Review Article

Malignant Transformation Rate in Patients Presenting Oral Epithelial Dysplasia: Systematic Review and Meta-Analysis

Jaffer A. Shariff¹ and Athanasios I. Zavras²

¹Section of Population Oral Health, College of Dental Medicine, Columbia University, 622 W. 168th Street, Suite PH17-306R, New York, NY 10032, USA

²Department of Pediatric Dentistry, Henry M. Goldman School of Dental Medicine, Boston University, 100 E. Newton Street, Boston, MA 02118, USA

Correspondence should be addressed to Athanasios I. Zavras; zavras@bu.edu

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Objective. To perform a systematic review and meta-analysis on studies that assess malignant transformation rates (MTR) of oral epithelial dysplasia. **Materials and Methods.** This review was planned and conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. PubMed, EMBASE, Google Scholar, and Cochrane databases were screened to identify observational studies. Quality assessments were completed by two reviewers independently using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Pooled-malignant transformation rate (MTR) in person years, subgroup, sensitivity, and publication bias analysis were calculated using STATA 13.0 and Comprehensive Meta-Analysis software. **Results.** Sixteen observational cohort studies were identified with a total of 3708 participants from Asia, North America, and Europe. Analysis showed a MTR of 10.5% (pooled-MTR: 10.5, 95% CI: 3.7 to 17.3; fixed effect model, $I^2 = 0.0\%$; Q -value = 2.389; $p > 0.05$) among patients with histologically confirmed oral epithelia dysplasia undergoing long-term follow-up. Higher MTR in person year were seen among the severe dysplastic cases (pooled-MTR: 14.4%, 95% CI: 5.3% to 23.5%), studies published in Europe (pooled-MTR: 12.6%, 95% CI: 8.0% to 24.3%), and retrospective studies (pooled-MTR: 11.0%, 95% CI: 2.2% to 19.9%). **Conclusion.** These studies show that oral epithelial dysplasia has a significant high rate of transformation to cancer.

1. Introduction

Oral cancer is a potentially fatal disease that affects the oral cavity (the mouth) or the oropharynx (the part of the throat at the back of the mouth) [1]. Oral cavity cancer is amongst the most prevalent cancers worldwide [1]. In the United States, approximately 42,440 people are expected to be diagnosed with oral cancer in 2014, among which 8390 will not be alive in five years [2]. In fact, it has also been classified as the sixth most frequent leading cause of cancer death worldwide. Though the oral cavity is accessible for direct examination, these malignancies are still detected at a late stage. Death rates due to oral cancer are particularly high not because it is hard to discover or diagnose, but because oral cancer in its early stage can be painless and go unnoticed in its development [2].

Oral epithelial dysplasia (OED) on the other hand is a potentially malignant lesion of the oral mucosa with an unpredictable course of progression [3], where there is expansion of immature cells (such as cells of the ectoderm), with a corresponding decrease in the number and location of mature cells [3]. The presence of epithelial dysplasia is generally regarded as one of the most vital predictors of malignant transformation [4]. The early and careful diagnosis is of extreme significance, which allows arresting the progression of oral epithelial dysplasia to oral squamous cell carcinoma. Therefore, it is important to understand the rate and duration of malignant transformation in these precancerous oral lesions so as to make them more amenable to treatment with the greatest chance of cure.

The primary objective of this systematic review and meta-analysis is to assess the progression of oral epithelial dysplasia

to cancer by examining observational cohort studies for outcome measure which include malignant transformation rate (MTR). The secondary objective is to examine the difference in the MTR measure based on the level of dysplasia.

2. Methods

2.1. Protocol and Registration. This review was planned and conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [5]. The protocol was not registered on any database.

