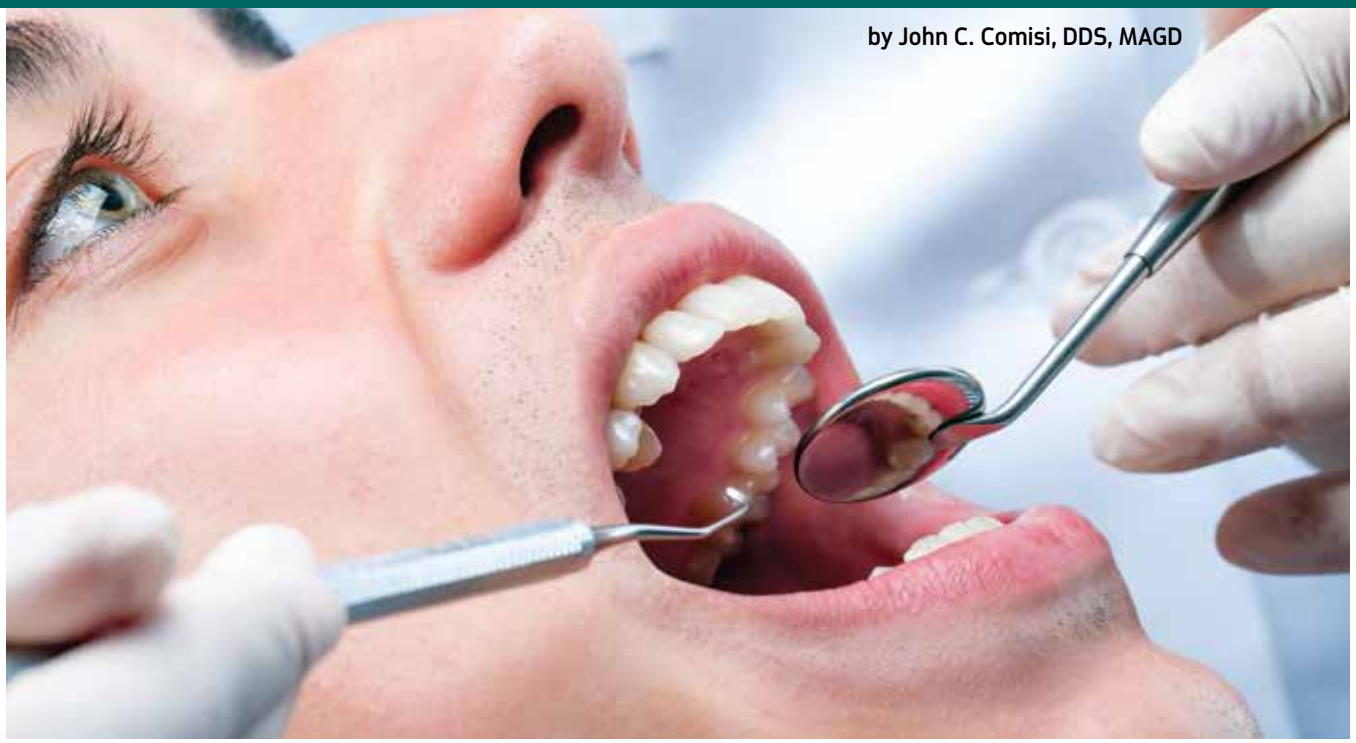
ORAL SQUAMOUS-CELL CARCINOMA DETECTION:

PAST, PRESENT AND FUTURE

by John C. Comisi, DDS, MAGD



Who is at risk? Everyone!

Oral Squamous Cell Carcinoma (OSCC) and Head and Neck Squamous Cell Carcinoma (HNSCC) have confounded the health-care profession for a long time. More than 90 percent of HNSCC are OSCC.

According to the Oral Cancer Foundation, approximately 44,000 Americans will be diagnosed with oral or pharyngeal cancer this year, and 8,000 deaths will occur due to this disease. That is equivalent to one person dying every hour for an entire year. The five-year survival rate of those newly diagnosed with oral cancer has not significantly improved over the last 50 years.

Additionally, the cost of treatment after diagnosis can be quite staggering. It has been estimated that approximately $3.2 billion is spent annually in the United States alone to treat these cancers.[1]

OSCC is an aggressive tumor with low response to chemotherapy and basic resistance to most standard-of-care anticancer drugs.[2] The death rate for oral cancer is higher than that of cervical cancer, Hodgkin's lymphoma, testicular cancer and skin cancer. In fact, oral cancer is three times more common than cervical cancer, with men twice as likely to be diagnosed. Additionally, oral cancer is the fourth leading cause of cancer in black men.

