16 (3):164—9.
82. Wu CL, Roz L, Sloan P, Read AP, Holland S, Porter S, et al. Deletion mapping defines three discrete areas of allelic imbalance on chromosome arm 8p in oral and oropharyngeal squamous cell carcinomas. Genes Chromosomes Cancer 1997;20 (4):347—53.
83. Sunwoo JB, Sun PC, Gupta VK, Schmidt AP, El-Mofty S, Scholnick SB. Localization of a putative tumor suppressor gene in the sub-telomeric region of chromosome 8p. Oncogene 1999;18 (16):2651—5.
84. El-Naggar AK, Coombes MM, Batsakis JG, Hong WK, Goepfert H, Kagan J. Localization of chromosome 8p regions involved in early tumorigenesis of oral and laryngeal squamous carcinoma. Oncogene 1998;16 (23):2983—7.
85. Ishwad CS, Shuster M, Bockmühl U, Thakker N, Shah P, Toomes C, et al. Frequent allelic loss and homozygous deletion in chromosome band 8p23 in oral cancer. Int J Cancer 1999;80 (1):25—31.
86. Garnis C, Coe BP, Ishkanian A, Zhang L, Rosin MP, Lam WL. Novel regions of amplification on 8q distinct from the MYC locus and frequently altered in oral dysplasia and cancer. Genes Chromosomes Cancer 2004;39 (1):93—8.
87. van der Riet P, Nawroz H, Hruban RH, Corio R, Tokino K, Koch W, et al. Frequent loss of chromosome 9p21—22 early in head and neck cancer progression. Cancer Res 1994;54 (5):1156—8.
88. Yamashita Y, Miyakawa A, Mochida Y, Aisaki K, Yama M, Shiiba M, et al. Genetic aberration on chromosome 10 in human oral squamous cell carcinoma. Int J Oncol 2002;20 (3):595—8.
89. Zhou X, Jordan RCK, Li Y, Huang BL, Wong DTW. Frequent allelic imbalances at 8p and 11q22 in oral and oropharyngeal epithelial dysplastic lesions. Cancer Genet Cytogenet 2005;161 (1):86—9.
90. Shuster MI, Han L, Beau MML, Davis E, Sawicki M, Lese CM, et al. A consistent pattern of RIN1 rearrangements in oral squamous cell carcinoma cell lines supports a breakage-fusion-bridge cycle model for 11q13 amplification. Genes Chromosomes Cancer 2000;28 (2):153—63.
91. Huang Q, Yu GP, McCormick SA, Mo J, Datta B, Mahimkar M, et al. Genetic dierences detected by comparative genomic hybridization in head and neck squamous cell carcinomas from dierent tumor sites: construction of oncogenetic trees for tumor progression. Genes Chromosomes Cancer 2002;34 (2):224—33.
92. Ogawara K, Miyakawa A, Shiba M, Uzawa K, Watanabe T, Wang XL, et al. Allelic loss of chromosome 13q14.3 in human oral cancer: correlation with lymph node metastasis. Int J Cancer 1998;79 (4):312—7.
93. Gebhart E, Liehr T, Wol E, Ries J, Fiedler W, Steininger H, et al. Pattern of genomic imbalances in oral squamous cell carcinomas with and without an increased copy number of 11q13. Int J Oncol 1998;12 (5):1151—5.
94. Largey JS, Meltzer SJ, Yin J, Norris K, Sauk JJ, Archibald DW. Loss of heterozygosity of p53 in oral cancers demonstrated by the polymerase chain reaction. Cancer 1993;71 (6):1933—7.
95. Huang MF, Chang YC, Liao PS, Huang TH, Tsay CH, Chou MY. Loss of heterozygosity of p53 gene of oral cancer detected by exfoliative cytology. Oral Oncol 1999;35 (3):296—301.
96. Lin SC, Chen YJ, Kao SY, Hsu MT, Lin CH, Yang SC, et al. Chromosomal changes in betel-associated oral squamous cell carcinomas and their relationship to clinical parameters. Oral Oncol 2002;38 (3):266—73.
97. Bockmühl U, Wolf G, Schmidt S, Schwendel A, Jahnke V, Dietel M, et al. Genomic alterations associated with malignancy in head and neck cancer. Head Neck 1998;20 (2):145—51.
