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# Oral epithelial dysplasia in non-users of tobacco and alcohol: an analysis of clinicopathologic characteristics and treatment outcome

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**Abstract: Oral epithelial dysplasia (OED) is a histopathological diagnosis that is associated with an increased risk of oral cancer. The purpose of this study was to compare the clinical features and long-term outcome of OED between users and non-users of tobacco and alcohol. The hospital records of 456 patients diagnosed as having OED were reviewed. Two groups of patients were selected based upon tobacco and alcohol usage: 37 patients who had neither smoked tobacco nor drank alcohol and 419 patients who both smoked tobacco and drank alcohol. OED in non-users of tobacco and alcohol was uncommon, accounting for only 8.1% of all OED. There was a male to female ratio of 1:1 in the group. The tongue and buccal mucosa were the most commonly affected sites. An erythro-leukoplakic-type lesion with mild dysplasia was the common presenting feature. Mixed type lesions with severe dysplastic changes, particularly of the gingiva, may progress to malignancy. These findings support the notion that OED may also develop in persons who have never used tobacco or alcohol. Lesions more commonly occurred in women, especially in the tongue and buccal mucosa, and were mostly of the erythroplakic type. The presence of OED in patients who do not smoke tobacco or drink alcohol suggests that risk factors other than alcohol and tobacco may exist. (J Oral Sci 52, 13-21, 2010)**

Keywords: alcohol; epithelial dysplasia; oral, tobacco.

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## Introduction

Oral epithelial dysplasia (OED) is a histopathological diagnosis that is associated with an increased risk of oral cancer. The roles of tobacco and alcohol as the two major risk factors of oral squamous cell carcinoma (SCC) (1-2) have been well documented; however, there are limited studies on the role of tobacco smoking and alcohol drinking as risk factors for OED (3-6). These substances are independent risk factors but exert a synergistic effect when combined (5-6). Individuals who smoke more than 20 cigarettes a day and consume more than 100 g of alcohol a day have an increased risk of developing OED. The risk of OED declined following smoking cessation, with ex-smokers of 10 or more years demonstrating no excess risk relative to non-smokers. In non-smokers, consumption of alcohol is not a significant predictor of OED (5). There is, however, a small population of patients diagnosed with OED without these major risk factors. These non-smoking and non-drinking (NSND) patients are an interesting subgroup, but they have rarely been studied. Analysis of this distinct group of patients may reveal several important issues – for example, specific clinicopathologic features of OED and common site, grade and rate of malignant transformation – and identify additional risk factors. There is a paucity of information regarding the occurrence of OED in persons who have never used tobacco or alcohol. The aims of this study were to define the clinical features of OED among tobacco and alcohol non-users, to compare

these features with OED among users of both these agents, and to assess the prognostic variables for non-users of tobacco and alcohol.

## Materials and Methods

The hospital records of 456 patients with the histopathological diagnosis of OED at the College of Dentistry, Ajman University of Science and Technology, Ajman, United Arab Emirates (UAE) between 1999 and 2007 (inclusive) were reviewed. Two groups of patients were selected based upon tobacco and alcohol usage: 37 patients who had neither smoked tobacco nor drank alcohol and 419 patients who both smoked tobacco and drank alcohol. Demographic and other data including age, gender, site of the primary lesions, histopathology, treatment, and disease behaviour, were examined.

Patients when first seen in the outpatient clinic were routinely screened for the consumption of alcohol and tobacco using a standardised structured questionnaire by the examining doctor, who recorded all information in the patients' records.

Questions related to alcohol consumption included the type of alcoholic beverage ingested, the average quantity of drinks consumed daily and the past history of drinking. Exposure rates were based subjectively upon the declaration of the patient. Patients who claimed to never or only occasionally indulge in alcohol consumption were considered abstainers. Information on smoking habits was elicited in a similar manner; i.e., based on the patients' own reporting. The data included the type of tobacco product used, the average number smoked per day and the period since cessation in ex-smokers. Three groups of patients were then defined. Patients who had never used tobacco or had stopped 10 years previously were considered to be non-users. Smokers who had stopped less than 10 years previously were included as current smokers classified by their previous intake. A second group of patients consisted of those smoking 1-19 cigarettes/day (moderate smokers) and a third group included patients smoking ≥20 cigarettes/day.

