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http://dx.doi.org/10.1111/odi.12289

http://medlib.mef.hr/2408

Potentially malignant oral disorders and high risk habits in liver cirrhosis and lung cancer patients

Running title: Potentially malignant oral disorders in high risk patients

Keywords: Oral cancer; cancer screening; precancerous conditions, smoking, alcohol drinking

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Date of submission: 30 March 2014

Abstract

OBJECTIVES*:* To analyze the role of smoking, drinking and their synergistic effect in the occurrence of potentially malignant oral disorders (PMOD).

SUBJECTS AND METHODS: We examined three groups: 50 lung cancer patients, 50 patients with liver cirrhosis and 50 patients with clear medical history. Scores were developed for drinking, smoking, drinking and smoking and PMOD.

RESULTS: All four scores were the lowest in the control group. The lung cancer group showed the highest Smoking, Alcohol & Smoking and Lesions score, while the liver cirrhosis group had the Alcohol score the highest. Compared to the control group, lung cancer group is more likely to develop a PMOD than the liver cirrhosis group (OR=12.31/ OR=6.71). Statistical significance between the groups was found in the Lesions score (χ^2=15.34; p=0.001).

CONCLUSIONS: The lung cancer and liver cirrhosis patients represent a high risk group for PMOD. Lung cancer and liver cirrhosis patients have never, to our knowledge, been categorized as high risk patients for PMOD. After diagnosed, lung cancer and liver cirrhosis patients should have a routine oral cavity examination, as they present a high risk group for PMOD and oral cancer.

Introduction

According to the WHO (World Health Organization), oral cancer (OC) is the eight most common cancer in the world (Petersen, 2009). More than 300,000 new cases worldwide are diagnosed with oral squamous cell carcinoma annually (Rivera, 2007). Approximately 40,000 new cases are recorded in the European Union annually (Tsantoulis *et al*, 2007). OC predominantly appears in middle aged people and older. Overall incidence and mortality attributed to oral cancer is increasing, with age-standardized incidence and mortality of 6.6/100,000 and 3.1/100,000 for males, and 2.9/100,000 and 1.4/100,000 for women (Mehrotta and Yadav, 2006). Many authors set an incidence ratio between men and women 2:1, but since more and more women are adopting unhealthy habits, the difference in future will surely decrease. At the beginning of the 20th century, the incidence ratio was 9:1 (Shah *et al*, 2003). According to WHO, in the developed countries, OC in the male population is the sixth most common cancer after lung, prostrate, colorectal, stomach and bladder cancer, while in female population, it takes the 10th place after breast, colorectal, lung, stomach, uterus, cervix, ovary, bladder and liver (Mehrotta and Yadav, 2006).

Alcohol is a carcinogenic via several mechanisms with a local and systemic effect on the oral mucosa. Tobacco generates carcinogens such as tobacco-specific nistrosamines and free radicals with a specific effect on the antioxidant enzymes. Smoking increases the acetalaldehyde burden following the alcohol consumption and alcohol consumption enhances the activation of pro-carcinogens present in tobacco (Scully and Petii, 2010).

In the 2005 WHO classification of oral lesions with a predisposition to malignant transformation, the term potentially malignant was preferred above premalignant or precancerous. It was recommended to abandon the terms "potentially malignant lesions" and "potentially malignant conditions" and to use the term "potentially malignant disorders" instead (PMOD). This was referred to erythroplakia, leukoplakia, lichen planus, oral submucous fibrosis and some miscellaneous potentially malignant disorders, like actinic cheilitis, inherited cancer syndromes and immunodeficiency (van der Waal, 2009).

In the last decade, there has been an increased interest in oral cancer screening (Logan *et al*, 2013). Unfortunately, till this day, there is no definitive evidence that un-targeted screenings are cost-effective. OC screenings in low-incidence areas could be more cost-effective if they targeted high-risk groups for oral cancer, heavy smokers and alcohol consumers.

