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Review article

Oral field cancerization: Genetic profiling for a prevention strategy for oral potentially malignant disorders

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ABSTRACT

Background: *Oral cancer therapy, such as radiation or surgical treatment, has pernicious long-term effects that patients suffer throughout their life, the disability being considerable with delayed diagnosis. It is well known that many oral cancers develop from oral potentially malignant disorders (OPMDs). Patients diagnosed with OPMDs may have an increased risk of developing cancer anywhere in the oral cavity. Early detection and intervention could be essential prevention strategies to inhibit oral cancer progression. OPMDs may not immediately develop into carcinoma. However, this condition provides a "field" of specific abnormalities wherein evolving altered genetic cells can be explained with the "field cancerization" concept.* ***Purpose:*** *This review aims to describe the "field cancerization" concept in oral cancer and OPMD, which is expected to contribute to a better clinical management strategy for oral cancer prevention.* ***Review:*** *"Oral field cancerization" describes oral cancers that develop in multifocal areas of pre-cancerous changes. It can be found as histologically abnormal tissue surrounding the tumor, suggesting that oral cancer often consists of multiple independent lesions.* ***Conclusion:*** *The oral field cancerization concept should prompt healthcare professionals to remind their patients that frequent oral examination with histological studies and molecular testing is mandatory for those at high risk of developing malignancies.*

Keywords: *genetically altered field; oral cancer; oral field cancerization; oral potentially malignant disorders*
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INTRODUCTION

Oral cancer is one of the most common malignancies worldwide, with approximately 5% of those with diagnosed cancer coming from developing countries. The prevalence of head-and-neck squamous cell carcinoma (HNSCC) worldwide is about 20 cases per 100,000 population per year.[1] Oral cancer, notably that induced by tobacco and alcohol consumption, may develop from an oral potentially malignant disorder (OPMD) or pre-cancerization lesion.[2–4] Some OPMDs might disappear, while others result in oral cancer. The proportion of cases of OPMD in oral cancers ranges from 3–50%.[5]

While the management of OPMD might improve the outcome, standard therapy does not prevent cancer transformation from OPMD.[6] Oral cancer therapies have pernicious long-term effects throughout the life of patients. These effects are substantial when the diagnosis is delayed.[7] The HNSCC 5-year survival rate is the lowest among aggressive cancers. The prognosis of oral squamous cell carcinoma (OSCC) depends on the presence of new tumor growth.[1]

In 1953, Slaughter published an article emphasizing the importance of examining and investigating the "field" surrounding an oral cancer lesion.[8] This should be done at the risk-assessment stage and must be part of the comprehensive management of oral cancer. Since then, many studies have used molecular techniques to explore this concept. The nature of oral cancer is genetically altered cells. During cancerization, several epithelial cells may undergo an altered genetic makeup called a field with a typical clinical appearance. These cells can provoke a process called "field cancerization."[9]

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Some oral lesions display field cancerization and are classified as OPMDs or pre-cancerization lesions. Common OPMDs are leukoplakia with a transformation possibility of 0.13–40.8%,[10–12] erythroplakia with 33.1%,[13] and oral lichen planus with 1.1–2.28%.[14,15] The differences in transformation depend on the predisposing or risk factors.[16]

Patients may develop cancer in the field of cancerization. Unfortunately, this condition is only confirmed with invasive excisional surgery. There is no effective intervention for preventing transformation and cancerization.[17] The purpose of this review is to discuss oral field cancerization, cancerization mechanisms, and deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and tissue markers to be considered as cancerization biomarkers to provide recommendations for dentists, oral medicine specialists, and oral surgeons for better patient management.