98. Imai FL, Uzawa K, Miyakawa A, Shiiba M, Tanzawa H. A detailed deletion map of chromosome 20 in human oral squamous cell carcinoma. Int J Mol Med 2001;7 (1):43—7.
99. Chen L, Wong MP, Cheung LK, Samaranayake LP, Baum L, Samman N. Frequent allelic loss of 21q11.1 approximately q21.1 region in advanced stage oral squamous cell carcinoma. Cancer Genet Cytogenet 2005;159 (1):37—43.
100. Reis PP, Rogatto SR, Kowalski LP, Nishimoto IN, Montovani JC, Corpus G, et al. Quantitative real-time PCR identifies a critical region of deletion on 22q13 related to prognosis in oral cancer. Oncogene 2002;21 (42):6480—7.
101. Miyakawa A, Wang XL, Nakanishi H, Imai FL, Shiiba M, Miya T, et al. Allelic loss on chromosome 22 in oral cancer: possibility of the existence of a tumor suppressor gene on 22q13. Int J Oncol 1998;13 (4):705—9.

102. el Naggar AK, Hurr K, Batsakis JG, Luna MA, Goepfert H, Hu V. Sequential loss of heterozygosity at microsatellite motifs in preinvasive and invasive head and neck squamous carcinoma. Cancer Res 1995;55 (12):2656–9.
103. Partridge M, Emilion G, Pateromichelakis S, A'Hern R, Lee G, Phillips E, et al. The prognostic significance of allelic imbalance at key chromosomal loci in oral cancer. Br J Cancer 1999;79 (11-12):1821–7.
104. Patmore HS, Cawkwell L, Staord ND, Greenman J. Unraveling the chromosomal aberrations of head and neck squamous cell carcinoma: a review. Ann Surg Oncol 2005;12 (10):831–42.
105. Normanno N, Luca AD, Bianco C, Strizzi L, Mancino M, Maiello MR, et al. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene 2006;366 (1):2–16.
106. Ishitoya J, Toriyama M, Oguchi N, Kitamura K, Ohshima M, Asano K, et al. Gene amplification and overexpression of EGF receptor in squamous cell carcinomas of the head and neck. Br J Cancer 1989;59 (4):559–62.
107. Nagatsuka H, Ishiwari Y, Tsujigiwa H, Nakano K, Nagai N. Quantitation of epidermal growth factor receptor gene amplification by competitive polymerase chain reaction in pre-malignant and malignant oral epithelial lesions. Oral Oncol 2001;37 (7):599–604.
108. Chen IH, Chang JT, Liao CT, Wang HM, Hsieh LL, Cheng AJ. Prognostic significance of EGFR and Her-2 in oral cavity cancer in betel quid prevalent area cancer prognosis. Br J Cancer 2003;89 (4):681–6.
109. Shiraki M, Odajima T, Ikeda T, Sasaki A, Satoh M, Yamaguchi A, et al. Combined expression of p53, cyclin D1 and epidermal growth factor receptor improves estimation of prognosis in curatively resected oral cancer. Mod Pathol 2005;18 (11):1482–9.
110. Shintani S, Li C, Mihara M, Yano J, Terakado N, Nakashiro ichi K, et al. Gefitinib ('Iressa', ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, up-regulates p27KIP1 and induces G1 arrest in oral squamous cell carcinoma cell lines. Oral Oncol 2004;40 (1):43–51.
111. Shintani S, Li C, Mihara M, Nakashiro ichi K, Hamakawa H. Gefitinib ('Iressa'), an epidermal growth factor receptor tyrosine kinase inhibitor, mediates the inhibition of lymph node metastasis in oral cancer cells. Cancer Lett 2003;201 (2): 149–55.
112. Cohen EEW, Rosen F, Stadler WM, Recant W, Stenson K, Huo D, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2003;21 (10):1980–7.
113. Kirby AM, A'Hern RP, D'Ambrosio C, Tanay M, Syrigos KN, Rogers SJ, et al. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. Br J Cancer 2006;94 (5):631–6.