The aim of the study is to determine the type, frequency and localization of the PMOD in patients with lung cancer and liver cirrhosis. These are chosen under consideration that the majority of the respondents have the risk habits for oral cancer development, smoking and alcohol consumption. We aim to correlate smoking, alcohol consumption, synergistic effect of alcohol and smoking with the appearance

of PMOD. Furthermore, we aim to emphasize that head and neck cancer screening clinics should target patients at high risk and attempt to ensure appropriate follow-up thereafter.

We haven't found any studies on PMOD in lung cancer and liver cirrhosis patients and never have lung cancer and liver cirrhosis patients been targeted as a risk group for PMOD or OC.

Materials and methods

One hundred and fifty respondents were examined in the General Hospital Pula, Croatia. The first group was made out of fifty respondents diagnosed with lung cancer, the second of fifty respondents that had liver cirrhosis and the third, the control group, was consisted of trauma patients with a clear medical history, admitted to the Department of Traumatology.

The study was reviewed and approved by the Ethic Committee of the School of Dental Medicine, University of Zagreb.

The respondents were examined in the departmental clinic by two doctors of dental medicine and two oral surgery specialists independently. Patients with suspicious findings, decubiti and PMOD were encouraged to follow-up and were given follow-up recommendations.

The respondents were given a questionnaire divided in two parts:

1. General information (age, gender, respondent's consent to participate in the research)
2. Anamnesis data (information about smoking habits, and alcohol consumption)

Four score variables were created:

1. Score "Smoking" = (duration of smoking (years) x number of cigarettes per day) / time since quitting smoking (years).
2. Score "Alcohol" = (duration of alcohol consumption (years) x alcohol units per day) / time since quitting drinking (years). Alcohol units were used to unify the criteria among alcoholic beverages. One alcohol unit contains 10g of pure alcohol. One alcohol unit is found in 125mL of wine, 300mL of beer and 30mL of strong liquor.
3. Score "Alcohol & Smoking" = ("Alcohol" + "Smoking") / 2

    Respondent had to drink and smoke in order to have a value different than 0.
4. Score "Lesions" = lesions in the oral cavity were evaluated according to their malignancy potential and localisation. Malignancy potential was graded, started from the smallest: lichen, leukoplakia, erythroplakia.

    The lesion's distinctive feature of the site appearance was described either as:

    - Characteristic – inside the "horseshoe"
    - Uncharacteristic – outside the "horseshoe"

    Lesions were scored from one to five:

- no lesion   0
- lichen   1
- uncharacteristic leukoplakia   2
- characteristic leukoplakia   3
- uncharacteristic erythroplakia   4
- characteristic erythroplakia   5

In case of multiple lesions, the values were summoned.

The data was organized into files (Microsoft Excel, Microsoft Inc., USA) and processed by JMP7 module from the software package SAS (SAS Institute Inc., Cary, NC, USA). Statistically significant results were found only if $p<0.05$. The value of χ^2 test was shown only when $p<0.05$. χ^2 test, where applicable, was used to compare qualitative data. Among other measures of association, relative risk and odds ratio were used. Quantitative data distribution was tested by Kolmogorov-Smirnov test. To compare more than two independent groups, the Kruskal-Wallis χ^2 test was used. Testing between groups was done by Mann-Whitney U test.

Results

The average age of the respondents in all groups is 61.51. The age distribution is shown in table 1. We examined 120 (80%) men and 30 (20%) women. Among the respondents there were 111 (74%) smokers and 39 nonsmokers (26%). Among 111 smokers 52 (47%) stopped smoking after the disease diagnosis and 59 (53%) are still smoking.

Among 133 of the respondents who drink alcohol, 84 (63%) of them consume only low alcoholic beverages (under 15% of alcohol) and 49 (37%) of them also drink stronger drinks. After their diagnosis, thirty of them (22.5%) stopped drinking, while the other (77.5%) are still consuming alcohol.

Duration of smoking in respondents with lung cancer is the longest (34.19 years), but there is no statistical significance in smoking duration between the three groups (p=0,107). On average, the largest amount of cigarettes per day is consumed by the respondents with lung cancer (27.54) and no statistical significance was found between the groups. The average score "Smoking" in the lung cancer group is 849.60, while in the control group the score is 412.35. The liver cirrhosis group has the average score 565.10.

