The challenge of the state of susceptibility to oral cancer.

Cancer is a complex and multifactorial group of diseases. Carcinogens, age, genetic predisposition, viral and bacterial infections, lifestyle and environment are highlighted among its factors associated.

Over the last few decades, the efforts of biomedical research in genomics and proteomics have focused on understanding the mechanisms which trigger cancer, including oral cancer. Despite the knowledge acquired so far, only 50% of our patients survive after 5 years[1].

What happened with the clinical utility of molecular evidence? The study of the molecular characteristics of malignant neoplasms has sought to contribute to the clinical management of cancer thus improving prognosis. In order to do this, recently, it has been sought to evaluate the benefit of integrating genomic and proteomic data (DNA copy number variation, DNA methylation and mRNA, microRNA and protein expression) from The Cancer Genome Atlas project[2] with traditional clinical variables for predicting survival of several types of cancer (kidney renal clear cell carcinoma, glioblastoma multiforme, ovarian serous cystadenocarcinoma and lung squamous cell carcinoma). The results are worrisome: 1) the information of clinical variables and molecular data are largely redundant in terms of survival 2) clinical variables are the most informative resource for prognosis 3) incorporating molecular data poorly increases without relevance the prediction models constructed from clinical variables.

The number of cancer prognostic molecular markers in clinical use is pitifully small, despite decades of tremendous and protracted efforts. Currently, many researchers make conclusions about the usefulness of the markers of interest by heavily relying on the p-value, rather than on the magnitude and uselfulness of registrying these markers in patients' clinical outcomes (response to therapy, relapse, survival, etc.) Still, the assessments and analysis are done on people who already have the disease and whose samples represent a profoundly altered biological system compared with a control group without the disease. Because of these many details, there are no biomarkers for oral cancer yet and the therapeutic alternatives available (surgery, radiation and chemotherapy) remain highly expensive and disfiguring[3]. Additionally, it may be more convenient for some areas of the pharmaceutical industry to focus on studies which use pathological samples, highlighting the role of isolated potential therapeutic targets and using medication to keep patients chronic stable without triggering their death.

Even when the molecular study has not enhanced prognosis in general, this could be highly relevant as far as predisposition to cancer concerns. It is known that early diagnosis of oral cancer is associated with high survival rates[4]. Therefore, if carcinogenesis is seen like an arrow from left to right, being placed leftmost of early diagnosis is even better.

It is necessary to define the actual state of susceptibility to the disease under a unifying concept: the "etiologic field effect", which states that various etiological factors (exposome, including diet, lifestyle, environment, microbiota, genetic and hormonal factors) and their interactions (interactome) contribute to form a tissue microenvironment which constitutes the "field of susceptibility" for neoplastic initiation, evolution and progression[5].

Unfortunately, exposome is not informed when describing the population in a study, not even when it is a complementary file to a main text. If the clinical variables are strongly related to the course of the disease, their registration should not be limited only to sex, age, TNM and whether there are smoking or drinking habits. The complexity of oral cancer deserves more than that, and the registration of variables must enable progress towards interactome and susceptibility status. What is

our patients' nutritional status? Is there presence of physiological stress? What is their immune system competition? Are there persistent infections? These questions should be answered when presenting a sample. Genomic and proteomic analysis can help to outline situations of biological normality, adaptation and, what concerns this letter, susceptibility. This will provide a panel of markers for population monitoring.

It is important to mention that the etiological fields are prior to acquiring the molecular aberrations that are considered to indicate the presence of a field cancerization. Therefore, the progress achieved at the beginning of the arrow will impact the current red numbers which are a testimony that there was much to be done but there are few alternatives already.

Clinical molecular research in areas of Oral Biology towards higher compression of the state of susceptibility to oral cancer is welcome but from a holistic point of view so that the pathology of systems synchronizes each of the chains and recorded items from the etiologic field.

CESAR RIVERA MARTÍNEZ. DDS MSc.
PhD student in Oral Pathology and Medicine.
Universidade Estadual de Campinas.

REFERENCES.

1   Rivera C, Gonzalez-Arriagada WA, Loyola-Brambilla M, de Almeida OP, Coletta RD, Venegas B. Clinicopathological and immuno-histochemical evaluation of oral and oropharyngeal squamous cell carcinoma in Chilean population. Int J Clin Exp Pathol. 2014;7(9):5968-77.

2.   Yuan Y, Van Allen EM, Omberg L, Wagle N, Amin-Mansour A, Sokolov A, Byers LA, Xu Y, Hess KR, Diao L, Han L, Huang X, Lawrence MS, Weinstein JN, Stuart JM, Mills GB, Garraway LA, Margolin AA, Getz G, Liang H. Assessing the clinical utility of cancer genomic and proteomic data across tumor types. Nat Biotechnol. 2014;32(7):644-52.

3.   Centers for Disease Control and Prevention. Oral Cancer. 2013 [Cited 2015 January 25]. Available at: *http://www.cdc.gov/OralHealth/oral_cancer/index.htm*.

4.   Dissanayaka WL, Pitiyage G, Kumarasiri PV, Liyanage RL, Dias KD, Tilakaratne WM. Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(4):518-25.

5.   Lochhead P, Chan AT, Nishihara R, Fuchs CS, Beck AH, Giovannucci E, Ogino S. Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression. Mod Pathol. 2015;28(1):14-29.