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Oral Leukoplakia in Arab Countries: A Review

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Abstract
Oral Leukoplakia (OL) is a term describing the white lesions of the oral mucosa; it is the most common potentially malignant lesion of the oral cavity. The epidemiology of this condition in Arab countries is not well studied. A computer-based search for literature through pub-med was performed using relevant keywords to retrieve studies conducted in Arab world related to OL. After searching PubMed database, local journals and cross-referencing; a total of 12 articles were used for this review. Eight studies were cross-sectional, of them, two studies estimated a prevalence that ranged between 1.9% and 3.6%. Studies about various risk factors and prognostic marker were conducted in a clinical setting using case-control design (n=4). Cultural determinants such as certain smokeless tobacco habits (e.g. Qat and Shammah chewing) and Cigarette smoking were among factors investigated in some Arab countries. The results demonstrate a strong relationship between OL and Qat and Shammah Chewing (OL prevalence was 22-27% among tobacco users). Further population-based studies should be conducted in Arab countries to identify a causal relationship between these factors and the development, onset and progression of OL.
Keywords: *Oral leukoplakia; Arab; epidemiology; premalignant; prevalence.*

Introduction

Oral leukoplakia (OL) is a wide range of oral white lesions that cannot be rubbed off nor diagnosed as another specific entity[(1)]. OL exhibits a significant tendency for malignant transformation and is usually diagnosed in middle-aged population [(1,2)]. Males are more affected than females possibly due tothe greater prevalence of tobacco use[(3)]. Leukoplakia is six times more common among smokers than among non-smokers[(8)]. Two main clinical types of OL wereidentified: homogenous and non-homogenous oral leukoplakia. Homogenous lesions are uniformly flat and thin, exhibiting shallow cracks of the surface keratin and have a relatively low risk of malignant transformation[(4)]. The estimated prevalence of OL, worldwide, is approximately 2% with prevalence variations due to differences in case selection criteria and methodology[(5)]. The annual malignant transformation rate is approximately 1%, which results in the development of oral cancer in20 persons per 100,000/year [(6,7)]. The previously mentioned evidence is mainly extracted from studies conducted in Western countries.

There are no review articles that assessed the OL studies in Arab countries. This study aims at summarizing the current state of knowledge on theepidemiology of OL in Arab World.

Methodology

An electronic search through PubMed was conducted to retrieve articles that met our inclusion criteria. Different keywords and

Boolean phrases were used to define the search (Appendix A). Articles in English language studying the epidemiology of OL in any of the 22 Arab countries until 2014 were included. Case reports and clinical trials whether preventive or curative in nature were excluded. Articles focusing on pathological/histological features, premalignant and malignant changes were excluded as well. A total of 17 articles were retrieved initially dating back to 1985; then nine articles were excluded based on the title and/or abstract reading. Full texts were retrieved and reviewed for eight articles at this stage, after which two more articles were excluded. Additional research was done by cross-referencing of included articles and searching the local journals in the Arab world that are not indexed in PubMed. Six articles were identified and included in this secondary research (Figure 1).

Results

A total of twelve articles were included in this review. The articles were grouped according to the specific area of research within OL to prevalence studies; risk factors studies and studies on prognosis. Prevalence studies (n=8) were conducted in different Arab countries and gave prevalence between 1.9 and 3.6% (Table1). Risk factors identified were focused on various forms and preparations of tobacco (smoking and smokeless). Immunosuppression was investigated about OL in one clinical study (Table 2).Various cytological markers were used to assess cell proliferation in patients with OL and squamous cell carcinoma (Table 3).

Table 1 Included studies on Prevalence of Leukoplakia in Arab countries (n= 8).

