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Long-term treatment outcome of oral premalignant lesions

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Summary The purpose of the present retrospective study was to learn the long-term outcome of oral premalignant lesions, leukoplakia and erythroplakia, with or without surgical intervention and to relate the outcome to factors supposed to be significant for malignant development including clinical type, demarcation, size, site, presence of epithelial dysplasia, smoking and surgery. A total of 269 lesions in 236 patients were included. Ninety-four lesions were surgically removed, 39 lesions (41%) being homogenous and 46 (49%) non-homogenous leukoplakias whereas nine (5%) were erythroplakias. Seventy-three percent of the lesions were associated with tobacco habits. The mean size of the lesions was 486 mm^2, and 71% of the lesions showed a degree of epithelial dysplasia. After excision the defects were closed primarily by transposition of mucosal flaps or they were covered by free mucosal or skin grafts. A few defects were left for secondary healing. After surgical treatment the patients were followed (mean 6.8 yrs, range 1.5–18.6 yrs), and new biopsies taken in case of recurrences. One hundred and seventy five lesions had no surgical intervention, 149 lesions (85%) being homogenous and 20 (11%) non-homogenous leukoplakias, and 6 (3%) erythroplakias. Eighty-one percent of the lesions were associated with smoking. The mean size of the lesions was 503 mm^2 and 21 of the lesions (12%) exhibited epithelial dysplasia. Sixty-five lesions were not biopsied. These patients were also followed (mean 5.5 yrs, range 1.1–20.2 yrs), and biopsies taken in case of changes indicative of malignant development. All patients were encouraged to quit smoking and candidal infections were treated. The possible role of different variables for malignant development was estimated by means of

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logistic regression analysis. Following surgical treatment 11 lesions (12%) developed carcinoma after a mean follow-up period of 7.5 yrs. Non-homogenous leukoplakia accounted for the highest frequency of malignant development, i.e. 20%, whereas 3% of the homogenous leukoplakias developed carcinomas. Surgically treated lesions with slight, moderate, severe and no epithelial dysplasia developed carcinoma with similar frequencies, i.e. 9—11%. Without surgical intervention 16% of the 175 lesions disappeared whereas seven lesions (4%) developed carcinoma after a mean observation period of 6.6 yrs. The highest frequency of malignant development (15%) was seen for non-homogenous leukoplakias, this figure being 3% for homogenous leukoplakias. Fourteen percent of lesions with slight epithelial dysplasia developed malignancy and 2% of lesions with no dysplasia showed malignant transformation. Logistic regression analysis showed a seven times increased risk (OR = 7.0) of non-homogenous leukoplakia for malignant development as compared with homogenous leukoplakia and a 5.4 times increased risk for malignant development for lesions with a size exceeding 200 mm^2. No other examined variables including presence of any degree of epithelial dysplasia, site, demarcation, smoking and surgical intervention were statistically significant factors for malignant development.

Introduction

The main purpose of identifying oral premalignant lesions is to prevent malignant transformation by initiating adequate intervention. It is widely approved that the oral premalignant lesions, leukoplakia and erythroplakia, show a significant tendency to malignant transformation. For the most common lesion, leukoplakia, the malignant transformation rate has been reported from 0.13% to 17.5%.[1] Various treatment modalities for oral leukoplakia have been reported, but there is currently no consensus on the most appropriate treatment.[2,3]

The treatment modalities include change of lifestyle factors such as tobacco and alcohol intake,[4,5] medication with retinoids or antimycotics,[6—8] surgical excision,[9—12] cryosurgery,[12—16] laser evaporation[17—19] or laser excision.[18,20—22] The outcome of these interventions appears to vary, and long-term follow-up studies are few. After surgical intervention, recurrencies and cancer development in areas of excised lesions have been reported in as much as 10—20% and 3—9%, respectively,[10,23,24] but no randomized clinical trials have been reported so far.[25]

Moreover, a number of paradigms about premalignant lesions, including factors significant for malignant development, have not been convincingly approved. These factors include clinical type,[4,26—32] demarcation, size,[33,34] site,[27,35,36] presence and grade of epithelial dysplasia,[4,11,27,37—40] and smoking.[41] Some of the factors have even been questioned in the past. This applies to site,[31] smoking,[4,31,42,43] and epithelial dysplasia.[4,30,31,38,40,41,43—51]

To challenge the above paradigms the hypothesis behind the present study was that the outcome after follow-up of oral premalignant lesions is independent of clinical type, demarcation, size, site, histopathology, smoking and surgery.

Therefore, the aim of the present study was to learn the long-term outcome of oral premalignant lesions, including leukoplakia and erythroplakia, after surgical intervention and after follow-up without surgery and to relate the outcome to factors supposed to be significant for malignant development including clinical type, demarcation, size, site, presence of epithelial dysplasia, smoking and surgery.

Material and methods

Lesions

In this retrospective study, a total of 269 lesions comprising 188 (70%) homogenous, 66 (25%) non-homogenous leukoplakias, and 15 (6%) erythroplakias in a total of 236 patients (132 women and 104 men; mean age: 60.8 yrs, range 23—92 yrs), referred between 1977 and 1997, were included. The clinical diagnosis of the lesions was based on the criteria provided by Axéll et al.,[52] adjusted to the most recent definition,[53] adopted by WHO,[54] and histopathological diagnosis of epithelial dysplasia was made according to WHO definitions.[27] All lesions were photographed as part of the first

examination and in case of changes. The approximated size of the lesions was recorded in mm^2 by multiplying the length with the width of the lesions.

The clinical set-up included antimycotic treatment of lesions with Candida infection as demonstrated by the presence of hyphae or pseudohyphae in PAS-stained sections or smears from the lesions. The patients were treated with amphotericin B, or miconazole for 4–6 weeks. Patients were informed about the premalignant nature of the lesions and smokers were encouraged to quit smoking throughout the entire follow-up period.

