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ORIGINAL PAPER

Malignant Transformation Rate of Non-reactive Oral Hyperkeratoses Suggests an Early Dysplastic Phenotype

Ivan J. Stojanov[1,2] · **Sook-Bin Woo**[3,4]

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Abstract

The presence of epithelial dysplasia (ED) in oral leukoplakia is the single most important predictor of malignant transformation (MT). The majority of leukoplakias, however, do not show evidence of ED and yet MT of these lesions is well-recognized. These lesions have been referred to as "hyperkeratosis/hyperplasia, no dysplasia," "keratosis of unknown significance" and "hyperkeratosis, not reactive (HkNR)." This study evaluates the MT rate of such leukoplakias. A literature review was performed to identify cohort studies on leukoplakias where (1) there was a recorded histopathologic diagnosis, (2) cases of "hyperkeratosis/hyperplasia, no dysplasia" comprised part of the cohort, and (3) follow-up information was available. There were 9,358 leukoplakias, of which 28.5% exhibited ED while 37.7% consisted of HkNR. Follow-up ranged from 15 to 73 months. The incidence of MT in leukoplakia exhibiting HkNR was 4.9%, compared to 15.3% for ED. Among oral squamous cell carcinomas (SCC) with previously biopsied, site-specific precursor lesions, 55.7% arose from ED/carcinoma in situ and 28.0% arose from HkNR. Leukoplakia exhibiting HkNR has a substantial MT rate, similar to that of mild ED, and must be recognized and managed appropriately to reduce oral SCC incidence.

Keywords Squamous cell carcinoma · Leukoplakia · Dysplasia · Oral cancer

Introduction

Keratotic lesions are commonly encountered in the oral cavity and their accurate histopathologic diagnosis is often necessary for appropriate patient management [1]. When hyperkeratotic/parakeratotic oral mucosa is encountered in routine pathology practice, a number of etiologies must be considered. The patterns of keratinization and epithelial maturation may represent (1) a reactive process, such as chronic frictional/factitial hyperkeratosis (morsicatio mucosae oris) or benign alveolar ridge keratosis, (2) a keratinizing epithelial dysplasia (ED), or (3) other well-defined conditions, such as lichen planus, candidiasis or white sponge nevus may that also be considered when appropriate [1–4].

In the oral cavity, as in the entire upper aerodigestive tract, the majority of EDs are keratinizing and present clinically as a keratotic plaque, that is, a leukoplakia. However, only a proportion of oral leukoplakias (19–46%) exhibit ED and this is the case even in studies that carefully exclude reactive/frictional keratoses with no malignant potential [5–9]. This implies that keratoses of uncertain malignant potential are commonly identified in routine practice. These are difficult to interpret histopathologically because they lack features of a reactive/frictional diagnosis and also because they lack the cytologic features of ED required by the World Health Organization (WHO) [10]. These have been referred to historically in the leukoplakia literature simply as 'hyperkeratosis/hyperplasia, no dysplasia' or 'keratosis of unknown significance' and in the proliferative (verrucous) leukoplakia literature more recently as 'hyperkeratotic lesion, not reactive,' and little is known about them except for the fact that

✉ Ivan J. Stojanov
ivan.stojanov@case.edu

1 Department of Oral and Maxillofacial Medicine and Diagnostic Sciences, Case Western Reserve University School of Dental Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA

2 Department of Pathology, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH, USA

3 Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA

4 Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, MA, USA

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they tend to present clinically as homogenous leukoplakias, often with corrugations and fissures [11–14].

A pathologic diagnosis of 'hyperkeratosis' has been previously considered adequate by the pathologist or clinician with the assumption that ED is not present. The presence of ED in leukoplakia is considered an important, if not the most important, predictor for malignant transformation (MT), and provides the basis for this historical approach [7, 15]. But this approach is challenged by the fact that MT can occur from leukoplakia not exhibiting ED [9] and also by a recent genomic characterization of a cohort of non-dysplastic leukoplakias that showed *KMT2C*, *TP53* and other genetic alterations at a similar frequency to bona fide EDs [16]. These lesions were considered clinically concerning for ED on the basis of their presentation as well-demarcated keratotic plaques of leukoplakia indistinguishable from lesions that exhibit ED, and histopathologically because they demonstrated no features of reactive/frictional keratoses.

The overlapping mutational profile of these leukoplakias, or hyperkeratoses that are not reactive (HkNR), with that of ED suggests that non-reactive, intrinsic keratinization of squamous mucosa may actually represent the earliest phenotype of keratinizing ED. Given the potential relationship between HkNR, ED, and squamous cell carcinoma (SCC), the aim of this study is to determine the rate of MT of HkNR in historical leukoplakia literature to provide insight into its biologic potential and to understand ramifications for leukoplakia/dysplasia reporting and management.

