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NARRATIVE REVIEW

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Investigating the factors proposed in oral lichen planus malignant transformation: A literature review

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Abstract

Background and Aims: Lichen planus is a chronic inflammatory disease that affects about 1% of the world's population. The World Health Organization has included oral lichen planus among potentially malignant disorders. Identification of reliable biomarkers for the diagnosis of malignant transformation may play a unique role in the development of standard screening and improvement of follow-up in patients with oral precancerous lesions. It is currently assumed that the molecular pathways controlling growth, maturation, proliferation, and apoptosis in epithelial cells may play an important role in the process of transformation into malignancy.

Methods: The search was done in PubMed, Scopus, Google Scholar, Embase, and Cochrane databases from 1960 to 2022.

Results: Based on the inclusion criteria, 23 articles were included.

Conclusion: In this review of articles, 34 different biomarkers that have been investigated in studies for the possibility of malignant transformation in OLP have been studied. Among all the risk factors related to malignant transformation, most studies have been done on the role of cytokines and tumor suppressors, in fact, the chronicity of the lesion which is the result of the reaction between the repair and the inflammatory response and the responses accompanied by the secretion of cytokines, may play a major role in the malignant transformation of OLP.

KEYWORDS

lichen planus, malignancy, malignant transformation, oral lichen planus

1 | INTRODUCTION

Lichen planus (LP) is a chronic inflammatory mucocutaneous disease affecting approximately 1% of the world's population. The disease prevalence is higher among women (female/male ratio 2:1) and the middle age group, but sporadic cases are also reported in very young patients or children. The oral mucosa is affected in 50% of patients with skin lesions.[1]

The two most important clinical characteristics of oral lichen planus (OLP) include its bilateral nature and spread in different oral areas. Oral lesions usually appear in the buccal region, especially on the lateral side and ventral surface of the tongue, the retromolar triangle, and the soft palate and palatine uvula complex. There are five clinical subtypes, which are classified into two main groups: Atrophic erosive (retinal, papular, and plaque) and atrophic erosive forms (ulcerative and bullous). The retinal form is one of the most common forms.[2]

OLP can cause general erosion of the oral mucosa, which leads to pain, burning, discomfort, and low quality of life.[3,4]

OLP diagnosis is based on clinical and histological features.

Histologically, OLP is characterized by lymphohistiocytic infiltration of subepithelial band-like, upregulation of intraepithelial lymphocytes, degeneration of basal keratinocytes, and absence of epithelial dysplasia (WHO).[5–8]

OLP was described in 1869, but its pathogenesis has not been fully defined so far. The main hypothesis indicates that the immunopathological reaction mediated by T lymphocytes and a series of exogenous factors, causes changes in endogenous antigens on the surface of oral mucosa keratinocytes.

It has been hypothesized that OLP is caused by heightened Th1 responses and T lymphocytes (CTLs). Several cytokines act as mediators between inflammatory cells and keratinocytes and play an important role in the immune-mediated destruction of keratinocytes in OLP.

Changes in epithelial membrane antigen expression can be induced by biological, pharmaceutical, or chemical factors. Among the most important factors that lead to these changes include: local and systemic cases, psychological stress, autoimmune phenomena, viral or bacterial infections (cytomegalovirus, herpes simplex virus types 1, 4, 6, HBV, HCV, HPv), and systemic disorders (diabetes mellitus, hypertension) and autoimmune phenomena including Hashimoto's thyroiditis (first reported in 1994) that can cause delayed hypersensitivity reactions through cells.[2]

There is still a debated question about its malignancy. The first malignant case of OLP was reported in 1910. Since then, many sporadic cancer cases have been reported in the literature. It is now assumed that the molecular pathways controlling growth, maturation, proliferation, and apoptosis in epithelial cells may play an important role in the malignancy transformation.[2]

WHO has included OLP among the potentially malignant disorders in this group, and its most serious complication can be oral squamous cell carcinoma (OSCC) based on the Vandermaji's & VanDerWal's criteria.[2] OLP lesions have been reported to develop into OSCC in 1%–2% of cases.[8,9]

Previous observations show that there is no gender bias in the risk of malignant changes in people over 40 years old, and the most common form of malignant changes is the erosive type.[10] However, malignant transformation may occur in all clinical types of OLP[7,11,12]

Because the annual risk of cancer in OLP patients is 100 times higher than that of people with normal oral mucosa, regular and accurate follow-ups are recommended for these patients.

