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A long-term follow-up study on the natural course of oral leukoplakia in a Swedish population-based sample

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AIM: To assess the natural course of screening-detected oral leukoplakia (OL) among non-consulting individuals.
METHODS: A cohort of 555 individuals with OL, confirmed in 1973–1974 during a population-based survey, were followed through January 2002 via record linkages with nationwide and essentially complete registers. A sample of 104 drawn from the 297 surviving cohort members who still were living in the area in 1993–1995 was invited to a re-examination. Sixty-seven of them attended.
RESULTS: At the time of re-examination OL had disappeared in 29 (43%) individuals. There was a statistically significant association between cessation of/no smoking habits in 1993–1995 and the disappearance of OL. Never/previous daily smokers were thus over-represented among individuals whose OL had disappeared compared to those with persisting OL [$n = 23$ (82%) vs. $n = 18$ (47%), $P < 0.01$]. Eighteen (78%) of the twenty three non-smokers with disappearing OL had quit after the initial examination. One man and two women developed oral cancer during follow-up while 0.7 and 0.07, respectively, were expected.
CONCLUSION: Smoking cessation was associated with an increased disappearance of OL. Hence, at least one-fourth had lesions that could be classified as tobacco-related. Small observed and expected numbers prohibited firm conclusions about a possible excess risk of developing oral cancer.
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Introduction

Oral leukoplakia (OL) denotes a white patch in the oral mucosa. The term contains connotations of a potential for malignant transformation and has done so since 1877 when Schwimmer reported squamous cell carcinomas evidently arising in tongue leukoplakias in patients with syphilis (1). However, the oral mucosa shows an array of white or whitish lesions, most of them either harmless or related to specific entities with or without potential malignant traits (2).

Attempts have been made to better define OL. One such attempt was to establish the term as a purely clinical one, carrying no other connotations and thus excluding histological characteristics (3). At two international seminars definitions have been further specified (4, 5). Thus, OL is defined as 'a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion' (5).

The prevalence of OL has been estimated to be 1–5% (6–9). The risk of malignant transformation is reported to be approximately 4%, but considerably higher figures have been reported from studies on selected populations at referral clinics (10).

Few population-based follow-up studies are available on OL. Most of them emanate from India (11) and focus on malignant transformation (8). No European studies on the natural course over time of OL have so far been published. The aim of the present study was to follow up screening-detected cases of OL in a Swedish general population examined in 1973–1974 (6) to register changes in clinical appearance and the possible transformation into oral cancer.

Study cohort and methods

In 1973–1974 a population-based prevalence study of oral mucosal lesions was carried out in Uppsala County, situated in central Sweden (6). The present follow-up study proceeded from 7890 and 8254 investigated men and women, respectively, who resided in a small town, a small municipality, or 15 surrounding rural parishes. All participants who had OL upon the initial examination formed our cohort (467 men and 88 women).

Follow-up of these 555 individuals was accomplished through record linkages with nation-wide and essentially complete registers of the total population, patients with

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cancer, and causes of death using the National Registration Numbers, assigned to all Swedish residents as unique identifiers.

Based on zip code numbers, a sample was drawn in 1993 from cohort members who had not died or moved out of the area. This sampling was deemed to be independent of outcome probability. The selected individuals were invited for a clinical re-examination and interview in 1993–1995, performed by one investigator (A.R.) at local dental clinics. If an individual failed to attend the first appointment, at least one new appointment was offered.

The ethics committee of the Medical Faculty, Uppsala University approved the study. Informed consent was obtained from all participants.

Clinical re-examination

Criteria for OL at re-examination were the same as in 1973–1974 (6). A criterion common to all sub-classes was that the lesion must be a whitish patch of the oral mucosa that cannot be attributed to any other diagnosable lesion. OLs were divided into the following subclasses:

1 OLs with demarcated margins or with indistinct boundaries blending into the adjacent normal mucosa (homogeneous).
2 OLs with one or more erythematous areas and/or with white, pinheaded-sized papules/nodules in parts of the lesion (non-homogeneous).