Materials and Methods

A review of all published English leukoplakia literature from 1990 to 2020 was performed. Data presented in this review were extracted from original research articles fulfilling 3 criteria: (1) leukoplakias with a recorded pathologic diagnosis; (2) presence of diagnoses of 'hyperkeratosis/hyperplasia' or 'no dysplasia' within the leukoplakia cohort; (3) follow-up information regarding MT of leukoplakia included, including length of follow up. Leukoplakia cohorts providing no information about subsequent MT were excluded, as were dysplasia-only cohorts. Additional exclusion criteria included: 'oral potentially malignant disorder' cohorts in which leukoplakia cases could not be specifically identified; and leukoplakia cohorts with study design assessing response to total excision only.

Results

A total of 786 records where identified, of which 689 were excluded after screening titles and abstracts (Fig. 1). Following this, 98 full-text articles, including one identified by manual search, were assessed for eligibility. Ultimately 18 studies were included in the review, including 16 leukoplakia cohorts and 2 oral SCC cohorts with paired pathologic diagnoses of previously biopsied leukoplakias. The most common reasons for article exclusion were lack of information regarding MT and lack of histopathologic diagnosis in leukoplakia cohorts.

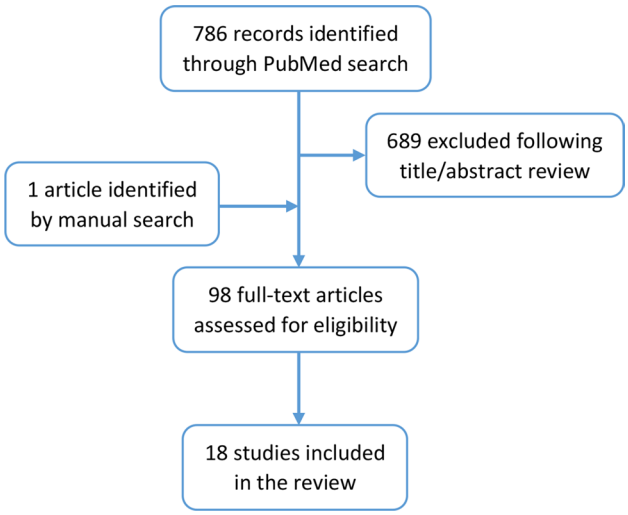

Fig. 1 Flow chart for article selection

The sixteen leukoplakia cohorts had sample sizes ranging from 24 to 5071, for a total of 9358 biopsied leukoplakias (Table 1) [9, 12, 17–30]. The prevalence of 'hyperkeratosis/hyperplasia' or 'no dysplasia' ranged from 7.8 to 70.3% in individual studies and was 37.7% (3532/9358) when pooled. The prevalence of ED ranged from 11.4 to 92.2% and was 28.5% (2665/9358) when pooled. Other diagnostic entities such as lichen planus or verrucous hyperplasia were inconsistently reported and not tabulated, though they accounted for a significant minority of two large studies [19, 21]. Ten studies reported mean follow-up duration ranging from 30 to 72 months; three studies reported median follow-up of 15, 29 and 41.1 months [12, 22, 23]; two studies reported interval time to MT of 33.6 and 61.8 months [21, 30]; and one study reported a 24–48 month range of follow-up with no mean or median [24].

During these follow-up periods, the incidence of MT of leukoplakias exhibiting only hyperkeratosis ranged from 0.0% to 28.6% and was 4.9% (172/3532) when pooled. The MT of leukoplakias with ED ranged from 4.8% to 51.3% and was 15.3% (408/2665) when pooled. Grade of ED was not reported across all studies, precluding calculation of incidence of MT by grade.

An additional two studies reported cohorts of oral SCC, a subset of which were paired with the pathologic diagnoses of pre-existing, site-specific (same-site) precursor lesions. Goodson et al. [31] reported 1248 and Chaturvedi et al. [32] 96 oral

Table 1. Incidence of malignant transformation of 'non-dysplastic' hyperkeratoses to SCC

