Review Article

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Archives in Cancer Research
ISSN 2254-6081

2018
Vol.6 No.1:3

DOI: 10.21767/2254-6081.100169

An Insight into Tumor Markers in Oral Cancer: A Review

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Citation: Kaur T, Dahiya S, Srivastava A (2018) An Insight into Tumor Markers in Oral Cancer: A Review. Arch Cancer Res. Vol.6 No.1:3

Abstract

Tumor markers are substances that are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign conditions that can aid in the diagnosis of cancer. These markers may be employed to predict primary or secondary tumor risk. Sometimes, non-cancerous conditions can also cause elevation of some tumor markers to be higher than normal. Besides, not every cancer patient may have raised level of a tumor marker. For these reasons, knowledge about cancer biomarkers is essential. This review highlights potential molecular markers relevant to oral neoplasia in terms of their perspective role of in prevention and detection.

Keywords: Biomarkers; Tumor; Oral cancer

Received: December 01, 2017; **Accepted:** January 23, 2018; **Published:** January 29, 2018

Introduction

Oral cavity cancer is amongst the most prevalent cancers worldwide and incidence rates are higher in men than women. There are an estimated 529,000 new cases of cancers of the oral cavity and pharynx each year, and more than 300,000 deaths. Oral cancers include the main subsites of lip, oral cavity, nasopharynx and pharynx and have a particularly high burden in South Central Asia due to risk factor exposures [1,2].

The diagnosis of cancer is based on the analysis of tissue and cytology specimens obtained through several procedures. When a cell becomes cancerous, new antigens unfamiliar to the immune system appear on the cell's surface. The immune system identifies these new antigens, called tumor antigens, as foreign and may be able to contain or destroy the cancerous cells [3,4].

A tumor marker can be defined as a molecule that indicates the likely presence of cancer or can also be defined as one that provides information about the likely future behavior of an existing cancer (e.g. ability to metastasize or to respond to therapy). Most existing tumor markers are mostly useful in making a clinical decision after initial suspicion of cancer or its behavior which has been already raised by more conventional means [5].

Review of Literature

Characteristics of an ideal tumor marker

a. It should be highly sensitive and should have low false negatives.

b. It should be highly specific and should have low false positive.

c. It should have high positive and negative predictive value.

d. 100% accuracy in differentiating between healthy individuals and tumor patients.

e. It should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.

f. It should predict early recurrence and have prognostic value.

g. It should be clinically sensitive i.e. detectable at early stage of tumor.

h. Its levels should be preceding the neoplastic process, so that it should be useful for screening early cancer.

i. It should be either a universal marker for all types of malignancies or specific to one type of malignancy.

j. It should be easily assayable and be able to indicate all changes in cancer patients receiving treatment [6,7].

Chan and Sell have summarized the potential uses of tumor markers as follows

a. Screening in general population.

b. Differential diagnosis in symptomatic patients.

c. Clinical staging of cancer.

d. Estimating tumor volume.

e. Prognostic indicator for disease progression.

f. Evaluating the success of treatment.

g. Detecting recurrences.

h. Monitoring responses to therapy.

i. Radio-immunolocalization of tumor masses.

j. Determining direction for immunotherapy [8].

Indications of tumor markers

For screening and early detection of cancer: Screening refers to looking for cancer in people who have no symptoms of the disease, while early detection is finding cancer at an early stage. Although tumor markers were first developed to test for cancer in people without symptoms, very few tumor markers have been found to be helpful in this way because most tumor markers have not been shown to detect cancer much earlier than they would have been found otherwise [5].

Diagnosing cancer: In most cases, cancer can only be diagnosed by a biopsy and tumor markers are usually not used to diagnose cancer. However, tumor markers can help determine if a cancer is likely in some patients. It can also help diagnose the origin of the cancer in patients presenting with advanced widespread disease.

Determining the prognosis (outlook) for certain cancers: Some newer tumor markers help to assess how aggressive a cancer is likely to be or even how well it might respond to certain drugs.

Determining the effectiveness of cancer treatment: One of the most important uses for tumor markers is to monitor patients being treated for cancer. If the initially raised tumor marker level goes down with treatment, it indicates that the treatment is working and is having a beneficial effect. On the other hand, if the marker level goes up, then the treatment is probably not working and change of treatment should be considered.