2.2. Eligibility Criteria. To be considered for review, studies had to meet the following criteria:

- (i) Type of studies: observational cohort studies (prospective and retrospective) evaluating the progression (MTR) of oral epithelial dysplasia to oral cancer were included.
- (ii) Study participants: histologically confirmed oral epithelial dysplasia participants were included. Studies reporting on oral leukoplakia patients as dysplasia were excluded.
- (iii) Outcome and outcome measure: the rate of malignant transformation (MTR) in person years of oral epithelial dysplasia to oral cancer was included.
- (iv) Length of follow-up: only studies with a minimum follow-up time of 2 years were included.
- (v) Reporting of results: studies that reported on MTR of oral epithelial dysplasia or reported on incidence of malignant cases during the follow-up period that could be used to calculate MTR were included.
- (vi) Accessibility of data: studies were eligible only if they were published as full papers in English language.

2.3. Literature Search. The following electronic databases were searched between the respective periods: PubMed/Medline (1966 to December 2014), Embase (1980 to December 2014), and Cochrane databases (CENTRAL, Cochrane Library, 1995 to December 2014). The literature search was constructed around the following search terms: “oral epithelial dysplasia”, “malignant transformation”, and “oral cancer” which were adapted for each database as necessary. For example, the following search strategy was used on the PubMed database: (“Oral” [MeSH] OR “Mouth” [All Fields] AND (“dysplasia,” [MeSH]) OR (“malignant transformation” [All Fields]) OR (“cancer” [All Fields] OR “neoplasm” [MeSH])). The reference lists of identified original articles or reviews were also searched manually for relevant articles.

2.4. Study Selection. Two independent investigators searched for articles that meet the aforementioned eligibility criteria. The two investigators compared search results to ensure completeness and then reviewed the full title and abstract of the articles retrieved in the initial literature search. Differences in eligible studies were reviewed and resolved by mutual agreement between the 2 reviewers. Duplicate articles and

those not meeting study eligibility criteria were removed. After removal of all duplicate papers, the reviewers screened the abstracts of the remaining papers individually. They went on to obtain the full papers for all potentially eligible studies, which were then checked for eligibility using the standard abstraction forms; the eligible papers were included in the systematic review. To ensure completeness of the systematic literature review, all of the references in the articles deemed eligible for inclusion in the study were searched by investigators for relevant articles.

2.5. Data Collection. Two reviewers independently extracted data using the standard data abstraction form on studies’ characteristics: study design, length of follow-up, exposure (OED presence and grade of OED), and time to outcome measure (MTR to oral cancer). The abstraction form also includes the title of the paper, authors’ information, country in which the study was conducted, and population characteristics (mean age, gender). Differences in paper selection and data abstraction were reviewed and resolved by mutual agreement between the 2 reviewers.

2.6. Data Analysis. Meta-analysis was conducted on the collected data from each of the selected observational cohort studies using STATA 13.0 and Comprehensive Meta-Analysis software v3.

2.7. Quality Assessment. The quality of the identified studies was assessed independently by the two reviewers using the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,” provided by the National Institute of Health (NIH) [6], by assessing the potential risk for selection bias, information bias, measurement bias, or confounding (confounding includes cointerventions, differences at baseline in patient characteristics, and other issues as shown in Table 3). Studies were rated as good, fair, and poor quality, where high risk of bias translated to a rating of poor quality (“-”) and low risk of bias translated to a rating of good quality (“+”).

2.8. Assessment of Heterogeneity. The degree of dissimilarity in the results of individual studies or heterogeneity was assessed graphically using forest plot and the exact binomial confidence intervals (CIs) were calculated. Statistical heterogeneity between the reviewed studies was quantified by determination of the DerSimonian and Laird estimate (I^2), where $I^2 > 30\%$, $I^2 > 50\%$, and $I^2 > 75\%$ were defined to indicate moderate, substantial, and considerable heterogeneity, respectively. Cochran’s Q test is a statistical test used in conjunction with the forest plot to determine the significance (p value ≤ 0.05) of heterogeneity among studies.

2.9. Subgroup and Sensitivity Analyses. Subgroup analyses were conducted on the identified studies by grouping them by their study design (prospective or retrospective study), the region in which they were published (Asia, North America, and Europe), and the grade of dysplasia (mild, moderate, and severe).