Lifestyle, environmental factors and genetic predisposition are the three main factors that affect the development and progression of malignant and premalignant lesions. The genetic factors involved include DNA repair disorder and pleomorphism of different genes, which are known as important risk factors for SCC. Malignancy is caused by disruption in several signaling pathways, which in turn leads to upregulation of some genes and disruption in cell differentiation and apoptosis.[13,14]

WHO suggested that the erosive type, female gender, and tongue site are risk factors for malignancy.[5]

Identification of reliable biomarkers for the diagnosis of malignant transformation may play a unique role in developing standard screening and improving follow-up in patients with oral precancerous lesions.[15–17]

According to the foregoing and the importance of identifying the effective factors in the transformation of OLP malignancy, a total of 34 factors and biomarkers, which are among the studied factors involved in n OLP malignancy from 1960 to 2022, are investigated in the present study.

2 | MATERIALS AND METHODS

The search process was performed in PubMed, Scopus, Google Scholar, Science Direct, Cochrane databases from 1960 to October 2020 using keywords “OLP” OR “LP” OR “Oral lichen planus” OR “lichen planus” AND malignant OR malignant transformation OR oral malignant transformation OR oral malignant. Besides, all the references of these articles were manually reviewed to identify other related articles that were not identified in the initial search (Figure 1).

2.1 | Eligibility criteria

The studies included in the present systematic review include case-control and cohort studies, which investigated effect of different markers on the malignant transformation in OLP patients without applying any time limit. The aim of the included studies was to focus on the role of different markers in causing malignant transformation among OLP patients. In the present review study, only English studies were included. Non-full-text and irrelevant studies, studies lacking WHO diagnostic criteria of OLP were excluded.

2.2 | Data extraction

At this stage, two researchers (G. H. M. and A. F.) individually reviewed the articles obtained from databases and manual search in three steps. In the first step, duplicate sources were removed by a manual recheck and using EndNote 20. In the second step, studies were screened by reviewing the titles and abstracts to exclude irrelevant studies. In the third step, the full-text of the studies was reviewed thoroughly for the eligibility of the studies based on the predetermined inclusion and exclusion criteria. Finally, two researchers shared their assessment of the eligibility of each article. If both agreed, the study was included in the final phase, and there was no need to consult with a third person in the present study.

3 | RESULTS

3.1 | Identification

A total of 249 studies (records) were obtained from five electronic databases (PubMed, Scopus, Embase, Chocrane, Google Scholar). Also, additional manual search of the cited references of the selected