Author	Number of biopsied leukoplakias	Number of 'non-dyplastic' hyperkeratoses	Incidence of MT of 'non-dysplastic' leukoplakia	Incidence of MT of leukoplakia exhibiting ED	Follow-up duration
Schepman et al. [12]	122[a]	53/122 (43.4%)	6/53 (11.3%)	12/69 (17.4%)	29 months (median)
Rosin et al. [17]	116	39/116 (33.6%)	6/39 (15.4%)	23/77 (30.0%)	37 months (mean)
Holmstrup et al. [18]	204[b]	116/204 (56.9%)	5/116 (4.3%)	10/88 (11.4%)	72 months (mean)
Hsue et al. [19]	1458	423/1458 (29.0%)	15/423 (3.5%)	8/166 (4.8%)	42.6 months (mean)[c]
Ho et al. [20]	148	67/148 (45.3%)	6/67 (9.0%)	8/33 (24.2%)	37.8 months (mean)[d]
Brouns et al. [9]	144	88/144 (61.1%)	8/88 (9.1%)	8/56 (14.3%)	51.2 months (mean)
Wang et al. [21]	5071	1684/5071 (33.2%)	49/1684 (2.9%)	72/1143 (6.3%)	33.6 months[e]
Kuribayashi et al. [22]	237	122/237 (51.5%)	2/122 (1.6%)	11/115 (7.8%)	41.1 months (median)
Mogedas-Vegara et al. [23]	65	21/65 (32.3%)	2/21 (9.5%)	8/44 (18.2%)	15.0 months (median)
Lima et al. [24]	24	7/24 (29.2%)	2/7 (28.6%)	4/17 (23.5%)	24–48 months (range)
Gandara-Vila et al. [25]	85	59/85 (69.4%)	2/59 (3.4%)	5/26 (19.2%)	49.5 months (mean)
Wang et al. [26]	835	490/835 (58.7%)	18/490 (3.7%)	84/345 (24.3%)	54 months (mean)
Wu et al. [27]	192	15/192 (7.8%)	0/15 (0.0%)	41/177 (23.2%)	34.8 months (mean)
Jayasooriya et al. [29]	93	20/93 (21.5%)	0/20 (0.0%)	7/73 (9.6%)	30 months (mean)
Sakata et al. [28]	165	116/165 (70.3%)	14/116 (12.1%)	11/49 (22.4%)	48 months (mean)
Li et al. [30]	399	212/399 (53.1%)	37/212 (17.5%)	96/187 (51.3%)	61.8 months[f]
Total	9358	3532/9358 (37.7%)	172/3532 (4.9%)	408/2665 (15.3%)	N/A

SCC squamous cell carcinoma, *MT* malignant transformation, *OSF* oral submucous fibrosis, *VH* verrucous hyperplasia, *LP* lichen planus/lichenoid

[a]Out of 166 total leukoplakias; 2/44 (4.5%) unbiopsied leukoplakias underwent MT

[b]Out of 269 total leukoplakias; 3/65 (4.6%) unbiopsied leukoplakias underwent MT

[c]During this time frame 10/324 (3.1%) VH, 8/402 (2.0%) OSF, and 3/143 (2.1%) LP underwent MT

[d]During this time frame 9/44 VH (20.5%) and 0/4 (0.0%) OSF underwent MT

[e]During this time frame 59/869 (6.8%) VH, 37/994 (3.7%) OSF, and 2/381 (0.5%) LP underwent MT

[f]Represents mean interval time to MT; follow-up information not reported

SCC, of which 58 and 71, respectively, had site-specific, previously biopsied precursor lesions that were reported. Table 2 presents the SCCs with previously biopsied, site-specific precursor lesions of these two studies as well as the SCCs of the other sixteen studies, as characterized by the presence or absence of ED in their precursor lesions. These 18 studies reported a total of 837 (range 6–219) SCCs arising from previously biopsied, site-specific precursor lesions. The incidence of hyperkeratosis alone in biopsied, site-specific precursor lesions ranged from 0.0 to 56.0% and was 28.0% (234/837) when pooled. The incidence of ED/carcinoma in situ (CIS) ranged from 18.2 to 100.0% and was 55.7% (466/837) when pooled. Other pathologic diagnoses such as verrucous hyperplasia, oral submucous fibrosis, and others were reported in only a subset of studies and comprised the remaining 21.6% (137/633) of this total.

Discussion

The findings of this review underscore the malignant potential of HkNR and corroborate genomic evidence of HkNR as an early or perhaps the earliest histopathologically detectable precursor lesion to oral SCC. The rate of MT of HkNR was 4.9%, approximately one-third of the 15.3% rate of MT of all ED in these studies. Additionally, the association between oral SCC diagnosis and pathologic diagnosis of previously-biopsied, site-specific precursor lesions in the historical leukoplakia literature suggests that

Table 2 Pathologic diagnoses of precursor lesions exhibiting subsequent MT to SCC