OED was graded by a single pathologist as mild, moderate and severe according to the level of dysplastic changes (7). Malignant transformation was considered to occur if a histopathologically proven oral squamous cell carcinoma (OSCC) arose in a lesion which had histopathological evidence of OED; recurrence of a dysplastic lesion was considered if a second histopathologically proven dysplastic lesion developed at the same oral site during follow-up; and second dysplastic lesions were considered to have occurred when a new histopathologically proven OED lesion developed at a site different from that of the index dysplastic lesion.

The follow-up study was continued through May 2007 and was attended by 359 (78.7%) patients. All patients in the study were followed up between 2 and 96 months, with a mean of 48 months.

Ethical approval for the study was obtained from the Ethics Committee for Research of the College of Dentistry, Ajman University, UAE.

Statistical procedures were carried out using the SPSS programme (version 12-0, SPSS Inc., Chicago, IL, USA for Windows). Chi-squared or Fissure exact test were used to compare between the two groups and the results were considered significant when $P < 0.05$.

## Results

### Patient demographics

Thirty-seven (8.1%) of 456 patients with OED had never used tobacco or alcohol. There was a male to female ratio of 1:1 in the group; most of them were in the sixth decade. There were no significant differences in the age, gender or ethnicity of patients with OED who were users or non-users of alcohol and tobacco (Table 1).

### Site of oral epithelial dysplasia

There was no significant difference in the distribution of oral sites of OED between non-users and users of tobacco and alcohol. In both groups, the tongue, floor of mouth and buccal mucosa were the most commonly affected sites. Tobacco and alcohol users tended to have an increased frequency of lesions in the retromolar area and commissure compared with non-users (Table 2).

### Clinical type and histology of dysplastic lesions

There were no notable differences in the clinical appearance of lesions in users and non-users of alcohol and tobacco, the majority of lesions in both groups being solitary white or red and white patches (Table 3). With respect to the histopathological features, there were more mild OED lesions (51.3%) in non-users than in users (35.3%), but users had more moderate OED (30.5%) than non-users (18.9%). However, these differences were not statistically significant.

### Treatment and clinical behaviour of the primary dysplastic lesions

Fifty-four percent (20/37) of non-users and 41.2% (173/419) of users were surgically treated, the remaining patients being managed with other treatment modalities (Table 4). The rates of OED recurrence and development of second OED were not significantly different in the two groups, although second OED lesions were more common

Table 1 Demographics of users and non-users of tobacco and alcohol with oral epithelial dysplasia

| | Non-users | | Users | | *P* value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Age (years) | | | | | |
| < 45 | 9/37 | 24.3 | 95/419 | 22.6 | 0.8 |
| 45-54 | 4/37 | 10.8 | 95/419 | 22.6 | 0.09 |
| 55-64 | 12/37 | 32.4 | 118/419 | 28.1 | 0.5 |
| 65-74 | 5/37 | 13.5 | 82/419 | 19.5 | 0.3 |
| 75+ | 7/37 | 18.9 | 29/419 | 6.9 | 0.01 |
| Gender | | | | | |
| Male | 18/37 | 48.6 | 251/419 | 59.9 | 0.1 |
| Female | 19/37 | 51.3 | 168/419 | 40.0 | 0.1 |
| Ethnic-background | | | | | |
| Asians | 24/37 | 64.8 | 260/383 | 67.8 | 0.7 |
| Arab | 10/37 | 27.0 | 93/383 | 24.2 | 0.7 |
| Africans | 3/37 | 8.1 | 20/383 | 5.2 | 0.4 |
| Others | - | - | 10/383 | 2.6 | |