114. Xia W, Lau YK, Zhang HZ, Liu AR, Li L, Kiyokawa N, et al. Strong correlation between c-erbB-2 overexpression and overall survival of patients with oral squamous cell carcinoma. Clin Cancer Res 1997;3 (1):3–9.
115. Werkmeister R, Brandt B, Joos U. Aberrations of erbB-1 and erbB-2 oncogenes in non-dysplastic leukoplakias of the oral cavity. Br J Oral Maxillofac Surg 1999;37 (6):477–80.
116. Werkmeister R, Brandt B, Joos U. Clinical relevance of erbB-1 and -2 oncogenes in oral carcinomas. Oral Oncol 2000;36 (1):100–5.
117. Caulin C, Nguyen T, Longley MA, Zhou Z, Wang XJ, Roop DR. Inducible activation of oncogenic K-ras results in tumor formation in the oral cavity. Cancer Res 2004;64 (15): 5054–8.
118. Xu J, Gimenez-Conti IB, Cunningham JE, Collet AM, Luna MA, Lanfranchi HE, et al. Alterations of p53, cyclin D1, Rb, and H-ras in human oral carcinomas related to tobacco use. Cancer 1998;83 (2):204–12.
119. Kiaris H, Spandidos DA, Jones AS, Vaughan ED, Field JK. Mutations, expression and genomic instability of the H-ras proto-oncogene in squamous cell carcinomas of the head and neck. Br J Cancer 1995;72 (1):123–8.
120. Sakata K. Alterations of tumor suppressor genes and the H-ras oncogene in oral squamous cell carcinoma. J Oral Pathol Med 1996;25 (6):302–7.
121. Matsuda H, Konishi N, Hiasa Y, Hayashi I, Tsuzuki T, Tao M, et al. Alterations of p16/CDKN2, p53 and ras genes in oral squamous cell carcinomas and premalignant lesions. J Oral Pathol Med 1996;25 (5):232–8.
122. Saranath D, Chang SE, Bhoite LT, Panchal RG, Kerr IB, Mehta AR, et al. High frequency mutation in codons 12 and 61 of H-ras oncogene in chewing tobacco-related human oral carcinoma in India. Br J Cancer 1991;63 (4):573–8.
123. Das N, Majumder J, DasGupta UB. ras gene mutations in oral cancer in eastern India. Oral Oncol 2000;36 (1):76–80.
124. Sathyan KM, Nalinakumari KR, Abraham T, Kannan S. Influence of single nucleotide polymorphisms in H-Ras and cyclin D1 genes on oral cancer susceptibility. Oral Oncol 2006.
125. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev 1999;13 (12):1501–12.
126. Koontongkaew S, Chareonkitkajorn L, Chanvitan A, Leelakriangsak M, Amornphimoltham P. Alterations of p53, pRb, cyclin D(1) and cdk4 in human oral and pharyngeal squamous cell carcinomas. Oral Oncol 2000;36 (4):334–9.
127. Miyamoto R, Uzawa N, Nagaoka S, Hirata Y, Amagasa T. Prognostic significance of cyclin D1 amplification and overexpression in oral squamous cell carcinomas. Oral Oncol 2003;39 (6):610–8.
128. Rousseau A, Lim MS, Lin Z, Jordan RC. Frequent cyclin D1 gene amplification and protein overexpression in oral epithelial dysplasias. Oral Oncol 2001;37 (3):268–75.
129. Myo K, Uzawa N, Miyamoto R, Sonoda I, Yuki Y, Amagasa T. Cyclin D1 gene numerical aberration is a predictive marker for occult cervical lymph node metastasis in TNM Stage I and II squamous cell carcinoma of the oral cavity. Cancer 2005;104 (12):2709–16.
130. Kushner J, Bradley G, Young B, Jordan RC. Aberrant expression of cyclin A and cyclin B1 proteins in oral carcinoma. J Oral Pathol Med 1999;28 (2):77–81.
131. Chen HM, Kuo MYP, Lin KH, Lin CY, Chiang CP. Expression of cyclin A is related to progression of oral squamous cell carcinoma in Taiwan. Oral Oncol 2003;39 (5):476–82.
132. Hassan KA, El-Naggar AK, Soria JC, Liu D, Hong WK, Mao L. Clinical significance of cyclin B1 protein expression in squamous cell carcinoma of the tongue. Clin Cancer Res 2001;7 (8):2458–62.