	Number of SCC exhibiting MT from previously biopsied, site-specific precursor lesion	Number of SCC arising from precursor lesion with pathologic diagnosis of hyperkeratosis	Number of SCC arising from precursor lesion with pathologic diagnosis of epithelial dysplasia/CIS	Number of SCC arising from precursor lesion with other pathologic diagnoses	Number of SCC arising from unbiopsied leukoplakias (as percentage of unbiopsied leukoplakias)
Schepman et al. [12]	18	6/18 (33.3%)	12/18 (66.7%)	N/A	2/44 (4.5%)
Rosin et al. [7]	29	6/29 (20.7%)	23/29 (79.3%)	N/A	N/A
Holmstrup et al. [18]	15	5/15 (33.3%)	10/15 (66.7%)	N/A	3/65 (4.6%)
Hsue et al. [19]	44	15/44 (34.1%)	8/44 (18.2%)	VH (10/44, 22.7%) OSF (8/44, 18.2%) LP (3/44, 6.8%)	N/A
Ho et al. [20]	23	6/23 (26.1%)	8/23 (34.8%)	VH (9/23, 39.1%)	N/A
Brouns et al. [9]	16	8/16 (50.0%)	8/16 (50.0%)	N/A	N/A
Wang et al. [21]	219	49/219 (22.4%)	72/219 (32.9%)	VH (59/219, 26.9%) OSF (37/219, 16.9%) LP (2/219, 0.9%)	N/A
Goodson et al. [31]	58	24/58 (41.4%)	25/58 (43.1%)	PVL (3/58) Candidiasis (3/38) PEH (2/58) Squamous papilloma (1/58)	N/A
Kuribayashi et al. [22]	13	2/13 (15.4%)	11/13 (84.6%)	N/A	N/A
Mogedas-Vegara et al. [23]	10	2/10 (20.0%)	8/10 (80.0%)	N/A	N/A
Lima et al. [24]	6	2/6 (33.3%)	4/6 (66.7%)	N/A	N/A
Gandara-Vila et al. [25]	7	2/7 (28.6%)	5/7 (71.4%)	N/A	N/A
Chaturvedi et al. [32]	71	38/71 (53.5%)	33/71 (46.5%)	N/A	N/A
Wang et al. [26]	102	18/102 (17.6%)	84/102 (82.4%)	N/A	N/A
Wu et al. [27]	41	0/41 (0.0%)	41/41 (100.0%)	N/A	N/A
Jayasooriya et al. [29]	7	0/7 (0.0%)	7/7 (100.0%)	N/A	N/A
Sakata et al. [28]	25	14/25 (56.0%)	11/25 (44.0%)	N/A	N/A
Li et al. [30]	133	37/133 (27.8%)	96/133 (72.2%)	N/A	N/A
Total	837	234/837 (28.0%)	466/837 (55.7%)	137/633 (21.6%)	5/109 (4.6%)

SCC squamous cell carcinoma, *CIS* carcinoma in situ, *VH* verrucous hyperplasia, *LP* lichen planus, *PVL* proliferative verrucous leukoplakia, *OSF* oral submucous fibrosis, *PEH* pseudo-epitheliomatous hyperplasia

a substantial proportion of cancer patients might have benefited from improved recognition and management of their previously biopsied keratosis. Just over half (55.7%) of oral SCC with biopsied site-specific precursor lesions in these studies were characterized by the presence of ED/CIS in the precursor lesion but 28.0% of SCC arose from site-specific precursor lesions diagnosed as hyperkeratosis/hyperplasia with 'no dysplasia' on biopsy.

Of note, the 4.9% rate of MT of HkNR is very close to the 5.7–6.0% rate of MT of mild ED according to the most commonly referenced figures for dysplasia of the upper aerodigestive tract [10, 33–35]. Furthermore, the 4.9% MT rate of oral leukoplakias without obvious ED is comparable to the 3.7% MT rate of laryngeal leukoplakia without ED as reported by Isenberg et al. [36]. Considering this as well as the findings of genomic alterations in a small study of oral HkNR [16], there is a strong suggestion that HkNR represents a "dysplastic" hyperkeratosis. In these lesions, marked intrinsic keratinization precedes the identification of an intraepithelial proliferation of atypical/dysplastic cells, which typically needs to be present to a substantial degree (higher grade dysplasia) before reasonable inter-pathologist concordance is achieved in conventional diagnosis of ED [37].