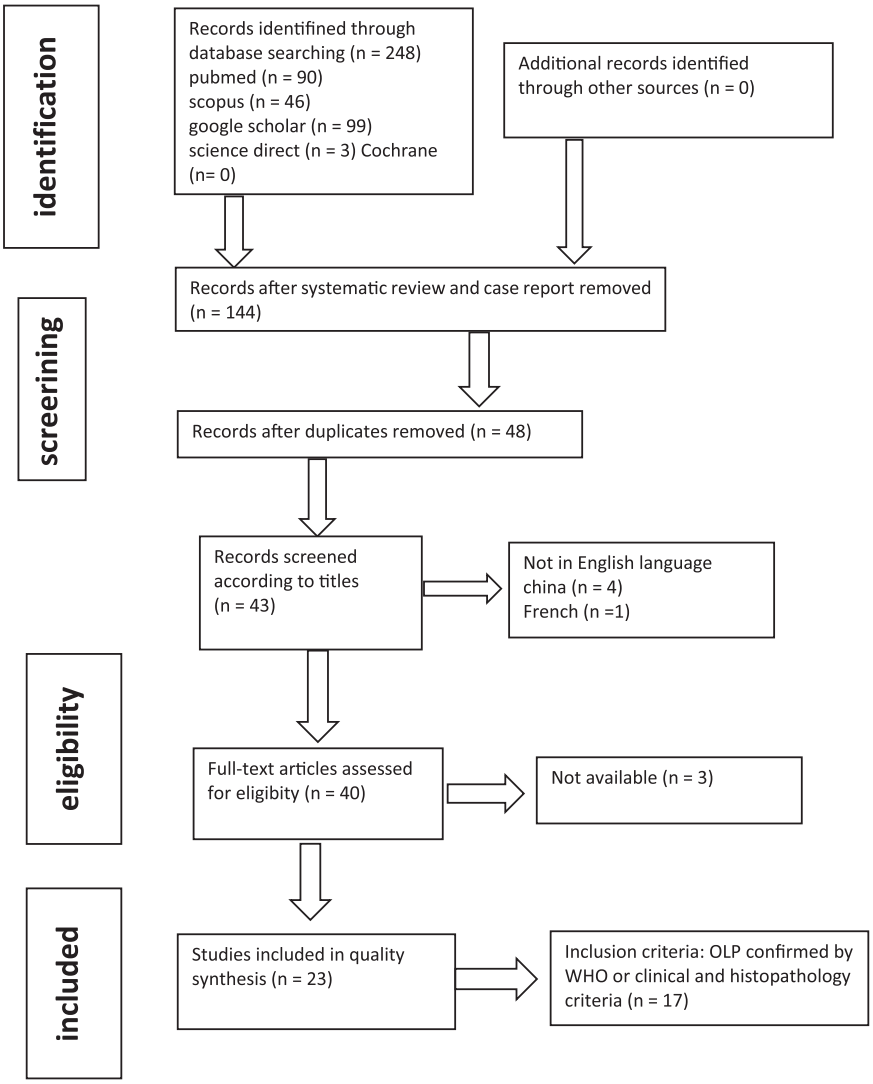

FIGURE 1 PRISMA 2009 flow diagram.

articles were performed and no any article was added. A total of 144 articles remained after removing the systematic review and case report articles, and 48 records were included in the screening stage after removing duplicates.

3.2 | Screening

At this stage, after screening the studies based on the title and abstract, five non-English-language studies were excluded ($n = 43$).

3.3 | Eligibility

To confirm the eligibility of the remaining 43 articles, full-text articles were assessed, and three studies were excluded due to unavailability of full text ($n = 40$). Of the remaining 40 studies, 17 studies were excluded due to lack of all approval criteria (OLP) based on clinical examination and histopathology. Finally, a total of 23 studies were included in the present review.

The reasons for the exclusion of studies are summarized in the PRISMA chart (Figure 1). The characteristics of each of the included studies are presented in Table 1.

From the total of 23 studies included in the present review, there was 1 cross-sectional study on 70 patients with tissue samples, there were 12 case-control studies on 13–190 patients with tissue, saliva and serum samples, and 10 cohort studies on 96–829 patients with tissue samples.[2,4,5,10,11,13,15,18–33]

4 | DISCUSSION

LP, as a relatively common chronic inflammatory autoimmune disease, can represent a cellular immune response to antigenic changes in the skin or mucosa of susceptible individuals. This disease was first described in 1869 and its exact mechanism is still not well known. Although skin lesions are self-limiting in most cases of this disease, chronic oral lesions are more difficult to control and are often resistant to conventional treatments. Unlike the cutaneous form, which has essentially no risk of malignant transformation,

TABLE 1 Characteristics of each of the included studies.