Detecting recurrent cancer: Markers are also used to detect cancers that recur after initial treatment. Some tumor markers can be useful once treatment has been completed and with no evidence of residual cancer left [9].

Limitations of Tumor Markers

a. False elevation may occur in non-neoplastic conditions as many tumor markers are proteins, over expressed not only by cancer cells but also by normal tissues.

b. Early detection is difficult, since low levels are seen in normal individuals.

c. Large volume of cancer needed for significant elevation above normal.

d. Many tumor markers are not specific to a particular type of cancer.

e. Tumor marker levels are not elevated in every person.

f. No simple tests are yet available with sufficient specificity to detect the presence of a cancer.

Types of Tumor Markers

a. Intermediate markers measure cellular and molecular alterations before the onset of the malignant neoplasm.

b. Diagnostic markers useful in confirming the malignant lesion established.

c. Prognostic markers determine the growth, metastasis and invasion potential of tumor.

d. Tumor specific markers specific for a single tumor.

e. Tumor associated markers are found with different tumors of the same tissue type [10,11].

f. Static tumor markers.

- **i.** Tend to remain constant throughout natural history of cancer.
- **ii.** Used as prognostic indicator.
- **iii.** Measured by IHC on tissue samples.
- **iv.** E.g. ER in breast cancer.

g. Dynamic tumour markers.

- **i.** Respond to changes in tumour due to therapy.
- **ii.** May be useful to predict response.
- **iii.** Measured in blood and body fluids.
- **iv.** E.g. CA-125, CA19-9

Classification of Tumor Markers

Earlier classification given by Neville AM & Cooper EH 2 is arbitrary with considerable overlap and grouped tumor markers into Hormones, Onco-fatal products, Enzymes/isoenzymes and other macromolecules. Even though broader classification was proposed in later years there is no single universally acceptable classification of tumor markers to date [12].

Neville AM and Cooper EH classification

a. Hormones.

b. Oncofetal products.

c. Enzymes/isoenzymes.

d. Macromolecules.

Markers to predict response to therapy

a. Estrogen and progesterone receptors.

b. Androgen receptors.

c. Steroid regulated proteins Cathepsin D and pS2.

d. c-erbB-2 Gene.

Markers to monitor drug resistance

a. P-glycoprotein (a transmembrane protein).

b. c-erbB-2.

Growth factors and receptors

a. Epidermal growth factor receptors, erb-2 oncoprotein, insulin and insulin like growth factor receptors, transforming growth factor receptors, fibroblast growth factor receptors and the somatostatin receptors.

Tumor angiogenesis

a. Microvascular density has been found to be an independent marker of prognostic relevance.

Tumor growth fraction

a. Ki 67 ANTIBODY, Proliferating Cell Nuclear Antigen (PCNA) and *P27 KiP1* Gene.

Tumor suppressor genes

a. p53 tumor suppressor gene and Retinoblastoma susceptibility suppressor gene.

Anti-apoptosis genes

a. *bcl-2*.

Nm23 Anti-metastasis gene

a. The *nm23* gene family was originally identified in a murine melanoma cell line and nm23-HI was found to be transcribed at a 10-fold higher rate in cells of lower metastatic potential.

DNA repair genes microsatellite instability (MSI)

a. The human genome is punctuated with an enormous number of short repetitive nucleotide sequences known as microsatellites. They are less likely to be associated with lymphatic and distant metastasis and the improved prognosis applies even they are stratified by stage.

Miscellaneous markers

a. K-ras and c-myc oncogenes, transforming factors TGF-a, TGG-b, adhesion proteins E-cadherin and CD 44, and the matrix metaloproteases and inhibitors, etc.

Broad Classification of Tumor Markers

Proliferation markers

a. Ki-67

b. PCNA

c. DNA polymerase alpha

d. *p27 Kip*/gene

e. p105

f. p120

g. Statin

Oncogenes

a. *c-erb-2* gene

b. *ras* gene

c. *myc* gene

d. *bcl-2* gene

Growth factors and receptors

a. EGFR

b. TGF β-HCC

c. FGFR

d. Insulin and IGFR

Tumour suppressor genes

a. p53

b. Retinoblastoma susceptibility suppressor gene

Serological tumour markers

a. Markers associated with cell proliferation.

b. To cell differentiation.

c. To metastasis.

d. To other tumor associated events.

e. To malignant transformation.

f. Inherited mutations.

g. Monoclonal Ab defined tumor markers.

