



Review

Oral precancer and cancer[☆]José López-López^a, Carlos Omaña-Cepeda^b, Enric Jané-Salas^{a,*}^a Departamento de Odontología, Facultad de Odontología, Universidad de Barcelona, l'Hospitalet de Llobregat, Barcelona, Spain^b Máster de Odontología en Pacientes Oncológicos e Inmunocomprometidos, Facultad de Odontología, Universidad de Barcelona, l'Hospitalet de Llobregat, Barcelona, Spain

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ABSTRACT

We reviewed the concept of oral precancerous lesions, oral cancer, and the possibility of early diagnosis. With the keywords: *pre-malignant oral lesions prevention*, a search was performed over the past 10 years. Also clinical trials are searched from January 2011 until today with the keywords: *oral cancer prevention AND dentistry*. It is emphasized that there can be no significant changes related to the concept of precancerous lesions and cancer, and those relating to the early diagnosis. Despite the numerous described methods of screening, biopsy remains the most useful test, and therefore it is essential, mainly if we consider the new possibilities of molecular studies.

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RESUMEN

Se revisa el concepto de lesiones precancerosas orales, de cáncer oral y su diagnóstico precoz. Con las palabras clave: *pre-malignant oral lesions prevention* se realiza una búsqueda de los 10 últimos años. También se buscan los ensayos clínicos desde enero de 2011 hasta la actualidad con las palabras clave: *oral cancer prevention AND dentistry*. Se destaca que no hay cambios significativos relacionados con el concepto de lesión precancerosa y cáncer, y que en cuanto al diagnóstico precoz, si bien se describen numerosos métodos de cribado, la biopsia sigue siendo la prueba más útil y, por tanto, imprescindible, más aún si consideramos las nuevas posibilidades de estudios moleculares.

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Introduction

Head and neck cancer accounts for 5% of all neoplasms of the body and 2% of oral cavity.¹ Overall mortality at 5 years is 50%, hence the importance of early diagnosis. It is relevant the increased prevalence in individuals aged under 40 years.² The oral health professionals are responsible for the early diagnosis of lesions that can become malignant and oral cancer in its earliest stages. There are several etiologic factors involved: tobacco (smoked or chewed), drinking, diet, immunosuppression, viruses such as human papil-

lomavirus (HPV), the presence of premalignant lesions and, in discussion for some authors, local trauma factors.³ Since 1978 WHO has defined injuries and premalignant oral conditions.⁴ Precancerous lesion is a morphological abnormality of tissue where oral cancer risk is higher. Precancerous condition is a systemic condition associated with increased oral cancer risk. This terminology is under review, and in 2007, Warnakulasuriya et al.⁵ introduced the name of potentially malignant lesions, which despite not having complete consensus, is prevailing over the former classification. These authors define them as potentially malignant lesions (lesions at risk of developing malignant tumors at higher rates than normal adjacent tissue).⁵

In this paper we review the literature on these entities and their diagnosis, in order to highlight the role of healthcare in their recognition and early diagnosis. To this purpose we have looked up the following keywords in PubMed: *pre-malignant oral lesions preven-*

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tion. Clinical trials have also been searched from January 2011 to date with the following keywords: *oral cancer prevention AND dentistry*.

Discussion

Of the 373 papers found, 139 in the last 10 years, 61 have been discarded when reading the title, 2 because they are related to HIV-AIDS and one for being a paper on angiogenesis inhibitory activity of thalidomide in an animal model in 70 hamsters. Nine of the remaining papers are on other entities, 17 are personal opinions or related to specific features of oral cancer, 39 of them are reviews (8 systematic reviews), one is a meta-analysis, and the other a controlled clinical trial in humans. Other 2 clinical trials of previous years were reviewed, both of 1998 and belonging to the group of the University of Helsinki.^{6,7} One of the 12 recent controlled clinical trials found is consistent with the previous search.⁶ Six of the remaining 11, after having read the full text are on the cancer treatment previously provided.^{6–11} One paper stresses the importance of lugol’s iodine staining in evaluating stages I and II of tongue cancer. Atalay et al. analyzed the potential usefulness of bisphosphonates,¹³ Pai and Prasad studied the effects of smoking on the levels of carbon monoxide,¹⁴ Lopes et al. studied whether or not antibiotic prophylaxis is convenient,¹⁵ and only one is a clinical trial.¹⁶ It is a work in Saudi Arabia that analyzes the knowledge that students, dental assistants, general practitioners and specialists have on precancer. The authors¹⁶ concluded that from 41.2 to 63.4% are competent to conduct a proper examination of the oral cavity and palpate the lymph nodes. Competence increases with the higher level of education, experience and access to continuing education studies. 82% are in favor of suspicious lesions. Uti and Fashina,¹⁷ in the first search, stress on this very same issue. In this paper the authors discuss about the poor knowledge on precancerous lesions by the odontology students of the School of Medicine, University of Lagos, Nigeria. We should also highlight a paper on chemotherapy,¹⁸ one on Intensity Modulated Radiation Therapy,¹⁹ one on cryotherapy²⁰ and another one on dental restoration techniques.²¹

We consider three aspects to analyze the most relevant data: oral precancer, oral cancer and methods for early diagnosis of oral cancer.