	Date author country	Main objective	Type of study	Number of patients (female/male)
1	2020 Guangzhao Guan New Zealand	Identifying the rate of malignant transformation in a retrospective cohort study	Longitudinal retrospective cohort	P (829) F (548) M (281)
2	2020 Eman Amr Egypt	Evaluation of miR-155 salivary levels before and after corticosteroid treatment	Case control	OLP (15) (F9) (M6) contol (15) (F9) (M6)
3	2020 Daniela Novembre Italy	Description of clinical features and prevalence of OLP	Retrospective cohort	OLP (96) (F61) (M35)
4	2020 Narges Gholizadeh Iran	Investigation of MAPK/ERK1/2 gene expression and miR-603, 4301, 8485, and 4731 in the MAPK signaling pathway in OSCC and OLP	Case control	Case (26) (F10) (M16) control (20)
5	2018 Sana Maher Hasan Aghbari Egypt	Comparison of microRNA27b and microRNA137 expression in tissues and saliva between OLP patients and controls	Case control	Case (20) (F14) (M6) control (20) (F7) (M13)
6	2018 Eman M. Amr Egypt	Measurement of serum and saliva levels of YKL-40 and IL-8 in OLP and OSCC patients	Case control	Control (15) OLP (15) OSCC (15)
7	2018 Eduardo Augusto Rosa Brazil	Evaluation of p16, Ki-67, Bub-3, and SOX4 expression levels	Retrospective cohort	P120 (F76) (M44)
8	2018 Ting Liu China	Analysis of p16 expression in OLP and malignant lesions of OLP and comparing its expression with normal mucosa	Case control	Case (40) (F24)(M16) control (24)
9	2016 Marcelo Sperandio Brazil	Image-based DNA ploidy analysis aids prediction of malignant transformation in oral lichen planus	Case control	Classical LP(68) control (80) unusual OLP (42)
10	2016 G. Suganya India	Immunohistochemical expression of survivin	Case control	p (70) OLP (50) OSCC (10) control (10)
11	2015 G. Shailaja India	Immunohistochemical expression of tumor markers Ki-67, p53, BCL-2, and BAX	Cross-sectional	Sample (70) normal (10) OLP (30) OED (30)
12	2013 Ziyuan Xu China	ALDH1 protein expression	Retrospective cohort	OLP not MT (89) (F70) (M19) MT (12) (F11) (M1)
13	2013 Elena Bardellini Italy	Epidemiological evaluation of OLP (in terms of clinical form, histopathological diagnosis, location of lesions, relationship with systemic diseases and alcohol, and tobacco consumption)	Retrospective cohort	P (204) (F163) (M41)
14	2012 Zheng-Yu Shen China	Investigating the epidemiological and clinical characteristics and changing the malignant form of 518 OLP patients in East China	Retrospective cohort	P (518) F (353) M (165)
15	2012 BoZana LonCar Brzak Croatia	Determining the frequency of OLP and its malignant transformation in the population	Retrospective cohort	OLP (F379) (M158)
16	2011 Gian Paolo Bombeccari Italy	Investigating the relationship between clinical features, pathological staging, and malignant recurrences in OLP	Retrospective cohort	P (327) (F229)(M98)
17	2010 Peng Shi China	Determination of podoplanin and ABCG2 protein expression in OLP with or without malignant transformation	Retrospective cohort	P (120) MT(9) (F8) (M1) UN MT (F84) M (26)

TABLE 1 (Continued)

	Date author country	Main objective	Type of study	Number of patients (female/male)
18	2010 Roseana de Almeida Brazil	Investigation of some characteristics of OLP lesions by immunohistochemistry and distinctive aspects such as apoptosis phenomenon through the expression of Bcl-2 protein, cell proliferation by PCNA, and possible malignant potential by p53 protein	Case control	Case (7) control (6)
19	2006 M. A. Gonzaalez-Moles Spain	Analysis of the expression of caspase-3 (an indicator of apoptosis) and p21 (an indicator of cell cycle arrest)	Case control	OLP (51) control (26)
20	2005 C. Bascones Spain	Quantitative investigation of cell cycle control arrest mechanisms, senescence, and apoptosis in oral epithelium affected by OLP	Case control	Case (32) (F20)(M12) control (20) (F10) (M10)
21	2001 Guido Valente Italy	Immunohistochemical staining for p53 as an early indicator of genetic predisposition to neoplastic transformation	Case control	OLP (28) (F13)(M15) control (7)
23	1997 A. K. Markopoulosulos Greece	Determination of the malignant potential of OLP based on the follow-up of 326 patients	Prospective cohort	P (326) (F/M 2/8:1)
22	1996 Anu Kilpi Australia	Analysis of c-erb-2 protein expression	Case control	Group1 (6) G2 (26) G3 (9) G4 (9)