The intra-departmental handling of patients with premalignant lesions included routine referral of the patients to two of the authors (PH and PV) if lesions exhibited epithelial dysplasia or were located on the lateral margin or the ventral surface of the tongue or in the sublingual region. These lesions were strongly recommended for surgical removal if the patient's general medical condition allowed such treatment. However, for unknown reasons, the routine referral was not followed systematically, why a number of patients with the above mentioned characteristics were seen for follow-up examination elsewhere in the department and not treated by surgery. Also, patients who denied surgical intervention and patients with lesions without epithelial dysplasia and outside the areas described above were seen for regular follow-up examination. The mean follow-up period for all patients was 6.0 yrs (range 1–20 yrs).

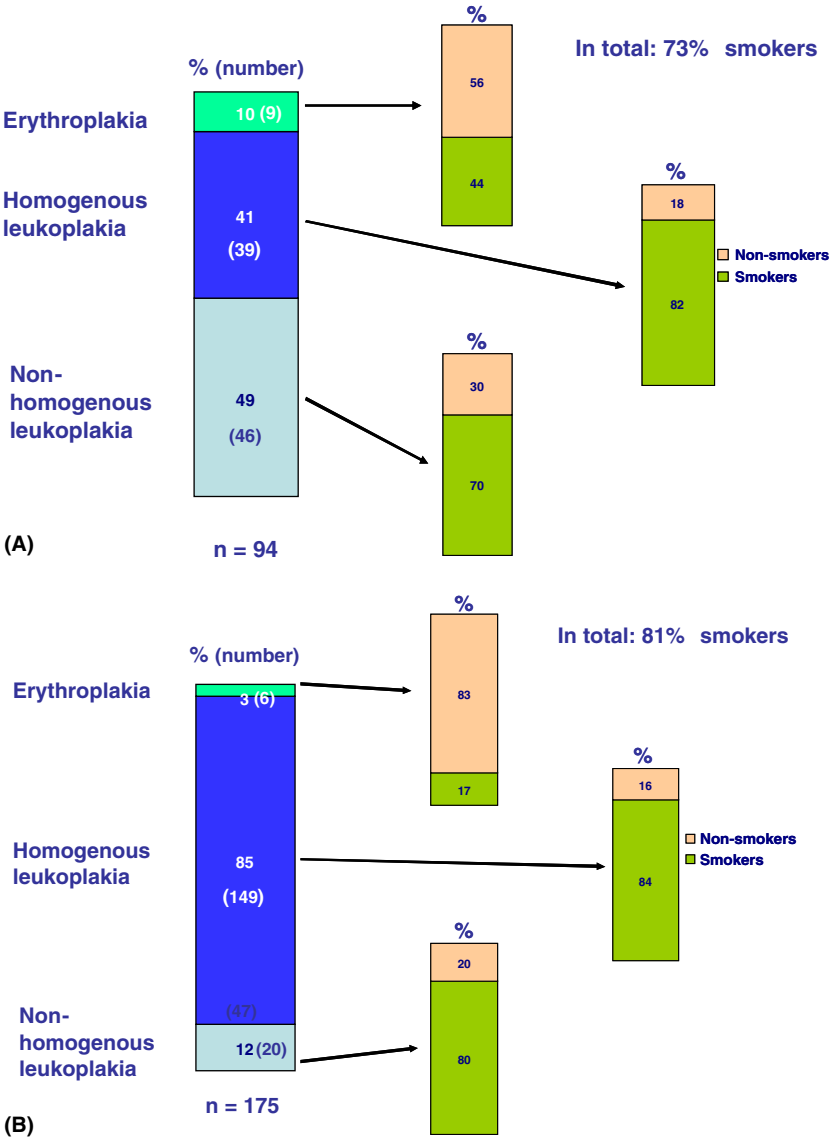

Figure 1 Smoking habits at first examination: (A) surgically treated lesions and (B) non-surgically treated lesions.

Lesions with surgical intervention

Ninety-four lesions in 89 patients, 51 lesions in 48 women and 43 in 41 men (mean age: 61.3 yrs, range: 23.3–92.4 yrs) were surgically removed. Short-term follow-up results for 40 of these lesions have previously been reported.[10] Thirty-nine lesions (41%) were homogenous and 46 (49%) non-homogenous leukoplakias, whereas nine (9%) were erythroplakias. The distribution of smokers and non-smokers by their lesions at the first examination is shown in Fig. 1A. Seventy-three percent of the lesions were associated with tobacco habits. The site-distribution of lesions is presented in Fig. 2A. The majority of lesions was situated in the floor of the mouth and in the buccal mucosa. The majority of lesions was sharply demarcated (Fig. 3A). The mean size of the lesions was 486 mm^2, (range: 10–3750 mm^2). The histological features of the lesions at the first examination are shown in Fig. 4A, the majority of lesions showing a degree of epithelial dysplasia or carcinoma in situ.