Oral cancers

The carcinogenesis process begins with a stem cell with one or more genetic or epigenetic alterations. Then, a clone from the altered cells forms a patch or cluster. Due to further genetic alteration, stem cells deviate from standard growth control patterns and enjoy advantages for the development of expanding clones. Furthermore, lesions develop and become a field that replaces normal epithelium laterally. This field has genetically altered clonal units and advantages in proliferation activity, and finally dominates the overall process. Additional genetic alterations occur along with enlargement of the lesion, creating various subclones within the field. Because of divergence and clonal selection, clones are altered at different times and produce adequate modified stem cells. However, these cells share the same clonal origin. This process culminates in invasive cancer formation.[18]

Histologically, it is considered a local recurrence when the distance between tumors is less than 2 cm; if it is more than 2 cm, it is regarded as a second primary tumor.[19] Even a single altered cell caused by tumor-suppressor gene inactivation and oncogene activation can overgrow and expand to form a clonal mass of tumor cells. Clinically, this is a dynamic process. Genetic alteration occurs from the accumulation of cell-growth phases and progresses from the benign to the pre-malignant and malignant stages.[20]

Oral field cancerization

The terms "field effect" and "field cancerization" are used when the pre-neoplastic process is in several locations.[21] This was previously assumed to be multiple conditions developing independently. However, this was challenged due to the clinical diagnosis of a second primary tumor located distant from the original tumor, found on genetic analysis to be arising from the clonal spreading of the initial lesion.[1] Field pre-cancerization and its correlation with oral cancers are explained in Figure 1.

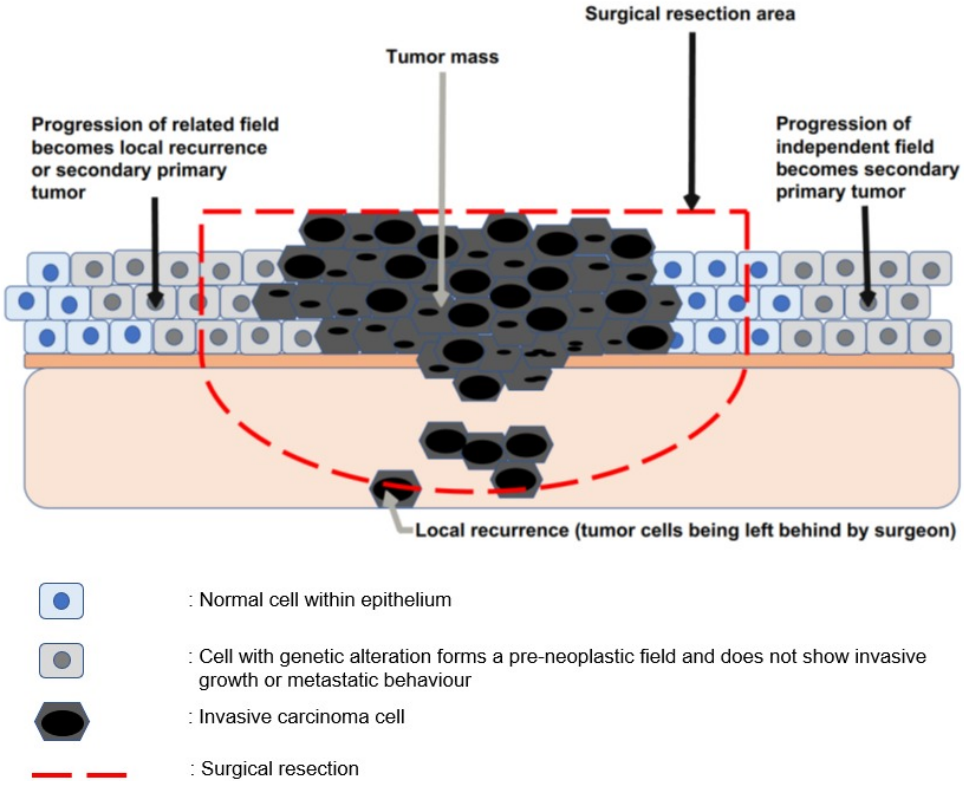

Figure 1. Field cancerization shows mucosal areas with normal cells (blue) and cells with cancer-associated genetic or epigenetic alterations (gray). A pre-neoplastic field is monoclonal in origin and does not show invasive growth or metastatic behavior, which are the hallmarks of invasive carcinoma (dark gray cells).