The 15.3% overall rate of MT of ED in this study is similar to the 12.1% rate reported in the systematic review and meta-analysis by Mehanna et al. [38] and lends credibility to these findings. But there are limitations entrenched within the leukoplakia literature which must be addressed. The first is inter-pathologist discordance in interpretation of ED, particularly in mild or low-grade dysplasia, which is substantial [18, 37, 39]. It is conceivable, and perhaps

likely that some "no dysplasia" specimens from the leukoplakia cohorts included in this study would be interpreted as mild dysplasia by some pathologists. For this reason it is appealing to conclude that the 4.9% MT rate of HkNR may be an overestimate due to the inclusion of mild ED; and likewise that the 28% of SCC that arose from HkNR may only represent a failure to appropriately recognize and manage low-grade ED. Such an observation is interesting because inter-observer variability is almost unavoidable when assessing highly differentiated hyperkeratotic mucosa using ED grading criteria that heavily emphasize cytologic features. The comparable MT rates of HkNR and mild ED (4.9% vs. 5.7–6.0%) suggest, actually, that low-grade dysplastic mucosa is just as likely to present with architectural atypia (such as epithelial atrophy or surface corrugations/papillomatosis) as with cytologic atypia and that inclusion of HkNR within the spectrum of low-grade ED may improve classification and recognition of at-risk patients for appropriate management, as well as improve rates of inter-pathologist concordance.

But what is HkNR, histopathologically? Previous studies as reviewed here do not specify the nature of the hyperkeratosis. In recent research on both solitary and proliferative (verrucous) leukoplakia, HkNR presents as abnormal architectural changes to the epithelium including marked hyperkeratosis, papillomatosis/corrugation, sharp demarcation, epithelial atrophy, hypergranulosis and/or skip segments [14, 40, 41]. Cytologic features of ED, on the other hand, are either absent (Fig. 2a–f) or consist of, at most, mild nuclear hyperchromasia and atypia restricted to basal/parabasal layers (Fig. 3), which may be sufficient for some pathologists to interpret as mild ED, particularly when correlated with a clinical image. The presence of a lymphocytic host response, as can be seen in keratinizing ED, can result in misdiagnosis as lichenoid mucositis (Fig. 2g–i). Importantly, no diagnostic features of a reactive/frictional keratosis are present (Fig. 4). Of note, a recent study by Wils et al. [42] presented a series of 84 biopsied oral leukoplakias, 25 of which subsequently transformed to SCC. Only 14/25 (56%) exhibited classic features of dysplasia as defined by the World Health Organization and the majority of the remaining exhibited histopathologic features reminiscent of differentiated vulvar intraepithelial neoplasia (VIN). However, the vast majority of differentiated VINs are p53 positive and more research will be needed to clarify if there is any relationship between HkNR and differentiated VIN [43, 44].