Abbreviations: OLP, oral lichen planus; OSCC, oral squamous cell carcinoma.

malignant transformation of OLP has been proved.[2] WHO has classified OLP as a potentially premalignant disorder.[3]

This disease is of particular importance due to its association with pain and burning and potentially malignant changes.[1] However, cancer triggers in OLP lesions are not known.[3]

The main problem associated with the study of the malignant transformation of OLP includes lack of universally accepted criteria for the OLP diagnosis. Clinical and histopathological criteria identification are used in a number of studies on OLP patients. For decades, the progression of OLP to OSCC has generated a long-standing debate about the malignant potential of OLP. It is hypothesized that the potential reduction of antitumor immune responses caused by immunosuppressive drugs could increase the risk of oral cancer in patients with OLP.[5]

Prognostic survival biomarkers can be valid tools to assess patient life expectancy and guide treatment toward specific goals.

A total of 34 different biomarkers for malignant transformation in OLP which were used in previous studies, are investigated in the present review study.

These 34 risk factors are related to cytokines ($n = 10$ factors), tumor suppressors ($n = 10$ factors), oncogenes and proto-oncogenes ($n = 5$ factors), infections ($n = 2$ factors), tobacco and alcohol ($n = 2$ factors), and other factors involved in the malignant transformation ($n = 5$ factors).

Of the 34 risk factors that were studied in OLP patients, the most frequently studied one included tumor suppressors ($n = 9$ studies), oncogenes and other factors ($n = 4$ studies), cytokines ($n = 3$ studies), and tobacco-alcohol and infections ($n = 1$ study).

Currently, all forms of tobacco and alcohol use are strongly proven factors in the transformation of oral malignancy.

Smoking has an effect on the transformation of the OLP malignancy through various mechanisms, including the increase in density in small vessels and the overexpression of epithelial mesenchymal factor. It has also been reported that alcohol increases the risk of oral malignancies by increasing the permeability of the oral mucosa and causing epithelial atrophy, which facilitates the penetration of carcinogens. The ethanol usually manifests its carcinogenic effect if is consumed more than 45 mL on a daily basis.[3] It has been suggested that the atrophic and ulcerative forms make the oral mucosa susceptible to damage caused by carcinogens such as alcohol and tobacco or infections such as *Candida albicans*. Although none of the patients who developed cancer were daily alcohol or cigarette users, this suggests that malignant transformation may be part of the natural course of OLP. Although malignant transformation is uncommon, it still has a significant risk. Findings of other studies show that atrophic/erosive forms have a higher rate of malignant transformation compared to hyperplastic forms.[3,5] The reason for the increased risk of oral cancer in OLP patients is unknown. The oral mucosal immunity may somehow be compromised by OLP to the extent it becomes more sensitive to exogenous mutagens in tobacco, alcohol, betel quid, and *C. albicans*.[21,34–37] Smoking and alcohol are important risk factors for malignant transformation. But recent studies showed no correlation between OLP and smoking and/or alcohol.[24]

Currently, cytokines and inflammatory response, as well as some infection-causing factors, are among the risk factors for the malignant transformation of OLP. A total of 10 different cytokines and their role in the malignant transformation of OLP have been investigated in the present study.

Chronic inflammatory response and simultaneous epithelial wound healing response in OLP may increase the probability of malignant gene mutations.[21] Long-term chronic inflammation in some conditions, such as inflammatory bowel disease, is associated with an increased risk of malignant transformations. Chronic inflammation always induces healing and thus improves cell survival and is accompanied by the release of a number of cytokines and other molecules into the local environment. Potentially, the genetic predisposition of basal keratinocytes in conjunction with chronic inflammation may lead to the initiation of carcinogenesis. In a research, it has been suggested that cytokines that are released as part of the chronic inflammation process may participate in malignant changes. Cytokines such as IL-6, IL-17, and IL-23 have been shown to be involved in tumor progression and tumor necrosis factor α (TNF-α), TNF-β, and IL-6 in the promotion of cancer cells for growth and survival. Several cells that expressed IL-17 have been found in both OLP and OSCC, suggesting that IL-17 may play a role in the pathogenesis of OSCC.[27–30,31] Besides, increased salivary levels of TNF alpha, IL-10, IL-6 have been found in the saliva of OLP/OLL patients with high-grade dysplasia and OSCC.[5,38–43] These inflammatory injuries lead to upregulation of inflammatory mediators such as TNF-α, interferon α/β, IL-1, and IL-6, which subsequently promote the expression of proinflammatory chemokines. Also, serum and salivary IL-8 level, which causes angiogenesis and tumorigenesis, was significantly higher in in OSCC and OLP groups compared to healthy individuals.[44–47]

