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THE PREVALENCE OF PRECANCEROUS LESIONS IN PRIMARY DENTAL HEALTH CARE

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Abstract

Benign and premalignant states of the oral cavity related to impairments of epithelial keratinization are classified as oral precancerous lesions, and can be hereditary, reactive, immunologic, infectious, idiopathic, or neoplastic. Epidemiologic studies conducted worldwide have identified the following types of oral precancerous lesions to be priorities according to their prevalence and clinical implications: leukoplakia, erythroplakia, oral lichen, actinic cheilitis, candidal leukoplakia, papillomatous lesions, tertiary syphilis, and oral submucous fibrosis. Five of these eight clinical entities, i.e. leukoplakia, erythroplakia, oral lichen, actinic cheilitis and candidal leukoplakia, and their importance in the prevention of oral carcinoma are discussed in detail. General practitioner and polyvalent practicing dental medicine doctor have a major role in the early diagnosis of neoplasms in the head, neck and oral cavity region. Early diagnosis is associated with better treatment options and lower probability of visible mutilations. The occurrence of oral precancerous lesions is influenced by the following factors: cigarette smoking and alcohol abuse, showing positive correlation with both the amount and duration of particular habit; exposure to detrimental factors (occupational and environmental) and radiation (sunlight and ionizing); uncontrolled medication; viruses; and inappropriate dietary habits. Successful prevention of oral precancerous lesions requires regular visits to dentist office, elimination of harmful habits, and healthy lifestyle. In case of clinical manifestation of an oral precancerous lesion, dental doctor should reach an accurate diagnosis by use of laboratory tests and not infrequently biopsy finding, i.e. clinical diagnosis should be verified or ruled out by pathohistology. Therapy and regular control visits are prescribed according to the diagnosis.

Key words: *oral cavity, precancerous lesions, diagnosis, prevention, dental practice*

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Introduction

Precancerous lesions are pathologic processes that tend to transform to malignancy (1). In general pathology, precancerous lesions are classified as neoplasms, which can be benign, premalignant, or malignant. Benign and premalignant states of oral mucosa that are related to impairments of epithelial keratinization are classified as oral precancerous lesions and are divided into the following types:

- hereditary – white sponge nevus, leukoedema
- reactive – orthokeratosis, parakeratosis, acanthosis, dyskeratosis (mechanical, chemical, thermal, radiation and microbial lesions)
- immunologic – oral lichen, lupus erythematosus (systemic and discoid)
- infectious – keratotic candidiasis, hairy leukoplakia, syphilitic leukoplakia
- idiopathic – lingua villosa, lingua geographica
- neoplastic – epithelial dysplasia (dyskeratosis), carcinomas (*in situ*, squamous cell, verrucous)

Oral precancers include precancerous lesions and precancerous states. Precancerous lesions are erythroplakia, leukoplakia, oral lichen, actinic cheilitis and keratotic candidiasis. Precancerous states are morsicatio buccarum, palatitis nicotinica, discoid lupus erythematosus, white sponge nevus, submucous fibrosis, Plummer-Vinson syndrome, glossitis luetica and xeroderma pigmentosum.

International epidemiologic studies (2) have pointed to the following entities as priorities according to their prevalence and clinical implications of oral precancerous lesions:

- leukoplakia
- erythroplakia
- oral lichen
- actinic cheilitis
- keratotis candidiasis
- papillomatous lesions
- tertiary syphilis
- oral submucous fibrosis

Of these eight clinical entities, the clinical significance of the following oral precancerous lesions in the prevention of oral carcinoma will be discussed in more detail: leukoplakia, erythroplakia, oral lichen, actinic cheilitis and keratotic candidiasis. A general practitioner and polyvalent practicing dental doctor play a major role in the early diagnosis of neoplasms in the head, neck and oral cavity region. Early diagnosis is associated with more favorable treatment prognosis and

lower rate of mutilating interventions in the most visible part of the body.

The occurrence of oral precancerous lesions is associated with cigarette smoking and alcohol abuse (positive correlation with both the amount and duration of these habits), exposure to detrimental noxae (occupational and environmental), radiation (sunlight and ionizing), uncontrolled drug intake, viruses, and inappropriate dietary habits. Dental prevention of oral precancerous lesions includes regular visits to dental office, giving up harmful habits, and healthy lifestyle.