Before the re-examinations the examiner in 1973–1974 (T.A.) and the examiner at follow-up in 1993–1995 (A.R.) calibrated their evaluations using clinical photographs. At both clinical examinations the OLs were registered with sub-class and site(s) and photographed in color. No biopsies were taken at re-examination.

In connection with both examinations, identical questions were asked about tobacco use (currently and in the past) and alcohol use.

Statistical methods

In the register-based follow-up we only considered first cancers. After having confirmed the validity of the National Registration Numbers through linkages with the population, cause of death and migration registries, person-time was calculated from the date of first examination until the date of death, occurrence of any cancer, emigration or end of follow-up (January 31, 2002), whichever occurred first. We considered the following oral cancers: WHO ICD7 codes 141: tongue; 143: floor of the mouth; 144: other parts of oral cavity. The expected number of cancers was calculated through multiplying the observed person-time in gender-, 5-year age- and calendar-year strata by cancer incidence rates in the corresponding strata in the entire Swedish population.

In the analyses of the participants re-examined in 1993–1995 Fisher's exact test (12) was used to test independence between change of observed lesions and smoking habit at the time of re-examination. Homogeneous and non-homogeneous OL were not separated because of small numbers of non-homogeneous OL. Smoking habit was defined as never/previous daily user (stopped >1 year ago) and current daily user. Age at entry to the cohort in 1973–1974 (categorized as 15–24, 25–34, 35–44, 45–54, ≥55 years) and alcohol user status (categorized as low: no consumption or less than once a week; moderate: one to two times a week; high: >2 times a week) were also tested for independence of OL lesion. The missing value category was not included in the tests (12).

Results

At the time of clinical re-examination, 186 and 12 individuals were lost because of death and emigration, respectively. In addition, 60 cohort members had relocated to places where personal examination was unfeasible (Fig. 1B).

In total, 104 of the remaining 297 individuals (35%) received an invitation to a clinical check up. Out of the invited individuals, 67 (64% of the sample) attended the examination. Reasons for non-participation were refusal/missed appointment (51%), no contact (27%), or physical or mental impediments (22%).

Table 1 provides details about the initial OL cohort ($n = 555$) and the group selected for re-examination in 1993–1995 ($n = 104$). Because of small numbers with non-homogeneous OL (5 out of the 555 individuals) we only analyzed overall OL. Relatively few individuals in the oldest age groups in 1973–1974 were included in the sub-sample as most of them had died. Nevertheless the re-examined group and the non-participants did not differ importantly from the total cohort of 555 with regard to age, smoking, or alcohol habits. Thus, the sample was deemed to be representative of the total cohort for these variables. During the follow-up period, there was a shift from living in a small town toward residence in a small municipality. This shift was largely due to a difference in selection of individuals for examination in 1993–1995; in the small municipality all individuals were selected, while a selection process that was deemed to be equivalent to random sampling was employed in the small town. As place of residence was unrelated to outcome in preliminary analyses, the artificial shift from a small town to a small municipality was deemed to be unimportant for results.

At re-examination, the OL had disappeared in 29/67 (43%) and persisted in 38/67 (57%). The relationships of age at entry in 1973–1974, smoking habit in 1993–1995, and alcohol use in 1993–1995 with the presence or absence of OL in 1993–1995 are shown in Table 2. Never/previous daily smokers were over-represented among those in whom OL had disappeared compared to those with persisting OL [$n = 23/29$ (82%) vs. $n = 18/38$ (47%), $P < 0.01$]. Smoking cessation after the initial encounter in 1973–1974 was reported by 18/29 (62%) and 12/38 (32%) of these individuals, respectively. This means that 78% of the 23 non-smokers in 1993–1995 with disappearing OL had quit smoking after the initial examination. None in the re-examined group had started smoking during follow-up. There were no