FIGURE 1: Flow chart showing the flow of article selection for meta-analysis.

Sensitivity analyses to test the robustness of any significant results were conducted by comparing the results of studies with high risk versus low risk at the domains selection bias, detection bias, attrition bias, and other risks. Significant Q-statistics (p value ≤ 0.05) or I^2 statistic greater than 30% was considered as evidence of significant heterogeneity in the respective meta-analysis.

2.10. Risk of Bias across the Studies. The risk of publication bias was assessed by visual analysis of funnel plots generated by Comprehensive Meta-Analysis v3. Roughly symmetrical funnel plots will indicate a low risk of publication bias, while asymmetrical funnel plots indicate a high risk of such bias.

3. Results

3.1. Study Selection. The literature search retrieved 3386 records of which 262 were duplicates. After title and abstract screening, 3176 records were excluded. Of the remaining 51 articles that were assessed for eligibility by full text review, 7 were cross-sectional studies, 24 did not report our primary outcome (MTR) and were thus excluded, and 4 reported on patients with oral leukoplakia without histologically confirmed diagnosis of dysplasia and were excluded. At the end, 16 studies with a total of 3708 patients were included in the qualitative and quantitative analysis (Figure 1).

3.2. Study Characteristics. The characteristics of the study samples, interventions, outcome measures, and results are shown in Table 1.

3.2.1. Setting and Participant Characteristics. Studies originated from all over the world: four from Asia: India [7], Taiwan [8, 9], and China [10]; six from Europe: Denmark [11], Northern Ireland [12], Hungary [13], England [14, 15], and Italy [16]; and six from North America: USA [17–20] and Canada [21, 22]. Six studies [15, 16, 19–22] had a sample size greater than 200 participants with the largest population of

1434 patients in one study [21]. Five studies [7, 8, 14, 17, 22] were prospective hospital based studies, ten [9–11, 13, 15, 16, 18–21] were retrospective hospital based studies, and one was retrospective laboratory based study [12]. Mean age of the study population ranged from 46.7 to 63.9 years as reported in 13 of the 16 studies with a mean follow-up period ranging from 2.5 to 9.3 years among all the 16 studies (Table 1).

3.2.2. Outcome Measures. Malignant transformation rate (MTR) was reported or calculated by using the incidence malignant cases over the total number of dysplastic cases across all 16 studies. MTR was also calculated by the histologic grade of dysplasia: mild, moderate, and severe (Table 2).

3.2.3. Risk of Bias in Individual Studies. No study was considered to be seriously flawed as per the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” [6].

Studies’ risk to performance bias was moderately low across all the 16 studies, with five studies [11, 12, 14, 20, 22] having some form of risk due to nonblinding. The risk of attrition bias due to incomplete outcome data was absent across all the studies (Table 3).

3.3. Malignant Transformation Rate in Oral Epithelial Dysplasia

3.3.1. Test for Heterogeneity and Pooled-Malignant Transformation Rate. All the studies looked at the rate of malignant transformation among individuals with histologically confirmed oral epithelial dysplasia followed over a range of mean follow-up years of 2.5 to 9.0 years. Using forest plots from the DerSimonian and Laird (D&L) random effects model (random effect model: pooled-MTR = 10.5%, CI: 3.7 to 17.3%), two studies were seen to be weighted higher than the others with no heterogeneity (I^2 : 0.0%; Q-value = 2.389, $p > 0.05$) across all the 16 studies. Hence, D&L fixed effects model was used to estimate the final pooled-malignant transformation

TABLE 1: Description of selected studies.