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Oral cancers, especially OSCCs, develop in pre-cancerous cells with clonal expansion of normal keratinocytes that have been altered genetically. The genetically unstable pre-cancerous keratinocyte manifests as aneuploidy, gaining or losing chromosomal material, or nucleotide sequence alteration. The instability of genomic support and further acquisition in genetic alteration leads to the growth superiority or inferiority of affected cells. Genetically inherited cells eventually acquire a cancerous phenotype. Although other oral cancers can develop from blood vessels or salivary glands, this mechanism underlies all cancer events.

The probability of cancer development from genetically altered stem cells depends on the nature of the stem cells and the additional alteration. The proposed carcinogenesis model is based on a monoclonal origin and involves three stages.[22,23] The first stage of patch formation is the conversion of a single stem cell (Figure 2A) into a cell cluster with genetic alteration and without appropriate growth-pattern control. The second stage, or clonal expansion, is additional genetic alteration; the patch proliferates and forms a field that replaces normal epithelium (Figure 2B). After exposure to another carcinogenic event, these cells turn to cancer cells with invasive growth or metastatic behavior, the third stage of tumor transition (Figure 2C, 2D). Surgical treatment is usually carried out at this stage (Figure 2E). Without proper molecular examination and prediction of field cancerization, cells with cancer-associated genetic or epigenetic alterations may be left behind (Figure 2F). Over time, with exposure to multiple carcinogenic events (unavoidable predisposing and risk factors), the remaining cells with cancer-associated genetics can develop into a second-field tumor, becoming overt carcinoma with invasive growth and metastases (Figure 2G, 2H).

Markers of field cancerization

Carcinogenesis is a complex phenomenon with multiple genetic lesions and interactions.[24] Since every tumor has a

