# Meta-analysis on clinicopathologic risk factors of leukoplakias undergoing malignant transformation

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## Abstract

**Context:** Leukoplakia is classified under the term potentially malignant disorder. This term does not suggest the clinician or the patient about the severity of the disease to undergo a malignant transformation. Thus, there arises a need to identify the risk factors associated with malignant transformation (MT) to predict it at the earliest.

**Aims:** To generate evidence regarding the clinicopathologic factors affecting MT in oral leukoplakias.

**Materials and Methods:** Meta-analysis was done by extracting data from all the previous studies published. Articles were searched in PubMed databases.

**Statistical Analysis:** Mixed model by using the PROC MIXED (SAS 9.3) was performed to estimate the effect of different factors such as gender, type of habit (smoking tobacco, gutka, paan (with tobacco) and no habit association), clinical type and histopathology on MT. The lower specific mean for MT was also calculated with respect to the above-mentioned factors.

**Results:** Speckled leukoplakias also known as erythroleukoplakia confirmed to be at the highest risk. Lateral border of the tongue followed by gingiva, buccal mucosa, floor of the mouth, lesions involving tongue and floor of mouth showed increased risk. Smoking tobacco (cigarette and bidi) and idiopathic leukoplakia (without habit) carried almost equal risk. Gender had minimal influence on MT. Histopathologic correlation of grades showed an insignificant bearing on MT.

**Conclusion:** The carcinogenic transformation of a preexisting lesion (leukoplakia) is multifactorial and patient specific. The protocol to delineate a high-risk lesion should include the clinical type and site.

**Key Words:** Epithelial dysplasia, malignant transformation, oral leukoplakia, speckled leukoplakia, tobacco, tongue

## INTRODUCTION

Oral precancerous lesions have been a subject of controversy ever since the term was introduced. They were defined as morphologically altered tissues in which cancer is more likely to occur than its apparently normal counterpart.[1] This group included leukoplakia, erythroplakia, lichen planus and palatal keratosis. Studies done later confirmed that not all precancerous lesions transformed into malignancy and some regressed after

the cessation of habit.[2-4] Thus, a new term potentially malignant disorders was introduced. However, this term does not imply to the patient nor the clinician about the severity of the risk of malignant transformation (MT) as it again includes lesions of differing risk with erythroplakia 14%, leukoplakia 0.3–17.5% and palatal lesions in reverse smoking 0.3% being the least.[2,5-7]

Oral leukoplakia is one of the most common lesions classified under the heading "Potentially malignant disorder" and is graded histologically as mild, moderate and severe dysplasia depending on the level of involvement of the epithelium by the WHO. The main purpose behind grading dysplasia was to predict and possibly prevent MT. However, a majority of studies have been unable to conclusively predict MT on the basis of grading dysplasia.[6,8,9] Thus, there arises a need to identify the risk factors associated with MT to predict it at the earliest.

The aim of the present study was to generate evidence regarding the clinicopathologic risk factors of leukoplakias undergoing MT by conducting a meta-analysis of the observational studies on leukoplakia.

## MATERIALS AND METHODS

As per the guidelines of the meta-analysis of the observational studies in epidemiology, a search was conducted in PubMed database. The search term included oral leukoplakia, dysplasia and potentially malignant disorders. Each of these terms was again combined with the terms observational studies, follow-up studies, clinicopathologic studies and outcome. Reference list of the obtained studies and personal reference lists were also searched manually.

### Selection criteria

Studies which confirmed diagnosis of dysplasia histologically were included in the review. For multiple publications from the same patient group, the longest follow-up period was considered. The cross-sectional studies of dysplasia were excluded and also cases which showed carcinoma changes at the initial biopsy or within 3 months of diagnosis was excluded as many authors were of the opinion that these lesions could be cancer at the initial biopsy, and the sample might have been from a nonrepresentative site. Proliferative verrucous leukoplakias were also excluded. Due to a limited number of follow-up/observational studies, we also extracted data of the follow-up cases in studies where conservative treatment was performed.