First author	Year	Location	Region	Study design	Mean follow-up year	Mean age	Sample size
Bánóczy [13]	1976	Hungary	Europe	Retrospective hospital	6.3	NR	68
Mincer [17]	1972	USA	North America	Prospective hospital	8.0	NR	45
Gupta [7]	1980	India	Asia	Prospective hospital	8.5	NR	90
Lumerman [18]	1995	USA	North America	Retrospective hospital	2.5	57.0	43
Cowan [12]	2001	Northern Ireland	Europe	Retrospective laboratory	4.0	57.7	165
Holmstrup [11]	2006	Denmark	Europe	Retrospective hospital	6.0	60.8	82
Hsue [8]	2007	Taiwan	Asia	Prospective hospital	3.6	47.5	166
Ho [9]	2009	Taiwan	Asia	Retrospective hospital	3.1	46.7	33
Arduino [16]	2009	Italy	Europe	Retrospective hospital	4.5	63.9	207
Bradley [21]	2010	Canada	North America	Retrospective hospital	3.7	57.5	1434
Liu [10]	2011	China	Asia	Retrospective hospital	5.1	52.7	138
Warnakulasuriya [15]	2011	England	Europe	Retrospective hospital	6.0	56.5	204
Zhang [22]	2012	Canada	North America	Prospective hospital	3.7	60.8	296
Ho [14]	2012	England	Europe	Prospective hospital	9.0	48.5	91
Sperandio [19]	2013	USA	North America	Retrospective hospital	9.3	55.0	201
Dost [20]	2014	USA	North America	Retrospective hospital	3.3	59.5	368

NR: not reported.

TABLE 2: Oral epithelial dysplasia (OED) count and malignant transformation rate (MTR).

First author	Year	Oral epithelial dysplasia				Malignant transformation				Malignant transformation rate			
		Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.
Bánóczy [13]	1976	68	13	43	12	9	1	3	5	13.2%	7.7%	7.0%	41.7%
Mincer [17]	1972	45	NA	32	13	5	NA	2	3	11.1%	NA	6.3%	23.1%
Gupta [7]	1980	90	NA	NA	NA	6	NA	NA	NA	6.7%	NA	NA	NA
Lumerman [18]	1995	43	19	18	6	7	3	3	1	16.3%	15.8%	16.7%	16.7%
Cowan [12]	2001	165	NA	NA	NA	24	NA	NA	NA	14.6%	NA	NA	NA
Holmstrup [11]	2006	82	42	26	14	8	5	2	1	9.8%	11.9%	7.7%	7.1%
Hsue [8]	2007	166	NA	NA	NA	8	NA	NA	NA	4.8%	NA	NA	NA
Ho [9]	2009	33	NA	NA	NA	8	NA	NA	NA	24.2%	NA	NA	NA
Arduino [16]	2009	207	135	50	22	15	4	2	9	7.3%	3.0%	4.0%	43.0%
Bradley [21]	2010	1434	959	326	149	139	47	43	49	9.7%	4.9%	13.2%	32.9%
Liu [10]	2011	138	92	NA	46	37	17	NA	20	26.8%	18.5%	NA	43.5%
Warnakulasuriya [15]	2011	204	104	70	30	24	5	11	8	11.8%	4.8%	15.7%	26.7%
Ho [14]	2012	91	40	31	20	23	8	11	11	25.3%	20.0%	35.5%	55.0%
Zhang [22]	2012	296	127	135	34	41	16	19	6	13.9%	12.6%	14.1%	17.7%
Sperandio [19]	2013	201	103	69	29	17	4	7	6	8.5%	3.9%	10.1%	20.7%
Dost [20]	2014	368	221	85	55	26	9	6	1	7.1%	4.1%	7.1%	1.8%

NA: not available.

rate over mean follow-up years (fixed effect model: pooled-MTR: 10.5%, CI: 3.7% to 17.3%) (Figure 2).

