

## Molecular markers as an indicator in the malignant potential of oral lichen planus: A systematic review

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### Review Article

#### Abstract

**BACKGROUND AND AIM:** Oral lichen planus (OLP) is a chronic, autoimmune, inflammatory disease. The progression of OLP to oral squamous cell carcinoma (OSCC) has generated a longstanding controversy about the details of this malignant transformation potential. This study aimed to do a systematic review on the molecular markers related to the malignant transformation of OLP.

**METHODS:** We searched the databases PubMed, Google Scholar, Science Direct, Scopus, Cochrane and Thomson Reuters Web of Science (1990-2015) with the MeSH key words of: (“oral lichenoid reaction”, “oral lichenoid lesion”, “oral lichenoid eruption”, “oral lichen planus” “lichen planus”, “lichenoid”) AND (“malignant transformation”, “pre-malignant character”, “cancerization”, “pre-neoplasm”, “squamous cell carcinoma”). The reviewers screened the identified publications in three steps according to title, abstract and full text, extracted all the investigated markers in screened articles and finally classified the markers according to the frequency. Extracted data were saved in Excel software.

**RESULTS:** Out of 570 articles, 66 were finally enrolled in the study. The most frequent evaluated markers were p53, cyclooxygenase-2 (COX-2), Ki67, B-cell lymphoma-2 (Bcl-2), Bax, p21, and caspase-3.

**CONCLUSION:** The present study concluded that there were some documented evidences for association between malignant transformation of OLP and seven molecular markers (p53, COX-2, Ki67, Bcl-2, Bax, p21, and caspase-3).

**KEYWORDS:** Biomarkers; Tumor; Gene Expression; Oral Lichen Planus

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Oral lichen planus (OLP) is an autoimmune muco-cutaneous chronic disease that commonly involves the oral cavity. The prevalence of OLP varies from 0.5% to 3.0%. It mainly occurs among females between the ages 30 and 60. OLP is classified as white (reticular or plaque) and red (atrophic or erosive) lesions.<sup>1-6</sup> Malignant transformation of OLP has been reported,<sup>7</sup> and its frequency ranges from 0% to 5.3%. The highest malignant transformation frequency rate occurs in erythematous and erosive lesions.<sup>7,8</sup> The World Health Organization (WHO) has categorized this lesion as precancerous, which is “a generalized state associated with

a significant increased risk of cancer”.<sup>7</sup> The transformation of OLP into oral squamous cell carcinoma (OSCC) has led to a longstanding controversy about its malignant potential.<sup>8</sup>

Fitzpatrick et al. conducted a systematic review in 2014.<sup>9</sup> They evaluated 16 studies on the malignant transformation of OLP and they focused on its prevalence in clinical evidence. The rate of malignant transformation ranged between 0% and 3.5%. The authors concluded that while there is little possibility of malignant degeneration in OLP, regular follow-up is necessary for OLP patients.<sup>9</sup> Molecular markers provide the possibility of identifying patients with

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potential malignancy that are progressing toward OSCC before histological detectability of malignant cells at the primary region. Previous studies have found various types of molecular pathways that are possibly involved in the transformation of OLP into OSCC, such as p53, CDKN1A, LCK, PIK3CA, BIRC5, IL-2, and PI3K.<sup>8</sup>

Nowadays, there are no specific markers to recognize which OLP lesions have a higher risk for malignant transformation. Every patient with OLP should be observed ultra-carefully to detect early findings for cancer development; thus, it is critical to identify the main molecular markers such as those mentioned. Since Fitzpatrick et al.<sup>9</sup> only evaluated the clinical characteristics of the malignant alteration of OLP, this study aimed to identify the specific molecular markers related to the malignant transformation of OLP.

### Methods

In the present study we systematically reviewed all the published papers in English since January 1990 to December 2015. Toward this end, the international electronic databases including PubMed, Google Scholar, Science Direct, Scopus, Cochrane, and ISI Web of Science were searched. Our search included (MeSH) the medical keywords “oral lichenoid reaction”, “oral lichenoid lesion”, “oral lichenoid eruption”, “oral lichen planus”, “lichen planus”, and “lichenoid” in combination with “malignant transformation”, “pre-malignant character”, “cancerization”, “pre-neoplasm”, and “squamous cell carcinoma”. In the next step, to identify other related articles we considered summaries of all presentations at international congresses in the field of oral health during the specified period (1990–2015). In addition, we used the references cited in the related papers in order to prevent us from missing any pertinent

data or studies. All the obtained articles were imported into EndNote software. The software eliminated duplicate studies. The investigator screened the relevant publications in three steps based on the titles, abstracts, and body text. The investigator also screened the articles according to the strength of their methods.<sup>10,11</sup>

Therefore, case-reports or studies without any comparison with a control group or without a reliable diagnostic test were excluded. The included papers were case-control studies with both human and biopsy samples. We extracted data in two phases. First, we evaluated the overall related qualified studies and we extracted all the investigated molecular markers. In the second data extraction phase, we categorized the molecular markers according to their frequency. The obtained data included papers that examined special molecular markers. The collected papers were classified based on the number of repeated markers they contained: repeated more than once and repeated once. The data were extracted and then saved separately in an Excel worksheet.