The group with liver cirrhosis drinks, on average, 12 alcohol units per day and there is a statistical significance between the three groups ($\chi^2=30.68$; p=0.001). The average score "Alcohol" is 391.63 in the liver cirrhosis group, 292.80 in the lung cancer group and 173.14 in the control group. The maximal

value of the one individual in the control was 1197.00, which significantly affects the mean. The median for the score was 320.00 for the liver cirrhosis group, 287.50 for the lung cancer and 90.00 for the control group.

The score "Alcohol & Smoking" was highest in the lung cancer group (530.48), followed by the liver cirrhosis (399.95) and the control group (231.73). Lung cancer group has 41, liver cirrhosis group 35 and the control group 21 tobacco and alcohol consumers.

The score "Lesions" is highest in the lung cancer group and amounts to 0.92, lowest in the control group (0.10) and in the liver cirrhosis group it amounts to 0.64. Statistical significance was found between the groups (χ^2=15.34; p=0.001).

The distribution of PMOD is shown in table 2. Due to their frequency, we found no statistical significance between the score "Lesions" and all other scores between the groups. The risk of developing a potentially malignant disorder between the risk groups and the control group is shown in table 3.

All of the respondents who were diagnosed with a lesion had either a smoking or a drinking habit or both. Table 4 describes the disorders with regards to the respondents habits. Each lichen lesion found was located outside the „horseshoe". Leukoplakia was found in 16 respondents (10.6%), out of which 12 (75%) was located outside the horseshoe. Erythroplakia was found in seven respondents, out of which five (71.4%) lesion were located inside the horseshoe.

The score comparison between groups is shown in table 5.

Discussion

The developed scores integrated several variables and allowed us to represent all the variables as quantitative data. Our limitations are our small sample size and an unequal gender distribution. Unfortunately, we cannot completely rule out some unevaluated confounders, like human papilloma virus infection. A biopsy of the lesions wasn't taken, however bias of the estimator has been minimized by the number of examiners. We selected healthy individuals for our control group from the Department of Traumatology. The selection bias here is possible, due to our selection of patients with clear medical history, under intention that these represent the non-targeted screening population. By targeting and defining the risk groups, we avoided the systemic bias.

According to studies on the topic, smoking and alcohol consumption is more prominent in men, however as mentioned before, the ratio between genders is dropping (Petti S, 2009).

Studies show that over 98% of oral cancer patients are over forty (Bonifazi *et al*, 2011). We only found one age-targeted prevention campaign for population over 60 in Sao Paulo (Martins *et al*, 2012). The campaign was beneficial to the oral health of elderly with a significant reduction of oral cancer cases. The average age of our respondents is 61.51. Even though age mean is similar between groups, the

control group was not age-matched to the risk groups. The oldest respondent in the control group is 93 years old, eleven years older than the oldest respondent in the risk groups. This could present a study limitation. However, we believe that the presented age difference is not a confounding factor.

As expected, the score "Smoking" is 35% higher in the lung cancer group than in the liver cirrhosis group and 50% higher than in the control group. The liver cirrhosis had the highest "Alcohol" score. By considering the time from quitting smoking and drinking, we avoided the upward bias in the smoking and drinking frequency. The synergistic effect of alcohol and smoking was already noticed in 1972 (Rothman and Keller, 1972). We didn't expect to find a 25% higher "Alcohol & smoking" score in the lung cancer group compared to the liver cirrhosis group. The reason for this is the higher "Smoking" score ratio than the "Alcohol" score ratio between the two high risk groups.

Score "Lesions" was most sensitive to the malignancy potential developed in respect to previous studies on the subject and its localization (van der Waal, 2009). As predicted, PMOD were more frequent in the high risk groups (p=0,001). In both high risk groups the score "Lesions" is ten times higher than in the control group. Even though we found no statistical significance in score "Lesions" between the lung cancer and liver cirrhosis group, score is 1.44 times higher in the lung cancer group. We couldn't calculate the χ^2, RR or OR for leukoplakia, erythroplakia and loral lichen individually because of the small sample size. Nevertheless, as shown in table 3, statistical significance was found between risk groups and the control group in PMOD distribution, when all lesions observed together.