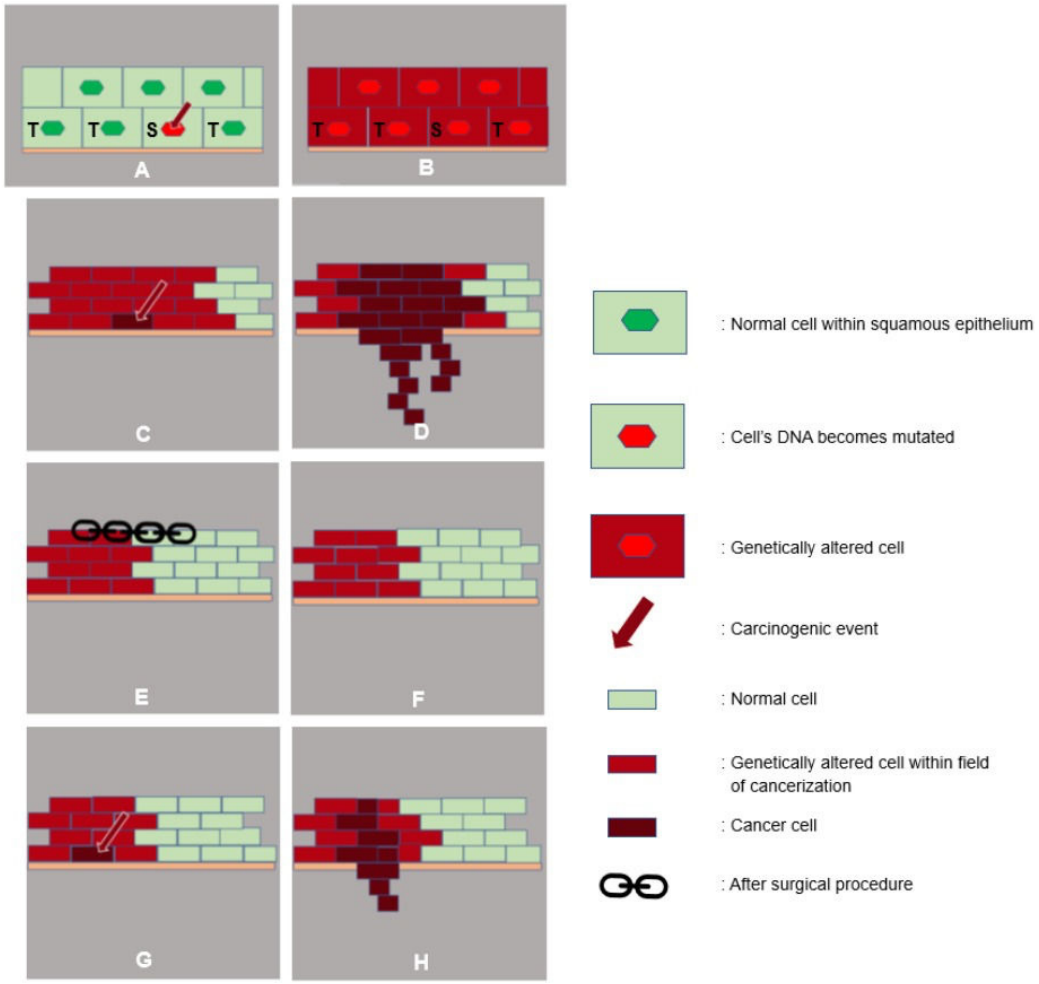

Figure 2. Second field tumor model; **A**. A normal clonal unit. A stem cell (S) exposed to the carcinogenic event becomes a genetically altered cell. **B**. Transit-amplifying cells (T) and daughter cells of the stem cell have the same genetic alteration. **C**. Genetically altered cells with uncontrolled growth develop. **D**. Cancer cells with invasive and metastatic behavior start to grow. **E**. The surgeon removes the carcinoma. **F**. Post-surgery, without a proper genetic examination, the surgeon has left a field behind. **G**. A cell in the field turns into a cancer cell after another series of carcinogenic exposures. **H**. Carcinoma develops in the same field: a second-field tumor.[1]

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unique alteration pattern, information about these markers can be used to measure the clonal correlation between lesions in a single patient. The presence of a field with genetically altered cells is a risk factor for cancer. Many pre-cancerization cells within the proliferating area may increase cancer risk significantly. The early genetic event can lead to clonal expansion from pre-malignant daughter cells in specific tumor fields. Subsequent genomic alteration in a few cells can induce a malignant phenotype.[1]

Biomarkers can be used to monitor tumor progression, thus preventing invasive cancer transformation in pre-cancerous lesions. The standard markers for identifying field cancerization are loss of heterozygosity, microsatellite alterations, chromosomal instability, and p53 gene mutations, generally detected by polymerase chain reaction, immunohistochemistry, and in situ hybridization.[9]

More specifically, some alteration or modification can detect both pre-cancerization and cancerization. In some instances of pre-cancerization, known as OPMDs, biomolecular markers have a significant role in detecting transformation to oral cancers. Available data state that the intratumoral heterogeneity,[25] proteome and lipidome profile,[26] myofibroblasts,[27] and cytokeratin markers like tissue polypeptide antigen (TPA) and tissue polypeptide specific antigen (TPS),[28] are the current biomarkers of pre-cancerization lesions.

Further, extensive analysis at the tissue and DNA level has been developed. DNA aneuploidy 29 and chromosome aberrations30 are commonly used to detect field cancerization at the DNA level. Several markers (p53, Ki-67,[31] cytokeratin fragments 21-1,[28] variations in nucleolar organizer regions,[32] phosphatases and tensin homolog deleted on chromosome 10 allelic loss,[33] DEK overexpression,[34] micro RNA [hsa-miR-221, hsa-miR-21, hsa-miR-135b, and hsa-miR-29c] detection,[35] ATP-binding cassette subfamily G member 2,[36] MutL protein homolog 1, methylguanine-methyltransferase methylation,[37] interferon-stimulated gene 15,[38] aldehyde dehydrogenase, Notch1,[39] and Bmi1[40]) have been identified in pre-cancerization transformation into oral cancer, stimulating the cell cycle and promoting DNA replication (Figure 3).

Various protein expressions or markers have been revealed at the tissue level and may be easier to replicate in clinical settings than DNA analysis. These include the expression of Ki-67,[38] kaiso, e-cadherin,[41] stathmin,[42] Oct^{4+}, Sox^{2+},[43] GLUT-3, GLUT 4,[44] substance p, NK-1R,[45] podoplanin,[36] matrix metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 1 (TIMP-1), vimentin (VIM),[46] cornulin,[38] transforming growth factor (TGF-β1) and interleukin 17-A (IL-17A).[47] These markers are essential in detecting oral cancer, especially OSCC. All these markers have demonstrated strong reactivity, and detecting these markers increased the survival rate (Figure 3).