### Results

First, 570 articles were collected from the previously mentioned databases (Cochrane: 8, PubMed: 347, Google Scholar: 141, Science Direct: 41, Scopus: 27, Web of Science: 6). after removing duplicate articles, the remaining records were evaluated based on their title and abstract. Finally, 66 records were selected (Figure 1). Reviewing the full texts of those 66 articles enabled us to clarify the most important molecular markers in these studies. The extracted and stratified data [regarding the author, year, study group(s), technique, and detection of markers in the OLP group] for these reviewed articles are shown in tables 1-3.



Figure 1. Flow diagram of study

**Table 1.** Description of the reviewed studies for the main seven markers

Studies/ Marker	Author	Year	Study group(s)	Technique	Detection of marker in OLP	
Twelve studies for p53	Acay et al. <sup>15</sup>	2006	22 OLP, 27 OLL	IHC	+	
	Agha-Hosseini and Mirzaei-Dizgah <sup>14</sup>	2015	35 OLP, 38 NM	ELISA	NC	
	Arreaza et al. <sup>15</sup>	2013	31 OLP, 34 OLR	IHC	+	
	de Sousa et al. <sup>29</sup>	2009	24 OLP, 24 OSCC	IHC	+	
	Gonzalez-Moles et al. <sup>55</sup>	2006	51 OLP, 26 NM	IHC	+	
	Lee et al. <sup>38</sup>	2004	56 OLP, 20 NM, 20 EH, 30 ED, 38 SCC	IHC	NC	
	Leyva-Huerta et al. <sup>39</sup>	2012	21 OLP, 16 OSCC, 4 NM	IHC	+	
	Ogmundsdottir et al. <sup>59</sup>	2002	55 OSCC, 48 OLP, 12 NM	IHC	NC	
	Oliveira Alves et al. <sup>56</sup>	2013	5NM, 25 IFH, 65 OLP, 16 OED, 19 OSCC	IHC	+	
	Safadi et al. <sup>65</sup>	2010	18 OLP, 10 NM, 10 OSCC, 13 NM, 20 OFK, 30 OED	IHC	-	
	de Sousa et al. <sup>29</sup>	2009	24 OLP, 24 OED	IHC	+	
	Seven studies for COX-2	Valente et al. <sup>15</sup>	2000	28 OLP, 7 NM	IHC	NC
Abdel Hay et al. <sup>12</sup>		2011	50 OLP, 50 NM	RFLP, RT-PCR, RIA	-	
Arreaza et al. <sup>16</sup>		2014	34 OLR, 31 OLP	IHC	+	
Cortes-Ramirez et al. <sup>26</sup>		2010	44 OLP	IHC	+	
Danielsson et al. <sup>28</sup>		2011	20 OLP, 20 NM	RT-PCR, IHC, Western blot	+	
Li et al. <sup>40</sup>		2013	33 OLP, 38 OSCC, 10 NM	IHC, RT-PCR	+	
Lysitsa et al. <sup>42</sup>		2007	30 OLP, 8 NM	Western blot	+	
Neppelberg and Johannessen <sup>53</sup>		2007	7 NM, 45 OLP	IHC	-	
Seven studies for Bcl-2		Arreaza et al. <sup>16</sup>	2014	34 OLR, 31 OLP	IHC	+
		de Sousa et al. <sup>29</sup>	2009	24 OLP, 24 OSCC	IHC	-
		Gonzalez-Moles et al. <sup>55</sup>	2006	51 OLP, 26 NM	IHC	+
		Leyva-Huerta et al. <sup>39</sup>	2012	21 OLP, 16 OSCC, 4 NM	IHC	+
	Nafarzadeh et al. <sup>51,52</sup>	2013	11 WOSCC, 30 OLP, 20 NM	IHC	?	
	Pigatti et al. <sup>57</sup>	2014	14 OLP, 14 OLL, 9 NM	IHC	+	
	Sousa et al. <sup>69</sup>	2009	24 OLP, 24 OED	IHC	+	
Six studies for Ki67	Acay et al. <sup>15</sup>	2006	22 OLP, 27 OLL	IHC	-	
	Gonzalez Moles et al. <sup>32</sup>	2009	Ninety OSCCs from 73 patients	IHC	+	
	Gonzalez-Moles et al. <sup>33</sup>	2006	51 OLP, 26 NM	IHC	NC	
	Mattila et al. <sup>46</sup>	2007	70 OLP	IHC	-	
	Pigatti et al. <sup>57</sup>	2014	14 OLP, 14 OLL, 9 NM	IHC	?+	
	Zargarani et al. <sup>75</sup>	2013	17 EH, 16 OLP, 10 MED, 10 SED, 10 WOSCC, 10 POSCC	IHC	+	
	Five studies for Bax	Bascones et al. <sup>17</sup>	2005	32 OLP, 20 NM	TUNEL assay, IHC	-
Bascones-Ilundain et al. <sup>18</sup>		2007	32 OLP (18 reticular and 14 atrophic-erosive)	IHC	NC	
de Sousa et al. <sup>29</sup>		2009	24 OLP, 24 OSCC	IHC	-	
Nafarzadeh et al. <sup>51,52</sup>		2013	11 WOSCC, 30 OLP, 20 NM	IHC	+	
Sousa et al. <sup>69</sup>		2009	24 OLP, 24 OED	IHC	+	
Four studies for p21	Bascones et al. <sup>17</sup>	2005	32 OLP, 20 NM	TUNEL assay, IHC	+	
	Bascones-Ilundain et al. <sup>19</sup>	2006	32 OLP, 20 NM	IHC, TUNEL assay	+	
	Gonzalez-Moles et al. <sup>55</sup>	2006	51 OLP, 26 NM	IHC	+	
	Safadi et al. <sup>65</sup>	2010	18 OLP, 10 NM, 10 OSCC, 13 OM, 20 OFK, 30 OED	IHC	+	
Four studies for Caspase-3	Bascones et al. <sup>17</sup>	2005	32 OLP, 20 NM	TUNEL assay, IHC	+	
	Bascones-Ilundain et al. <sup>18</sup>	2007	32 OLP (18 reticular and 14 atrophic-erosive)	IHC	-	
	Bascones-Ilundain et al. <sup>19</sup>	2006	32 OLP, 20 NM	IHC, TUNEL assay	+	
	Gonzalez-Moles et al. <sup>55</sup>	2006	51 OLP, 26 NM	IHC	+	