The most common localisations (75-85%) of oral cancer are the sublingual and paralingual region. The anatomical structures most commonly affected (soft palate, front pharyngeal arch, retromolar region, ventral and lateral parts of the tongue) are less keratinized and therefore more prone to dysplasia (Shenoi et al, 2012). In the western countries, 80% of all carcinomas develop in 20% of the oral cavity surface. This area forms a horseshoe shape and covers the mouth floor, ventral and lateral surface of the tongue, retromolar trigonum and the palatal arches. A horseshoe shape area represents a "reservoir" in which the carcinogens dissolved in saliva gather. Macan et al (2007) showed that among alcoholics, these parts are exposed to carcinogens for 24 hours after consumption, since alcohol is retained in the oral cavity for a while and then afterwards exuded through saliva. The interesting fact is that we found 75% of leukoplakia lesions outside the horseshoe. However, 75% of all erythroplakia lesions were located inside the horseshoe, while we found none in the control group. Unfortunately, size of the lesions, as a predictive factor, wasn't recorded. Brouns et al. (2014) showed that the size of the leukoplakia lesions over 4cm could be the only predictive factor of malignant transformation.

Sarode et al (2011) suggested a new classification where leukoplakia is a habit related morphologically altered tissue and oral lichen a morphologically altered tissue where chronic inflammation is responsible for malignant transformation. Erythroplakia hasn't been described as a

potentially malignant disorder in this classification, probably because they are considering it a carcinoma in situ.

Since the scientists haven't agreed on the malignancy potential of lichen, it is conditional to call it a potentially malignant disorder. This is the reason why lichen was given less points in the score "lesions". Brzak *et al* (2012) did a retrospective study on 12508 patients with lichen and leukoplakia and during the period of ten years did not find any malignant transformation in patients with lichen. On the other hand, Tovaru *et al* (2013), in an another retrospective study, out of 633 patients with lichen, after 0.5-20 years after its diagnosis, found six cases of oral squamous cell carcinoma (OSCC) at the site of previously confirmed lichen. The percentage (0.95%) isn't big, but has to be taken into account. Manojlovic *et al* (2007) described five OSCC lesions which aroused from the preexisting oral lichen planus. All of the respondents with oral lichen were recommended to an oral medicine specialist.

Clinical examination by a specialist of oral and maxillofacial surgery was recommended to all the respondents diagnosed with erythroplakia or leukoplakia. This referred to 23 respondents: twelve in the lung cancer group, nine from the liver cirrhosis group and two from the control group. Eighteen out of 23 drank and smoked, and the rest just smoked. Five of them drank strong liquor, which could support the observation that the amount of alcohol is more influential than the type of alcohol, highlighting the local effect of alcohol. The localisation of the higher concentrations of direct alcohol and alcohol excreted in saliva are in correlation with typical localisations of oral cavity cancer (Macan, 1999; Macan *et al*, 2007). Bagnardi *et al* (2013) showed that even light drinking (up to 1 drink/day) increases the risk of oropharyngeal cancer (RR =1.30; 95% CI 1.09-1.56).

In the lung cancer group we found three erythroplakia lesions located on the soft palate, while in the liver cirrhosis group we found none on that localisation. This is consistent with the studies by which smoking more frequently causes PMOD and OC located on the palate, while alcohol is considered to be more responsible for lesions located on the floor of the oral cavity (Macan, 1999). This could depict the local effect of tobacco and alcohol.

Other PMOD than the ones mentioned, weren't detected in this study.

Despite the efforts in early detection of oral cancer, surgery, radiation and chemotherapy, a five-year survival rate is 50% or less (Markopoulos, 2012). Most of the patients seek for medical opinion only when they experience lasting pain, dysphagia or swelling, which are often signs of an advanced malignant disease. Needless to state, treatment is more effective in the initial stages and the morbidity is minimal. Early diagnosis provides a higher survival rate, less mutilating surgery, faster recovery and less expense.