133. Shang ZJ, Li ZB, Li JR. VEGF is up-regulated by hypoxic stimulation and related to tumour angiogenesis and severity of disease in oral squamous cell carcinoma: in vitro and in vivo studies. Int J Oral Maxillofac Surg 2006;35 (6):533–8.
134. Li C, Shintani S, Terakado N, Klosek SK, Ishikawa T, Nakashiro K, et al. Microvessel density and expression of vascular endothelial growth factor, basic fibroblast growth factor, and platelet-derived endothelial growth factor in oral squamous cell carcinomas. Int J Oral Maxillofac Surg 2005;34 (5): 559–65.
135. Kishimoto K, Sasaki A, Yoshihama Y, Mese H, Tsukamoto G, Matsumura T. Expression of vascular endothelial growth factor-C predicts regional lymph node metastasis in early oral squamous cell carcinoma. Oral Oncol 2003;39 (4):391–6.
136. Tanigaki Y, Nagashima Y, Kitamura Y, Matsuda H, Mikami Y, Tsukuda M. The expression of vascular endothelial growth factor-A and -C, and receptors 1 and 3: correlation with lymph node metastasis and prognosis in tongue squamous cell carcinoma. Int J Mol Med 2004;14 (3):389–95.

137. Moriyama M, Kumagai S, Kawashiri S, Kojima K, Kakihara K, Yamamoto E. Immunohistochemical study of tumour angiogenesis in oral squamous cell carcinoma. Oral Oncol 1997;33 (5):369–74.
138. Thomas GT, Lewis MP, Speight PM. Matrix metalloproteinases and oral cancer. Oral Oncol 1999;35 (3):227–33.
139. de Vicente JC, Fresno MF, Villalain L, Vega JA, Vallejo GH. Expression and clinical significance of matrix metalloproteinase-2 and matrix metalloproteinase-9 in oral squamous cell carcinoma. Oral Oncol 2005;41 (3):283–93.
140. Patel BP, Shah PM, Rawal UM, Desai AA, Shah SV, Rawal RM, et al. Activation of MMP-2 and MMP-9 in patients with oral squamous cell carcinoma. J Surg Oncol 2005;90 (2):81–8.
141. Vicente de JC, Fresno MF, Villalain L, Vega JA, Arranz JSL. Immunoexpression and prognostic significance of TIMP-1 and -2 in oral squamous cell carcinoma. Oral Oncol 2005;41 (6): 568–579.
142. Pande P, Mathur M, Shukla NK, Ralhan R. pRb and p16 protein alterations in human oral tumorigenesis. Oral Oncol 1998;34 (5):396–403.
143. Sartor M, Steingrimsdottir H, Elamin F, Gäken J, Warnakulasuriya S, Partridge M, et al. Role of p16/MTS1, cyclin D1 and RB in primary oral cancer and oral cancer cell lines. Br J Cancer 1999;80 (1–2):79–86.
144. Reed AL, Califano J, Cairns P, Westra WH, Jones RM, Koch W, et al. High frequency of p16 (CDKN2/MTS-1/INK4A) inactivation in head and neck squamous cell carcinoma. Cancer Res 1996;56 (16):3630–3.
145. Wu CL, Roz L, McKown S, Sloan P, Read AP, Holland S, et al. DNA studies underestimate the major role of CDKN2A inactivation in oral and oropharyngeal squamous cell carcinomas. Genes Chromosomes Cancer 1999;25 (1):16–25.
146. Shintani S, Nakahara Y, Mihara M, Ueyama Y, Matsumura T. Inactivation of the p14(ARF), p15(INK4B) and p16(INK4A) genes is a frequent event in human oral squamous cell carcinomas. Oral Oncol 2001;37 (6):498–504.
147. Weinberger PM, Yu Z, Haty BG, Kowalski D, Harigopal M, Sasaki C, et al. Prognostic significance of p16 protein levels in oropharyngeal squamous cell cancer. Clin Cancer Res 2004;10 (17):5684–91.
148. Gorgoulis VG, Vassiliou LVF, Karakaidos P, Zacharatos P, Kotsinas A, Liloglou T, et al. Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature 2005;434 (7035):907–13.