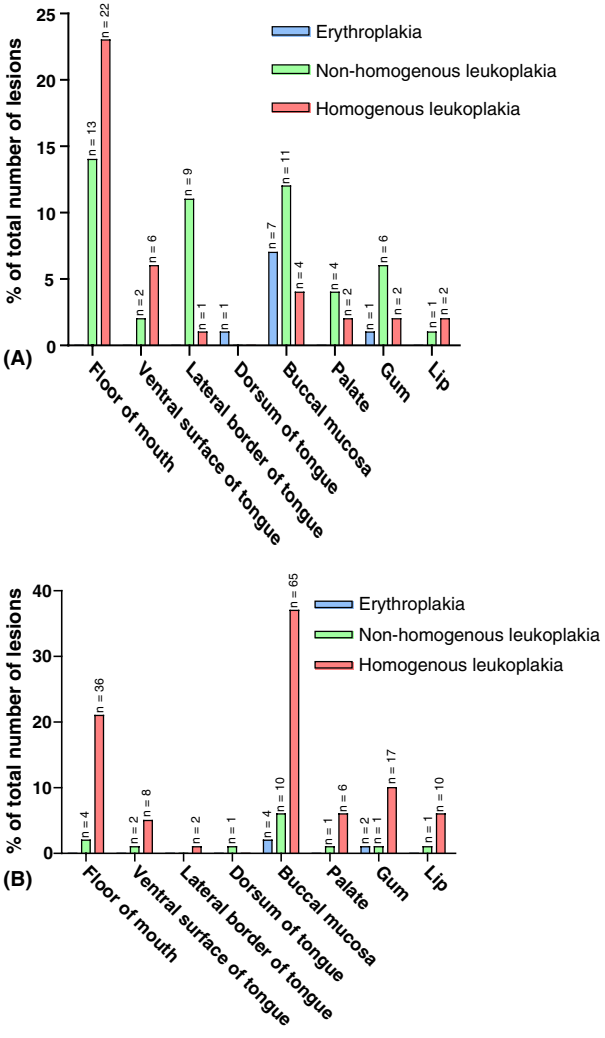

Figure 2 Lesions at first examination by site: (A) surgically treated and (B) non-surgically treated.

Surgical excision of the lesions with scalpel was made under local or general anaesthesia depending on size of the lesion and general health of the patient. Prior to injection of local anaesthesia the lesion was marked with ink and the lesion was excised with scalpel including 3–5 mm of clinically normal mucosa peripheral to the lesion as described previously.[10] The lesions were usually separated from underlying tissue structures by blunt dissection at an attempted depth of 4–5 mm. Sublingual lesions involving the orifice of the duct of the submandibular gland, included establishment of a new opening of the duct more dorsally. The mucosal defects after excision of the lesions were closed primarily or by transposition of local mucosal flaps. In cases not allowing these methods and where sufficient normal buccal mucosa was available, the defects were covered by a free buccal mucosal graft. Where these methods were not applicable, the defects were covered by split skin grafts or the defects were left for secondary healing.

The surgical treatment involved secondary healing (three lesions), coverage of defect by transposition of local mucosal flaps and primary closure (57 lesions), free mucosal (four lesions) or free skin grafts (30 lesions).

If histopathological examination of the surgically removed lesions in contrast to the initial biopsy revealed frank carcinoma, the patient was excluded from the study.

After the immediate postoperative period, the patients were examined every 3 months for the first 2 yrs and thereafter every 6 months during the following years (mean: 6.8 yrs, range: 1.5–18.6 yrs). In case of recurrences, new biopsies were taken.

Lesions with no surgical intervention

One hundred and seventy five lesions in 147 patients, 100 lesions in 84 women and 75 lesions in 63 men (mean age: 60.6 yrs, range: 28.1–89.7 yrs) had no surgical intervention. One hundred and forty nine lesions (85%) were homogenous and 20 (11%) non-homogenous leukoplakias, whereas 6 (3%) were erythroplakias. The distribution of smokers and non-smokers by their lesions at the first examination is shown in Fig. 1B. Eighty-one percent of the lesions were associated with smoking. The distribution of lesions by site is presented in

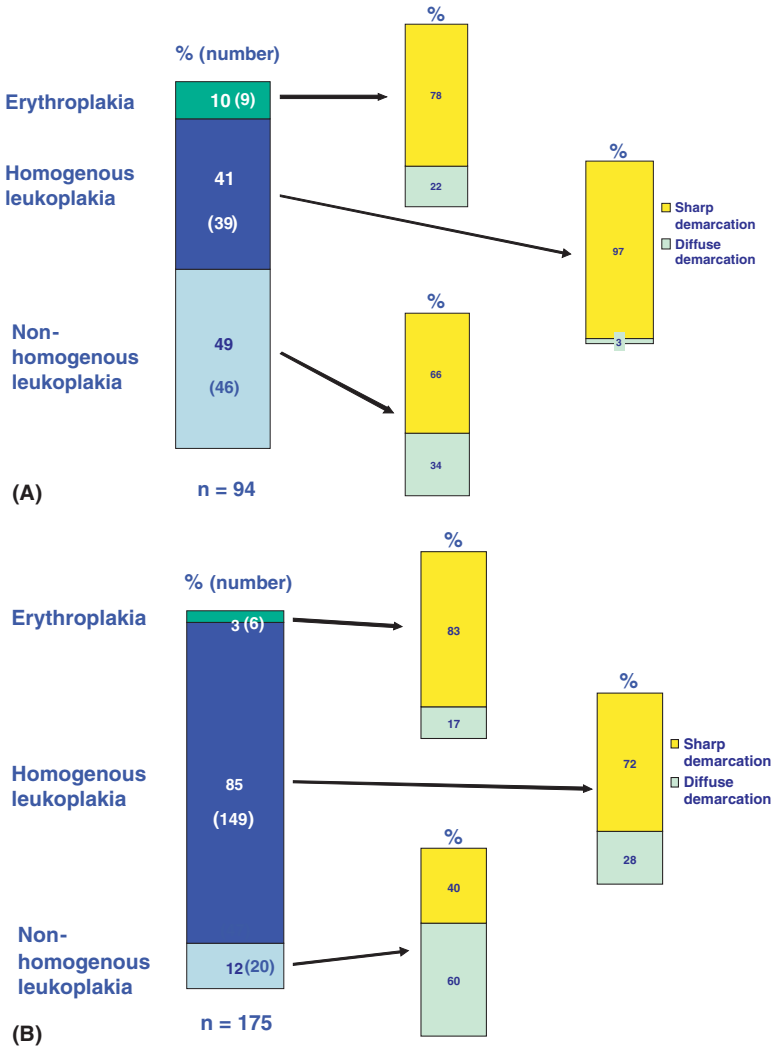

Figure 3 Demarcation of lesions at first examination: (A) surgically treated lesions and (B) non-surgically treated lesions.