3.3.2. Subgroup and Sensitivity Analyses. A subgroup analysis by study design showed a higher pooled-MTR in person years among the eleven retrospective studies (pooled-MTR: 11.4%, CI: 2.2% to 19.9%; fixed effect model: $I^2 = 0.0\%$, Q-value: 1.134, and $p > 0.05$) as compared to the five prospective

studies (pooled-MTR: 9.7%, CI: -0.9% to 20.4%; fixed effect model: $I^2 = 0.0\%$, Q-value: 1.221, and $p > 0.05$) (Figure 3). Six studies published from Europe were shown to have a higher pooled-MTR in person years (pooled-MTR: 12.6%, 95% CI: 0.8% to 24.3%; fixed effect model: $I^2 = 0.0\%$, Q-value: 0.815, and $p > 0.05$) as compared to the six studies from North America (pooled-MTR: 9.9%, 95% CI: -1.3% to 21.0%; fixed effect model: $I^2 = 0.0\%$, Q-value: 0.175, and $p > 0.05$) and

TABLE 3: Risk assessment of individual studies.

First author	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Criteria 12	Criteria 13	Criteria 14
Bánóczy (1976) [13]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Mincer (1972) [17]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Gupta (1980) [7]	+	+	+	+	-	NR	-	+	+	+	+	NR	+	+
Lumerman (1995) [18]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Cowan (2001) [12]	+	+	+	+	-	+	+	+	+	+	+	-	+	+
Holmstrup (2006) [11]	+	+	+	+	-	+	+	+	+	+	+	-	+	+
Hsue (2007) [8]	+	+	+	+	-	NR	+	+	+	+	+	NR	+	+
Ho (2009) [9]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Arduino (2009) [16]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Bradley (2010) [21]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Liu (2011) [10]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Warnakulasuriya (2011) [15]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Zhang (2012) [22]	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Ho (2012) [14]	+	+	+	+	-	+	+	+	+	+	+	-	+	+
Sperandio (2013) [19]	+	+	+	+	-	+	+	+	+	+	+	-	+	+
Dost (2014) [20]	+	+	+	+	-	+	+	+	+	+	+	-	+	-

NR: not reported.

¹ Was the research question or objective in this paper clearly stated?² Was the study population clearly specified and defined?³ Was the participation rate of eligible persons at least 50%?⁴ Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?⁵ Were a sample size justification, power description, or variance and effect estimates provided?⁶ For the analyses in this paper, was the exposure(s) of interest measured prior to the outcome(s) being measured?⁷ Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?⁸ For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?⁹ Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?¹⁰ Was the exposure(s) assessed more than once over time?¹¹ Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?¹² Were the outcome assessors blinded to the exposure status of participants?¹³ Was loss to follow-up after baseline 20% or less?¹⁴ Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

FIGURE 2: DerSimonian and Laird fixed effect model: malignant transformation rate (MTR) of dysplasia.

FIGURE 3: Subgroup analysis (D&L fixed effect model): malignant transformation rate, by study design.

four studies from Asia (pooled-MTR: 8.9%, 95% CI: -3.8% to 21.6%; fixed effect model: $I^2 = 0.0\%$, Q-value: 1.209, and $p > 0.05$) (Figure 4). Severe grade of dysplasia was reported

in twelve studies which were shown to have a higher pooled-MTR in person year (pooled-MTR: 14.4%, 95% CI: 5.3% to 23.5%; fixed effect model: $I^2 = 0.0\%$, Q-value: 10.218, and $p >$

TABLE 4: Sensitivity analysis showing MTR in studies using different exclusion criteria.

	Number of studies	Pooled-MTR*	LCI	UCI	Q-stats (<i>p</i> value)	<i>I</i> ² %
All trials	16	10.5%	3.7%	17.3%	1.010 (>0.05)	0.0%
Single- or double-blinded	9	11.4%	1.9%	21.0%	2.389 (>0.05)	0.0%

*Fixed effect model; LCI: 95% lower confidence interval; UCI: upper confidence interval.

Asia: I^2 : 0.0%; Q-value: 1.209, df: 3, and p = 0.751.

North America: I^2 : 0.0%; Q-value: 0.175, df: 5, and p = 0.999.

Europe: I^2 : 0.0%; Q-value: 0.815, df: 5, and p = 0.976.

FIGURE 4: Subgroup analysis (D&L fixed effect model): malignant transformation rate, by region.