When a patient presents with an oral precancerous lesion, dental doctor should reach an accurate diagnosis by use of laboratory tests and quite frequently biopsy finding for the clinical diagnosis to be confirmed or excluded by pathohistology. The diagnosis will dictate the choice of therapy and regular control visits.

In Europe, health institutions have developed a program of prevention with a motto 'Europe Against Cancer'.

In this paper, literature data and results of our own studies of oral precancerous lesions are presented.

Epidemiologic data

In the USA, the distribution of oral carcinoma in 14253 patients according to the involvement of oral mucosa, i.e. the seat of carcinoma, was as follows: lower lip 38%, tongue 22%, base of the mouth 17%, gingiva 6%, palate 5.5%, tonsils 5%, upper lip 4%, buccal mucosa 2%, and uvula 0.5% (3). In Croatia, the incidence of oral carcinoma in 583 patients in 1999 according to the seat of carcinoma was as follows: tongue 187 (32%), lip 122 (21%), salivary glands 102 (17.5%), base of the mouth 44 (7.6%), and other seats in the oral cavity 94 (16%). The male to female ratio was 441 *vs.* 142 (76% *vs.* 24%) cases (4). In Bosnia & Herzegovina (B&H), there were 6722 patients with malignant neoplasms, and 2986 deaths from malignant neoplasms in 2000 (5). Comparison of the causes of death in B&H and Croatia revealed circulatory system diseases to be the leading cause with 53% in B&H and 52% in Croatia, followed by neoplasms with 17.4% and 22%, respectively (6,7), indicating that about 70% of deaths in B&H were due to circulatory system diseases and neoplasms.

Leukoplakia and erythroplakia

Pindborg *et al.* (8) define leukoplakia as a white lesion of oral mucosa which has no characteristic of any other type of lesion. Leukoplakia is a hyperkeratosis which can be homogeneous or inhomogeneous according to its clinical appearance. Inhomogeneous

leukoplakia is characterized by the occurrence of red and white areas that may be atrophic, nodular, verrucous, or ulcerative (erythroplakia). On differential diagnosis, leukoplakia should be differentiated from friction keratosis, wind keratosis, bite keratosis, chemical mucosal lesions, leukoedema, white sponge nevus, oral lichen, hairy leukoplakia, and pseudomembranous candidiasis.

The prevalence of leukoplakia in the general population of Europe is from 0.9% in Germany to 3.6% in Sweden, 2.9% in the USA, and from 0.7% to 11.7% in India (9). In the epidemiologic study performed in a representative sample of 5552 subjects from B&H, there were 110 (1.8%) subjects with leukoplakia (10). During the 1996 – 2001 period, 6668 new patients were recorded at the Department of Oral Medicine, Zagreb University School of Dental Medicine, 56 of them with leukoplakia. The incidence of leukoplakia among the newly recorded patients was 0.84% (11).

Among 7820 subjects examined in Budapest, mean age 57.1 years, there were 104 (1.33%) subjects with leukoplakia. The percentage of cigarette smokers in the groups of subjects with and without leukoplakia was 86.5% and 29.0%, respectively (12). A study conducted in Nairobi indicated the relative risk of leukoplakia to be 14.7% and 6.7% in those smoking >10 and <10 cigarettes daily, respectively. In those who had been smoking for less than 10 years the incidence of leukoplakia was 7.4% *vs.* 10.8% in those with a >30-year history of smoking (13).

The diagnosis of leukoplakia is made on the basis of personal history (cigarette smoking, alcohol consumption), inspection, palpation, and biopsy finding. Differentiation between benign and malignant leukoplakia cannot be made on the basis of the clinical picture alone but also requires biopsy finding. Pathohistologic diagnosis of leukoplakia is characterized by the basal layer finding, which includes loss of cell polarity, hyperplasia, increased nucleus to cytoplasm ratio, increased number of mitoses, atypical mitoses, irregular epithelial stratification, mitoses in the upper epithelial layers, cellular and nuclear polymorphism, nuclear hyperchromatism, nuclear enlargement, loss of intercellular adhesion, and keratinization in the spinous layer.

