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On the natural course of oral lichen lesions in a Swedish population-based sample

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OBJECTIVES: The aim was to assess the natural course of oral lichen lesions (OLL) among unselected, non-consulting individuals.

SUBJECTS AND METHODS: A cohort of 327 subjects with OLL, confirmed in 1973–1974 during a population-based survey in two Swedish municipalities, was followed through January 2002 via record linkages with nationwide and essentially complete registers. A sample of 80 drawn from the 194 surviving subjects who still resided in the area in 1993–1995 was invited for interview and oral re-examination.

RESULTS: At the end of follow-up, one case of oral cancer was detected, while 0.4 were expected. The overall mortality among subjects with OLL was not significantly different from that in the 15 817 OLL-free subjects who participated in the initial population based survey in 1973–1974. The lesion had disappeared in 14 (39%) of 36 re-examined subjects with white OLLs in 1973–1974, and four (11%) had transformed into red types. In the corresponding group of 19 with red forms initially, five (26%) had become lesion free and four (21%) had switched to white types. Although the cohort size does not permit firm conclusions regarding oral cancer risk, the natural course over up to 30 years appears to be benign in the great majority.

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Introduction

While several hypotheses have been suggested (1), the aetiology and pathogenesis of oral lichen planus (OLP) remain unclear. OLP lesions can appear in various forms (2) and the appearance may change over time (3). The term 'oral lichenoid reactions' (OLR) has been used for lesions with the same clinical and histopathological appearance as OLP but with an obvious triggering factor. According to WHO criteria, OLP is a precancerous condition (4) but the link to oral malignancies has been debated (5, 6). Small sample sizes and possible selection of high-risk patients limit the interpretation of follow-up data from published case series (7–10), some of which show increased incidence rates of oral cancer (7). Our aim was to study the natural course of oral lichen lesions (OLL), including OLP and OLR, in a population-based cohort of non-patients.

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Subjects and methods

During 1973–1974, a population-based prevalence study of oral mucosal lesions was carried out in Uppsala County, situated in central Sweden (11). The present follow-up study was restricted to a subset of the 20 333 investigated subjects, namely those coming from a small municipality (Bålsta), a small town (Enköping), and 15 surrounding rural parishes. Out of 7890 and 8254 investigated men and women, respectively, 118 and 209 had OLL according to set criteria (11). They formed our cohort.

Follow-up was accomplished through record-linkages with the nationwide and essentially complete registers of cancer (12), causes of deaths (13) and total population (14), using the National Registration Numbers as unique identifiers.

Among cohort members who were still alive and lived in the same area in 1993–1995 a sample was drawn. Because of limited resources, not all of the 194 individuals were invited to re-examination. The sampling procedure differed between Enköping, Bålsta and the surrounding parishes. In Enköping and the 15 rural parishes, the selection was restricted to a few zip code areas chosen to preserve the sociodemographic distribution of the source population. In these zip code areas, all individuals were invited to re-examination. In Bålsta, the entire study cohort was selected and invited to re-examination. As the selection of

subjects was unrelated to individual characteristics, and thus to outcome probability, it was deemed equivalent to random sampling, but it simplified the practical arrangements around the re-examinations. The selected individuals were invited to a clinical re-examination and interview, performed by one investigator (AR) at local dental clinics. If a subject failed to attend the first appointment, at least one new appointment was offered. Questions were asked about tobacco use currently and in the past, alcohol use and prescription drugs. These questions were identical to those used in 1973–1974.

Clinical re-examination

Our criteria for OLL at follow-up were the same as in 1973–1974 (11), see Table 1.