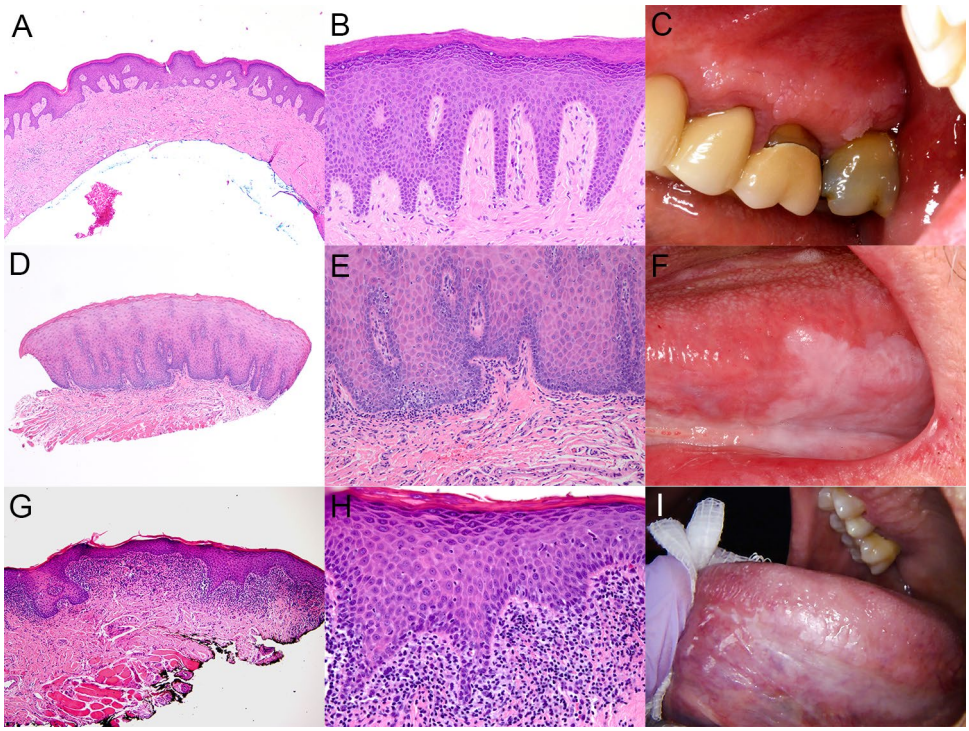

Fig. 2 Keratinizing squamous mucosa with surface corrugation and hypergranulosis (**A**) but with no identifiable cytologic atypia (**B**), presenting clinically as a well-demarcated leukoplakia of the attached gingiva (**C**). Thinly parakeratinizing and acanthotic mucosa (**D**) with no appreciable cytologic atypia or basal cell hypeplasia even in the presence of acanthosis (**E**) and presenting clinically as a well-demarcated leukoplakia of the ventral tongue (**F**). Keratinizing squamous mucosa with variable atrophy/acanthosis, hypergranulosis, and a lymphocytic host response at the interface (**G**), without cytologic atypia or lichenoid epithelial changes (**H**). The clinical presentation is of a well-demarcated leukoplakia of the ventral tongue with no reticulations. (**A** and **G**, original magnification ×40; **B** and **E**, original magnification ×100; **D** original magnification ×60; **H** original magnification ×200; hematoxylin and eosin stain)

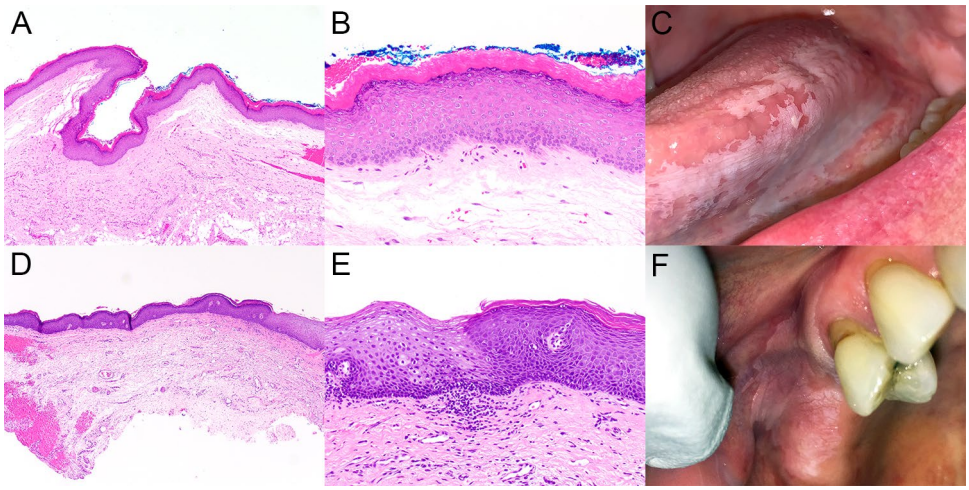

Fig. 3 Keratinizing squamous mucosa in two separate patients exhibiting epithelial atrophy, surface corrugation and hypergranulosis (**A**, **D**); epithelial atypia, chiefly in the form of nuclear hyperchromasia and increased nuclear/cytoplasmic ratio of basal and parabasal cells, is borderline for mild epithelial dysplasia (**B**, **E**); the clinical presentations are of leukoplakia with irregular but well-demarcated borders involving the ventrolateral tongue (**C**) and attached gingiva (**F**). (**A** and **D**, original magnification ×40; **B** and **E**, original magnification ×200; hematoxylin and eosin stain)

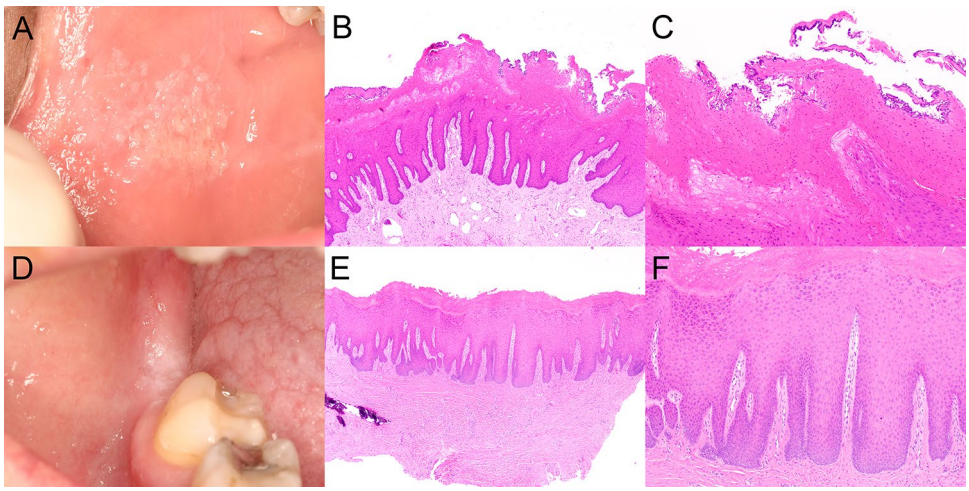

Fig. 4 Chronic frictional/factitial keratosis (**A**–**C**) exhibiting shaggy parakeratosis with acanthosis and keratinocyte edema; parakeratosis is extensive and superficially colonized by bacteria. Benign alveolar ridge keratosis of retromolar pad (**D**–**F**) exhibiting hyperkeratosis with surface undulations and wedge-shaped hypergranulosis; epithelium is acanthotic with slender and elongated rete ridges are occasionally confluent at the tips without cytologic atypia. (**B**, **E** original magnification ×40, and **C**, **F** original magnification ×100; hematoxylin and eosin stain)