Tissue Markers of Potential and Established Malignancy

Cell surface markers

a. Carbohydrates

b. Squamous carcinoma antigens

c. Histocompatibility antigens

d. Growth factors and receptors

Intracellular markers

- **a.** Cytokeratin's
- **b.** Filaggrin
- **c.** Involucrin
- **d.** Desmosomal proteins
- **e.** Carcinoma antigen 17.13
- **f.** Quantitative DNA
- **g.** Ag NOR
- **h.** Oncogenes
- **i.** Arachidonic acid products
- **j.** Enzymes

Basement membrane markers

- **a.** Laminin
- **b.** Collagen IV

Matrix markers

- **a.** Tenascin

Cell Surface Markers

Carbohydrates

Cell surface carbohydrates may be important in the interaction of cells with matrix and other cells and therefore have attracted interest as markers for epithelial maturation, differentiation and neoplastic change. There are regional variations in cell surface carbohydrates in normal oral epithelium, but malignancy can be associated with synthesis of new carbohydrates, deletion of complex structures, and the accumulation of precursors [13].

ABH blood group antigens

The ABH blood group antigens are cell surface carbohydrates that may change in oral dysplastic lesions and malignant lesions. The expression of antigens A and B is lost and there is extended expression of precursor antigens. Some leukoplakias showing such cell surface carbohydrate changes but no dysplasia on conventional criteria have later developed into carcinomas suggesting these changes may be of predictive value.

Lectins

Ulex europaeus agglutinin 1 (UEA-1) is a lectin that binds to α-L-fucose and is an approximate marker for the blood group antigen H. The lectin Bandeiraea simplicifolia (BSA-1) binds to a-D-galactose and is specific to blood group antigen B, Peanut agglutinin (PNA) binds to the carbohydrate D-galactose-P 1-3-N-acetylgalactosamine in normal oral epithelium, UEA stains mainly the stratum spinosum, BSA the upper stratum spinosum, and PNA the stratum basale of normal oral epithelium.

Thomsen-Friedenreieh carbohydrates

The Thomsen-Friedenreich antigen (T antigen) is a carbohydrate which is carried on the same protein as the human blood group antigen system MN on erythrocytes. Antigen Tn is a precursor of T in this system. The sialosyl-T form is found on cell surfaces of basal and some parabasal epithelial cells in normal oral epithelium and, in non-secretors of ABH blood group antigens, also in the stratum spinosum. In contrast, in normal epithelium the less mature carbohydrates Tn and sialosyl-Tn are found in the cytoplasm of some spinous but not basal cells. In dysplastic oral epithelium, sialosyl-Tn expression in basal cells disappears and conversely, sialosyl-Tn expression extends to the basal cells. The changes in these mucin type carbohydrates increase with increasing severity of dysplasia but are not specific to potentially malignant lesions.

Histocompatibility antigens

HLA class 1 antigens continue to be expressed in normal, potentially malignant and malignant oral epithelium though there is partial loss in a few carcinomas. HLA class antigens are expressed on some oral carcinomas, most frequently in poorly differentiated tumors.

Beta-2 microglobulin (β2m)

β2M is 11 KD light chain constituent of HLA antigen. The Beta 2 M is used clinically as a marker of first choice for B-cell leukemia, lymphomas and multiple Myeloma. However, due to its non-specificity its moderate elevation is observed in cases of solid tumors and also in various inflammatory diseases, benign infectious disorders, and primary biliary cirrhosis and in acquired immune deficiency syndrome. It is used routinely for evaluating tumor cell load, disease activity and prognosis. It is also used to monitor efficacy of patient's response to treatment. Elevated levels of Beta 2-M are also reported in cerebrospinal fluid (CSF), acute lymphobalstic leukemia, Lymphoma and other Lymphoproliferative metastases disorders/diseases. Hence, the determination of β2M in CSF helps in identifying and managing CNS. Normal value <2.5 mg/L.