Fig. 2B. The majority of lesions was situated in the buccal mucosa and in the floor of mouth and the majority of lesions were sharply demarcated (Fig. 3B). The mean size of the lesions was 503 mm^2 (range: 12–2800 mm^2). The histological findings at the first examination are presented in Fig. 4B. A total of 21 of the lesions (12%) exhibited epithelial dysplasia. Sixty-five lesions (37%) were not biopsied either because the patient refused, or because the lesions were considered as having a low risk of malignant development.

The patients were followed with varying intervals dependent on characteristics of their lesions. Non-homogenous lesions and lesions with epithelial dysplasia were seen every third month whereas homogenous lesions were seen twice annually during the follow-up period (mean: 5.5 yrs, range: 1.1–20.2 yrs). In case of change of clinical features indicative of malignant transformation, biopsies were taken.

Statistical data

Analysis of data was performed using the package SAS (version 8.02, SAS Institute, Inc., Cary, NC). The possible role of different factors for malignant development of the premalignant lesions was estimated by means of logistic regression analysis. The factors were incorporated as independent variables in the analysis if they had an association with the outcome variable (malignant transformation) at a $p < 0.20$. Smoking habits were included in the first analysis both in terms of smokers/non-smokers at the first examination and in terms of ever smokers/never smokers throughout the follow-up period. The criterion of the first analysis was not

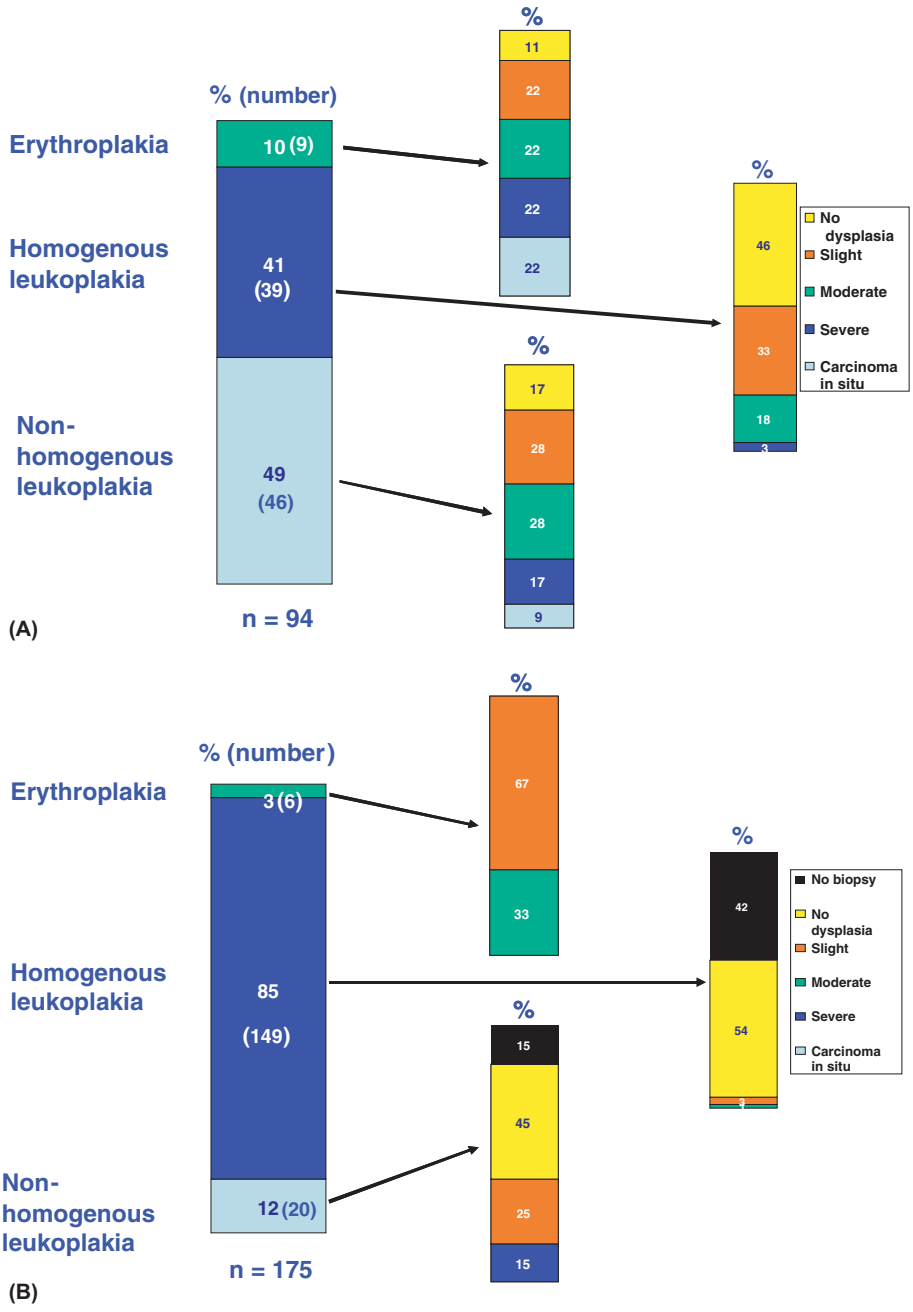

Figure 4 Histological characteristics of lesions: (A) surgically treated lesions and (B) non-surgically treated lesions.

fulfilled for smoking habits registered as ever smokers or never smokers and for site, why these factors were excluded from the regression analysis. The included independent variables are shown in Table 1.

In connection with the logistic regression analysis the odds ratios and the corresponding confidence intervals were calculated. Ordinary level of significance: 0.05.

To examine the effect of surgical treatment on malignant development of non-homogenous leukoplakias with epithelial dysplasia at the ''risk sites'' mentioned, a logistic regression analysis was used again.