A second important limitation in the leukoplakia literature and within the term leukoplakia itself refers to the tremendous heterogeneity in what is considered leukoplakia, as attested to by the wide range in the prevalence of HkNR of 7.8–70.3% within the included studies. The term leukoplakia itself frequently functions descriptively in the hands of clinicians, typically only denoting the identification of a hyperkeratotic patch to be biopsied. Since clinicians, out of concern for ED, rightly have a low threshold for biopsy when encountering hyperkeratosis (especially in smokers), published leukoplakia cohorts ultimately represent heterogeneous admixtures of keratinizing ED, HkNR, and reactive keratoses with no malignant potential. As an example of this heterogeneity, in a report of 1347 biopsied leukoplakias by Cowan et al. [45] (not included in this review) 88% showed hyperkeratosis, but the authors frankly stated that their non-ED cohort contained a much wider group of lesions "and

therefore would not be easily compared with studies based on the clinical diagnosis of leukoplakia."

A recent study showed that 75% of all biopsies submitted as "leukoplakia" or "hyperkeratosis" histopathologically represented chronic frictional/factitial keratosis, benign alveolar ridge keratosis or another reactive keratotic lesion with no malignant potential [6]. This speaks to the heterogeneity in published leukoplakia data sets based on a clinical diagnosis of leukoplakia alone and raises the question as to whether published MT rates of leukoplakia, prevalence rates of ED in leukoplakia cohorts, and even the MT rate of HkNR may be underestimated. The challenges in defining leukoplakia, ultimately, are related to the challenges in diagnosing hyperkeratotic mucosa clinically and histopathologically, which is clearly critical for correct patient management and risk stratification. It is imperative that HkNR be recognized at the very least as "not reactive," if not as mild ED, on account of comparable MT rates and histopathologic features. "Leukoplakia" would simply become, in the latter case, a homogenous category of keratotic, preneoplastic mucosa, generally well-demarcated and occasionally with clinically discernable patterns of keratinization (fissuring, verrucous changes) or with erythematous components (erythroleukoplakia). And, likewise, risk stratification of "leukoplakia" would be accomplished histopathologically on the basis of varying combinations of architectural and cytologic atypia,currently interpreted into two- or three-tiered grading systems. Regarding HkNR, it does appear simpler, instead of adding an additional "tier," to consider, if not actually classify, it as within the histopathologic spectrum of mild or low-grade ED on account of shared clinical, histopathologic, biological and possibly even genomic similarities, even though overt "intraepithelial" neoplasia is frequently absent or subtle.

One putative model of oral carcinogenesis can be based on the "three strikes" to cancer proposed by Vogelstein and Kinzler (Fig. 5) [46]. In such a model, low-grade dysplasia (HkNR/mild ED) would represent strike 1 (breakthrough phase); high-grade dysplasia (moderate/severe ED/CIS) would represent strike 2 (expansion phase); and invasive carcinoma would represent strike 3 (invasive phase). Such an approach may complement a two-tiered grading system for oral ED, as already adopted in the larynx and other mucosal sites, and more work is needed to determine whether a genomic progression model would consistently predict these phenotypes.

Improved recognition of dysplastic squamous mucosa ultimately is foundational to improving patient outcomes.