*P* value for chi-square test

Table 2 Sites of the oral epithelial dysplastic lesions in users and non-users of tobacco and alcohol

| Site | Non-users | | Users | | *P* value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Labial mucosa | 3 | 8.1 | 41 | 9.7 | 0.7 |
| Tongue | 11 | 29.7 | 113 | 26.9 | 0.7 |
| Gingiva | 6 | 16.2 | 37 | 8.8 | 0.1 |
| Floor of mouth | 6 | 16.2 | 86 | 20.5 | 0.5 |
| Buccal mucosa | 7 | 18.9 | 84 | 20.0 | 0.8 |
| Soft palate | 4 | 10.8 | 31 | 7.3 | 0.4 |
| Retro-molar area | - | - | 24 | 5.7 | - |
| Commissure | - | - | 3 | 0.7 | - |
| Total | 37 | 100.0 | 419 | 100 | |

*P* for chi-square test

Table 3 Clinical type and histopathology of oral epithelial dysplastic lesions in users and non-users of tobacco and alcohol

| | Non-users | | Users | | *P* value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Clinical type | | | | | |
| White patch | 16/37 | 43.2 | 216/419 | 51.5 | 0.3 |
| Red patch | 2/37 | 5.4 | 7/419 | 1.6 | 0.1 |
| Mixed | 17/37 | 45.9 | 182/419 | 43.4 | 0.7 |
| Ulcer | 1/37 | 2.7 | 14/419 | 3.3 | 0.6 |
| Lump | 1/37 | 2.7 | - | - | - |
| Histology | | | | | |
| Mild dysplasia | 19/37 | 51.3 | 148/419 | 35.3 | 0.05 |
| Moderate dysplasia | 7/37 | 18.9 | 128/419 | 30.5 | 0.1 |
| Severe dysplasia | 10/37 | 27.0 | 96/419 | 22.9 | 0.5 |
| Carcinoma in-situ | 1/37 | 2.7 | 11/419 | 2.6 | 1.0* |

* Fisher's exact test

*P* for chi-square test

Table 4 Treatment and clinical behaviour of oral epithelial dysplasia in users and non-users of tobacco and alcohol

| | Non-users | | Users | | *P* value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Treatment | | | | | |
| Surgery | 20/37 | 54.0 | 173/419 | 41.2 | 0.8 |
| Use of drug therapy | 7/37 | 18.9 | 42/419 | 10.0 | 0.09 |
| Others | 10/37 | 27.0 | 204/419 | 48.6 | 0.01 |
| Recurrence after initial therapy | 6/37 | 16.2 | 39/233 | 16.7 | 0.9 |
| Second dysplastic lesions | 5/37 | 13.5 | 18/232 | 7.7 | 0.06 |
| Transformation to malignancy | 4/37 | 10.8 | 13/322 | 4.0 | 0.08* |
| Status when last reviewed | | | | | |
| Alive disease free | 13/23 | 56.5 | 160/235 | 68.1 | 0.2* |
| Alive with dysplastic lesions | 9/23 | 39.1 | 74/235 | 31.5 | 0.4 |
| Dead-oral cancer | - | - | 1/235 | 0.4 | |
| Dead-other causes | 1/23 | 4.3 | - | - | |

* Fisher's exact test
*P* for chi-square test

Table 5 Features of subsequent oral squamous cell carcinoma in users and non-users of alcohol plus tobacco

| Oral squamous cell carcinoma | Non-users | | Users | |
|---|---|---|---|---|
| | No | % | No | % |
| Site | | | | |
| Labial mucosa | 1/4 | 25.0 | - | - |
| Tongue | - | - | 2/13 | 15.3 |
| Gingiva | 2/4 | 50.0 | - | - |
| Floor of mouth | 1/4 | 25.0 | 6/13 | 46.1 |
| Buccal mucosa | - | - | 2/13 | 15.3 |
| Soft palate | - | - | 3/13 | 23.0 |
| Degree of dysplasia | | | | |
| Mild | - | - | 2/13 | 15.3 |
| Moderate | 1/4 | 25.0 | 2/13 | 15.3 |
| Severe | 3/4 | 75.0 | 7/13 | 53.8 |
| Carcinoma in-situ | - | - | 2/13 | 15.3 |
| Clinical type of primary lesion | | | | |
| White patch | - | - | 4/13 | 30.7 |
| Red patch | 1/4 | 25.0 | 4/13 | 30.7 |
| Mixed | 3/4 | 75.0 | 4/13 | 30.7 |
| Ulcer | - | - | 1/13 | 7.6 |
| Lump | - | - | - | - |