Results

Lesions with surgical intervention

The outcome of surgical treatment of the various types of lesions is presented in Figs. 5A–C, 6A

Table 1 Odds ratio estimates for carcinoma to occur

	Variable	Point estimate	95% Confidence limits	
Clinical type	2 vs 3	7.0	1.7	28.5
Clinical type	1 vs 2	1.0	0.1	13.1
Size	1 vs 2	5.4	1.1	26.1
Histology	1 vs 3	4.3	0.4	49.6
Histology	2 vs 3	0.9	0.2	3.5
Surgery	1 vs 2	1.6	0.4	5.9
Border	1 vs 2	0.9	0.3	2.5
Tobacco habit	1 vs 2	0.6	0.2	1.8

Clinical type: 1. Erythroplakia, 2. Non-homogenous leukoplakia, 3. Homogenous leukoplakia.
Size: 1. $\geqslant$200 mm^2, 2. <200 mm^2.
Histology: 1. Carcinoma in situ, 2. Slight, moderate or severe dysplasia, 3. No dysplasia.
Surgery: 1. With surgical intervention, 2. Without surgical intervention.
Border: 1. Sharp demarcation, 2. Diffuse demarcation.
Tobacco habit: 1. Smokers at the first examination, 2. Non-smokers at the first examination.

and B, 7A and 8A. Out of the 94 surgically treated lesions approximately two thirds had a successful treatment outcome characterized by normal mucosa or skin graft (Fig. 8A). The successful outcome was equally distributed among homogenous and non-homogenous leukoplakias, with erythroplakia showing slightly less.

Recurrences occurred in 12 cases (13%) (eight non-homogenous and two homogenous leukoplakias, two erythroplakias), five (5%) of these (three non-homogenous and two homogenous leukoplakias) had two recurrences and two lesions (2%) (one non-homogenous and one homogenous leukoplakia) exhibited three recurrences during the follow-up period.

A total of 11 lesions (12%) developed carcinoma after a mean follow-up period of 7.5 yrs (range 2.7—15.1 yrs) (Fig. 8A). The clinical type of lesion accounting for most of the malignant developments among surgically treated lesions, i.e. 20%, was non-homogenous leukoplakia (Fig. 5A), whereas 3% of the homogenous leukoplakias were associated with malignant development after surgical intervention (Fig. 5B). One (11%) out of nine surgically treated erythroplakias developed carcinoma. Among the 12 recurring lesions, four lesions (33%) (one erythroplakia and three non-homogenous leukoplakias) later developed carcinoma.

Homogenous leukoplakias showed a much higher rate of persistence (31%) than did non-homogenous leukoplakias (5%) after surgical intervention (Fig. 5A and B).

Surgically treated lesions in, what was considered sites of increased risk of malignant development, developed carcinoma in 13% of the surgically treated cases, whereas 72% of these lesions became normal mucosa or skin (Fig. 6A). Lesions in other sites developed carcinoma in 10% of the cases (Fig. 6B).

The histological feature associated with the highest proportion (33%) of malignant development (Fig. 7A) after surgical intervention was carcinoma in situ, this figure being 11% for lesions with slight dysplasia, 9% for lesions with moderate or severe dysplasia and 11% for lesions with no dysplasia.

Lesions with no surgical intervention

Lesions without surgical intervention demonstrated an outcome after follow-up as presented in Figs. 5A—C, 6B, 7B and 8B. Whereas 16% of the 175 lesions disappeared, seven lesions (4%) developed carcinoma after a mean observation period of 6.6 yrs (range: 1.0—17.2 yrs) (Fig. 8B). The highest frequency of malignant development (15%) was seen for non-homogenous leukoplakias (Fig. 5A) whereas 3% of homogenous leukoplakias showed such a course (Fig. 5B).

Homogenous leukoplakias showed a much higher rate of persistence (81%) than did non-homogenous leukoplakias (10%), which became homogenous in 55% and disappeared in 20% of the cases without surgical intervention.

Not surgically treated lesions in, what was considered sites of increased risk of malignant development, developed carcinoma in 4% of the cases, whereas 13% of these lesions became normal mucosa (Fig. 6A). However, lesions in other sites also developed carcinoma in 4% of the cases (Fig. 6B).

The histological feature at first examination associated with the highest frequency of malignant development, i.e. 14%, was slight dysplasia. 2% of lesions with no dysplasia and 5% of non-biopsied lesions developed carcinoma (Fig. 7B).

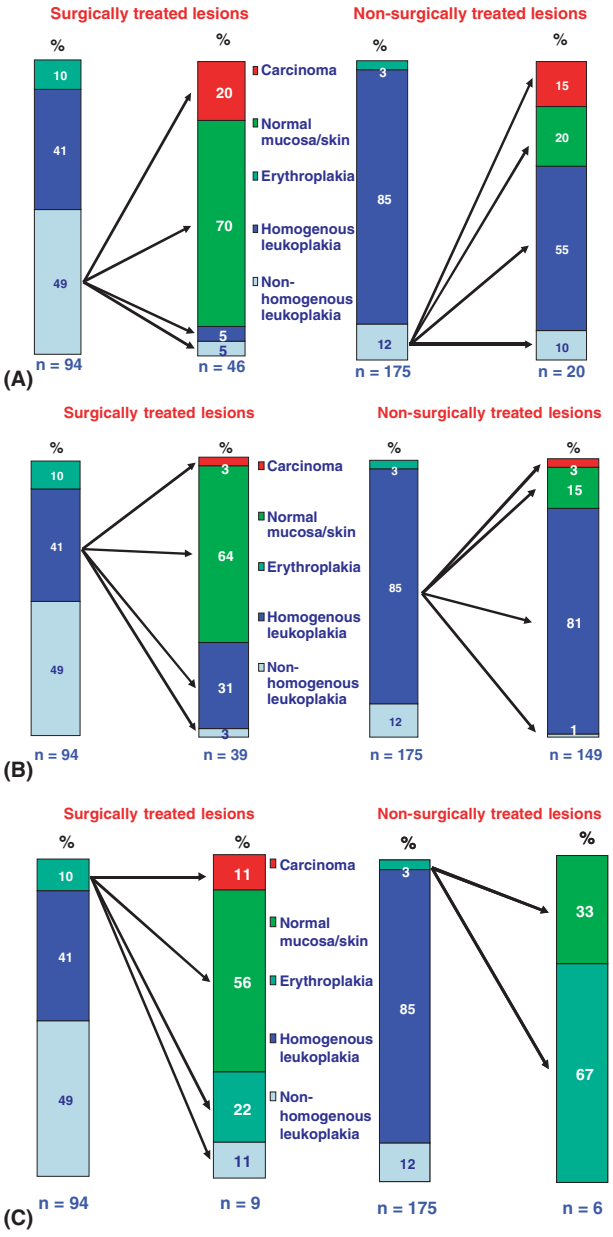

Figure 5 Clinical type at first and last examination: (A) non-homogenous leukoplakia, (B) homogenous leukoplakia and (C) erythroplakia.