We were unable to differentiate between OLP and OLR as no such distinction had been made in the original examination in 1973–1974; henceforth, both are referred to as OLL. Before the re-examinations the examiner in 1973–1974 (TA) and the examiner at follow-up (AR) calibrated their evaluations using clinical photos. The lesions were grouped into two main categories: (1) White forms which included the papular, reticular and plaque types; and (2) red forms including all the erythemathous/atrophic and ulcerative/erosive types irrespective of any coexisting white forms. In a subsequent blinded evaluation of 10 new photos, the inter-examiner agreement, measured as Kappa value (15) was 0.74 (95% CI 0.26–1.0). AR's intra-examiner agreement was 0.74 (95% CI 0.26–1.0). At the clinical examinations, all OLLs were documented photographically. No biopsies were taken. Furthermore, the presence and type of dental materials was recorded for each subject.

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

Statistical methods

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 cancer, emigration or the end of follow-up (31 January 2002), whichever occurred first. To identify oral cancers in the Cancer Register, the ICD7 codes 141 (tongue), 143 (floor of the mouth), 144 (other site of the oral cavity) were used. The standardized incidence ratio (SIR), the ratio of observed to expected number of cancers, was used to estimate relative risk for cancer.

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. Hence, the SIRs are inherently adjusted for potential confounding by gender, age and calendar period. Confidence intervals of SIRs were calculated with the assumption that the observed number of events followed a Poisson distribution (16). Analogously, standardized mortality ratios (SMRs) were calculated for overall mortality and some cause-specific deaths. In the latter analyses, there was no censoring after cancer occurrence.

So as to control for any 'healthy participant effect', we further made direct comparisons of incidence rates between the OLL cohort and the 15 817 survey participants who were found to be without OLL in 1973–1974. We used a generalized linear model of the log type with the model distribution being Poisson, adjusted for age at entry, follow-up and gender. Mortality rates were compared in a similar way.

Table 1 Criteria for a oral lichen lesions (OLL) in 1973–1974 and 1994–1995

1. White, pinheaded-sized papules
2. White, distinct striae forming patterns
3. White plaque-like lesions with striae at the margins
4. Red, erythemathous areas with striae at the margins
5. Atrophy of tongue papillae. The atrophic area has a whitish, dry surface
6. Areas of erosions or ulcerations with striae at the margins
7. Vesicles or bullae in areas with lesions compatible with criterion 1, 2, 3, 4 or 5
8. The white structures cannot be rubbed of

Papular type = 1 + 8; reticular type = 2 + 8; plaque type = 3 + 8; atrophic type = 4 + 8 or 5 + 8; erosive type = 6 + 8; bullous type = 7 + 8.

Results

In Table 2, the OLL cohort is characterized with regard to gender, age, place of residence, smoking, alcohol, prescription drugs and OLL type at entry. Censoring because of death occurred in 88 subjects and two subjects had emigrated. In addition, 43 subjects had relocated to places were personal re-examinations were unfeasible (Fig. 1).

The 327 subjects in the OLL cohort were followed for an average of 22.7 years. In all, 7440 person-years were under surveillance.

Table 3 shows observed and expected cancer occurrences in the OLL cohort up to 29 years. One case of oral cancer was observed in an 84-year-old woman, consistent with an expected number of no more than 0.4 (0.2 for both men and women respectively). In both sexes combined, the SIR for oral cancer was 2.6 (95% CI 0.1–14.8). The corresponding SIR for overall cancer was 1.2 (95% CI 0.9–1.5).

In our direct comparison with lichen-free attendees, the incidence rate ratio (overall cancer, both sexes) was 1.2 (95% CI 0.9–1.5). The incidence rate ratio for oral cancer was 2.0 (95% CI 0.3–15.3).

Table 4 describes the number of deaths for women and men in the OLL cohort. The all-cause SMR for both men and women was 0.8 (CI 95% 0.6–1.0). The deficit of deaths was fairly evenly distributed across cause-specific categories. The direct comparison with lichen-free participants yielded similar results (detailed data not shown); the all-cause mortality rate ratio was 1.0 (95% CI 0.8–1.1).