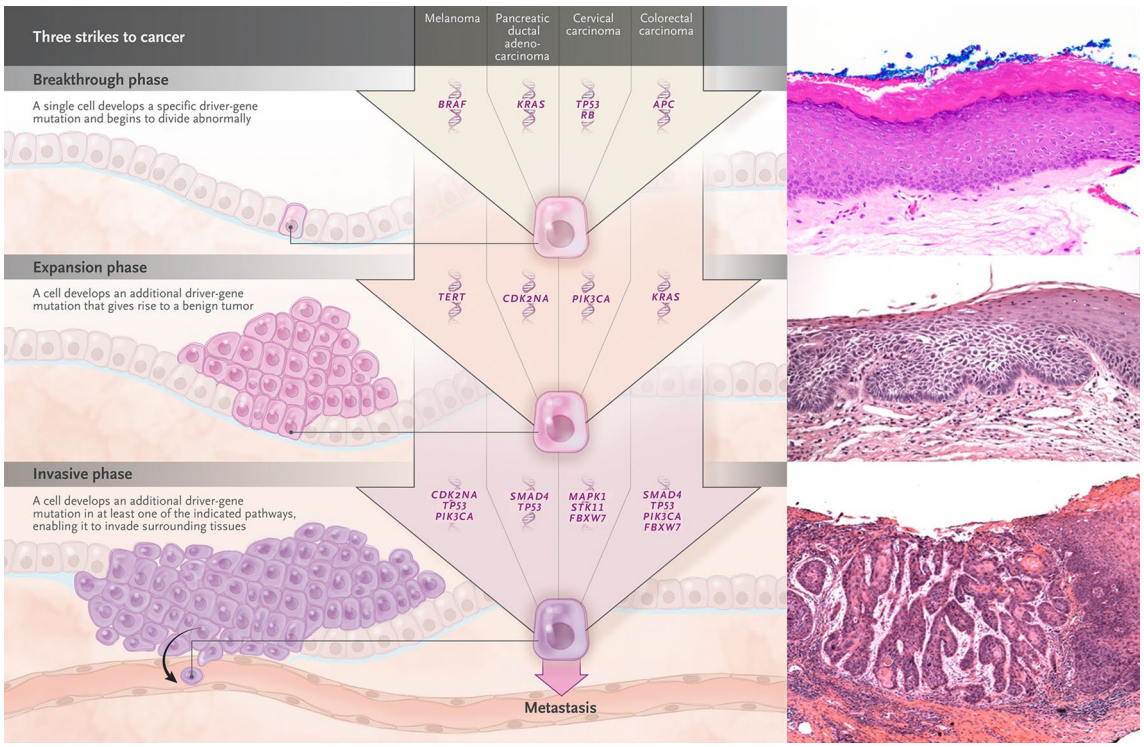

Fig. 5 Within the 3 strikes to cancer model, intrinsically keratinizing stratified squamous epithelium in the absence of or with mild epithelial dysplasia corresponds to the breakthrough phase, high grade keratinizing dysplasia (moderate-to-severe epithelial dysplasia) corresponds to the expansion phase, and invasive carcinoma corresponds to the invasive phase. Three strikes to cancer diagram reproduced with permission from *N Engl J Med* 2015; 373:1895–1898, Copyright Massachusetts Medical Society

Mehanna et al., who documented a 12.1% overall rate of MT in ED, found that the rate of MT was 14.6% in patients managed by observation alone and 5.4% in those treated surgically, a nearly three-fold reduction in risk [38]. Clearly, interrupting the process of sequential acquisition of mutations slows the process of cancer development and is beneficial, even if the leukoplakia recurs [47]. Since HkNR appears to represent the earliest dysplastic phenotype, then recognition of this as such followed by conservative, narrow excision to normal mucosa holds true promise in reducing the incidence of or at least delaying MT.

Limitations of this study include electronic database search restricted to PubMed, such that the possibility of article omission cannot be entirely excluded. However, this is considered less likely as the full-text articles evaluated in this study accounted for all of the articles included in two recent systematic reviews on the MT of oral leukoplakia (with and without pathologic diagnoses) [7, 48]. A meta-analysis was not performed to identify clinical variables, such as tobacco or alcohol abuse, which may be related to HkNR and the heterogeneity between studies was not analyzed via I^2 test. More work is need to see if HkNR and ED associate with similar clinical variables, which would further support HkNR as an early dysplastic phenotype.

In conclusion, our data in this review show the following:

- HkNR is commonly encountered in leukoplakia biopsies (37.7%)
- A 4.9% rate of MT in HkNR on the basis of historical studies, which is similar to the 5.7–6.0% rate of MT in mild ED
- Only approximately half (55.7%) of oral SCC included in these studies arose from a site-specific precursor lesion diagnosed as ED/CIS
- 28.0% of oral SCC arose from precursor lesions exhibiting hyperkeratosis alone (HkNR), indicating room for improvement in recognition and management of precursor lesions with atypical patterns of epithelial keratinization and maturation in the absence of prominent intraepithelial neoplasia.

On the basis of this and recently published genomic data, HkNR likely represents an early phenotype of keratinizing ED that must be accurately diagnosed as such to direct patient management. Identification and incorporation of HkNR histopathologic features into the category of low-grade dysplasia may facilitate patient stratification, improve patient outcomes, and clarify leukoplakia research.

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Declarations

Conflict of interest None.

Consent to Participate Not applicable.

Consent for Publication Both authors consent to publication of the manuscript.

Ethical Approval Not applicable.

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