149. Bartkova J, Horejs Z, Koed K, Krmer A, Tort F, Zieger K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 2005;434 (7035):864–70.
150. Ogden GR, Kiddie RA, Lunny DP, Lane DP. Assessment of p53 protein expression in normal, benign, and malignant oral mucosa. J Pathol 1992;166 (4):389–94.
151. de Vicente JC, Gutiérrez LMJ, Zapatero AH, Forcelledo MFF, Hernández-Vallejo G, Arranz JSL. Prognostic significance of p53 expression in oral squamous cell carcinoma without neck node metastases. Head Neck 2004;26 (1):22–30.
152. Nees M, Homann N, Discher H, Andl T, Enders C, Herold-Mende C, et al. Expression of mutated p53 occurs in tumor-distant epithelia of head and neck cancer patients: a possible molecular basis for the development of multiple tumors. Cancer Res 1993;53 (18):4189–96.
153. Ogden GR, Chisholm DM, Morris AM, Stevenson JH. Overexpression of p53 in normal oral mucosa of oral cancer patients does not necessarily predict further malignant disease. J Pathol 1997;182 (2):180–4.
154. Homann N, Nees M, Conradt C, Dietz A, Weidauer H, Maier H, et al. Overexpression of p53 in tumor-distant epithelia of head and neck cancer patients is associated with an increased incidence of second primary carcinoma. Clin Cancer Res 2001;7 (2):290–6.
155. Xie X, Clausen OP, Angelis PD, Boysen M. The prognostic value of spontaneous apoptosis, Bax, Bcl-2, and p53 in oral squamous cell carcinoma of the tongue. Cancer 1999;86 (6):913–20.
156. González-Moles MA, Galindo P, Gutiérrez-Fernandez J, Sanchez-Fernandez E, Rodriguez-Archilla A, Ruiz-Avila I, et al. P53 protein expression in oral squamous cell carcinoma. survival analysis. Anticancer Res 2001;21 (4B):2889–94.
157. Yamazaki Y, Chiba I, Hirai A, Sugiura C, Notani ichi K, Kashiwazaki H, et al. Specific p53 mutations predict poor prognosis in oral squamous cell carcinoma. Oral Oncol 2003;39 (2):163–9.
158. Shintani S, Mihara M, Nakahara Y, Terakado N, Yoshihama Y, Kiyota A, et al. Apoptosis and p53 are associated with eect of preoperative radiation in oral squamous cell carcinomas. Cancer Lett 2000;154 (1):71–7.
159. Alsner J, Sørensen SB, Overgaard J. TP53 mutation is related to poor prognosis after radiotherapy, but not surgery, in squamous cell carcinoma of the head and neck. Radiother Oncol 2001;59 (2):179–85.
160. Jayasurya R, Francis G, Kannan S, Lekshminarayanan K, Nalinakumari KR, Abraham T, et al. p53, p16 and cyclin D1: molecular determinants of radiotherapy treatment response in oral carcinoma. Int J Cancer 2004;109 (5):710–6.
161. zur Hausen H. Papillomavirus infections—a major cause of human cancers. Biochim Biophys Acta 1996;1288 (2):F55–78.
162. Münger K, Schener M, Huibregtse JM, Howley PM. Interactions of HPV E6 and E7 oncoproteins with tumour suppressor gene products. Cancer Surv 1992;12:197–217.
163. Syrjänen K, Syrjänen S, Lamberg M, Pyrhönen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. Int J Oral Surg 1983;12 (6):418–24.
164. Gassenmaier A, Hornstein OP. Presence of human papillomavirus DNA in benign and precancerous oral leukoplakias and squamous cell carcinomas. Dermatologica 1988;176 (5):224–33.
165. Chatterjee R, Mukhopadhyay D, Chakraborty RN, Mitra RB. Evaluation of argyrophilic nucleolar organizer regions (AgNORs) in oral carcinomas in relation to human papillomavirus infection and cytokinetics. J Oral Pathol Med 1997;26 (7):310–4.
166. Woods KV, Shillitoe EJ, Spitz MR, Schantz SP, Adler-Storthz K. Analysis of human papillomavirus DNA in oral squamous cell carcinomas. J Oral Pathol Med 1993;22 (3):101–8.