Squamous carcinoma antigens

Several squamous carcinoma antigens have been described but these have not been fully studied in potentially malignant oral lesions are as follows:

- **a.** Antigen Ca-1-Ca-1 antigen is a cell surface glycoprotein found on malignant but not normal cells but is also unfortunately found on non-malignant lesions and this is therefore highly unreliable in distinguishing malignant lesions.
- **b.** Antigen (SCC-Ag) TA-4- SCC-Ag-(TA-4) is found on squamous carcinomas and in serum, preceding recurrence.
- **c.** Antigen SQM1-SQMl is an antigen detectable on oral and various other carcinomas in the head and neck.
- **d.** Antigen 3H-1 A monoclonal antibody 3H-1 has recently been reported to stain squamous carcinomas but also stains other rapidly dividing squamous cells.
- **e.** Differentiation antigens, two tumor associated antibodies

MAb K 984 and MAb K 928 recognizing surface antigens dependent on squamous differentiation have been generated using viable cells of squamous cell carcinomas. MAb K 984 reacts with undifferentiated basal cells and is apparently associated with the proliferative fraction of squamous carcinomas; MAb K 928 binds to suprabasal cells.

Growth factors and receptors

Epidermal growth factor: Epidermal growth factor (EGF) is a polypeptide, mitogenic to epithelial cells, and acting by binding to a cell surface receptor (EGF receptor: EGFR) thereby stimulating a cellular protein kinase which catalyses the phosphorylation of tyrosine found in various proteins. EGF is found in small amounts in normal oral mucosa, mainly in the upper lamina propria close to the epithelium; the cellular source is unclear but it seems likely to be mesenchymal, possibly fibroblasts. Increased amounts of EGF at this site are seen in dysplastic and malignant oral epithelial lesions but the epithelia do not express EGF.

Transforming growth factor α: Transforming growth factor alpha (TGF-α), which is related to EGF, can stimulate epithelial growth by binding to and activating the EGF receptor, and is not expressed in normal epithelium but is expressed in oral squamous cell carcinomas. Messenger RNAs from TGF-α and EGFR have been demonstrated in oral carcinomas. High levels of TGF- α are associated with poor tumor differentiation. TGF-α appears to be derived mainly from tumor- infiltrating eosinophils.

Transforming growth factor β: Transforming growth factor, TGF-β, binds to distinct cell surface receptors, may stimulate or inhibit cell proliferation, and may play a role in the growth of carcinomas by modulating an autocrine growth control loop. Carcinoma cell lines appear to express fewer TGF-β receptors. Tumor cell lines have altered responses to both EGF and TGF-β, which appears to give the tumor a growth advantage over normal keratinocytes.

Intracellular markers

Cytokeratin's

Cytokeratin's constitute the main structural proteins in epithelial cells. At least 19 cytokeratin's have been described and they fall into 2 sub-tamilies acidic (type 1 or A) and basic (type II or B). Normally, each acidic cytokeratin is co-expressed with a specific basic one, as a "keratin pair".

Filaggrin

Filaggrin is a histidine-rich basic protein found in the granular and cornified layers in normal oral and another epithelium. Filaggrin is responsible for aggregating keratin intermediate filaments in the final and crucial steps of keratinocyte terminal differentiation and ortho-keratinization. In oral leukoplakias, filaggrin appears in the stratum corneum and in oral carcinomas it appears in keratin pearls but is less evident in undifferentiated or anaplastic lesions. No differences have been found between leukoplakias with and without dysplasia, though others report that filaggrin expression correlates with the degree of oral epithelial dysplasia.

Involucrin

Involucrin is a precursor of the cross-linked envelope present mostly in and above the stratum spinosum where there is a commitment to terminal differentiation of the keratinocyte. Both proliferative and neoplastic oral mucosa show decreased overall staining for involucrin but positive foci scattered throughout the epithelium and especially positive staining of keratinized areas in carcinomas. No differences have been found in involucrin expression in oral leukoplakias with and without dysplasia.