Improved patient outcome is the aim of screening and its benefit, while on the other hand, testing and investigating a healthy population, highly fluctuating geographic incidence of oral cancer, resources required, false positive referrals and poor cost-benefit ratio do not state its precedence. Neither the US

Preventive Services Task Force, The American Academy of Family Physicians nor the Canadian Task Force on Preventive Health Care recommend routine screening for head and neck cancer (Moyer 2013; Shuman *et al*, 2013). They all state the lack of evidence that screening for oral cancer led to improved health outcomes.

Due to self-selection among patients presenting for screening, traditional risk factors may not be associated with the likelihood of detecting the oral cancer. Prior publications suggest that screening clinics should target patients at high risk (Linkov *et al*, 2007; Sankaranarayanan *et al*, 2013).

In conclusion, lung cancer and liver cirrhosis patients present a high risk group for PMOD and should, after diagnosed, attend a routine oral examination, as they present a high risk group for PMOD and oral cancer. The four scores developed gave a clear and broad picture of the respondent's habits. All four scores developed were lowest in the control group. The liver cirrhosis group had the score "Alcohol" the highest, while the lung cancer group had the scores "Smoking", "Alcohol & smoking" and "Lesions" the highest. Lung cancer patients had almost twice the OR for developing a PMOD than the liver cirrhosis patients.

Acknowledgements:

References

Bagnardi V, Rota M, Botteri E *et al* (2013). Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol* **24**:301-308.

Bonifazi M, Malvezzi M, Bertuccio P *et al* (2011). Age-period-cohort analysis of oral cancer mortality in Europe: The end of an epidemic? *Oral Oncol* **47**:400-407.

Brzak BL, Mravak-Stipetić M, Canjuga I *et al* (2012). The frequency and malignant transformation rate of oral lichen planus and leukoplakia – a retrospective study. *Coll Antropol* **36**:773-777.

Brouns EREA, Baart JA, Karagozoglu KH, Aartman IHA, Bloemena E, van der Waal I (2014). Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. *Oral Dis* **20**:e19-e24.

Linkov F, Lisovich A, Yurkovetsky Z *et al* (2007). Early detection of head and neck cancer: development of a novel screening tool using multiplexed immunobead-based biomarker profiling. *Cancer Epidemiol Biomarkers Prev* **16**:102–107.

Logan HL, Shepperd JA, Pomery E *et al* (2013). Increasing screening intensions for oral and pharyngeal cancer. *Ann Behav Med* **46**:96-106.

Macan D (1999). The role of alcohol in the etiology of oral cancer. Dissertation, University of Zagreb.

Macan D, Virag M, Bozikov J (2007). Alcohol in saliva related to the anatomical site of oral carcinoma. Abstracts of the First World Congress of the International Academy of Oral Oncology (IAOO); 17-20 May, Amsterdam. *Oral Oncol Suppl* **2**:128.

Manojlovic S, Mravak Stipetic M, Luksic I, Macan D, Manojlovic Z (2007). Malignant transformation of oral lichen planus. Book of abstracts of the 21st European Congress of Pathology; September 8-13; Istanbul, Turkey. *Virchows Archiv* **451**:544-545.

Markopoulos AK (2012). Current aspects on oral squamous cell carcinoma. *Open Dent J* **6**:126-130.

Martins JS, Abreu SC, Araújo ME *et al* (2012). Strategies and results of the oral cancer prevention campaign among the elderly in São Paulo, Brazil 2001 to 2009. *Rev Panam Salud Publica* **31**:246-252.

Mehrotta R, Yadav S (2006). Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. *Indian J Cancer* **43**:60-66.

Moyer VA (2014). Screening for Oral Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* **160**:55-60.

Petersen PE (2009). Oral cancer prevention and control: The approach of the World Health Organization. *Oral Oncol* **45**:454-460.

Petti S (2009). Lifestyle risk factors for oral cancer. *Oral Oncol* **45**:340-350.

Rivera MCA (2007). 4NQO Carcinogenesis: A Model of Oral Squamous Cell Carcinoma. *Inl J Morphol* **30**:309-314.

Rothman K, Keller A (1972). The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis* **25**:711-716.

Sankaranarayanan R, Ramadas K, Thara S *et al* (2013). Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol* **49**:314-321.