Table 2 The oral lichen lesion (OLL) cohort identified in 1973–1974

	Lichen cohort, n = 327 (%)
Gender	
Men	118 (36)
Women	209 (64)
Age (years) at entry	
15–24	20 (6)
25–34	38 (12)
35–44	48 (15)
45–54	77 (24)
55–64	83 (25)
65–74	41 (13)
75–84	17 (5)
≥85	3 (1)
Residence	
Rural	53 (16)
Small municipality	48 (15)
Small town	226 (69)
Smoking habits	
Never daily	205 (63)
Previous daily	50 (15)
Current daily	85 (26)
Alcohol use	
Never	131 (40)
Sometimes	174 (53)
Often/daily	22 (7)
Prescription drugs	
None	205 (63)
1	53 (16)
>1	61 (19)
Missing information	8 (2)
OLL form	
White	212 (65)
Red	115 (35)

Alcohol use: never = beer or wine less than once a week; sometimes = beer or wine more than once a week but wine or liquor less than twice a week; often/daily = wine or liquor 2–3 times a week or more frequent. Prescription drugs is the number of prescribed drugs used/day.

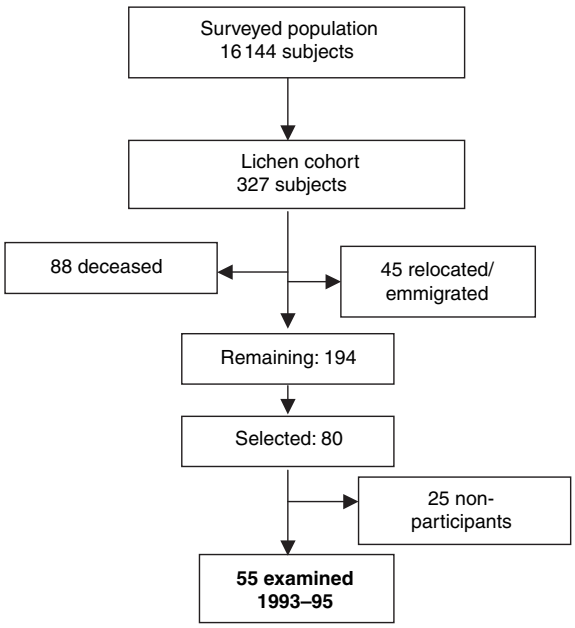

Figure 1 Flow chart of the total cohort to the re-examined group.

Table 3 Observed versus expected first cancer occurrences by gender in the lichen cohort during 1973–1974–2002, along with standardized incidence ratios (SIRs) and 95% confidence intervals (CI)

Type of cancer	*Observed*	*Expected*	*SIR*	*95% CI*
Women				
All cancers	43	31.9	1.3	0.98–1.8
Breast	12	8.4	1.4	0.7–2.5
Colon/rectum	6	4.0	1.5	0.5–3.3
Lung	2	1.3	1.6	0.2–5.5
Gastric	0	1.0	0.0	0.0–3.0
Cervix	1	0.8	1.2	0.0–7.0
Bladder	0	0.8	0.0	0.0–3.7
Renal	2	0.7	2.7	0.3–9.0
Oral	1	0.2	5.2	0.1–27.9
Other	19	14.7	1.3	0.8–2.0
Men				
All cancers	22	23.5	0.9	0.6–1.4
Prostate	7	6.8	1.0	0.4–2.1
Colon/rectum	3	2.9	1.0	0.2–3.0
Lung	0	2.1	0.0	0.0–1.4
Bladder	2	1.7	1.2	0.1–4.2
Gastric	3	1.2	2.5	0.5–7.3
Renal	1	0.7	1.4	0.0–8.0
Oral	0	0.2	0.0	0.0–15.0
Other	6	7.9	0.8	0.3–1.7

Table 4 Observed versus expected deaths by gender in the OLL cohort during 1973–1974–2002, along with Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals (CI)