### Data extraction

The following data were extracted: Gender of the patients; type of habit association (tobacco smoking [TS], bidi, cigarette--in some studies bidi habit was mentioned specifically so it was taken as a separate group, tobacco chewing [TC]--gutka, pan [with tobacco], TS + TC, nonhabit--when there was

no history of habit association [idiopathic leukoplakia], in some studies tobacco with pan was mentioned without mentioning the form of tobacco whether chewed or smoked, so it was taken as tobacco and pan); site-few studies mentioned the exact location of the lesion, whereas a few combined different site, so it was taken as it is; type of leukoplakia; histopathologic grade of dysplasia; time at which MT took place after initial biopsy and the rate of MT. While extracting data on the type, we noticed that some studies had not specifically mentioned the type of nonhomogenous leukoplakias, so they were included under combined nonhomogenous group which may be any type of nonhomogenous leukoplakia.

When extracting data on histopathologic grades, we noticed that there was no uniformity in grading, a number of studies did not grade dysplasia, and therefore they were included under combined/ungraded dysplasia. Few studies clubbed mild and moderate, few other moderate and severe, so they were included in the same way.

### Statistics

Mixed model by using the PROC MIXED (SAS 9.3) (SAS 1976) was performed to estimate the effect of each of the above-mentioned factors on MT of leukoplakia. The lower specific mean for MT was also calculated with respect to the above-mentioned factors.

The model fit was done taking study as random effect as follows:

$$Y_{ij} = B_0 + B_1 Xij + B_2 Xij^2 + S_i + b_i * X_{ij} + \epsilon_{ij}$$

Where i = 1–13 studies

J = 1 to $n_1$ values, $B_0 + B_1 Xij + B_2 Xij^2$ is fixed effect part of the model and $S_i + b_i * X_{ij} + \epsilon_{ij}$ is random effect part of the model. PROC MIXED as implemented in the version of 9.3 S.A.S was used.

## RESULTS

The meta-analysis comprised a total of 13 studies starting from 1975 to 2009. One fact that stood out was that there was no uniformity in reporting of cases in terms of habit history, site, type and grade of dysplasia.

A correlation of gender with MT rate showed minimal or no difference. However, there was a trend toward female predilection [Table 1 and Figure 1].

When habit association and MT rate were compared, smoking had the highest risk, followed by no habit history, tobacco and pan, chewing tobacco, pan, bidi smoking, smoking and chewing tobacco [Table 2 and Figure 2].

On correlating site of the lesions with MT, we noticed that lateral border of tongue had the greatest risk followed by gingiva; buccal mucosa; floor of the mouth; lesions involving tongue and floor of mouth; palate; lip; mandibular ridge and mucobuccal fold; maxillary ridge and mucobuccal fold [Table 3, Table 4 and Figure 3].

Speckled leukoplakias demonstrated utmost risk for MT followed by combined nonhomogenous, nodular, homogenous, verrucous and ulcerated type of leukoplakia [Table 5 and Figure 4].

Histopathologic correlation of grades showed that hyperkeratosis without dysplasia had the maximum risk of MT followed by ungraded dysplasia, moderate dysplasia, severe dysplasia, mild dysplasia, verrucous hyperplasia without dysplasia, moderate + severe dysplasia and mild + moderate dysplasia. [Table 6 and Figure 5].

### DISCUSSION

Precancerous lesion and precancerous condition were proposed by the WHO in 1978, wherein the term precancer in itself suggested a clinical presentation that may have a tendency to develop cancer.[10] This conveyed that carcinogenesis is a two-step or multistep process. Later, studies done by Gupta et al. in 1980, Silverman et al. in 1984 and Schepman et al. in 1998 revealed that not all lesions having dysplasias developed cancer, suggesting that it is patient specific.[2,7,11] Further studies suggested that cancer may develop in the contralateral or any other apparently normal mucosa.[12]

A recent consensus thus proposed a new term "potentially malignant disorder" in the place of precancer. The consensus was of the opinion that not all lesions and conditions described under the term precancer may transform to cancer, rather that there is a family of morphological alterations among which some may have an increased potential for MT.[10] However, term potentially malignant disorder fails to subclassify lesions that have an increased potential for MT among the group. The term is more generalized, including in its gamut reticular lichen planus having a negligible tendency when compared to erythroplakia which has a higher tendency for MT. Thus, the term neither completely suggests to the clinician nor the patient about the severity of the disease or its MT potential.