167. Matzow T, Boysen M, Kalantari M, Johansson B, Hagmar B. Low detection rate of HPV in oral and laryngeal carcinomas. Acta Oncol 1998;37 (1):73–6.
168. Elamin F, Steingrimsdottir H, Wanakulasuriya S, Johnson N, Tavassoli M. Prevalence of human papillomavirus infection in premalignant and malignant lesions of the oral cavity in UK subjects: a novel method of detection. Oral Oncol 1998;34 (3):191–7.
169. Snijders PJ, Scholes AG, Hart CA, Jones AS, Vaughan ED, Woolgar JA, et al. Prevalence of mucosotropic human papillomaviruses in squamous-cell carcinoma of the head and neck. Int J Cancer 1996;66 (4):464–9.
170. Paz IB, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP. Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. Cancer 1997;79 (3):595–604.
171. Koh JY, Cho NP, Kong G, Lee JD, Yoon K. p53 mutations and human papillomavirus DNA in oral squamous cell carcinoma: correlation with apoptosis. Br J Cancer 1998;78 (3): 354–9.
172. Riethdorf S, Friedrich RE, Ostwald C, Barten M, Gogacz P, Gundlach KK, et al. p53 gene mutations and HPV infection in primary head and neck squamous cell carcinomas do not

correlate with overall survival: a long-term follow-up study. J Oral Pathol Med 1997;26 (7):315—21.
173. Miguel RE, Villa LL, Cordeiro AC, Prado JC, Sobrinho JS, Kowalski LP. Low prevalence of human papillomavirus in a geographic region with a high incidence of head and neck cancer. Am J Surg 1998;176 (5):428—9.
174. Cruz IB, Snijders PJ, Steenbergen RD, Meijer CJ, Snow GB, Walboomers JM, et al. Age-dependence of human papillomavirus DNA presence in oral squamous cell carcinomas. Eur J Cancer B Oral Oncol 1996;32B (1):55—62.
175. Bouda M, Gorgoulis VG, Kastrinakis NG, Giannoudis A, Tsoli E, Danassi-Afentaki D, et al. ''High risk'' HPV types are frequently detected in potentially malignant and malignant oral lesions, but not in normal oral mucosa. Mod Pathol 2000;13 (6):644—53.
176. Nielsen H, Norrild B, Vedtofte P, Praetorius F, Reibel J, Holmstrup P. Human papillomavirus in oral premalignant lesions. Eur J Cancer B Oral Oncol 1996;32B (4):264—70.
177. D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR. Detection of HPV-16 genome in human oral cancers and potentially malignant lesions from India. Oral Oncol 1998;34 (5):413—20.
178. Fouret P, Martin F, Flahault A, Saint-Guily JL. Human papillomavirus infection in the malignant and premalignant head and neck epithelium. Diagn Mol Pathol 1995;4 (2): 122—7.
179. Sexton CJ, Proby CM, Banks L, Stables JN, Powell K, Navsaria H, et al. Characterization of factors involved in human papillomavirus type 16-mediated immortalization of oral keratinocytes. J Gen Virol 1993;74 (Pt 4):755—61.
180. Oda D, Bigler L, Lee P, Blanton R. HPV immortalization of human oral epithelial cells: a model for carcinogenesis. Exp Cell Res 1996;226 (1):164—9.
181. Oda D, Bigler L, Mao EJ, Disteche CM. Chromosomal abnormalities in HPV-16-immortalized oral epithelial cells. Carcinogenesis 1996;17 (9):2003—8.
182. Anand P, Foley P, Navsaria HA, Sinicropi D, Williams-Chestnut RE, Leigh IM. Nerve growth factor levels in cultured human skin cells: eect of gestation and viral transformation. Neurosci Lett 1995;184 (3):157—60.
183. Bryan D, Sexton CJ, Williams D, Leigh IM, McKay IA. Oral keratinocytes immortalized with the early region of human papillomavirus type 16 show elevated expression of interleukin 6, which acts as an autocrine growth factor for the derived T103C cell line. Cell Growth Dier 1995;6 (10):1245—50.