Oral lichen rubber

Lichen ruber is a noninfectious, inflammatory disease of the skin and mucosa, characterized by T lymphocyte destruction of the epithelial basal layer. Lichen is classified in the group of chronic mucocutaneous autoimmune diseases of as yet obscure etiology. Genetic predisposition (HLA-DR9), drugs, dental material, chronic diseases of the hepatobiliary system, diabetes mellitus, intestinal

diseases (Crohn's disease) and psychogenic factors have been most commonly reported as factors contributing to the genesis of lichen ruber. Concerning the basic pathogenetic mechanism with unknown antigen, the antigenic structure of epithelial cell is modified. Thus, the autoimmune reaction is triggered, failing to recognize native antigens as its own and leading to epithelial destruction.

Clinically, the disease presents with morphologically diverse manifestations. The basic classification of the various clinical forms is based on the occurrence of efflorescences at various levels of mucosal surface and includes lichen ruber planus, lichen ruber bullosus, and lichen ruber erosivus with the following subtypes: papular, reticular, annular, atrophic, bullous, erosive and ulcerative. Clinical diagnosis should be verified by biopsy, i.e. pathohistologic finding showing hyperkeratosis, acanthosis, epithelium of dentate appearance, liquefaction degeneration of the basal layer, and subepithelial inflammatory cellular infiltrate.

The prevalence of the disease in the general population ranges from 0.5% to 2.5% (14). Its onset usually occurs at 40 to 60 years of age, and shows a 2:1 male to female ratio (15). During a 10-year period (1990-1999), the diagnosis of oral lichen was made in 343 (3.92%) of 8751 patients at the Department of Oral Medicine, Zagreb University School of Dental Medicine. Thus, every 25th patient had oral lichen (16).

The rate of malignant transformation of oral lichen ruber differs among various authors, ranging from 0.4% (17) to 3.3% (18). The number of oral lichen ruber patients in pooled data reported by 11 researchers from different countries ranges from 214 to 2071. During the period of observation that ranged from 2 to 10 years, malignant transformation occurred in 59 (0.9%) of a total of 6529 patients with the diagnosis of oral lichen ruber (19). Patients with a clinical diagnosis of erosive oral lichen ruber showed malignant transformation of the epithelium.

Actinic cheilitis

Actinic cheilitis is labial (more commonly lower lip) alteration due to chronic sun exposure. Ultraviolet (UV) rays of the sunlight spectrum lead to cellular destruction in the labial epithelium and connective tissue. Collagenous and elastic fibrils of the connective tissue are destroyed, resulting in the microscopic appearance known as basophilic degeneration. Longterm continuous sun exposure (20-30 years) is needed for the dysplastic lesion to occur (20). Fair-complexion subjects are at a greater risk of actinic cheilitis than those dark-colored. Individuals aged >60 spending most of the time outdoors for sports or

work (farmers, bricklayers/stonemasons, fishermen, sailors, hunters, mountaineers, skiers, oarsmen, etc.) are usually affected.

Actinic cheilitis shows a male predominance. In women, lipstick is a major protective factor. Smoking, and especially pipe smoking, is a predisposing factor for the development of actinic cheilitis (21,22).

Lower lip mucosa in the region of vermilion is thin, atrophic, homogeneous, with milky-white, smooth, irregular or dentate patches with sharply delineated peripheral margin. Macular pigmentation with scaling may be seen on perioral skin surface. Suspicion of malignant alteration is raised by color heterogeneity, rough thickening, absence of sharp margins, and presence of erosions/ulcerations that would not heal (23). Some 10% of cases of actinic cheilitis show malignant transformation to squamous cell carcinoma (24,25).

Keratotic candidiasis

Keratotic candidiasis or candidal leukoplakia is a unique clinical picture of chronic hyperplastic candidiasis among other forms of oral candidiasis. It is a white plaque-like lesion that can be scraped off. The lesion is well demarcated, white with occasional red patches, thickened or verrucous, mostly localized on the anterior part of buccal mucosa or palate. Clinically, it resembles leukoplakia, whereas histologic finding shows epithelial atypia, especially if biopsy specimen has been obtained from the erythematous area of the lesion.