Sarode SC, Sarode GS, Karmarkar S, Tupkari JV (2011). A new classification for potentially malignant disorders of the oral cavity. *Oral Oncol* **47**:920-921.

Scully C, Petti S (2010). Overview of cancer for the healthcare team: Aetiopathogenesis and early diagnosis. *Oral Oncol* **46**:402-406.

Shah JP, Johnson NW, Batsakis JG (2003). Global epidemiology. In: Shah JP, Johnson NW, Batsakis JG, editors. Oral cancer. London: Dunitz Martin Ltd. p. 3-33.

Shenoi R, Devrukhkar V, Sharma BK, Sapre SB, Chikhale A (2012). Demographic and clinical profile of oral squamous cell carcinoma patients: a retrospective study. *Indian J Cancer* **49**:21-26.

Shuman AG, McKiernan JT, Thomas D *et al* (2013). Outcomes of a head and neck cancer screening clinic. *Oral Oncol* **49**:1136-1140.

Tovaru S, Parlatescu I, Gheorghe C, Tovaru M, Costache M, Sardella A (2013). Oral lichen planus: a retrospective study of 633 patients from Bucharest, Romania. *Med Oral Patol Oral Cir Bucal* **18**:201-206.

Tsantoulis PK, Kastrinakis NG, Tourvas AD, Laskaris G, Gourgoulis VG (2007). Advances in the biology of oral cancer. *Oral Oncol* **43**:523-534.

van der Waal I (2009). Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol* **45**:317-323.

Table 1. Respondents age, alcohol and smoking information

Feature		Liver cirrhosis group	Lung cancer group	Control group
Age	Mean; Standard deviation	58.58; 11.44	64.84; 8.11	61.12; 17.10
	Minimal; Maximal value	38; 82	43; 77	38; 93
Duration of smoking	Mean; Standard deviation	31.80; 13.38	34.19; 14.21	27.06; 14.71
No. cigarettes per day	Mean; Standard deviation	26.57; 13.21	27.54; 10.83	23.16; 16.47
No. alcohol units per day	Mean; Standard deviation	12.00; 6.06	9.20; 5.03	5.71; 6.17
Duration of drinking	Mean; Standard deviation	32.80; 10.10	37.50; 10.14	37.05; 14.03

Table 2. Potentially malignant oral disorders

Lesion	Liver cirrhosis group	Lung cancer group	Control group
Lichen	6	10	1
Leukoplakia	6	8	2
Erythroplakia	3	4	0
Total	15	22	3

Table 3. Potentially malignant disorder risk between the risk groups and the control group

Feature	Liver cirrhosis - Control group	Lung cancer – Control group
RR	5.00	7.33
OR	6.71	12.31
CI (95%)	1.80 – 25.00	3.38 – 44.89
z; p	2.839; 0.005	3.803; 0.001

Table 4. Potentially malignant oral disorders in relation to smoking and alcohol consumption

Habit	Leukoplakia	Erythroplakia	Lichen	All
Smoking N (%)	13 (81.3)	7 (100.0)	15 (88.2)	35 (87.5)
Alcohol N (%)	15 (93.8)	6 (85.7)	15 (88.2)	36 (90.0)
Smoking and alcohol N (%)	12 (75.0)	6 (85.7)	13 (76.5)	31 (77.5)
Don't drink & smoke N (%)	1 (6.3)	0 (0.0)	2 (11.8)	3 (7.5)
All N (%)	16 (100.0)	7 (100.0)	17 (100.0)	40 (100.0)

Table 5. Score comparison between two groups (Mann Whitney U test)

Lung cancer and control group

	Smoking	Alcohol	Smoking and Alcohol	Lesions
U	668.00	764.50	680.50	772.00
p	0.003	0.003	<0.001	0.001

Liver cirrhosis and control group

	Smoking	Alcohol	Smoking and Alcohol	Lesions
U	1030.00	469.00	884.5	947.50
p	0.363	0.003	0.017	0.038

Lung cancer and liver cirrhosis group

	Smoking	Alcohol	Smoking and Alcohol	Lesions
U	879.00	983.00	989.00	1079.50
p	0.030	0.195	0.099	0.242