The specific techniques to obtain satisfactory results are whole-exome sequencing and targeted ultra-deep sequencing,[48] DNA high-resolution flow cytometry, array-comparative genomic hybridization,[30] mass spectrometry imaging based on matrix-assisted desorption-ionization,[26] and liquid biopsy.[49]

DISCUSSION

The World Health Organization has proposed the term OPMD for classifying fifteen conditions, including leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral submucous fibrosis, and oral lichen

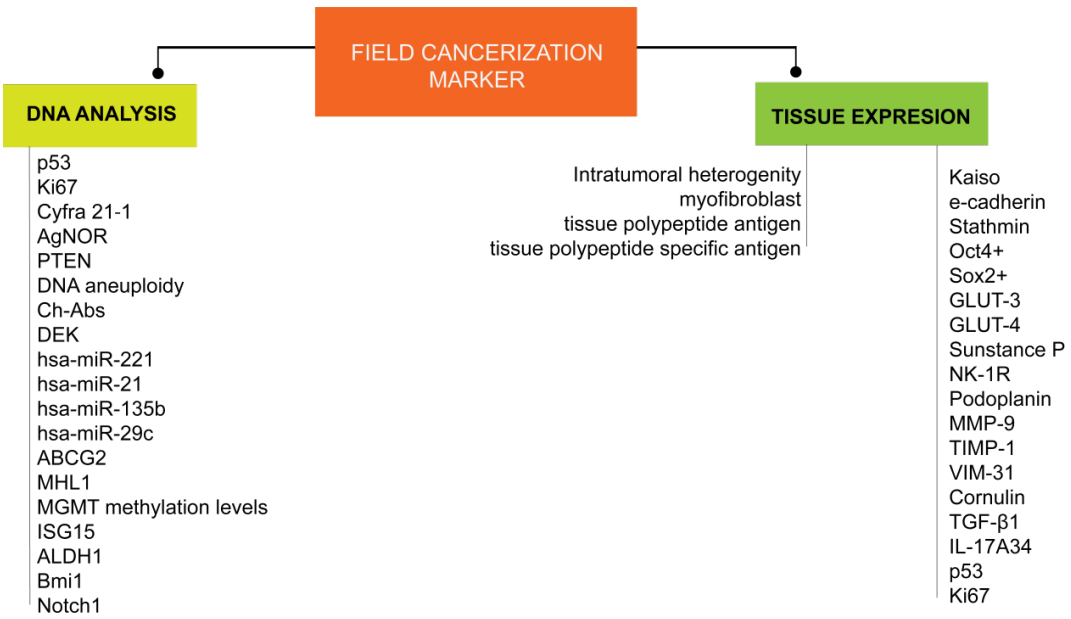

Figure 3. The markers of OSCC, including DNA analysis and tissue expression, are purposed for field cancerization to prevent malignant transformation or recurrence.

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planus.[5] OPMDs are determined to be pre-cancerization lesions because some of the cells carry cancer-associated genetic or epigenetic alterations. Some oral cancer specimens from the border of malignant lesions, showing a histologically normal appearance, have a genetic alteration, indicating that not all pre-cancerous fields can be identified histologically.[50] Genetic markers must be used to identify all potentially malignant areas.[5] Alteration can happen within the epithelium and/or the stroma.[1] In the oral cavity, tobacco and alcohol work synergistically as primary carcinogens in developing OSCCs. Environmental carcinogens reach a broader area simultaneously, destroy in more significant proportions and contribute to pre-malignant conditions within the exposed area and can manifest as micro-metastatic deposits.[51] A pre-malignant field often needs a long time, about 67–96 months, to develop and become invasive carcinoma. An analysis of 783 patients by Slaughter suggested that exposure to carcinogen-induced mucosal changes causes vulnerability of the surrounding area to multiple malignant foci.[52]