Desmosomal proteins

Desmosomal proteins are complex entities, major components of desmosomes. Potentially malignant oral lesions appear not to have been studied but oral squamous carcinomas as do all carcinomas, mesotheliomas and carcinoid tumors show strong positive reactivity for desmoplakin, and this correlates with the cytokeratin positivity.

Intercellular substance antigen

Intercellular substance antigen is totally or partially absent from 92% of oral leukoplakias with dysplasias and 26.3% of leukoplakias without dysplasia. The degree of antigenic loss correlates with the degree of dysplasia and in carcinomas there is 95% loss.

Other cytoplasmic antigens

A monoclonal antibody raised to a specific cytoplasmic antigen in oral squamous carcinoma stains basal cells in normal oral mucosa and benign epithelial lesions but homogeneously stains carcinomas, allowing a good assessment of microinvasion.

Silver-binding nucleolar organizer regions

In a cancer cell, chromosome disarray with multiple nucleoli appears to result in an increase in AgNORs and higher AgNOR counts suggest poor prognosis for oral cancer. Ag-NORs appear not to have been examined in potentially malignant oral lesions.

Oncogenes

Genetic alterations are involved in the deregulation of cell growth and differentiation that leads to cancer. Specific karyotypic abnormalities involving particularly chromosomes 1 and 11, often at 11ql3 have been found in some head and neck carcinomas. Oncogene expression is a widespread phenomenon and thus quantitative analysis of expression is essential, but the enhanced expression or amplification of c-erb-B with c-myc oncogenes may be related to the biological behaviour of oral carcinomas. The bcl-1 locus on chromosome 11 may be highly susceptible to mutation in individuals who smoke tobacco and it may be that mutation and amplification of this and closely related oncogenes such as int-2 and hst-1 are involved in some oral carcinogenesis, acting via production of factors similar to fibroblast growth factor.

Arachidonic acid products: Lipoxygenase metabolites including prostaglandin E2, 5, 12 and 15 hydroxyeicosatetraenoic acids and leukotriene B4 are increased in oral squamous carcinomas but potentially malignant lesions have not been studied.

Enzymes: Gamma-glutamyl transpeptidase (GGT) is a membrane associated enzyme involved in transport of amino acids, GGT is expressed in non-dysplastic epithelium of high risk patients and in dysplasias and carcinomas of the oral, pharyngeal and laryngeal mucosa. High activity of lactate dehydrogenase and changes in the isoenzyme pattern have been found in oral carcinoma cells but not in adjacent normal oral epithelium. The protease guanidinobenzoatase which is capable of breaking down extracellular matrix, is found in cells with active locomotion and in most malignant tumor cells. In oral squamous cell carcinomas, guanidinobenzoatase can be demonstrated in areas of invasion and it has therefore been advocated as a marker of tumor cells.

Basement membrane markers

Epithelial basement membranes are complex structures composed of glycoproteins, proteoglycans and collagens. The basal lamina contains principally type IV collagen, laminin and heparin sulphate, Entactin, nidogen and fibronectin are also present. The lamina reticularis contains collagens types I and III and type VII collagen anchors the basal lamina to the connective tissue. Fibronectin is consistently present in basement membrane and adjacent connective tissue in normal oral mucosa, leukoplakia and carcinomas, while irregular discontinuities and loss of laminin occur in areas of carcinoma *in-situ* and tumor invasion.

The basal lamina fragments in malignant neoplasms and, although this may be a consequence of neoplastic invasion, some components such as laminin might actually promote invasion and metastasis. Changes in epithelial basement membranes may help distinguish invasive from *in-situ* neoplasia.

Matrix markers

Tenascin is an extracellular glycoprotein found in mesenchyme during embryogenesis and in some normal adult tissues, healing wounds and neoplasms, including oral squamous carcinomas. However, it is absent or reduced in areas where the tumor is infiltrating and it has been proposed that this could be a contributory factor to invasion.

Discussion and Conclusion

Tumor markers cannot be construed as primary modalities for the diagnosis of cancer. Their main utility in clinical medicine has been a laboratory test to support the diagnosis. New investigative techniques at the cellular and molecular level show great promise at defining potentially malignant lesions but further prospective, in depth studies are required to determine their practical usefulness.

Conflict of Interest

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript.

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