OLP: Oral lichen planus; OLL: Oral leukoplakia; OLR: Oral lichenoid reaction; NM: Normal mucosa; OSCC: Oral squamous cell carcinoma; EH: Epithelial hyperplasia; OED: Oral epithelial dysplasia; MED and SED: Mild; Moderate and severe epithelial dysplasia; OFK: Oral focal keratosis; WOSCC and POSCC: Well-differentiated and poorly-differentiated OSCC; NC: Non-conclusive; OM: Oral mucositis; IHC: Immunohistochemistry; ELISA: Enzyme-linked immunosorbent assay; RFLP: Restriction fragment length polymorphism; RT-PCR: Reverse transcription polymerase chain reaction; RIA: Radioimmunoassay; TUNEL assay: Terminal deoxynucleotidyl transferase dUTP nick-end labeling assay

**Table 2.** Markers repeated in two studies

Marker	Author	Year	Study group(s)	Technique	Detection of marker in OLP
PCNA	Lee et al. <sup>38</sup>	2004	56 OLP, 20 NM, 20 EH, 30 ED, 38 SCC	IHC	?
	Sousa et al. <sup>69</sup>	2009	24 OLP, 24 dysplasia	IHC	+
MMPs	Chen et al. <sup>22</sup>	2008	27 OLP, 15 OSCC, 11 NM*	IHC	+
	Li et al. <sup>40</sup>	2013	33 OLP, 38 OSCC, 10 NM	IHC, RT-PCR	+
E-cadherin	Mattila et al. <sup>47</sup>	2008	70 OLP	IHC, static	-
	Neppelberg and Johannessen <sup>53</sup>	2007	7 NM, 45 OLP*	DNA cytometry IHC	-

MMP: Matrix metalloproteinases; PCNA: Proliferating cell nuclear antigen; OLP: Oral lichen planus; NM: Normal mucosa; EH: Epithelial hyperplasia; ED: Epithelial dysplasia; SCC: Squamous cell carcinoma; OSCC: Oral squamous cell carcinoma; NM: Normal mucosa; IHC: Immunohistochemistry; RT-PCR: Reverse transcription polymerase chain reaction

As shown in those tables, the main result of the reviewed studies denotes the significant existence of a particular marker in OLP. Table 1 shows the collected data for

seven markers repeated in more than two studies: p53, cyclooxygenase-2 (COX-2), Ki67, B-cell lymphoma-2 (Bcl-2), Bax, p21, and caspase-3.