Oral field cancerization is caused by either cell migration or from an independent cell. Multiple tumors from the original primary cells and genetically altered cells from the primary cell are brought to their progenitor cells. Investigating the development of primary lesions and their progression through cell expansion is crucial for measuring clonal markers based on the early identification of genetic events.[18]

Clinically, oral cancer lesions may appear as white plaques, red plaques, ulcers, or verrucous forms, with a low degree of hyperplasia. However, the surrounding tissue may have a well-differentiated, verrucous hyperplasia, severe dysplasia, and even a carcinoma in situ.[53] Why the surrounding tissues transform into cancer is still not fully understood. The possible mechanism is that the adjacent tumor microenvironment and cancer occur through dynamic interactions by direct cell-to-cell communication or extracellular and intracellular agents. Some hypotheses for cancer transformation are cell fusion, horizontal gene transfer, genetic instability, and microenvironment involvement.[54]

Noncoding and microRNAs represent the dynamic interaction between tumor and nontumor cells.[55] This process may induce cancer-associated fibroblasts, the dominant cell type within the reactive stroma of many tumor types.[56] Other causal factors include cytokine involvement, growth factors, and reactive oxygen species (ROS) as cell signaling molecules that aid cell-to-cell communication.[57] Field cancerization replaces the normal cell population with a histologically nondysplastic but pro-tumorigenic mutant cell clone.[58] This mechanism is demonstrated in Figure 2E; after surgical treatment, the surrounding tissue can progress to oral cancer because a single cell with cancer-associated genetic or epigenetic alterations can induce a neighboring cell to transform (Figure 4).

During the biopsy, it suggested that the sample should be larger than a single clonal unit, i.e., containing at least 200 cells in width and reaching 10 cm in diameter.[19] This could identify pre-cancerization at the periphery of the incision, making the examination of possible areas of field cancerization more precise and adequate. However, it should be noted that some lesions and anatomical locations are a barrier to carrying out comprehensive biopsies.

Comprehensive biopsies aid in the adequate detection of field cancerization. Clinical symptoms do not correlate with the pathogenesis and development of oral cancer in the early stages. Thus, diagnostic biomarkers are crucial for determining histopathology grading and prognosis. When cancer has invaded, there are increased clinical symptoms, and the need for biomarker diagnostics is decreased. Since