Study	Country/Setting	Study design/Sample Size/Population	Histopathological verification	Main results
Mani [9]	Saudi Arabia, College of Dentistry, King Saud University Riyadh	Cross-sectional 674 dental out patients	No	Patients screened over 1 year period. OL Point prevalence was 1.9% (Male 3.2%, Female 1.2%). A relation to oral tobacco was found. Prevalence distribution among males by type of tobacco habit as follows: 14.3% cigarette, Shisha 20%, Shammah 100%.
Salem [10]	Saudi Arabia, King Fahad Central Hospital Gizan	Cross-sectional 1436	Yes	Patients screened over 1 year. The prevalence rates of OL and pre-oral leukoplakia in this study were 11.4% and 4.3%, respectively. Of the affected subjects, 99% were dippers of snuff known as Shammaa.
Aiman et al [11]	Sana'a Yemen College of Dentistry	Cross-sectional 2500 dental outpatients	No	Dental patients screened over one and half year, OL point prevalence was 22.4% among Qatb Chewer and 0.6% for non-chewers (P < 0.001). Lesions in qat chewers vary in their clinical features (14%, 5.9% and 2.4% were grade I, II and III) OL among qat chewers occurred more frequently in females (33 %) than in males (21%). (P<0.0000)
Scheifel et al [12]	Yemini villages and cities, Yemen	Cross-sectional 200 dental outpatients	No	Patients examined for the presence of OL over six months period. For males; age ranged from 11 to 74 years. Prevalence of OL was 27% among Yemeni shammah users and it was not related to daily duration of Shammah application (P value=0.87). Homogeneous OL accounted for 74% of OL cases, thevestibule and buccal mucosa were the most frequently affected locations with 50% cases. Non homogeneous OL were found mostly on the ventral surface of the tongue in (57%) cases.
Mohammed et al [13]	Kuwait, Kuwait University Dental Center	Cross-sectional 530 dental outpatients	Yes	Patients were screened over a two-year period and a higher percentage of smokers had oral mucosal lesions than did non-smokers (p < 0.01). OL point prevalence was 3% (male 2%, female 1%)
Alattas [14]	Saudi Arabia, King Abdul Aziz University, Faculty of Dentistry Jeddah	Cross-sectional 599	No	Patients examined for the presence of various oral lesions over a 2-year period. Males accounted for 75% of OL cases. OL Point prevalence was 2.3%. Tobacco habits of participants were: Cigarette smoking 66% Shisha 38 % and chewable tobacco 21%. Chewable) tobacco was associated with higher level of suspicious or potentially malignant lesions (P-value<0.001),
Abd-Sada [15]	Iraq/ College Dentistry University of Sulaimani, Kurdistan Region	Cross-sectional 500 dental outpatients	No	Patients screened for common white lesions in the oral cavity. OL Point Prevalence was 3.6% with male predominance (Male 2.3 and Female 1.4%).
Al-Sharabi [16]	Yemen, Faculty of Dentistry University of Sana'a	Cross-sectional 650 healthy Yemen Patients	No	Majority of patients chewed tobacco (75%) they were recruited and divided into. Male (79.20%) and females (20.80%) with M/F ratio of 4: White lesions were found on buccal mucosa at chewing sites (99.7%) compared to (8.5%) among non-chewers (P-value<0.05)

Table 2. Included studies on Risk factors of Leukoplakia in Arab countries (n= 3)

Study	Country/Setting	Study design/Sample Size/Population	Histopathological verification	Main results
Ahmed and Mahgood [17]	Sudan/ Department of Histopathology and Cytology, Faculty of Medical Laboratory Science, University Khartoum	Case-control/ 82 patients with and without Tobacco habits	Yes	Majority of patients were Toombakd users (70%), and 21% were diagnosed with OL. Oral cancer and cytological atypia were histologically diagnosed among the study population as well. Almost all lesions were found on buccal mucosa or lower lip.
Al Mohya et al [18]	Saudi Arabia/Renal Transplant Clinic, King Abdulaziz Medical City (KAMC), Riyadh	Case-control/ 110 Renal transplant patients (RTP) and age/gender matched dental outpatients	Biopsy for questionable cases only	RTPs had higher prevalence of hairy leukoplakia 8.6% compared to controls (P value=0.04). Hairy leukoplakia was proposed as marker of significant over-immunosuppression.
Noam et al [19]	Yemen/Israel Research Committee of the School of Dental Medicine, Tel Aviv University	Case- control/102 Khat chewers and gender and ethnic background matched controls	No	Prevalent of OL among the Khat chewers was 83% (P < 0.001). OL lesions were noticed in 84% of smoking chewers compared with 20% of patients who were smokers but did not chew Khat. An association was found between Khat chewing and white changes of the mucosa (P<0.001) but not between occurrence of white lesions and smoking habits

Table 3. Included study on Prognosis of Leukoplakia in Arab countries (n=1)

Study	Country/Setting	Study design/Sample Size/Population	Histopathological verification	Main results
Abbas and Hussain (20)	Sudan/ Department of Histopathology and Cytology Faculty of Medical Laboratory Sciences, Alneelain University and Sudan University of Science and Technology	Case-control 210/ Toombak users, patients with SCCe and non-tobacco users	Yes	Cytological atypia was identified in 4% of Toombak users but not among control group (p<0.04). Cytological marker (Micronuclei frequencies) were higher in toombak users (1.026) than in the control (0.356) (p<0.0001) The mean AgNORf counts in Toombak users (2.423) were higher than control group (1.303) (P<0.0001). Neither Toombak users nor control group showed mitotic figures in 1% crystal violet method. Toombak dipping was cited as a high risk factor that increases the cellular proliferation in the oral mucosa.