**Table 3.** Markers repeated in one study

Author	Year	Marker(s)	Detection of marker in OLP
Rivarola de Gutierrez et al. <sup>63</sup>	2014	CK1	-
Chen et al. <sup>44</sup>	2008	TIMP-2, TGF-b1	+
Cheng et al. <sup>23</sup>	2014	DUSP1; H3F3A; OAZ1; S100P; SAT1	+
Cheng et al. <sup>24</sup>	2011	ET-1	+
Czerninsk et al. <sup>27</sup>	2013	SCCA	+
Czerninsk et al. <sup>27</sup>	2013	TPS, VEGF	-
Danielsson et al. <sup>28</sup>	2011	miR-26b	+
Gonzalez Moles et al. <sup>29</sup>	2009	SP, NK-1R	+
Hakkinen et al. <sup>36</sup>	1999	Integrin a9 subunit, tenascin	+
Li et al. <sup>40</sup>	2013	CXCL9	-
Ma et al. <sup>43</sup>	2013	Bmi1	+
Mattila et al. <sup>46</sup>	2007	CK-19	-
Mattila et al. <sup>46</sup>	2007	Topoisomerase II	+
Mattila et al. <sup>47</sup>	2008	cdk-1, Rad-51	-
Mattila et al. <sup>47</sup>	2008	desmocollin-1	+
Montebugnoli et al. <sup>49</sup>	2011	p16INK4A	-
Nafarzadeh et al. <sup>51,52</sup>	2013	Smad3	+
Oliveira Alves et al. <sup>56</sup>	2013	SUMO-1	-
Oliveira Alves et al. <sup>56</sup>	2013	MDM2	+
Pimenta et al. <sup>58</sup>	2004	hMSH2	+
Poomsawat et al. <sup>59</sup>	2011	cdk6	-
Poomsawat et al. <sup>59</sup>	2011	cdk4, p16	+
Prodromidis et al. <sup>60</sup>	2013	p-Akt, p-mTOR, phospho-pS6	+
Rhodus et al. <sup>62</sup>	2005	NF-Kb, TNF-a,	+
Rivarola de Gutierrez et al. <sup>63</sup>	2014	CK13, CK14	-
Segura et al. <sup>66</sup>	2013	MYC status	+
Shi et al. <sup>67</sup>	2010	Podoplanin, ABCG2	+
Sun et al. <sup>70</sup>	2013	CD133	+
Thongprasom et al. <sup>72</sup>	1998	Telomerase activity	+
Valente et al. <sup>73</sup>	2000	MIB-1	-
Xu et al. <sup>74</sup>	2013	ALDH1	+
Zhang et al. <sup>76</sup>	1997	LOH	+

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It is important to note that these markers were highlighted in 45 studies. The marker studied most often was p53 (in 12 studies). The markers that were least often studied were p21 and caspase-3 (in four studies). The markers that were only repeated in two studies are listed in table 2. The markers that were only repeated in one study are presented in table 3.

### Discussion

This review focused on the most frequent molecular markers of OLP malignancy, which were examined in 66 articles, and reported on the frequency of these markers. Based on those 66 studies, there were seven principal markers for malignant transformation: p53, COX-2, Ki67, Bcl-2, Bax, p21, and caspase-3.<sup>12-77</sup>

p53 is the marker that is most frequently investigated in the studies in this systematic review. In the normal development of a cell, the p53 protein level is low because it has a short half-life; otherwise, in situations in which a cell can tolerate additional pressure the production of this marker saves the cell and it would not prevent apoptosis. The wild-type p53 protein has an opposite effect on cell proliferation, and it can inhibit the cell cycle process between the G1 and S phases. It has been shown that the p53 mutation increases proliferative activity; the expression of this protein is altered in OSCC and in potentially malignant oral lesions.<sup>13,15,38,39,73</sup> COX-2 and Bcl-2 (the second most frequent markers found in this systematic review) are important factors in inflammation and carcinogenesis. Overexpression of COX-2 is indicated in cancer development, including invasion, metastasis, angiogenesis, and other cancer-related steps. The increased expression of COX-2 has been reported in pre-cancerous lesions, including squamous cell carcinoma and OLP.<sup>12,26,28,40,42</sup>