Warnakulasuriya et al. in 2007 proposed that the term leukoplakia should be used to recognize white plaques of

**Table 1: Comparing gender with malignant transformation**

| Serial number | Study | Gender | |
|---|---|---|---|
| | | Male | Female |
| 1 | Waldron et al. (Emory material) | 818 | 808 |
| 2 | Bancozy et al. (conservative group) | NM | NM |
| 3 | Silverman et al. | 4687 (5) | 75 (1) |
| 4 | Hogewind | 50 (0) | 34 (3) |
| 5 | Pogrel et al. | 7 (2) | 12 (1) |
| 6 | Silverman et al. | 125 (19) | 132 (26) |
| 7 | Lind et al. | 102 (8) | 55 (6) |
| 8 | Gupta et al. | NM (12) | NM (7) |
| 9 | Schepman et al. | 76 (4) | 90 (16) |
| 10 | Cowan et al. | 464 (16) | 482 (25) |
| 11 | Hsue et al. | NM | NM |
| 12 | Ho Shan et al. | 148 (22) | 0 |
| 13 | Ho et al. | 49 (9) | 42 (11) |

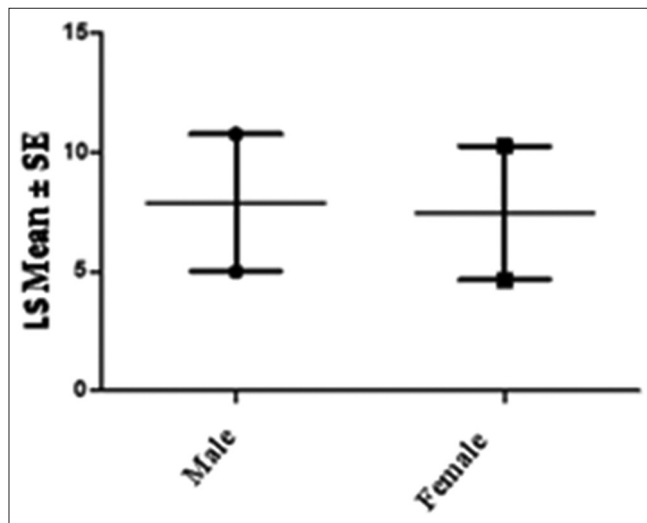Figures within bracket represent a number of MT cases. NM: Not mentioned, MT: Malignant transformation



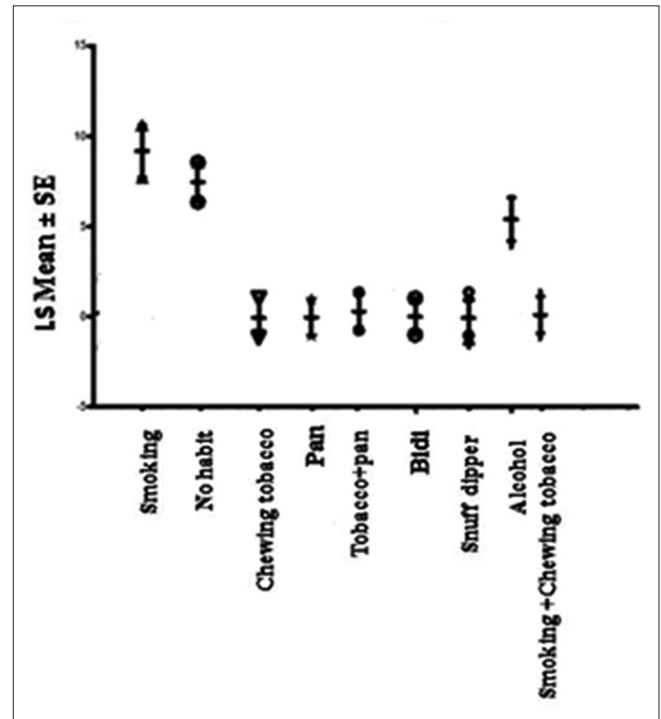**Figure 1:** Effect of gender on malignant transformation