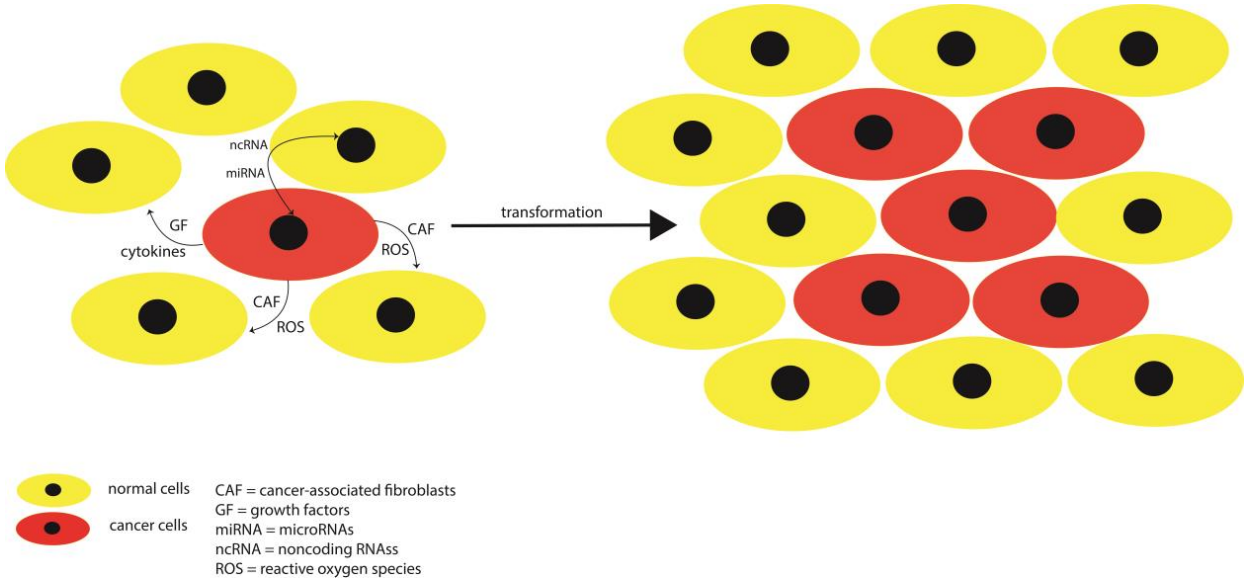

Figure 4. Mechanism of field cancerization and cell transformation through noncoding RNA, microRNA, cytokines, growth factors, and reactive oxygen species.

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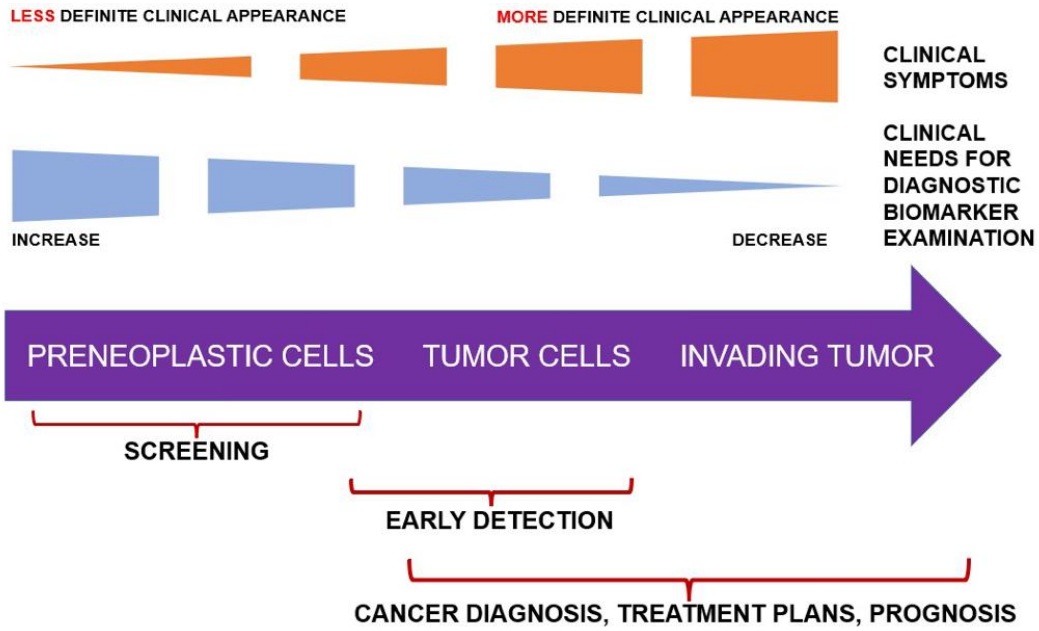

Figure 5. Carcinogenesis model and clinical need for diagnostic biomarkers.

the cancer is already in the final stage, the clinician focuses on the diagnosis and treatment plan with the possibility of a poor prognosis (Figure 5).

Management strategies for OPMD or pre-cancerization lesions should follow a strict protocol, including counseling emphasizing the patient's commitment to discontinuing their bad habits. The clinician must provide a long-term follow-up and patient monitoring with an estimation of 67 – 96 months to detect invasive carcinoma transformation. Based on the clinical characteristics, it is essential to examine and observe the entire oral area and not just the area with lesions. Specific biomarkers must be used appropriately.[17]

These steps should contribute to improving prognosis.[17] Identifying molecular markers is essential in genetically transformed cells with normal histological appearance.[59] Thus, tumor-specific biomarker identification has an excellent role in monitoring tumor progression and, if possible, preventing invasive cancer transformation. Early identification and management of field cancerization are critical for cancer mortality and morbidity prevention. In the clinical setting, oral field cancerization should prompt healthcare professionals to remind patients that frequent oral examination with histological studies and molecular testing is mandatory for those at high risk of developing malignancies.

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