[a]Shammah:is a traditional form of chewing tobacco{smokeless tobacco, (ST)}. It is commonly used In the Middle East especially in Saudi Arabia,Yemen and Sudan and consists of a mixture of powdered tobacco, lime, ash, black pepper, oils and flavoring. It is usually placed in the buccal or lower labial vestibule of the mouth.

[b]Khat or Qat: (Catha Edulis) a flowering plant native to the horn of Africa and Arab Peninsula.

[c]Shisha: (a.k.a Hookah or water pipe)a single or multi-stemmed instrument for vaporizing and smoking flavored tobacco.

[d]Toombak:is a native tobacco plant of the species Nicotiana rustica.

[e]SCC: Squamous Cell Carcinoma.

[f]AgNOR argyrophilic nucleolar organizer region:are loops of DNA possessing ribosomal RNA gens. Some of the NOR associated proteins are argyrophilic and can be demonstrated by silver colloidal staining methods in formation fixed , paraffin embedded sections, in which they appear as brown or black dots within nucleus. Increase in the AgNOR count reflects cellular proliferative activity.

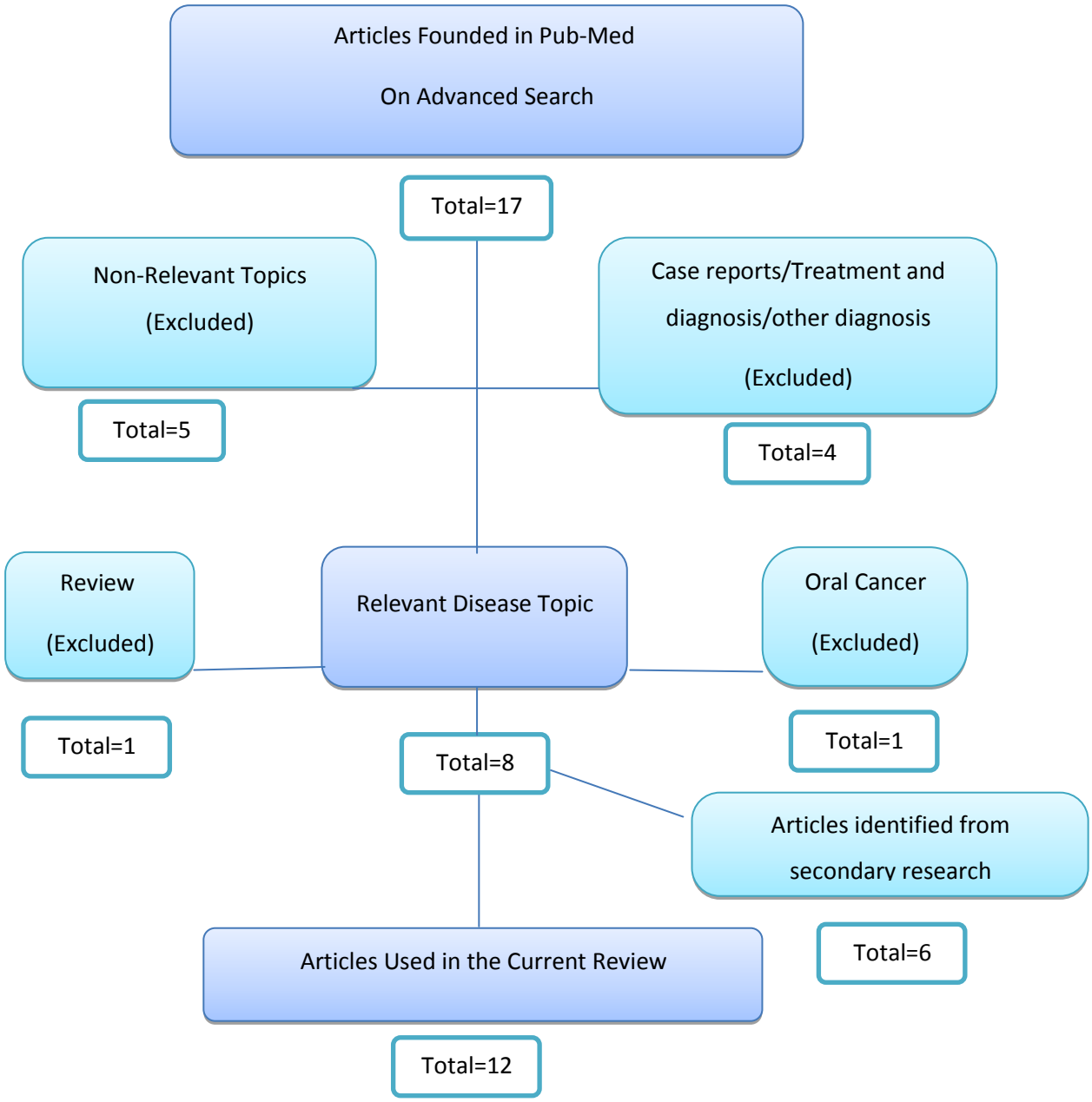

Figure 1. The electronic research strategy used to identify articles for inclusion.

Discussion

Eight prevalence studies were reviewed giving an overall prevalence that ranged from 1.9to3.6%, and prevalence among participants with habits was much higher[9-15]. Prevalence studies were conducted in 4 out of the 22 included countries. In Arab countries population prevalence was severely lacking, and studies were almost exclusively carried out in dental centers.While this would have resulted in high numbers of detected cases, it might not reflect the prevalence of OL at population levels. Prevalence from studies mentioned above gave a higher prevalence (1.9-3.6%) than the range is taken from some international studies (0.9-1%). Internationally oral leukoplakia is uncommon, possibly occurring in less than 1% of adults[25]. Fluctuations in OL prevalence could be reflecting a true increase in the condition in Arab counties or due to differences in diagnostic criteria.

Tobacco smoking or chewing was one risk factor that has been highly associated with OL in some studies[14,17,20]. Qat chewing habits are also prevalent in some Arab countries (e.g. Yemen)

and were associated with OL as well [16,19]. In Saudi Arabia, smoking habits were reported to be anywhere between 12% and 52%[21,22]. Despitethe high level of tobacco use among Saudis and the reported associated risk of OL, it was found that there is as carcity of studies that assessed the prevalence of OL in Saudi Arabia and Arab world generally[14].