Hepatitis C virus infection has been suggested to be a risk factor for both SCCs and OLP, however, the relationship between HCV and malignant transformation is difficult to interpret.[48]

Tumor suppressors are genes that make proteins called tumor suppressor proteins that help control cell growth. Mutations in tumor suppressor genes may lead to cancer. They are also called anti-oncogenes

Ten different tumor suppressors have been investigated in the present study, which include p16, p21, p53, and BAX proteins, as well as various genes such as BUb3, as well as RNA factors including miR155, miR603, miR137, miR4731, and miR27b.[49,50]

P16 is an inhibitor of cell cycle progression involved in the inhibition of cyclin-dependent kinases (CDK), namely CDK4 and CDK6. According to previous studies, the diagnostic and prognostic value of p16 has been suggested in different types of cancer, especially in cervical cancer. Despite this important role in the cell cycle, its value as a malignant progression predictor is controversial and depends on the anatomical site (e.g., in cervical or breast cancer). An early event in the development of oral carcinomas is a change in the 9p21 locus, which leads to p16 suppression.[4]

p21 is a protein that arrests the G1 cell cycle and causes differentiation and senescence. The basal epithelial layer is the only layer where cell proliferation is expressed normally and should not express p21. Cyclin D1, considered a cell growth stimulator, may overcome the inhibitory effect exerted by p21 in the oral mucosa. OLP Patients showed basal expression of p21 in approximately half of cases, a protein that causes cell cycle arrest to ensure DNA repair, and can strengthen cells that grow in adverse conditions by resisting apoptosis.[30]

p53 is a tumor suppressor that is important in cell cycle control (from G1 to S phase), DNA repair, and apoptosis. p53 mutation, which may result in expression of defective p53, is associated with increased cell proliferation and early malignant transformation. P53 can also be considered as a reliable prognostic biomarker for malignancy. p53 overexpression in OLP patients is essentially due to the wild-type form, which inhibits the cell cycle for DNA repair or apoptosis induction. p53 in OLP patients is more likely to cause cell cycle arrest as compared to apoptosis.[22,51,52]

Budding uninhibited by benzimidazole 3 (Bub-3) is known as a mitotic checkpoint gene that inhibits mitosis. Besides, as a member of the mitotic checkpoint protein complex, BUB3 plays an essential role in pairing with other proteins of the same family to prevent premature entry of cells into anaphase. This marker may be less sensitive compared to p16 and ki67.[15]

BAX is a BCL-2-related protein that stimulates apoptosis, and BAX overexpression is associated with favorable prognosis in several cancers and plays a tumor suppressor role.[22]

miRNAs are short (20–22 nucleotides) single-stranded noncoding RNAs that regulate gene expression. There is a positive correlation between the release of inflammatory cytokines and the miR-155 expression. Impaired miR-155 expression negatively affects immune responses, which may lead to various diseases. A positive relationship between IFN-γ and miR-155 was identified, leading to a Th1-mediated immune response in OLP. Furthermore, miR-155 has been suggested to be involved in the differentiation of T cells toward Th1 through IFN-γ signaling. However, the specific role of miR-155 in the pathogenesis of OLP is still largely unclear. In one study, the mean miR-155 level in OLP patients were higher than the control group at baseline, while it decreased about 4 weeks after corticosteroid treatment.[18,53]