While the smoking habits in the two treatment groups were slightly different at baseline, the proportion of smokers was similar at the final examination (Fig. 8A and B). Thus, among surgically treated patients 73% smokers was reduced to 63% and 81% smokers among non-surgically treated patients was reduced to 62% at the final examination. In both groups reduced smoking was obtained in equal proportions, i.e. 18–19%.

Only the variables in Table 1 fulfilled the inclusion criteria of the logistic regression analysis. The analysis showed a seven times increased risk (OR = 7.0) of non-homogenous leukoplakia for malignant development as compared with homogenous leukoplakia. Further, a 5.4 times increased risk for malignant development was observed when the size of the lesions exceeded 200 mm^2. No other variables were statistically significant.

The result of logistic regression analysis of the effect of surgical treatment on malignant development of non-homogenous leukoplakias with epithelial dysplasia at the ''risk sites'' mentioned was an estimated odds ratio of 1.9, the 95% confidence limits being 0.6–6.5.

Discussion

The present study includes two groups of patients with premalignant lesions. One group had surgical intervention whereas the other group had no surgical treatment. The study is not a randomized clinical trial and the two groups under investigation are not directly comparable, because the composition of lesions in the groups is different. Surgically treated lesions comprised 49% non-homogenous leukoplakias in contrast to 12% non-homogenous leukoplakias in the group of non-surgically treated patients. Moreover, while 71% of the surgically treated lesions showed epithelial dysplasia or carcinoma in situ, only 12% of biopsied non-surgically treated lesions displayed epithelial dysplasia and none of these lesions exhibited carcinoma in situ.

The study has demonstrated that the surgical approach applied did not prevent all premalignant lesions from malignant development. This is consistent with findings in other studies of surgically treated premalignant lesions.[9–11,23,24]

Our challenging hypothesis was that the risk of cancer development could not be eliminated or significantly reduced by surgical intervention. The surgically treated lesions developed cancer at a higher rate (13%) than did surgically untreated lesions (4%). Since the two groups were not directly comparable due to differences in types of lesions, comparisons were only made on the basis of the various factors characterizing the lesions i.e. clinical type of lesion, demarcation, size, site, tobacco habit, histology and surgical intervention, all factors believed to be important for the lesions' potential of malignant development.[4,11,27,33,37–40]

However, the logistic regression analysis showed that the various factors characterizing the lesions in most instances were insignificant. The only two significant factors identified with a prognostic value was the clinical type of leukoplakia, and the size of the lesion.

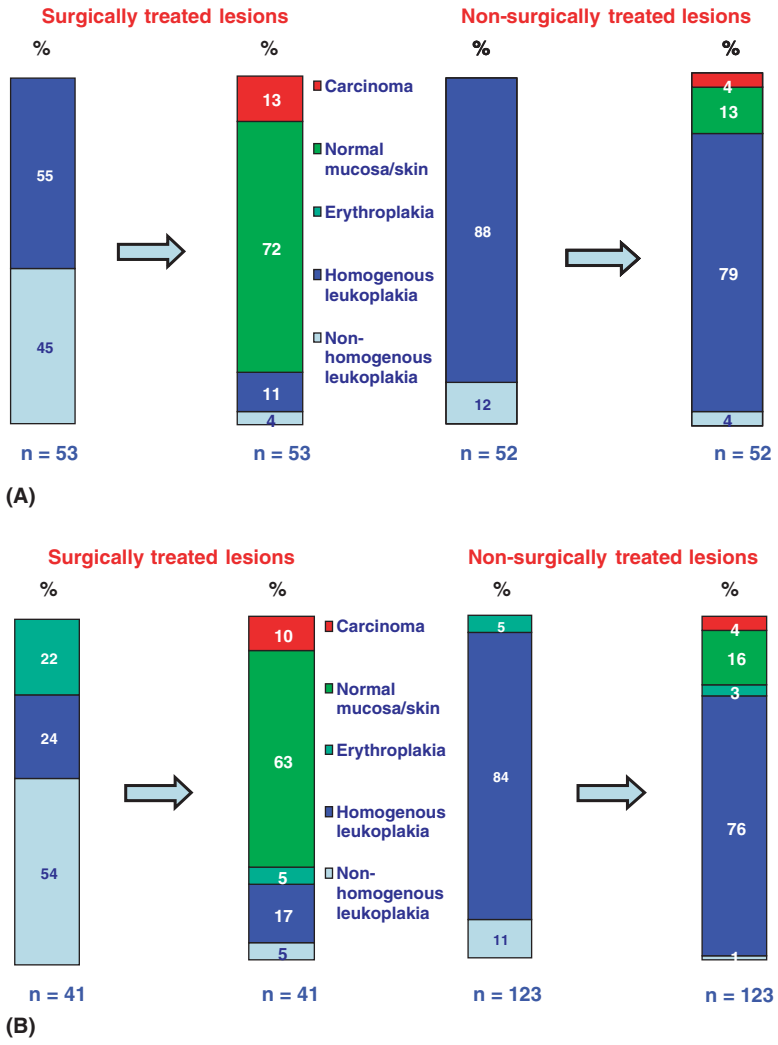

Figure 6 Clinical type at first and last examination. (A) Risk areas: lateral border and ventral surface of tongue, floor of mouth; (B) non-risk areas: dorsum of tongue, buccal, palatal, gum and lip mucosa.