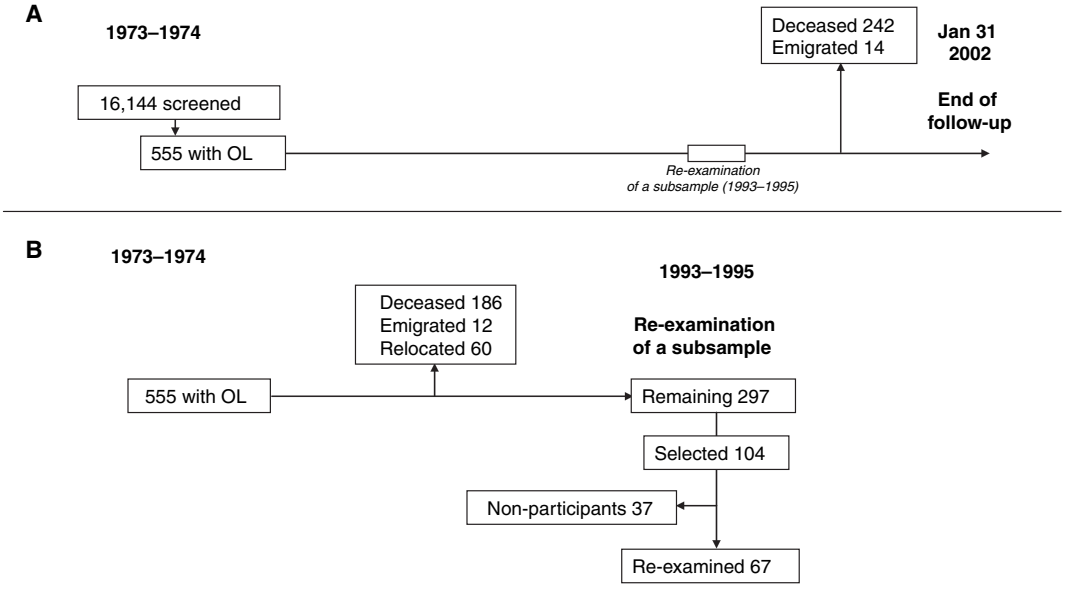

Figure 1 Flow chart of the total cohort to the re-examined group.

Table 1 Description of the total study cohort and individuals selected for re-examination in 1993–1995

	Total cohort (OL 1973–1974), n = 555 (%)	*Re-examined (1993–1995), n = 67 (%)*	*Non-participant (1993–1995), n = 37 (%)*
Age at entry, years (1973–1974)			
15–24	12 (2)	2 (3)	0 (0)
25–34	63 (11)	10 (15)	5 (14)
35–44	111 (20)	17 (25)	15 (41)
45–54	137 (25)	22 (33)	8 (22)
55–64	143 (26)	16 (24)	7 (19)
65	89 (16)	0 (0)	2 (5)
Gender			
Male	467 (84)	59 (88)	31 (84)
Female	88 (16)	8 (12)	6 (16)
Residence (1973–1974)			
Rural	99 (18)	17 (25)	11 (30)
Small municipality	80 (14)	24 (36)	10 (27)
Small town	376 (68)	26 (39)	13 (43)
Smoking habit (1973–1974)			
Never/previous daily	88 (16)	11 (16)	3 (8)
Current daily	467 (84)	56 (84)	34 (92)
Alcohol use[a] (1973–1974)			
Low	126 (23)	10 (15)	9 (24)
Moderate	340 (61)	45 (67)	23 (62)
High	89 (16)	12 (18)	5 (14)

OL, oral leukoplakia.
[a]Low: no consumption or less than once a week; moderate: one to two times a week; high: >2 times a week.

Table 2 Examined in 1993–1995, by presence or absence of OL

	No OL lesion in 1993–1995, n = 29 (%)	*OL lesion n = 38 (%)*
Age at entry, years (1973–1974), $P = 0.9$[a]		
15–24	1 (3)	1 (3)
25–34	3 (10)	7 (18)
35–44	8 (28)	9 (24)
45–54	10 (34)	12 (32)
55	7 (24)	9 (24)
Gender ($P = 1.0$)[a]		
Male	26 (90)	33 (87)
Female	3 (10)	5 (13)
Smoking habit (1993–1995), $P < 0.01$[a]		
Never/previous daily	23 (82)	18 (47)
Current daily	5 (18)	20 (53)
Missing	1 ()	0 ()
Alcohol use[b] (1993–1995), $P = 0.6$[a]		
Low	4 (14)	3 (8)
Moderate	20 (69)	30 (79)
High	5 (17)	5 (13)

OL, oral leukoplakia.
[a]Fisher's exact test of equal proportions across strata.
[b]Low: no consumption or less than once a week; moderate: one to two times a week; high: >2 times a week.

significant differences between individuals with remaining OL and disappearing OL concerning age, gender, or alcohol use.