It is a controversial issue whether the dysplastic alteration in chronic hyperplastic candidiasis is caused by colonization, candidal infection and penetration to the pre-existing plaque-like leukoplastic lesion, or leukoplakia has been induced by Candida. Experimental hyperkeratotic lesion can be reproduced on the dorsal side of mouse tongue if inoculated with *Candida albicans*. *Candida albicans* is known to produce nitrosamine, a carcinogen (26). Nitrosamine is a chemical mitogen. Metabolic activation of nitrosamine proceeds *via* P-450 cytochrome, whereby a potent methylating mutagen, methyldiazohydroxide, is released. In some nitrosamines, potent alkylating intermediaries can be produced. The mutagenic action of nitrosamine manifests by the generation of bonds between DNA molecules and alkylating and methylating metabolites of the compound (27).

In some patients, squamous cell carcinoma developed from candidal leukoplakia in the absence of other risk factors (26).

In dental casuistics, oral mucosa candidiasis is more common than leukoplakia. In each case of leukoplakia, dental doctor should determine the possible presence of Candida as a pathogenic microorganism in the patient's oral cavity.

Discussion

Oral precancerous lesions are pathologic processes that frequently progress to carcinoma. According to a medical axiom, diseases have their causes. If the cause can be eliminated, the disease can be prevented. However, this simple logic does not hold for cancer. Cancer is not a disease that could be ascribed exclusively to one factor but is ultimate result of consecutive or simultaneous activity of a number of factors connected in the causative network. Different factors contribute to the genesis of cancer. Extrinsic factors are smoking habit, alcohol consumption, and UV rays, and intrinsic factors are systemic conditions such as fatigue, malnutrition, sideropenic anemia (Plummer-Vinson syndrome), HIV infection, prior antibiotic therapy, syphilis (glossitis luetica, tertiary stage). Of all these, smoking habit and alcohol abuse require special attention.

There is a significant association between smoking habit and oral carcinoma. The risk of oral carcinoma is proportional to the frequency and duration of smoking habit. The proportion of smokers is on a fast decrease thanks to large-scale health education, ban on cigarette advertising (except at car races), and high tobacco tax rates. However, those who continue smoking do it at a higher rate and with greater passion, so there is no decrease in the rate of oral carcinoma in the general population, although data on oral carcinoma in smokers show 3- to 5-fold figures found in nonsmokers. The more so, alcohol consumption enhances the effect of smoking on the occurrence of oral carcinoma. Studies of the effect of alcohol and its interaction with smoking are hampered, because it is quite difficult to recruit adequate number of subjects in particular groups (e.g., alcoholics non-smokers). According to some literature data, the prevalence of oral carcinoma in heavy smokers and alcohol users is 35-fold that recorded among those neither using alcohol nor smoking.

Ethanol is not carcinogenic in experimental animals, thus it is difficult to explain exactly how alcohol drinks increase the risk of carcinoma. The clue may be some dietary deficiency accompanying longterm alcohol abuse, or contamination (e.g., nitrosamines), or maybe greater mucosal permeability for other carcinogens. The hypothesis of local action appears to be supported by data on the use of oral alcohol containing mouthwash solutions that increase the risk of oral carcinoma (28). The systemic effect of alcohol in the development of liver cirrhosis is crucial. Alcohol consumption and cigarette smoking have a synergistic, cumulative action, resulting in several-fold increase in the incidence of oral carcinoma.

Almost all precancerous lesions and oral malignancies localized on soft tissues of the oral cavity can be detected by properly taken

history, thorough inspection and palpation. Inspection of the oral cavity is a precondition for detection of a risky lesion in its initial stage. Among oral malignancies, oral squamous cell carcinoma is most common. It is for months or even years preceded by the presence of whitish (leukoplakia) and/or reddish (erythroplakia) discoloration known as precancerous lesion. Oral malignancies increase with age, in individuals aged >40. Besides inspection of oral mucosa, palpation with rubber gloved hands is of utmost importance. Resistance to palpation with induration of the lesion area should be a signal to the clinician suggesting a potential malignancy.

The prognosis of patients with oral carcinoma greatly depends on the primary tumor size. Small lesions without metastases have a high percentage of >5-year survival in treated patients. Therefore, early clinical diagnosis when the tumor is still small and free from metastases is crucial for successful therapeutic outcome.