**Figure 2:** Effect of habit on malignant transformation

**Table 2: Data comparing habit with malignant transformation**

| Study | TS | TC | Pan | Alcohol | TC + TS | Tobacco + pan | Bidi | NH/I |
|---|---|---|---|---|---|---|---|---|
| Waldron et al. (Emory material) | NM | NM | NM | NM | NM | NM | NM | NM |
| Bancozy et al. (conservative group) | NM | NM | NM | NM | NM | NM | NM | NM |
| Silverman et al. | 1980 (2) | 148 (0) | 100 (0) | 0 | 205 (1) | 1571 (2) | 0 | 90 (1) |
| Hogewind | NM | NM | NM | NM | NM | NM | NM | 9 (3) |
| Pogrel et al. | 7 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Silverman | NM (17) | 0 | 0 | 0 | 0 | 0 | 0 | 74 (18) |
| Lind et al. | NM | NM | NM | NM | NM | NM | NM | NM (6) |
| Gupta et al. | NM (0) | NM (15) | NM | NM | NM (1) | NM (0) | NM (2) | NM (0) |
| Schepman et al. | NM | 0 | 0 | 0 | 0 | 0 | 0 | NM |
| Cowan et al. | NM | NM | NM | NM | NM | NM | NM | NM |
| Hsue et al. | NM | NM | NM | NM | NM | NM | NM | NM |
| Ho Shan et al. | 11 (7) | 0 | 0 | 49 (8) | 0 | 0 | NM | 132 (18) |
| Ho et al. | 71 (24) | 0 | 0 | 49 (19) | 0 | 0 | 0 | 20 (9) |

Figures within brackets indicate the number of MT cases. NM: Not mentioned, TS: Tobacco smoking, TC: Tobacco chewing, NH/I: No habit/idiopathic

**Table 3: Comparing single site with malignant transformation**

| Study | L | C | B | G | T | FOM | P |
|---|---|---|---|---|---|---|---|
| Waldron et al. (Emory material) | NM | NM | NM | NM | NM | NM | NM |
| Bancozy et al. (conservative group) | NM | NM (0) | NM (0) | 0 | NM | NM (0) | NM (0) |
| Silverman | 1 (1) | NM (2) | 31 (2) | 1 (1) | 0 | 0 | 2 (0) |
| Hogewind | 3 (0) | 6 (0) | 12 (0) | 0 | 10 (0) | 3 (0) | 4 (0) |
| Pogrel et al. | 0 | 0 | 0 | 0 | 0 | 19 (3) | 0 |
| Silverman et al. | 23 (4) | 0 | 29 (5) | 63 (11) | 74 (13) | 40 (7) | 29 (5) |
| Lind et al. | NM (1) | 0 | NM (4) | NM (3) | NM (4) | 0 | 0 |
| Gupta et al. | NM | NM (1) | NM (10) | NM | NM (0) | NM (1) | NM (1) |
| Schepman et al. | 0 | 13 (0) | 13 (NM) | 0 | 54 (0) | 37 (NM) | 3 (0) |
| Cowan et al. | 0 | 0 | NM (4) | 0 | NM (13) | NM (9) | NM (4) |
| Hsue et al. | NM | NM | NM | NM | NM | NM | NM |
| Ho Shan et al. | 0 | 0 | 97 (8) | 0 | 22 (11) | 0 | 0 |
| Ho et al. | 0 | 0 | 16 (5) | 0 | 15 (8) | 40 (3) | 7 |

Figures within bracket represent a number of MT cases. MT: Malignant transformation, NM: Not mentioned, L: Lip, C: Commissure, B: Buccal mucosa, G: Gingiva, T: Tongue, FOM: Floor of mouth, P: Palate
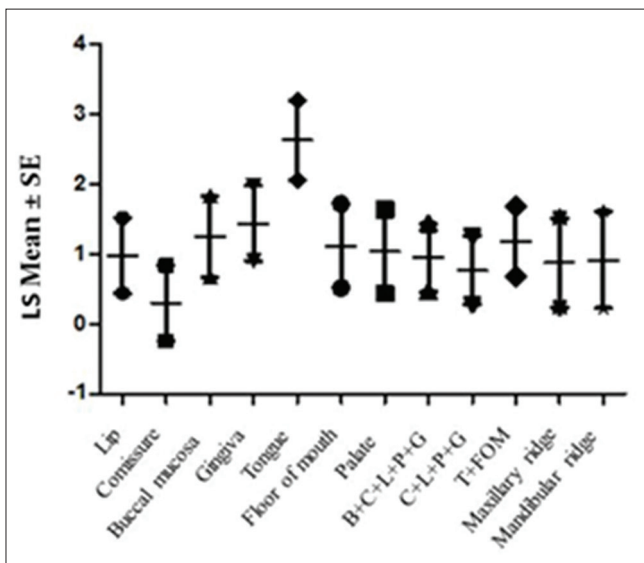