Thus non-homogenous leukoplakia exhibited an odds ratio of 7.0 for cancer to occur as compared with homogenous leukoplakia. The finding is consistent with previous results demonstrating a higher potential for malignant development of non-homogenous leukoplakia.[4,26,28–32]

If the size of the lesions exceeded 200 mm^2 the odds ratio for cancer to occur was 5.4 as opposed to smaller lesions. A significance of size of the lesions for cancer development is not substantially evidenced in the literature, but has been reported previously.[33]

The logistic regression analysis also showed that the histological features of the initial biopsy were insignificant factors, i.e. presence of carcinoma in situ or any degree of epithelial dysplasia versus no dysplasia. The reason for considering presence of any degree of dysplasia versus no dysplasia, was that the diagnosis of epithelial dysplasia and degrees thereof to some extent is subjective.[46,51]

The distribution of cancer by degree of epithelial dysplasia (Fig. 7A and B) on the other hand showed that the degree of epithelial dysplasia did not appear to be correlated with the course of the lesions in any of the groups examined, a finding consistent with that of others.[16,50,51] However, our finding of 11–14% malignant development of surgically and non-surgically treated lesions exhibiting slight epithelial dysplasia is particularly interesting in the light of those previous studies, in which lesions with slight epithelial dysplasia have been regarded harmless.[37,45,47] A similar comment applies to surgically treated lesions without epithelial dysplasia developing carcinoma in 11% of the cases and to non-biopsied leukoplakias developing cancer in 5% of the cases. The

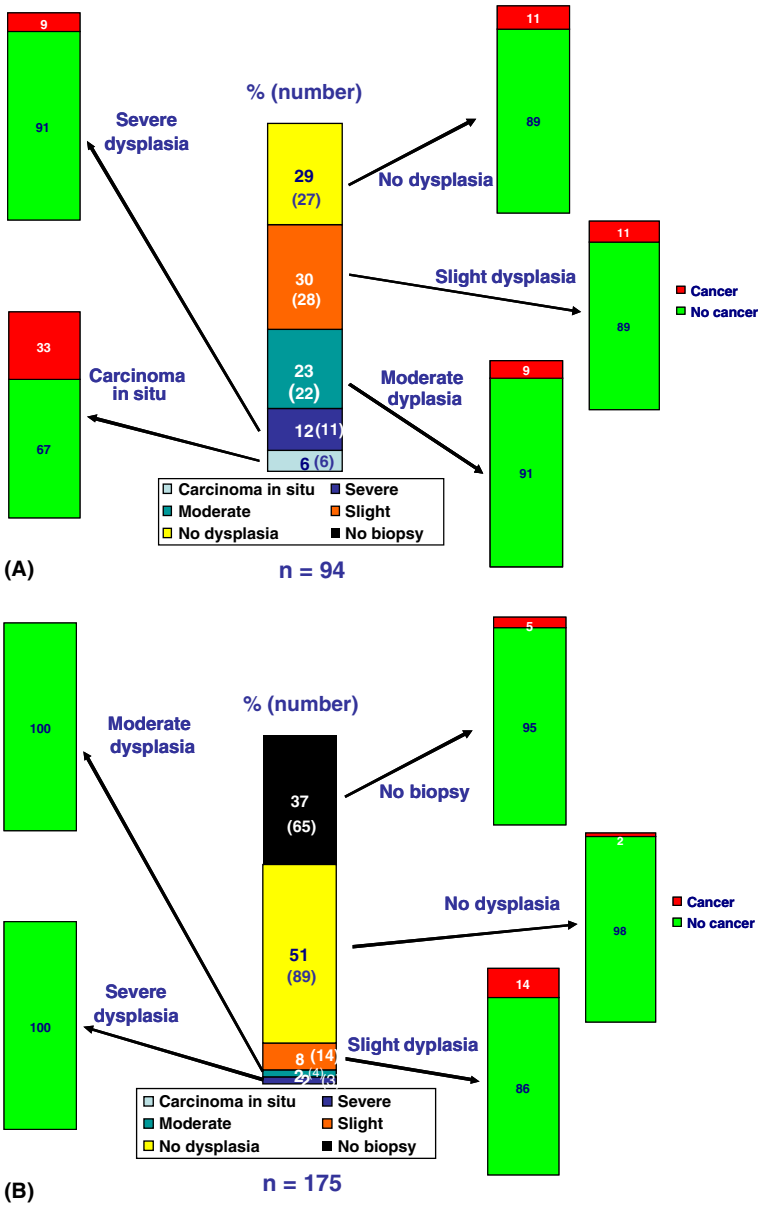

Figure 7 Cancer development by epithelial dysplasia: (A) surgically treated lesions and (B) non-surgically treated lesions.

reason for not taking biopsies must be that the lesions were regarded harmless. The lack of correlation between histological feature and outcome of the lesions with or without treatment should be considered in the light that the biopsies were taken at the first examination years before termination of the study. Meanwhile, of course the histological features may have changed in lesions without surgical intervention even without such changes being observed clinically. Also, the initial biopsy is considered one of the important factors determining how to handle the lesion. However, whether the initial biopsy is representative of the entire lesion is an open question to be addressed in a future report.

Lack of correlation between histological features of biopsy and outcome of lesions may also be explained by biopsy features not being representative of the entire lesion.