The present study show a statistically significant decrease in miRNA 27b expression in the tissues and saliva of OLP groups compared to the control group, which may indicate the role of miRNA 27b in the pathogenesis of OLP.[54,55] In addition, the lowest miRNA 27b level has been reported in the erosive form, followed by atrophic, papular, reticular, and plaque forms, which indicates a decrease in keratinocyte activity in the atrophic and erosive forms of OLP. miRNA 137 has been proposed as a tumor suppressor gene that is downregulated in OSCC, and can probably be used as a biomarker for early detection of cancer. There is a significant decrease in the salivary and serum miRNA 137 levels of the OLP group compared to the control group.[56,57] The erosive form of OLP shows a lower salivary and serum miRNA 137 expression, which may indicate a malignancy transformation. miRNA 27b has been shown to improve keratinocyte migration and miRNA 27b inhibition increases keratinocyte apoptosis and mitochondrial reactive oxygen species.[19]

It was reported in a study that miR-603 and miR-4731 act as tumor suppressors in OSCC, in such a way that the down- or nonregulation of miR-603 and miR-4731 contributes to the upregulation of MAPK/ERK1/2 and miR-603 is an important predictive factor for the malignant transformation of OLP into OSCC.[13]

Proto-oncogene plays a role in normal cell growth. A proto-oncogene mutation may change it in to an oncogene, which can cause the growth of cancer cells. In the present review, five oncogenes and proto-oncogenes and their effects on LP was investigated.

Ki-67 is a cell cycle-associated nuclear antigen located in the perichromosomal region that is associated with cell proliferation and is widely used in pathology as a proliferative marker to measure cell growth in human tumors.[46] Ki-67 half-life is estimated 60–90 min. ki67 expression begins in the S phase, and gradually increases in the G2 phase and reaches a plateau in mitosis. After mitosis, cells return to G1 with Ki-67 antigen storage, the level of which decreases rapidly during this phase. Also, Ki-67 has been evaluated as a predictor of metastasis and as an indicator for prognosis and recurrence of OSCC.[22,58]

The Bcl-2 proto-oncogene is the first discovered antiapoptotic gene that regulates the apoptotic pathway. BCL-2 blocks a distal step in the evolutionarily conserved pathway for apoptosis.[46] BCL-2 overexpression in genetically modified cells such as tumor cells helps to expand the damaged cell clone and leads to cell immortality by preventing turn over (programmed cell death). Permanent acquisition of mutations and transformation into malignancy is facilitated by promoting BCL-2 cell survival. Besides, BCL-2 overexpression in cancer cells probably reflects the resistance of tumor cells to apoptosis and may have consequences for their response to treatments. Also, BCL-2 can be considered as a reliable prognostic biomarker for malignancy.[22]

Survivin is a protein that inhibits apoptosis and regulates cell division. Survivin expression has been observed in basal layer cells in OLP cases, which was of moderate intensity while mild to zero expression is observed in different layers of healthy epithelium. Survivin expression in the basal layer of the epithelium in OLP cases indicates apoptosis inhibition, which may act as a molecular signature in malignant transformation.[21]

SOX4 is a member of the SOX transcription factor family. Previous studies show that SOX4 is involved in cell cycle arrest and apoptosis by activating p53, which suggests that SOX4 may be an indirect biomarker of carcinogenesis.[15]

The human proto-oncogene c-erbB-2 encodes a putative transmembrane receptor similar to the epidermal growth factor receptor. Amplification of the c-erbB-2 gene and subsequent overexpression of the c-erbB-2 protein have been reported in a significant number of human neoplasms.

Other factors that have been proposed in the malignant transformation of OL include the following:

YKL-40 is a glycoprotein that is secreted by 23 different types of cells, including endothelial cells, cartilage, inflammatory cells, and cancer cells. Although its exact role is unknown, it has been associated with several inflammatory and immune diseases, including multiple malignancies. The YKL-40 expression increases during inflammation, and plays an important role in chemotaxis and the activation and recruitment of inflammatory cells, because it participates in differentiation, proliferation, apoptosis, and angiogenesis. The poor prognosis of various inflammatory and tumor diseases is due to serum YKL-40 overexpression. In addition, YKL-40 is considered a proinflammatory factor and has been described to promote the induction of chemokines such as IL-8 from cancer cells. Serum and salivary YKL-40 levels in OSCC and OLP patients are significantly higher than that of healthy individuals and the highest in the OSCC group.[10]