Risk factors studies were not comprehensive in the Arab world. Furthermore, size sample ranging from 530-2500 in Yemen, Saudi Arabia, and Kuwait studies was significantly smaller in comparison with some India and U.S.A studies that examined l1,6128 and 48,700 patients, respectively[23,24]. Inaddition, most studies reported that OL patients were diagnosed through routine dental examination; this could have underestimated the prevalence as patients with symptoms might have sought treatment elsewhere. Some OL risk factors that were investigated in some Arab countries cannot be generalized to others due to geographical variations in the distribution of tobacco habits. For instance smokeless tobacco seems to be more prevalent in some parts (e.g. Yemen and Sudan); but not so in many Arab countries.

Most studies reviewed were cross-sectional conducted to assess OL prevalence among selective populations. Future studies should focus on surveying the extent of OL in Arab countries. Proper sampling at the population level should be considered rather than sampling from the clinical setting. The low response rate of participants may have introduced non-response bias into the results. Case-control studies can help in identifying certain behavioral risk factors that relate to cultural habits (e.g. smoking and smokeless tobacco habits). Choice of volunteers as controls in case-control studies might have caused a degree of selection bias. The reviewed studies lacked mentioning sample size calculation or technique used for sampling, and occasionally not all measures of association (e.g. odds ratio) were reported.

Conclusion

In the essence of this review, it is apparent that prevalence of OL requires being explored at the population level in different geographical countries. An appropriate sampling of particular populations should be used to ensure representativeness of studies. Prevalence of OL among khat and Shammah chewers ranged from 22 to 27% in studies reviewed. Smoking was associated with OL, and lesions suspicious for oral malignancy were more linked with chewable tobacco forms. Patients with OL, especially non-homogenous type, should be followed carefully for any sign of malignant transformation. Future clinical studies should consider exploring genetic predisposition to OL development and/or malignant changes.

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Appendix A – Key Words Used

Keyword used in Pub-Med's advanced search and secondary search to identify articles. They included a combination of Disease of interest (oral leukoplakia), epidemiological terms and geographical locations (names of 22 Arab countries).

Mortality
Factor
Determinant
Distribution
Incidence
Odds
Pattern
Prognosis
Trend
Rate
Prevalence
Epidemiology