**Figure 3:** Effect of sites on malignant transformation



**Figure 4:** Effect of clinical type on malignant transformation

questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer.[10] This
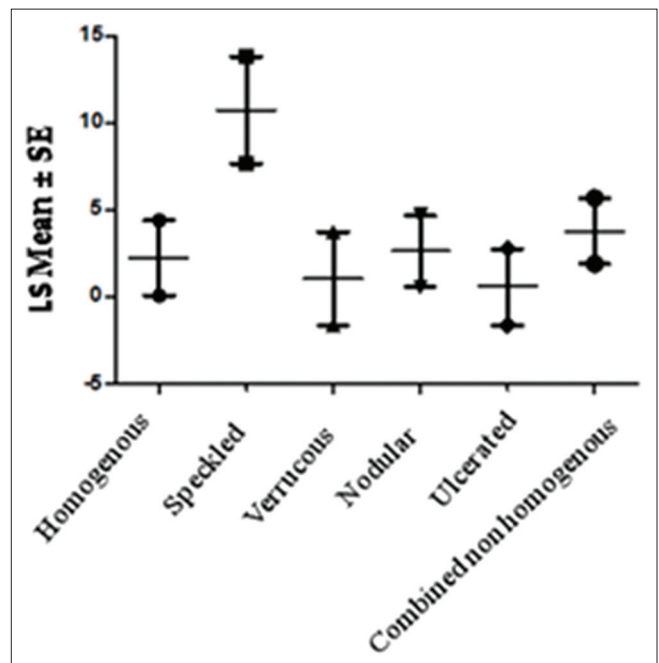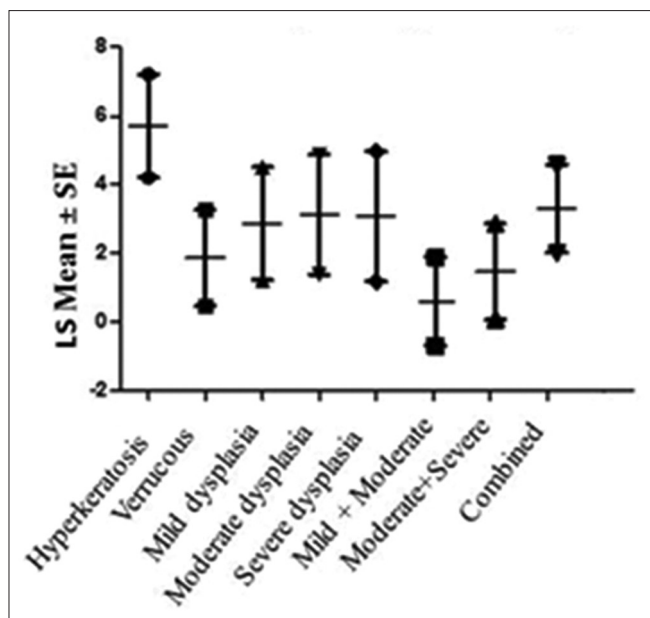
**Figure 5:** Effect of histopathology on malignant transformation

definition too does not suggest which lesions exactly have to be excluded whether it is erosive lichen planus or nodular leukoplakia.

Thus, there arises a need to clinically and/or histologically identify lesions that have an increased risk for MT so as to caution the patient and the clinician about the severity of the disease process. Hence, a meta-analysis was conducted to identify features of the lesions that underwent MT.