There is little information about the biological function of ALDH1 as a marker of cancer stem cells in potentially malignant oral lesions, but ALDH1 expression was significantly associated with malignant transformation in a series of OLP patients with an average 5-year follow-up. The present study also showed that ALDH1 may be a useful biomarker to identify high risk of potentially malignant oral lesions progressing to OSCC.[23]

ABCG2: ATP-binding cassette, G2 is known as a molecular determinant of side population phenotype in stem cells. This phenotype has been found in various types of cancer cell lines including esophagus, nasopharynx, and oral cavity. Besides, ABCG2 expression has been found in retinoblastoma solid tumors and squamous cell carcinomas of the liver, esophagus, and head and neck. ABCG2 has been significantly associated with the risk of transformation into malignancy in OLP patients. The risk of malignant transformation was 6.04 times higher in patients with ABCG2 expression compared to people who did not express ABCG2.[11]

Podoplanin is a mucin-type membrane glycoprotein cultured in human lymphatic endothelial cells. Podoplanin expression has been reported in squamous cell carcinoma of esophagus, lung, skin, and oral cavity. It is also expressed in hyperplastic and dysplastic areas adjacent to primary tumors, suggesting that its abnormal expression occurs early in oral tumorigenesis. This glycoprotein has been used as a specific marker for lymphatic vessels, and its upregulation has been observed in several cancers. It has been reported that podoplanin is expressed in about 90% of OSCCs and is limited to squamous cell carcinoma invasion. Podoplanin has been significantly associated with the risk of malignant transformation in OLP patients.[10]

PCNA is an auxiliary enzyme of DNA polymerase-delta, which is involved in DNA synthesis during the S phase of the cell cycle. It is used to evaluate cell proliferation. PCNA overexpression is reported in patients with OLP lesions.[45]

According to these studies, it seems that different forms of alcohol and tobacco, which play an important role in other cancers, probably do not play an important role in OLP. In this review (Table 1), oncogenes and proto-oncogenes biomarkers have mostly been investigated in a study with a limited number of patients; therefore, to confirm their malignant transformation, further studies with a larger sample size, and longer follow-ups are needed.

The relationship between inflammation and cancer has been recognized since the 17th century, but there is now sufficient information about cells, cytokines, and physiological processes that play an essential role in inflammation and cancer.[59–62]

Inflammation plays an important physiological role because its ultimate goal is to repair tissue damage. Various internal and external factors can trigger a chronic state of inflammation. When chronic inflammation occurs (conditions such as OLP), it stimulates molecular and cellular networks that create a suppressive environment for the immune system that can cause cancer.[63]

Carcinogenesis and inflammation are complex processes that result from the combined effects of many immunological and cellular signaling forces. It is accepted that there is a cause and effect relationship between inflammation and the development of cancer, which indicates the fact that why does chronic inflammation cause cancer in some people but not in others? The answer may lie in an individual's relative ability to repair accumulated DNA damage. Individuals with a greater ability to repair DNA damage have a lower risk of cancer.[64] In fact, the chronic lesion chronicity, that is, the phenomenon during which the interaction between healing and inflammation is carried out, which is due to the reaction between the repair and the inflammatory response and the responses that lead to the secretion of of cytokines, may play a major role in the transformation of the malignant transformation of OLP. Therefore, if it is possible to somehow reduce the secretion of cytokines, which are a common factor between OLP and OSCC, or in other words, reduce inflammation, it may be effective in preventing the transformation of OLP.

Therefore, it is suggested that all OLP patients should be managed with the aim of completely eliminating the lesions. Also, the longer the lesions recede and the longer the intervals between recurrences, and in other words, recurrences occur less frequently, the odds ratio of developing malignancy will be lower.

AUTHOR CONTRIBUTIONS

Farzaneh Agha-Hosseini: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. **Mahdieh-Sadat Moosavi**: Methodology; supervision; writing—original draft; writing—review and editing. **Mahdieh Ghaffarpour**: Conceptualization; investigation; methodology; writing—original draft; writing—review and editing. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Mahdieh Ghaffarpour affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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