184. Li SL, Kim MS, Cherrick HM, Doniger J, Park NH. Sequential combined tumorigenic eect of HPV-16 and chemical carcinogens. Carcinogenesis 1992;13 (11):1981—7.
185. Park NH, Gujuluva CN, Baek JH, Cherrick HM, Shin KH, Min BM. Combined oral carcinogenicity of HPV-16 and benzo(*a*)pyrene: an in vitro multistep carcinogenesis model. Oncogene 1995;10 (11):2145—53.
186. Itakura M, Mori S, Park NH, Bonavida B. Both HPV and carcinogen contribute to the development of resistance to apoptosis during oral carcinogenesis. Int J Oncol 2000;16 (3):591—7.
187. Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med 2001;344 (15):1125—31.
188. Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 2003;95 (23):1772—83.
189. Ringström E, Peters E, Hasegawa M, Posner M, Liu M, Kelsey KT. Human papillomavirus type 16 and squamous cell carcinoma of the head and neck. Clin Cancer Res 2002;8 (10):3187—92.
190. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained ecacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367 (9518):1247—55.
191. Maeda H, Kubo K, Sugita Y, Miyamoto Y, Komatsu S, Takeuchi S, et al. DNA vaccine against hamster oral papillomavirus-associated oral cancer. J Int Med Res 2005;33 (6):647—53.
192. Sand LP, Jalouli J, Larsson PA, Hirsch JM. Prevalence of Epstein-Barr virus in oral squamous cell carcinoma, oral lichen planus, and normal oral mucosa. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93 (5):586—92.
193. González-Moles M, Gutiérrez J, Ruiz I, Fernández JA, Rodriguez M, Aneiros J. Epstein-Barr virus and oral squamous cell carcinoma in patients without HIV infection: viral detection by polymerase chain reaction. Microbios 1998;96 (383):23—31.
194. González-Moles MA, Gutiérrez J, Rodriguez MJ, Ruiz-Avila I, Rodriguez-Archilla A. Epstein-Barr virus latent membrane protein-1 (LMP-1) expression in oral squamous cell carcinoma. Laryngoscope 2002;112 (3):482—7.
195. Mao EJ, Smith CJ. Detection of Epstein-Barr virus (EBV) DNA by the polymerase chain reaction (PCR) in oral smears from healthy individuals and patients with squamous cell carcinoma. J Oral Pathol Med 1993;22 (1):12—7.
196. Cruz I, Brule AJVD, Brink AA, Snijders PJ, Walboomers JM, Waal IVD, et al. No direct role for Epstein-Barr virus in oral carcinogenesis: a study at the DNA, RNA and protein levels. Int J Cancer 2000;86 (3):356—61.
197. Iamaroon A, Khemaleelakul U, Pongsiriwet S, Pintong J. Co-expression of p53 and Ki67 and lack of EBV expression in oral squamous cell carcinoma. J Oral Pathol Med 2004;33 (1):30—6.
198. Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T. High prevalence of hepatitis C virus antibody and RNA in patients with oral cancer. J Oral Pathol Med 1995;24 (8): 354—60.
199. Porter SR, Lodi G, Chandler K, Kumar N. Development of squamous cell carcinoma in hepatitis C virus-associated lichen planus. Oral Oncol 1997;33 (1):58—9.
200. Carrozzo M, Gandolfo S, Carbone M, Colombatto P, Broccoletti R, Garzino-Demo P, et al. Hepatitis C virus infection in Italian patients with oral lichen planus: a prospective case-control study. J Oral Pathol Med 1996;25 (10):527—33.
201. Muzio LL, Mignogna MD, Favia G, Procaccini M, Testa NF, Bucci E. The possible association between oral lichen planus and oral squamous cell carcinoma: a clinical evaluation on 14 cases and a review of the literature. Oral Oncol 1998;34 (4):239—46.
202. Nagao Y, Sata M, Noguchi S, Seno'o T, Kinoshita M, Kameyama T, et al. Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. J Oral Pathol Med 2000;29 (6):259—66.
203. Carrozzo M, Quadri R, Latorre P, Pentenero M, Paganin S, Bertolusso G, et al. Molecular evidence that the hepatitis C virus replicates in the oral mucosa. J Hepatol 2002;37 (3):364—9.