Dental doctors have a major role in the prevention of oral carcinoma by reaching an accurate diagnosis and differential diagnosis of oral precancerous lesions. In suspect cases, biopsy is required to confirm or rule out the diagnosis of precancerous lesion. May some dilemma arise on pathohistologic diagnosis, the methods of immunohistochemistry, immunofluorescence, immunoprecipitation and molecular pathology (polymerase chain reaction, *in situ* hybridization) should be employed.

Biopsy is required in relatively small chronic ulcerative lesions caused by mechanical irritation, if they fail to heal within some 20 days from the cause elimination.

The opinion about the method of treatment of oral carcinoma differs among different centers of head and neck oncology. Some centers primarily perform surgical therapy followed by postoperative radiotherapy (Zagreb), whereas in other institutions radiotherapy is considered the method of choice (Ljubljana). In Sarajevo, a selective approach is used.

Conclusions

1. Benign and premalignant states of oral cavity that are related to impairments of epithelial keratinization are classified as precancerous lesions, and can be hereditary, reactive, immunologic, infectious, idiopathic, or neoplastic.
2. Oral precancers include precancerous lesions and precancerous states (potential precancerous lesions).
   a) Precancerous lesions include erythroplakia, leukoplakia, oral lichen, actinic cheilitis, and candidal leukoplakia.

b) Precancerous states include leukokeratosis palatina nicotinica, morsicatio buccarum, discoid lupus erythematosus, white sponge nevus, submucous fibrosis, Plummer-Vinson syndrome, glossitis luetica, and xeroderma pigmentosum.

3. Precancerous lesions also include paraneoplastic mouth syndromes, which represent the existence of some oral diseases that are in some way associated with neoplastic processes elsewhere in the body.
4. Smoking habit and alcohol consumption have a synergistic, cumulative effect that results in several-fold increase in the risk of oral precancerous lesions and their transformation to oral carcinoma.
5. Dental doctors have a major role in the prevention, diagnosis and therapy of oral precancerous lesions as well as in the diagnosis of oral mucosa carcinoma.

Apstrakt

Udio oralnih prekanceroza u stomatološkoj praksi primarne zdravstvene zaštite

Benigna i premaligna stanja usne šupljine koja su vezana za poremećaje keratinizacije epitela pripadaju oralnim prekancerozama. Oni mogu biti: hereditarni, reaktivni, imunološki, infekcijski, idiopatski i neoplazmatski. Prema svjetskim epidemiološkim istraživanjima, po učestalosti i kliničkom značenju oralnih prekanceroza, važnim za stomatološku praksu prioritetnu listu čine: leukoplakija, eritroplakija, oralni lihen, aktinički heilitis, kandidialna leukoplakija, papilomatozne lezije, tercijarni sifilis i oralna submukozna fibroza. Od navedenih osam kliničkih entiteta, detaljno se raspravlja o pet i to: leukoplakiji, eritroplakiji, oralnom lihenu, aktiničkom heilitisu i kandidialnoj leukoplakiji kao i o njihovom značenju u prevenciji oralnog karcinoma. Liječnik opće prakse i stomatolog polivalentne prakse imaju najznačajniji udio u ranoj dijagnostici neoplazmi u području glave, vrata i usne šupljine. Rana dijagnoza daje veće šanse za liječenje i manje šanse za mutilacijama vidljivog dijela tijela. Na nastanak oralnih prekanceroza značajno utiču pušenje i konzumiranje alkohola, kako količinski tako i vremenski; zatim izlaganje štetnim faktorima (profesionalnim i okoliša), zračenja (sunčana i jonizirajuća), nekontrolirana upotreba lijekova, virusi, i neadekvatna prehrana. Prevencija oralnih prekanceroza traži redovite posjete ordinaciji liječnika – stomatologa, eliminaciji štetnih navika i življenju zdravih stilova života. Kada se klinički manifestira u ustima neka od prekanceroza stomatolog bi morao imati točnu dijagnozu koristeći laboratorijske nalaze, vrlo često i biopsiju odnosno patohistološkom dijagnozom potvrditi ili isključiti postavljenu kliničku dijagnozu. Prema dijagnozi provodi se terapija i redoviti kontrolni pregledi.

Ključne riječi: *usna šupljina, prekanceroze, dijagnoza, prevencija, stomatološka praksa.*

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