in non-users (13.5%) than users (7.7%). A total of 17 (4.7%) of 359 lesions transformed to squamous cell carcinoma. While malignant transformation was higher in non-users (10.8%) than users (4%), there was no significant difference in the rates of transformation between the two groups. The long-term outcome of the two groups appeared to be similar.

## Characteristics of squamous cell carcinoma in tobacco/alcohol users and non-users

Details of the SCC in both groups are presented in Table 5. Among non-users, malignant transformation occurred in the gingiva in 50% (2/4) compared with none among users. Forty-six percent of the tobacco and alcohol users, however, had SCC of the floor of the mouth, compared to 25% of non-users (Table 5).

## Discussion

The difficulty of correctly diagnosing and classifying OED lesions has been emphasised by various studies (8-9), and is an inherent problem of any study of OED. The histologic grading is partially subjective, since the pathologist must make a decision which often is based on his or her individual past training and experience. The validity and uniformity of the diagnostic criteria in the current study were strengthened by the availability of a single qualified oral pathologist throughout the study period.

Most oral cancers are squamous cell carcinomas, and some oral squamous cell carcinomas are preceded by precursor lesions that can present as leukoplakia, erythroplakia, or erythroleukoplakia. Microscopically, these lesions may exhibit OED, a histopathologic diagnosis characterised by cellular changes and maturation disturbances indicative of developing malignancy (7). Oral epithelial dysplasia is an important risk factor in predicting subsequent development of invasive carcinoma. Despite the malignant potential of OED, the current state of knowledge regarding aetiological risk factors associated with OED is limited. The current study investigated the demographic, clinical, histological and prognostic aspects of OED in patients who had not been exposed to both alcohol and tobacco, the two widely recognised risk factors for OED and invasive squamous cell carcinoma (4-6). The presence of OED in patients who do not smoke tobacco or drink alcohol suggests that risk factors other than alcohol and tobacco may exist, and perhaps may reveal if patients without these risk factors are clinically different from those who smoke tobacco and drink alcohol.

Only 8.1% of the group of 456 studied patients were identified as non-users of both tobacco and alcohol. This is higher than the figure of 4.4% reported by Farshadpour et al. (10) in one of the few studies on oral squamous cell carcinoma solely in non-users of tobacco and alcohol, but less than the figure of 31% reported by Wey et al. (11). Perhaps the acknowledged contributions of tobacco and alcohol, and the prevalence of their use, obscure the attention given to other aetiologic factors in the development of OED, oral precancers and cancer.

Just over 50% of the non-users of tobacco and alcohol were female. Studies have shown that OED has a predilection for males, but the decrease in the male:female ratio suggests that the picture may be changing. This lack of gender differences between users and non-users may indicate that the increasing incidence of OED in women cannot be explained by lifestyle changes alone.

The number of lesions in this study was adequate for detailed analysis of the differences between adjacent locations within the oral cavity. There were no significant differences in the sites of presentation of OED between users and non-users of tobacco and alcohol, although non-users had fewer lesions on the floor of the mouth than users. To some degree, this finding would support the suggestion that oral tumourogenesis may be related to the direct effects of tobacco and alcohol at the site where the greatest dose is supplied. For example, the carcinogens in alcohol, thought to be promoters of oral cancer, may be delivered in a greater concentration to the floor of the mouth compared to the relatively dilute carcinogens of tobacco smoke and saliva may lead to a pooling of tobacco-derived carcinogens in the floor of mouth (12).