Gender association with MT did not show a major difference, but there was a trend toward female association, especially in nonhabit associated cases, which is in agreement with other studies.[7,13]

It is generally accepted that tobacco in any form is carcinogenic. Our study revealed that smoking tobacco and nonhabit association carries relatively equal risk for MT followed by other forms of tobacco such as gutka and pan (with tobacco) which is in agreement with previous studies.[7,9,11,13]

Next, when we focused on the risk of a specific site to undergo MT, we noted that lateral border of the tongue followed by gingiva had the highest tendency for MT. The transformation time for tongue lesions was the least with an average 6.4 years when compared to other sites which is similar to previous studies. We believe that nonkeratinized lateral border of tongue and dentogingival junction show an increased turnover rate and are subjected to mechanical trauma, microbial biofilm formation, along with superimposed tobacco habits make it susceptible for increased transformation rate. The incidence of oral carcinoma in other sites is related to the geographical

### Table 4: Comparing multiple sites with malignant transformation

| Study | B+C + L+P + G +T + FOM | C+L + P+ G | Max. R and MB fold | Man. R and MB fold |
|---|---|---|---|---|
| Waldron et al. (Emory material) | NM | NM | NM | NM |
| Bancozy et al. (conservative group) | 0 | 0 | 0 | NM |
| Silverman | 0 | 0 | 0 | 0 |
| Hogewind | 35 (0) | 0 | 3 (0) | 4 (0) |
| Pogrel et al. | 0 | 0 | 0 | NM |
| Silverman et al. | 0 | 0 | 0 | 0 |
| Lind et al. | 0 | 0 | 0 | NM (2) |
| Gupta et al. | 0 | 0 | NM | NM (2) |
| Schepman et al. | 101 (15) | 65 (5) | 14 | 6 (0) |
| Cowan et al. | 0 | 0 | NM (1) | NM (3) |
| Hsue et al. | NM | NM | NM | NM |
| Ho Shan et al. | 0 | 26 | 0 | 0 |
| Ho et al. | 0 | 0 | 1 | 4 |

Figures within bracket represent a number of MT cases. MT: Malignant transformation, NM: Not mentioned, L: Lip, C: Commissure, B: Buccal mucosa, G: Gingiva, T: Tongue, FOM: Floor of mouth, P: Palate, Max. R and MB: Maxillary ridge and Mucobuccal fold, Man. R and MB: Mandibular ridge and Mucobuccal fold

### Table 5: Comparing clinical type with malignant transformation

| Study | H | S | V | N | U | CNH |
|---|---|---|---|---|---|---|
| Waldron et al. (Emory material) | NM | NM | NM | NM | NM | NM |
| Bancozy et al. (conservative group) | NM | NM | NM | 0 | 0 | 0 |
| Silverman et al. | NM (4) | NM (2) | 0 | 0 | 0 | 0 |
| Hogewind | 10 (2) | NM | NM | NM | NM | 13 (1) |
| Pogrel et al. | 0 | 0 | 0 | 0 | 0 | 0 |
| Silverman et al. | 107 (7) | 128 (23) | NM (15) | 0 | 0 | 0 |
| Lind et al. | 35 (1) | 28 (3) | 41 (2) | 28 (8) | 0 | 91 (13) |
| Gupta et al. | 489 (3) | NM (0) | NM (0) | 13 (6) | 105 (1) | 118 (7) |
| Schepman et al. | 35 (2) | NM | NM | NM | NM | 12 |
| Cowan et al. | NM | NM | NM | NM | NM | NM |
| Hsue et al. | NM | NM | NM | NM | NM | NM |
| Ho Shan et al. | NM | NM | NM | NM | NM | NM |
| Ho et al. | 65 (10) | 18 | 0 | 0 | 2 (NM) | 26 (8) |

Figures within bracket represent the number of MT cases. MT: Malignant transformation, NM: Not mentioned, H: Homogenous, S: Speckled, V: Verrucous, N: Nodular, U: Ulcerated, CNH: Combined nonhomogenous

variations of the studies conducted and also due to varied habit patterns such as buccal mucosa owing to studies on Kerala population with chewing habits, floor of mouth due to extensive study on sublingual keratosis, palate because of reverse smoking in Andhra Pradesh population and lip in rural areas engaged in agriculture exposed to prolonged sunlight. The authors also accept the bias subjected to biopsy referrals from tumor clinics.[3,7,9,14-17]