The re-examined individuals showed OL lesions in various sites in the oral cavity and there were changes over time from 1973–1974 to 1993–1995 in some. Figure 2 summarizes the propensity for change in occurrence or site according to smoking habit in 1993–1995. Lesions occurring in new sites were much more common among current daily smokers than among never/previous daily smokers ($P < 0.01$).

In the register-based follow-up, all 555 cohort members were followed up for a total of 11 050 person-years (Fig. 1A). Three individuals (one man and two women) developed oral cancer (Table 3). The expected number, based on the incidence in the age- sex-and period-matched population, was no more than 0.7 and 0.07 among men and women, respectively. There was no consistency between site of oral cancer and site of lesion.

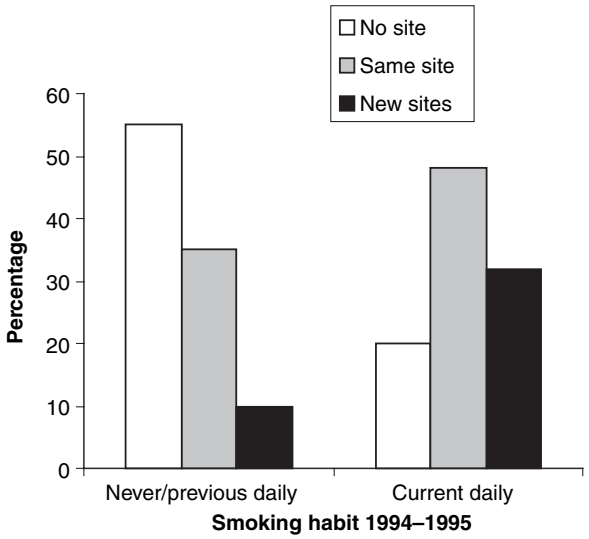

Figure 2 Oral leukoplakia (OL) lesions at re-examination by no OL/OL in same site(s)/OL in new site(s) in relation to smoking habits in 1993–1995.

All individuals in whom cancer developed were smokers and moderate alcohol users in 1973–1974.

Discussion

This study showed that a sizable proportion of screening-detected OL lesions disappear over a 20-year period and that smoking habits, but not age, gender or alcohol use, appear to be linked to their tendency to vanish.

We noted that two women developed oral cancers while only 0.07 were expected to do so. This excess is statistically significant, but as events can only occur in whole integers and the chance occurrence of one single case dramatically changes the relative risk estimate, no firm conclusion can be drawn regarding cancer risk in this study.

Oral leukoplakia may present with different clinical characteristics, and some lesions are considered to be more precancerous than others. First, the site of the OL lesion has been claimed to be of importance, with the floor of the mouth being the most risky location (13, 14). However, our findings show that in none of the three cases was the initial OL lesion or the oral cancer located in the floor of the mouth. Further, there was no concordance between the site of the OL lesion in 1973–1974 and location of the tumor diagnosed 10–15 years later. On the other hand, as many re-examined subjects showed OL at new sites, we cannot exclude the possibility that the oral cancer actually arose from a new OL lesion.

Second, the macroscopic appearance is purportedly linked to the risk for malignant transformation. Specifically, non-homogeneous OLs are considered to be at higher risk for cancer development than are homogeneous OLs (15–17). In contrast, all three oral cancers in the present study were found among individuals showing homogeneous OL in 1973–1974. However, we cannot rule out that a shift from the homogeneous to the non-homogeneous sub-class occurred after the first examination but prior to cancer development.

Third, according to previous studies, idiopathic OL is at higher risk for malignant transformation than tobacco-associated OL (10, 15, 18). In the present study this could not be confirmed, as all oral cancers occurred in ever tobacco-users.