Type of death	*Observed*	*Expected*	*SMR*	*95% CI*
Women				
All deaths	84	106.0	0.8	0.6–1.0
Cardiovascular	47	56.1	0.8	0.6–1.1
Cancer	22	23.3	0.9	0.6–1.4
Respiratory	2	7.6	0.3	0.0–0.9
Trauma	3	3.5	0.8	0.2–2.5
Other	10	15.5	0.6	0.3–1.2
Men				
All deaths	62	77.4	0.8	0.6–1.0
Cardiovascular	31	42.0	0.7	0.5–1.0
Cancer	17	17.5	1.0	0.6–1.6
Respiratory	4	5.8	0.7	0.0–1.8
Trauma	1	3.3	0.3	0.0–1.7
Other	9	8.8	1.0	0.5–1.9

An invitation to a clinical re-examination was sent to 80 of the 194 surviving OLL subjects who still resided in the area 1993–1995. Fifty-five subjects (69%) attended (Fig. 1). Reasons for non-participation were death between selection and re-examination ($n = 5$), refusal/missed appointment ($n = 11$), no contact ($n = 3$) or physical or mental impediments ($n = 6$). There were no participants from the oldest age-groups in 1973–1974 as most of them had already died. Thus, the mean age at entry among the 55 subjects who were re-examined in 1993–1995 was lower than the average in the entire OLL cohort. On the other hand, as a group the re-examined individuals did not differ importantly from the entire OLL cohort with regard to smoking, prescription drugs or OLL type (red or white), but the re-examined subjects reported, on average, a slightly higher alcohol consumption.

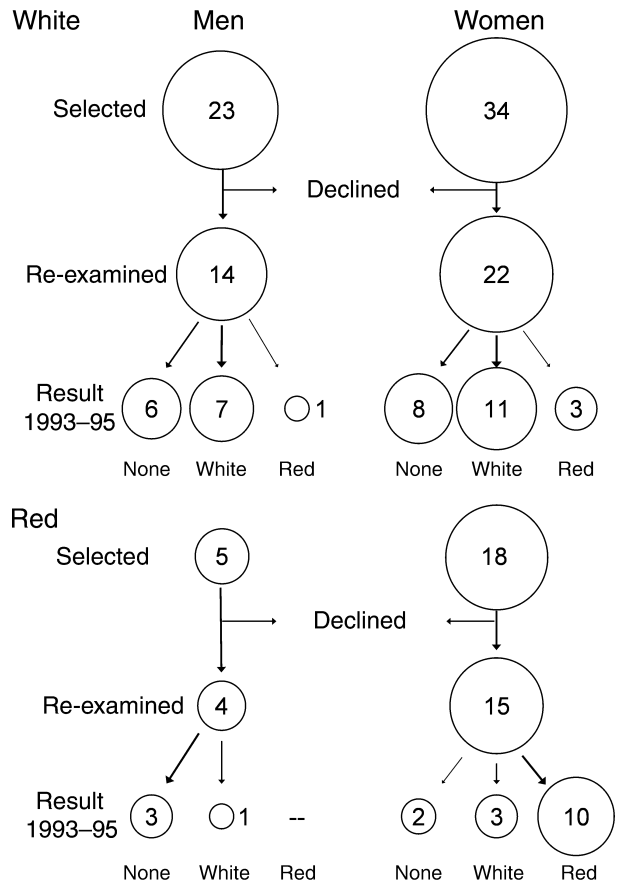

Figure 2 Development of oral lichen lesions (OLLs) in participating individuals between 1973–1974 and 1993–1995 by type of initial lesion (white or red) and gender.

The clinical course of the OLLs in re-examined subjects is described in Fig. 2. At follow-up 18 (50%) of the white OLLs recorded in 1973 were still present in its original form. Four subjects (11%) had changed from white to red type; however, in 14 (39%) the lesion had disappeared. This pattern was similar for men and women. The course of the red forms seemed to differ by gender, but the numbers were small (four men and 15 women). Among men, all the red OLLs had disappeared ($n = 3$) or converted to a white type ($n = 1$), while a majority of the women still had red OLLs present ($n = 10$; 67%). Re-examined subjects with red lesions tended to be somewhat older and to use more medications in 1993/1995 than those with white lesions or no remaining lesion, but the differences were far from statistically significant (data not shown). No conspicuous relationships emerged between the long-term development of OLLs and use of prescription drugs in 1973/1974, smoking or alcohol use in 1973/1974 or 1993–1995, or exposure to specific filling/restoration materials (data not shown). However, the power to detect clinically important differences was poor. No malignant lesions were noted at re-examination in any of the OLL categories.