Moreover, the result of the statistical analysis also showed that what was considered risk sites, i.e. lateral border and ventral surface of tongue and floor of mouth exhibited no increased risk of malignant development as compared with other sites of the oral mucosa. This is in contrast to some previous findings,[3,27,36] but in support of others.[31]

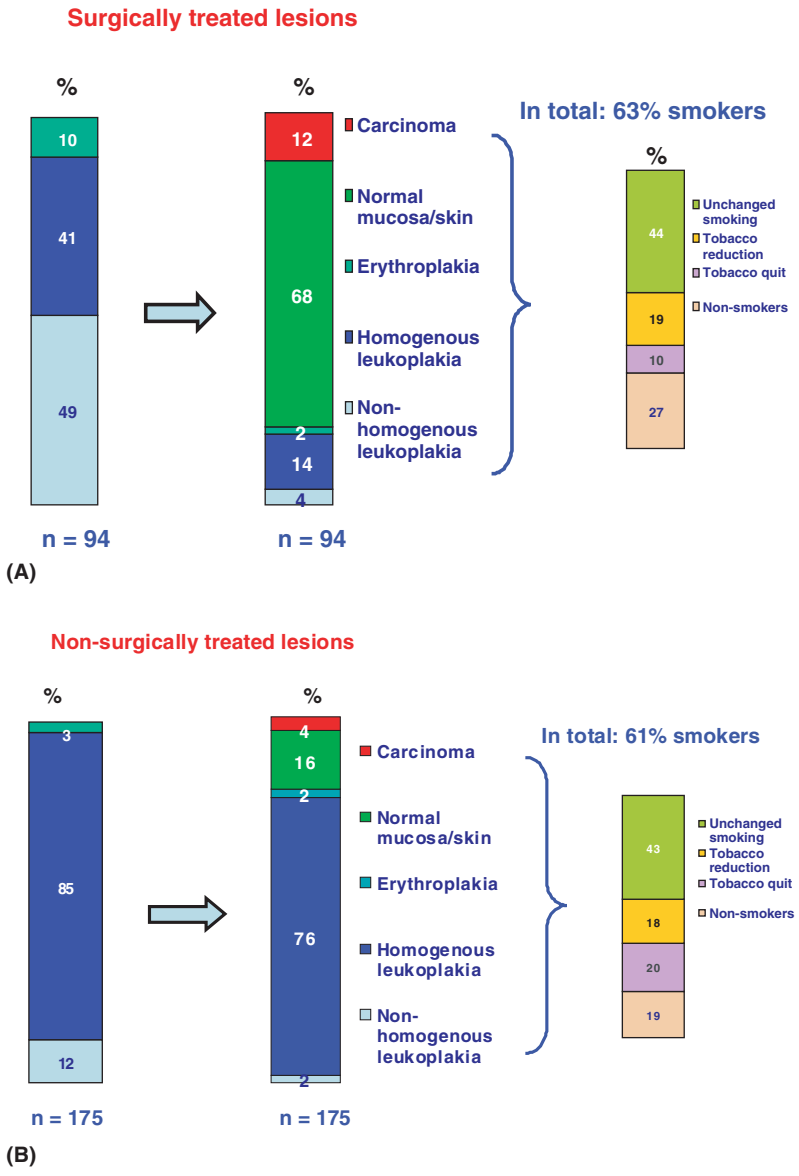

Figure 8 (A, B) Clinical type at first and last examination and tobacco habits.

The present study did not reveal any evidence supporting that surgical treatment was protective against cancer development. Neither was the opposite effect substantially evidenced.

The result of logistic regression analysis of the effect of surgical treatment on malignant development of non-homogenous leukoplakias with epithelial dysplasia at the ''risk sites'' mentioned was an estimated odds ratio of 1.9, the 95% confidence limits being 0.6—6.5. Although the effect of surgical intervention was considered insignificant, the result may suggest an increased risk of malignant transformation after surgery rather than surgery being protective for such a course.

Furthermore, it is remarkable that as much as 20% of surgically treated non-homogenous leukoplakias developed carcinoma, since the present frequency of malignant development of such lesions without surgical intervention appeared to be less. Also a Norwegian follow-up study has revealed a smaller frequency of malignant development of non-homogenous leukoplakias without intervention, i.e. 13.4%.[28] Whether surgical treatment acts as a cancer promotional stimulus on premalignant oral lesions is an open question, which obviously needs further investigation. Such an effect has been reported in an experimental study by Maeda and Kameyama,[55] who found an increased incidence of carcinomas after excision of hamster tongue mucosa treated with carcinogen.

Another explanation of the lacking success of surgical treatment may be a multiclonal origin of

the affected areas as seen in field cancerization.[56,57] Such a concept includes persistence of cancer stigmatized cells outside the removed lesions.[58,59] This hypothesis is supported by studies on DNA content in cells of oral leukoplakia, [41–43,50] which revealed cariotypic changes in the oral mucosa outside the clinically and histologically visible affections.

It was a hypothesis, that a limited number of clones involved might clinically manifest as a sharp demarcation of the lesions. Therefore we examined the prognostic value of the type of demarcation of the lesions, but failed to demonstrate any association.

An interesting finding was that homogenous leukoplakias showed a much higher rate of persistence (31%) after surgery than did non-homogenous leukoplakias (5%). This also applies to non-surgically treated lesions, where 81% of the homogenous leukoplakias persisted as opposed to only 10% of non-homogenous leukoplakias. Non-homogenous leukoplakias became homogenous in 55% and disappeared in as much as 20% of the cases without surgical intervention. Antimycotic treatment and altered smoking habits may account for part of the later changes, which demonstrates a reversible nature of some of the lesions irrespective of their non-homogenous clinical appearance.

In conclusion, the present study has shown that surgical intervention does not appear to prevent oral premalignant lesions from developing malignancy. The only significant factors associated with malignant transformation are clinical type of leukoplakia and size of the lesion. Other factors, including site, demarcation, presence of any type of epithelial dysplasia, smoking and surgical intervention appear to be insignificant with respect to future malignant development.

The present findings emphasize the need for new treatment modalities to effectively prevent cancer development as well as other methods for prediction of cancer development in susceptible lesions. The study may also serve as a background for establishing randomized clinical trials, because within the limitations of the retrospective design it demonstrates that there is no obvious advantage of surgical intervention.

Acknowledgements

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