Recent reports have suggested that only size of the lesion and presence of dysplasia have a bearing on the potential for malignant transformation (19). As biopsies were not taken in all subjects in 1973–1974, it is not possible to evaluate the influence of dysplasia in this follow-up.

The reversibility of OL lesions observed in our study is supported by earlier studies (15). Twenty (53%) out of 38 individuals with persisting OL in 1993–1995 were smokers but only 5 (18%) of 28 had disappearing OL and complete smoking information. In addition, OL disappeared in 18 (60%) out of 30 who quit smoking but in only 5 (20%) out of 25 smokers who did not quit. This is consistent – although not conclusive – with a causal role of tobacco use, at least in some. While disappearance of OL after smoking cessation does not constitute proof of causation, it appears appropriate to refer to the lesions that disappeared after quitting as, truly, tobacco-associated. However, there were indeed a number of OL lesions that persisted after smoking cessation; in these cases the causal role of tobacco use is even more uncertain and the lesions might be referred to as, more likely, idiopathic OL. An alternative explanation for the persistence of some lesions after tobacco cessation could be misdiagnosis. The validity of the clinical diagnosis was tested in 1973–1974 and was found to be good; 93% of 179 cases with a clinical OL diagnosis was consistent with the histological picture of OL (6). The diagnoses most commonly mistaken for OL were oral lichen planus and white frictional lesions. As

Table 3 Description of oral cancer cases in the OL cohort

Gender/age at entry	*Type of OL (1973–1974)*	*Site(s) of OL (1973–1974)*	*Year of diagnosis*	*Site of oral cancer*	*Smoking habit (1973–1974)*	*Alcohol use*[a] *(1973–1974)*
Male/63	Homogeneous	Right/left cheek	1984	Right lateral border of tongue	Yes, daily	Moderate
Female/69	Homogeneous	Inside lower lip	1985	Right side cheek, molar region	Yes, daily	Moderate
Female/40	Homogeneous	Right/left cheek	1990	Base of the tongue, left side	Yes, daily	Moderate

OL, oral leukoplakia.
[a]Low: no consumption or less than once a week; moderate: one to two times a week; high: >2 times a week.

these two alternative conditions are sometimes reversible, they could possibly also explain some instances of OL disappearance both among quitters and among those who continued smoking.

The results of the present study suggest that an OL lesion, if not misdiagnosed, in a tobacco user could be either idiopathic or tobacco-associated. It has previously been argued (19) that it is inappropriate to use the term tobacco-associated when provisionally classifying newly detected OL among smokers. As the definitive clinical diagnoses can only be made after elimination of suspected etiologic factors such as smoking, the classification among smokers must inherently be retrospective. Thus, according to this view, confidence in the classification into tobacco-related or idiopathic OL will be greatest among individuals whose lesions healed after smoking cessation (tobacco-associated) and among never-smokers (idiopathic). From our data 18/67 (27%) and 11/67 (16%), respectively, could be classified in these two categories.

The strengths of this study include the prospective design, its anchoring in the general population, and the long observation time. Caveats that should be highlighted are considerable losses to follow-up because of death and relocation, and the lack of histological confirmation. In the planning phase we assumed that the addition of invasive procedures such as biopsies could possibly inflate non-participation and hence aggravate possible selection bias. Another important weakness is the limited statistical power due to the small numbers in the cohort and very few malignant outcomes. It should, however, be pointed out that the identification of 555 population-based OL cases required oral examinations in more than 16 000 individuals.

In conclusion, close to half of screening-detected OL disappear within 20 years of follow-up. An overwhelming majority of individuals with disappearing lesions are non-smokers, and in this investigation most of the latter had quit after the lesion was first observed. Thus, our data indicate that approximately one-fourth of screening-detected OL in the general population is tobacco-associated if stringent criteria for this sub-classification are applied. In addition, an unknown but probably large proportion among continuing smokers also has tobacco-associated OL. Hence, smoking cessation appears to be a logical piece of advice to individuals with OL. The limited size of our study precludes firm conclusions regarding risks for oral cancer, with all the observed cases occurring among smokers.

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