At the re-examination five individuals reported that they had received treatment for their OLL during the period from 1973–1974 to 1994–1995. Two showed red lesions at both examinations, two had white lesions at both times and one was registered with a white OLL in 1973–1974 and had red OLLs at the re-examination.

Discussion

This long-term population-based follow-up study of non-consulting subjects with OLL revealed no statistically significant elevated risk of oral cancer. The cohort, however, was small with only 327 subjects and the expected number of oral cancers was only 0.4. Our result does not support previous reports of markedly elevated risks among referred patients in specialist clinics (7–10). Had the risk been 20-fold, as suggested in a recent clinic-based Swedish study among patients referred for specialist evaluation (7), we should have observed four oral cancer cases, but we found one. There was no association between OLL and cancer overall.

Upon re-examination, one-third of the lesions had disappeared. Such spontaneous remissions and changes in appearance over time have been described earlier (3). Our data suggest that red lesions may be more persistent in women than in men. Because of the putative relapsing nature of the condition, often noticed in clinical practice, lesions might come and go. Hence, the appearance (or absence) of lesions at a single point in time during follow-up might not always truly represent the subsequent course of the disease.

Dental amalgam has been proposed to be a pathogenetic factor of OLL. Replacement of amalgam restorations has been shown to result in healing or improvement of OLL (17). In contrast, we were unable to detect any effects on OLL corresponding to change of dental materials among our population-based subjects, but the power of our study was limited.

Strengths of our study include the prospective and population-based design and the comparatively long observation time. The major weakness is the limited size of the cohort, which precludes detection of weak or moderately strong associations with rare outcomes. Moreover, because of death or relocation, and limited investigative resources, only a fraction of the cohort underwent clinical investigation in 1993–1995.

However, the register-based follow-up for cancer and mortality was close to complete thanks to the National Registration Numbers in Sweden and well-managed population- and health registers. Essentially all occurrences of cancer are ascertained in the more than 98% complete nationwide Cancer Register (18, 19), all deaths are recorded in the Causes of Death Register (20), and practically, all emigrations are recorded in the Migration Register.

The observed numbers of deaths among both men and women in the OLL cohort were lower than expected based on age-, sex-, and period-specific rates in the general Swedish population. Although some geographical variations in longevity are conceivable, the most likely explanation is a 'healthy participant effect' among people who consented to an oral examination in 1973–1974. This selection bias may limit the generalizability of

our findings. There were no important differences in overall or cause-specific mortality between the OLL cohort and the surveyed population from 1973–1974 without OLL. Interestingly, however, a slight survival advantage compared with the general population was noted among patients with OLL at a specialist centre (7).

The inconsistent results in the literature regarding the association between OLL and risk of oral cancer may have several explanations. One explanation might be chance findings. Because of the low prevalence of OLL (about 2%) (11), published follow-up studies have rarely observed more than a handful of cancers. Furthermore, if exposures that are in themselves risk factors for oral cancer, e.g. smoking, increased medical attention and thus the probability of detection of OLL, selection bias may inflate risk estimates from clinic-based case series. Another conceivable explanation is that the risk varies with severity of the lesion and that a risk elevation becomes evident only in subjects with lesions that bring them to the attention of health care, either because of symptoms or a conspicuous appearance or size. It appears that previous studies on OLL showing an increased risk for cancer development primarily included patients who had been referred for evaluation by specialists (7–10, 21).

Although our data are limited by poor statistical precision, we conclude that OLL detected incidentally in non-patients may be less harmful than suggested in some previous studies among referred patients. More precise risk estimates by type and appearance of the lesion are clearly needed for future recommendations regarding management and surveillance.

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