Some differences were noted in the distribution of histopathological severity of OED in users and non-users of alcohol and tobacco. Just over 51% of the non-users had mildly dysplastic lesions and only 27.0% had severely dysplastic lesions. While the tobacco and alcohol users had fewer mildly dysplastic lesions (35.3%), they also had fewer severely dysplastic lesions than the non-users. This unpredictable association of disease severity and tobacco usage is reflected in the high frequency of mildly dysplastic lesions in smokeless tobacco users (13-14).

Oral epithelial dysplasia is not associated with any specific clinical appearance. However, leukoplakia and erythroplakia are the lesions classically associated with dysplastic changes. Thus, white, red, or mixed white and red changes are those most frequently revealing OED. The frequency of OED in leukoplakia varies between <1 and >30% (15-20).

In the present study, tobacco and alcohol use did not influence later disease progression. Studies report progression of OED to SCC at rates ranging from 6.6 to 36.4% after mean follow-up periods of 1.5 to 8.5 years (21-24). Results of other studies have shown that malignant transformation of leukoplakias is more common in non-smokers than in smokers (25-28). In the present study, 4.0% of the users group and 10.8% of non-users transformed to malignancy after a follow-up period ranging from 2 to 96 months with a mean of 4 years; these differences were not statistically significant. Silverman et al. (17) monitored 257 patients with oral leukoplakia; 22 had a diagnosis of epithelial dysplasia, and the remaining 235 had hyperkeratosis. Eight (36.4%) of the 22 with epithelial dysplasia developed carcinoma. Of the 107 patients with a homogeneous leukoplakic lesion and a diagnosis of hyperkeratosis, seven (6.5%) developed carcinoma. However, 30 (23.4%) of the 128 patients with erythroplakic lesions and a diagnosis of hyperkeratosis were eventually diagnosed with carcinoma. The time from initial diagnosis of either epithelial dysplasia or hyperkeratosis to carcinoma

ranged from 6 months to 39 years. In another study reported by Lumerman et al. (21), 15.9% of 44 patients with oral epithelial dysplasia identified in a biopsy service developed carcinoma; the mean time from biopsy to cancer diagnosis was 33.6 months.

The concept of a two-step process of cancer development in the oral mucosa – i.e., the initial presence of a precursor (pre-malignant, pre-cancerous) lesion subsequently developing into cancer – is well-established. Oral leukoplakia is the best-known precursor lesion. It is not known how many oral squamous cell carcinomas arise from precursor lesions and how many develop from apparently normal oral mucosa. However, studies have shown that between 16 and 62% of oral carcinomas are associated with leukoplakic lesions when diagnosed (28-29), and an Indian house-to-house survey showed that about 80% of oral cancers were preceded by oral pre-cancerous lesions or conditions (29). Others consider the vast majority of oral cancers to arise from otherwise clinically normal mucosa (30).

Greater risk of malignant change in an epithelial dysplasia may be associated with erythroleukoplakia, a proliferative verrucous appearance, location at a high-risk anatomic site such as the tongue or floor of mouth, the presence of multiple lesions, and a history of not smoking cigarettes (17).

There was a trend of increased risk of second OED lesions in non-users compared with users, but there were no significant differences in the frequency of new lesions between users and non-users. It has been suggested that second primary malignancies in tobacco and alcohol users may reflect chronic mucosal irritation by agents that "prime" the entire oral mucosa for neoplastic development even before the clinical appearance of disease (31); however, the present observations of no increased risk of new OED lesions or malignant transformation in users of alcohol and tobacco compared with non-users seems to disprove this notion. The concept of second primary tumours was studied by van Oijen et al. (32), who investigated the proliferation index of epithelium from adjacent, histologically normal mucosa taken from smoking and non-smoking squamous cell carcinoma patients. They observed a significantly increased proliferation index in epithelia from smoking patients, but not in epithelia from the non-smoking patients. The authors concluded that multiple tumors might be the result of continuous exposure to tobacco; however, this does not explain the high frequency of second primary tumors in non-smoking non-drinking patients. Another author (33) examined a cohort of 11 patients with multiple squamous cell carcinoma, including nine non-smoking and non-drinking patients, and found some identical novel microsatellite alleles indicating early genetic aberrations and a common clonal origin. They suggested that multiple lesions in these patients arise due to lateral spread from a common precursor and thus are clonally related. Thus, it appears that in non-smoking and non-drinking patients, SCCs arise from clonal spread and not independently. More recently, Farshadpour et al. (34) reported that non-smoking and non-drinking patients with squamous cell carcinoma have the same risk for developing multiple tumours as their smoking and drinking counterparts without an increased expression of p53 or Ki-67.