0.05) as compared to eleven studies that looked at moderate dysplasia (pooled-MTR: 9.1%, 95% CI: 1.6% to 16.7%; fixed effect model: I^2 = 0.0%, Q-value: 2.588, and p > 0.05) and eleven studies that looked at mild dysplasia (pooled-MTR: 6.5%, 95% CI: 0.0% to 13.0%; fixed effect model: I^2 = 0.0%, Q-value: 2.142, and p > 0.05) (Figure 5).

No sensitivity analyses were conducted for low versus high risk of selection bias as no study had high risk (Table 3). Analysis regarding blinding showed an increase in the MTR in person years within nine blinded studies (fixed effect model: pooled-MTR = 11.4%; CI: 1.9% to 21.0%) after exclusion of five nonblinded and two studies that did not report on blinding (Table 4).

3.4. Risk of Bias across Studies. Funnel plot shows a fairly symmetrical distribution of the studies across the mean line, suggesting no strong evidence of publication bias (Figure 6).

4. Discussion

4.1. Summary of Main Result. The results of the meta-analysis showed a malignant transformation rate of 10.5% amongst patients with histologically confirmed oral epithelial dysplasia undergoing long-term follow-up. This was lower than the previous estimate of 12.1% from the most recent meta-analysis paper, published in 2009 [23]. This difference in malignant transformation rates could be due to the exclusion of studies

FIGURE 5: Subgroup analysis (D&L fixed effect model): malignant transformation rate, by grade of dysplasia.

that linked oral leukoplakia as a form of oral dysplasia from this current meta-analysis. However, seven studies [7, 8, 11–13, 17, 18] from the previous meta-analysis [23] were eligible in the current meta-analysis.

Our current meta-analysis found that prospective cohort and studies published in regions with high prevalence of oral cancer reported higher MTR (Europe > North America > Asia). These analyses also show that individuals with severe form of dysplasia have a high rate of malignant

transformation in person years as compared to moderate and mild form of dysplasia (Severe > Moderate > Mild).

4.2. Applicability of Evidence. The reviewed studies were all observational cohorts (prospective and retrospective) that were conducted at hospital and in laboratory based settings from all parts of the world. The diagnosis and grading of oral epithelial dysplasia were histologically confirmed across all

FIGURE 6: Funnel plot, assessing publication bias.

the studies and excluded oral leukoplakia studies that might overestimate MTR. The population among all the studies had similar mean ages with adequate follow-up time and, as most of the studies were focused at high risk regions for oral cancer, these review results potentially apply to the majority of the adults with histologically confirmed oral epithelial dysplasia. However, it would give us a better picture to generalize these results even further after examining results from studies from other regions of the world.

4.3. Added Values of This Study. By combining these 16 studies for the purpose of the current meta-analysis, we have been able to increase the sample size (3708 participants) and thus the power to detect the true malignant transformation rate (MTR) by mean follow-up year. We have summarized the results of the same number of studies devoted to the same MTR analysis. The findings from the current study, as a result, could serve for evidence based medicine issues.

4.4. Strength and Weaknesses. This review and meta-analysis study was conducted in accordance with the MOOSE guidelines [5]. The meta-analysis included studies that only investigated histologically confirmed oral epithelial dysplasia cases and their malignant transformation rate, while excluding the ones that looked at oral leukoplakia, so as to provide a more reliable histopathologic classification and prevent OED misclassification.

A limitation of this meta-analysis was that only papers published in English literature were included. More effort in identifying the non-English studies is necessary. The assessment of the quality of observational studies was challenging, as there are no standard tools currently in wide use. To overcome this problem, we used the tool provided by the NIH for assessing the risk of bias and quality of the study. Further, this study did not investigate any of the predictive risk factors, such as smoking, alcohol use, and site and its effect on malignant transformation rate.

5. Conclusion

This study shows that oral epithelial dysplasia has a significant rate of transformation to cancer, which increases significantly among severe grades of dysplasia. These findings suggest that developed countries (regions) with higher incidence of oral cancer may have higher rate of transformation that might be attributed to other predictive risk factors.

Conflict of Interests

The authors declare no conflict of interests.

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