Speckled leukoplakia showed an increased risk for MT in most of the studies.[9,15,17,18] The presence of carcinoma *in situ*/ frank carcinoma in the erythematous areas suggests that the biologic behavior of the lesion to show transformation is due to its increased permeability to carcinogens through the thin epithelium as hypothesized for oral submucous fibrosis

**Table 6: Data comparing histopathology with malignant transformation**

| Study | HK* | VH† | Grade of Dysplasia | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | m | M | S | m + M | M + S | m + M + S |
| Waldron et al. (Emory material) | NM (1) | NM | NM | NM | NM | 327 (2) | 113 (12) | 0 |
| Bancozy et al. (conservative group) | 0 | 0 | 25 (1) | 72 (3) | 23 (4) | 0 | 0 | 0 |
| Silverman et al. | NM (6) | 0 | NM (0) | NM (0) | NM (0) | 0 | 0 | 0 |
| Hogewind | 22 (2) | 0 | 2 (0) | 3 (1) | 5 (0) | 0 | 0 | 0 |
| Pogrel et al. | 3 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Silverman et al. | 235 (37) | 0 | NM | NM | NM | 0 | 0 | 22 (8) |
| Lind et al. | 105 (3) | 0 | 15 (1) | 20 (1) | 3 (3) | 0 | NM (3) | 38 (3) |
| Gupta et al. | NM | NM | NM | NM | NM | 0 | 0 | 0 |
| Schepman et al. | NM (6) | 0 | 20 (2) | 26 | 19 | 0 | NM (14) | 0 |
| Cowan et al. | 781 (17) | NM | NM | NM | NM | 0 | 0 | 165 (20) |
| Hsue et al. | 423 (15) | 324 | 138 (6) | 15 (2) | 13 (0) | 0 | 0 | 0 |
| Ho Shan et al. | 67 (6) | 44 (9) | NM | NM | NM | 0 | 0 | 33 (8) |
| Ho et al. | 0 | 0 | 40 (10) | 31 (10) | 20 (5) | 0 | 0 | 0 |

*Without dysplasia, †With dysplasia. Figures within bracket represent a number of MT cases. MT: Malignant transformation, NM: Not mentioned, HK: Hyperkeratosis, VH: Verrucous hyperplasia, m: Mild, M: Moderate, S: Severe

undergoing MT.[19] The present study also confirmed the potential of homogenous leukoplakias to undergo MT.[7,9] This suggest the possible role of other risk factors such as site, genetic mutation and mechanical trauma association in the causal of transformation.

When we checked the efficacy of grading on predicting malignant potential, it was noted that there was no significant relationship between the number of mild, moderate and severe dysplasia undergoing malignant conversion.

We also observed that a significant number of hyperkeratosis without dysplasia cases underwent MT. In a study by Silverman et al. 1984 on 257 patients, of the 45 patients that underwent MT, only 8 had dysplasia; however, the author failed to subclassify the grades of dysplasia.[7] The rest 34 patients did not harbor any dysplasia. Yet, in another study by Lind 1987, of the 157 patients studied, 14 underwent a transformation. In these 14 patients, 6 patients had severe, 4 moderate, 1 mild dysplasia and 3 showed absence of dysplasia (2 gingiva, 1 mandibular sulcus). The author suggests that histopathology is mandatory, but dysplasia grading was unreliable.[9] Many other studies also have show similar lack of clarity on dysplastic grading and also report mild/non dysplastic lesions undergoing MT.[18] This suggests the mere absence of dysplasia does not exclude the possibility of MT. Similar conclusion is drawn by other authors.[3,15] Since the invasion of tumor cells occurs from the basal layer and basal cells are prone to mutations responsible for MT, we believe that mild dysplasia involving basal third is largely underestimated and concluded as having a lower risk. In the present study, hyperkeratosis without dysplasia showed a higher rate of transformation even compared to the dysplastic group. This may be due to the lack of uniformity in grading as some clubbed mild with moderate and others moderate with severe, some clubbed all the dysplastic cases under one heading, and some have separated all the three grades resulting in a distribution of dysplastic cases reducing the sample size.