The Bcl-2 protein is responsible for translocation in follicular lymphoma. Bcl-2 could protect cells against apoptosis. Bcl-2 is located in the inner mitochondrial

membrane, and to a lesser extent in the nuclear membrane and the endoplasmic reticulum. Bcl-2 activity correlates with p53 because its expression prevents apoptosis. Cell proliferation and apoptosis are altered in the carcinogenesis process. Bcl-2 and Bax have an important role in this alteration. Therefore, any altered expression and function of Bcl-2 and Bax could be an indicator of malignant transformation in a lesion. This mechanism has been described for oral cancer.<sup>30,34,39,52</sup> In the present study, the expression of Ki67 was ranked fourth in terms of its effect on the creation of precancerous and cancerous oral lesions. It has been described that Ki67 has an effect on the active phases of a cell cycle (G1, S, G2). Its expression rate depends on cellular proliferation. It might be promising as a first index of malignancy.<sup>13,46</sup> p21 tumor suppressor genes produce the p53 protein. p21 induces suppressive outcome on the function of cyclin-dependent kinase. This enzyme plays a controlling role in G1 to S phase (cell cycle). It has been shown that p21 overexpresses in oral epithelial dysplastic lesions and OSCC. Therefore, this gene expression could be used to identify the prognosis of oral malignancy.<sup>65</sup> Apoptosis is a defensive factor. It might protect cells from malignant transformation. The process of apoptosis depends on many molecular effectors. Caspase-3 is involved in proteolysis, and this special factor leads to the activation of apoptosis.<sup>17</sup>

In almost all the reviewed studies, the case group consisted of a number of cases with the diagnosis of lichen planus, unlike the control groups that showed a remarkable diversity of diseases, including oral leukoplakia, OSCC, oral epithelial dysplasia, and epithelial hyperplasia as well as normal mucosa. The wide clinical and histological spectra of these entities in the control groups are significant. Safadi et al.<sup>65</sup>, Zargarani et al.<sup>75</sup> and Lee et al.<sup>38</sup> divided their studied patients into five groups. Nevertheless, it seems that comparing more than two groups in one study causes

complexity in the data interpretation. Significantly, studies, such as those conducted by Bascones-Ilundain et al., have examined the high-risk clinical view of lichen planus (atrophic-erosive) for malignancy.<sup>17-19</sup>

In the present study, review of the 66 articles also found a notable diversity in the sample sizes, ranging from 14 to 70 cases for OLP in the examined studies. It seems that using the average number from that range (almost 40 cases of lichen planus) is reliable.

As shown in tables 1 and 2, the reviewed articles used eight different diagnostic methods to determine the presence of the molecular markers mentioned in their samples. These eight methods included immunohistochemistry (IHC), Enzyme-linked immunosorbent assay (ELISA), Restriction fragment length polymorphism (RFLP), Reverse-transcription polymerase chain reaction (RT-PCR), double-antibody radioimmunoassay (RIA), Western blot, the Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, and static DNA cytometry. IHC was the primarily used method (45 out of 66 studies). The influence that using a specific test had on the result of the studies is unclear. Abdel Hay et al.<sup>12</sup> were the only researchers who used RFLP and RIA, and Agha-Hosseini and Mirzaii-Dizgah exclusively utilized ELISA in their study.<sup>14</sup> Some researchers, such as Danielsson et al.<sup>28</sup> and Abdel et al.<sup>12</sup> used three different techniques in one study; however, the advantage of this approach is unclear.

Giacomelli et al.<sup>8</sup> studied the relationship between OLP and OSCC in a new way using the leader genes approach. In this method,

the data search for genes involved a specific process done systematically. Then, the data are ranked based on the number of interconnections with the other identified genes. This suggests that some key genes and encoded proteins are possibly involved in the malignant potential of OLP;<sup>8</sup> hence, that study has a good agreement with the findings of this study.

One of the limitations of this study was that the collected data could not be pooled due to different methods that were used and the study groups that were examined; thus, there was not a possibility to carry on a meta-analysis.

### Conclusion

The present study concluded that several molecular alterations, including p53, COX-2, Ki67, Bcl-2, Bax, p21, and caspase-3, which are involved in pre-neoplastic alterations, are measurable in OLP. It seems that three factors have serious implications for the lack of agreement in this field of research: 1) using different diagnostic tests, 2) choosing different numbers for the sample sizes, and 3) considering miscellaneous features for the case and control groups. To identify a definite relationship, we suggest further studies on both the most possible and the uncertain groups of molecular markers in this field.

### Conflict of Interests

Authors have no conflict of interest.

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