Precancer

In addition to the exogenous factors that can stimulate dysplastic transformation, there is a number of endogenous factors involved: the various potentially malignant lesions (Table 1). Among them we will review leukoplakia, erythroplasia and lichen planus (LP).⁵

Leukoplakia

Leukoplakia is the most frequent precancerous lesion of the oral mucosa; it is defined as a predominantly white lesion, which cannot be detached by scraping and clinically and histologically does not

Table 1
Potentially malignant lesions in the oral cavity.

Leukoplakia
Erythroplasia
Palatal lesions in reverse smokers
Oral submucous fibrosis
Actinic keratosis
Lichen planus
Discoid lupus erythematosus

Source: Warnakulasuriya et al.⁵

Table 2
Clinical classification of leukoplakia based on the criteria provided by the Conference of Uppsala.

Classification: appearance
<i>Homogeneous</i>
Injury predominantly white, uniform, firm, thin, smooth or wrinkled surface, which sometimes has shallow grooves
<i>Nonhomogeneous</i>
Injury, predominantly white, which can alternate with other red areas and/or irregular, nodular or exophytic surface
Erythroleukoplakia: mixed white and red areas
Nodular leukoplakia: red and/or white rounded excrescences
Exophytic leukoplakia: formerly called warty. Grows in volume outwardly with rounded or pointed projections
Classification: etiology
<i>True leukoplakia.</i> No associated factors other than smoking
<i>Idiopathic leukoplakia.</i> No associated factors
<i>Secondary leukoplakia.</i> A causal factor is detected

Source: Axéll et al.²⁵

belong to any other entity.⁴ Since the criteria provided in 2002,²² a provisional diagnosis is suggested, then the potential etiologic factors are removed for 2–4 weeks (not enough time if the etiology is smoking) and, if it does not disappear, confirm histologically. Today, a lower incidence than a few years ago is accepted. Thus, the paper by Scheifele et al.²³ in 16,128 individuals, reports a prevalence of 0.66% in men and 0.21% for women. The most frequent sites were the buccal mucosa and tongue. The study conducted in 1586 Brazilian subjects by Carrard et al.²⁴ also reports low percentages for leukoplakia (1.01%) and LP (1.02%), highlighting the potential relationship with some viruses. We should recall that from a clinical point of view the classification used is the provided by the Conference of Uppsala 1994²⁵ (Table 2). If we focus on the possible malignancy, Pindborg in 1968,²⁶ reports figures ranging from 0.1 to 17%. However, Scheifele et al., in 2003,²³ suggested that the annual malignant transformation was under 1%, being of most risk the lesions on the floor of the mouth, the nonhomogeneous lesions, dysplasias and those with certain molecular markers (particularly the p53, Loss of heterozygosity, DNA content and classification of nucleolar organizer regions related to Ag “AgNOR”). As for the treatment, to remove, if any, the etiological factors, and perform tumor excision is recommended, if possible. Drug therapies have been tested with vitamin A, calcipotriol, retinoic acid, beta carotene, bleomycin, curcumin, etc., with inconclusive results.^{26,27}

Erythroplasia

Erythroplasia and its most common mixed form, the erythroleukoplakia, fall within the concept of red lesions of the oral cavity, and as such deserve special diagnosis, because sometimes we are facing a carcinoma in situ. These lesions should always be biopsied, and some authors recommend the biopsy to be performed in the department of head and neck surgical oncology surgery, since the result is usually malignancy. In its pathogenesis etiologic agents in common with leukoplakia are suggested.²⁸ Clinically it is generally an asymptomatic red spot, which cannot be diagnosed as any other definable injury.²⁵ Usually located in the soft palate, floor of the mouth and buccal mucosa. The male/female ratio is 1:1 and it is more frequent in Asian patients.²⁸ Malignancy rate is higher compared to leukoplakia.²⁹ Reichart and Philipson,²⁸ for example, reported that in the homogeneous forms, 51% are invasive carcinomas, 41% carcinoma in situ, and the remaining 9% are mild or moderate dysplasia. The factor enhancing the evolution to malignancy is unknown, but chronic infection by *Candida albicans* or by HPV have been considered, among others.^{28,30} Their treatment is surgical excision and full histopathology study, but there are some promising papers with photodynamic therapy, both for this entity

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