Reported recurrence rates for premalignant lesions are as high as 34.4% (17). One study found an 18% recurrence rate in cases of severe epithelial dysplasia or carcinoma in situ in which the lesion had been excised with a 3- to 5-mm margin of normal tissue (35). Whether recurrence relates to continued exposure to risk factors or to an underlying mechanism that initiated the original lesion is unclear, but patients should be closely monitored for recurrence regardless.

From studies on the outcome of treatment of oral pre-malignant lesions by excision, it appears that the risk of malignant development may not change significantly (36-37). Recurrences are seen in 10-20% and cancer development in 3-9% of areas of excised lesions (35,38-39). In another study, carcinoma development in treated and untreated leukoplakias was compared (40). Therapy was not randomised; most small lesions underwent surgical excision, whereas large lesions apparently were not surgically removed unless severely dysplastic. Among 75 surgically treated leukoplakias, one patient later developed a carcinoma, whereas among 51 leukoplakias that did not receive treatment, four patients developed carcinoma. Thus, the carcinoma development in this study may be related to size of the lesion in addition to the lack of treatment. Saito et al. (41) suggested that widespread leukoplakias had a higher rate of malignant transformation.

The possible association between nutritional deficiencies and SCC remains controversial, but a number of case-control studies have consistently shown patients with oral cancers to have a poor diet (42). Also, dietary increase in vegetables and fruit may confer an advantage in reducing the incidence of laryngeal cancer. The nutritional status of our patients was not available.

Other possible aetiological factors for OED among non-users may include chronic mechanical irritation (43) anaemia (44), immunosuppression (45), infectious agents such as *Candida albicans* (46-47), or alcohol-containing mouth wash (48); however, the exact causes remain elusive.

The association of chronic periodontitis with oral cancer was recently reported. Tezal et al. (49) reported that chronic

periodontitis may be a significant factor in the natural history of HPV infection in patients with tongue cancers. In another study, Michaud et al. (50) reported that periodontal disease was associated with a small but statistically significant increase in overall cancer risk among non-smokers of tobacco. Our patients' periodontal health status was not available for analysis and further studies are needed to investigate the possible association of OED with chronic periodontitis.

The absence of any known potential risk factor suggests that specific molecular and genetic mechanisms may be involved in the tumorigenesis of the OED population. Sorensen et al. (51) found no p53 mutations in six NSND patients younger than 40 years. Koch et al. (52) found a lower p53 mutation rate and a higher HPV infection rate in a non-smoking HNSCC population. They also found that non-smokers were likely to have less loss of heterozygosity at chromosomes 3p, 4q, and 11q13, and a lower overall percentage of microsatellite alterations. These genetic differences in NSND patients indeed suggest a different pathogenesis. Further studies are needed to clarify this issue.

It is thus evident that OED can arise in non-users of tobacco and alcohol and the histopathological spectrum, clinical features and long-term behaviour are similar to those in users of alcohol and tobacco. Further studies in the NSND OED patient population are warranted. Potential factors that may contribute to OED development in NSND individuals include nutritional deficiency and HPV infection. Evaluation of these factors, along with the molecular mechanisms that underlie tumorigenesis and progression of dysplastic lesions in these patients, may provide researchers with clues fundamental to their understanding of the biology of the disease in a greater patient population.

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