Our meta-analysis concludes that carcinogenic transformation of a preexisting lesion is multifactorial and is patient specific. Therefore, all lesions diagnosed as leukoplakia should be biopsied not with the intention to grade dysplasia but to make sure that there is no existing cancer. The protocol to delineate a high-risk lesion should include gender (as an increased tendency for female to show transformation) and site (as accentuated tendency for the lateral border of tongue, gingiva, floor of mouth and buccal mucosa to demonstrate transformation is observed). Speckled leukoplakias, nonhomogenous and homogenous in any of the above-mentioned sites should indicate a high degree of caution.

Habit association and histopathologic grade of dysplasia have the least significance as tobacco history, nonhabit, nondysplastic, mild, moderate and severe are all associated with more or less similar degree of transformation.[20-24]

Therefore, we demarcate:

High-risk lesions in this order:
A. Any gender, ±TS, any site, speckled leukoplakia, ±dysplasia
B. Any gender, ±tobacco habit, tongue/gingiva/floor of mouth/buccal mucosa, homogenous/nonhomogenous, ±dysplasia
C. Females, nonhabit association, any clinical type, ±dysplasia
D. Any gender, ±tobacco habit, any site, nodular/verrucous/ulcerated leukoplakia, ±dysplasia
E. Any gender, nonhabit association, any type.

Low risk:
A. Any gender, +tobacco habit, buccal mucosa/palate/lip/commissure, homogenous, ±dysplasia

**Table 7: Overall comparison between number of cases and malignant transformation**

| Study | No treatment given | | | | | |
|---|---|---|---|---|---|---|
| | Total cases[‡] | disease free | Reduced in size | Increased in size | Unchanged | MT |
| Waldron *et al.* (Emory material) | 1626 | NM | NM | NM | NM | 15 |
| Bancozy *et al.* (conservative group) | 23 | NM | 2 | 0 | 10 | 8 |
| Silverman *et al.* | 4762 | 1502 | 0 | 0 | 2538 | 6 |
| Hogewind | 46 | NM | NM | NM | NM | 3 |
| Pogrel *et al.* | 19 | NM | 4 | NM | 3 | 3 |
| Silverman *et al.* | 257 | 73 | 0 | 0 | 138 | 45 |
| Lind *et al.* | 157 | NM | NM | NM | NM | 14 |
| Gupta *et al.* | 10,209 | NM | 3 | 0 | 4 | 10 |
| Schepman *et al.* | 166 | NM | NM | NM | NM | 20 |
| Cowan *et al.*\* | 946 | NM | NM | NM | NM | 33 |
| Hsue *et al.*[†] | 913 | NM | NM | NM | NM | 33 |
| Ho Shan *et al.* | 148 | NM | NM | NM | NM | 22 |
| Ho *et al.* | 91 | 0 | 63 | 5 | 0 | 23 |

*Data excluding lichen planus, lupus erythematosus, epithelial atrophy, carcinoma groups. [†]Data excluding lichen planus, submucous fibrosis. [‡]Excluding number lost for follow-up. Figures within bracket represent a number of MT cases. MT: Malignant transformation, NM: Not mentioned

B. Any gender, snuff dippers, buccal mucosa/palate/lip/commissure, homogenous, ±dysplasia.

## Draw backs

Lack of uniformity in reporting data among different studies resulted in the distribution of samples under different headings reducing the sample size. Some studies failed to mention the total number of cases studied under each factor such as age, sex, clinical subtypes and histologic grades. Some studies did not mention all the data pertaining to cases that underwent MT and cases that regressed [Table 7]. Therefore, precise values were difficult to obtain.

The reason behind the unanswered questions about the most often spoken topic dysplasia is lack of expression of sufficient data, non-uniformity among studies and fewer numbers of follow-up studies.

## Future directions
- We suggest better structured follow-up studies involving a total number of cases studied under each parameter and MT under that parameter to be mentioned. It also applies for lesions that have regressed to get a clear picture of characteristics of lesions that regressed or disappeared completely
- Molecular studies should be the next path toward grading leukoplakia as high risk or low risk.

## Acknowledgement

## Conflicts of interest
There are no conflicts of interest.

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