Who is at risk? Everyone! Twenty-five percent of oral-cancer patients are nonsmokers and nondrinkers.[3] The other 75 percent have the classic risk factors, including smoking, using chewing tobacco, betel-quid chewing and alcohol consumption. Individually, these factors increase the risk of developing oral cancer, but when combined, the probability of disease development drastically increases.[4] Studies also show that there is a 16 percent to 36 percent chance of oral-cancer reoccurrence, in addition to the probability of developing subsequent cancers elsewhere in the body.[5-7]

Although the oral cavity is easily accessible for examination and evaluation, several factors limit the successful identification

and early treatment of premalignant lesions. First, the gold standard for screening and detection is visual and tactile palpation during an extra- and intraoral examination by the health-care professional during a routine dental or physical examination. This head-and-neck examination entails bimanual palpation of various external areas of 1. the head and neck, including the lower jaw, neck, glands and lymph nodes of this area, and 2. the oral cavity, including the tongue, cheeks, floor and roof of the mouth, lips, and back of the throat. Second, this disease is not easy to identify in its earliest stages and has often eluded medical and dental professionals. The reason? It can be "occult," or hidden from plain view. Normal-looking tissue may often hide the truth within cells below the mucosa's surface.

If the disease is identified in Stage I or Stage II—the ideal time for identification—before the dysplastic cells have been able to break through the basement membrane, the overall five-year survival rate is greater than 80 percent. All too often, however, the manifestations of this invasive and devastating disease are found in the late Stage III or Stage IV periods, for which the five-year survival rate falls to 20 percent. These "frank" lesions—when a lesion is apparent and easily and visually identified—are often the hallmark in the identification process. Yet when found at this stage, the lesion has typically advanced so deeply that it is impossible to treat without radical surgical intervention and significant loss of the patient's quality of life.

Over the last 12 years, this need to identify these hidden lesions as early as possible—and reduce the need for aggressive treatment and its ramifications—has promoted various efforts to "visualize" or otherwise screen these early lesions using a variety of techniques. While better than simple visual inspection with visible light and bimanual palpation alone, these visualization modalities do present some challenges. First, the operator must be able to clearly evaluate all structures in the oral and oropharyngeal cavity. This task can be difficult, especially with an uncooperative patient. Second, the resulting observation can be misleading. This is due to the subjective nature and interpretation of results obtained via the current visualization modalities that lack strong clinical research support. As a result, lesion screening or visualization systems still do very little to address the clinical unmet need for early detection and intervention.

Only a definitive test can determine the biologic behavior of a lesion.[8] Currently, the gold standard for oral-cancer diagnosis is histopathological examination of surgical biopsy specimens.[9] Yet, if lesions are biopsied only when they are visible in the oral cavity, typically Stage III or Stage IV, we most certainly are not identifying disease at the earliest possible moment, leading to late-stage identification and lowering the long-term prognosis and survivability of the patient.

Clearly, a better mechanism is needed

The National Institute of Dental and Craniofacial Research (NIDCR) created initiatives in 2002 for the development of saliva diagnostic modalities for disease identification.[10] Of the salivary biomarkers studied, only a few have been—or are currently being—translated for use in clinical practice. Among the promising ones are protein measurements that include assessing total protein concentration and levels of CD44, a cell-surface transmembrane glycoprotein involved in cell proliferation and migration.[11-12] CD44 is also a key tumor-initiation marker that is over-expressed in the earliest stages of carcinogenesis.[13] Soluble CD44 (solCD44) is released by proteinases, is detectable in body fluids,[16-17] and can be measured with simple, inexpensive assays.[18-21]

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Research shows that the combination of solCD44 and total protein levels in oral rinses can distinguish OSCC cases from controls.[20-21] More recent work suggests that sensitivity can reach 88 percent for Stages I-III cancer, and specificity as high as 95 percent, depending on the population studied (unpublished data). Recently, this technology has been converted to a lateral-flow test strip point-of-care, and a laboratory test, both of which will be commercially available soon. The inclusion of a cancer stem-cell marker allows assessment of risk sufficiently early that a reversal of carcinogenesis via behavioral change could be possible even before a lesion is clinically identified.

This testing mechanism will be easy, quick, inexpensive and highly accurate. It will not interfere with the workflow of dental offices. It is believed that the point-of-care test, with results easily obtained in minutes, will play a critical role in alerting and directing the clinician to action long before a lesion can be visibly detected. Once available, this testing mechanism will create a paradigm shift in our understanding of OSCC and how we classify, identify and treat it in the future. ■

References

1. *http://www.oralcancerfoundation.org/facts/*
2. *Martin Grimm, Marcel Cetindis, Max Lehmann, Thorsten Biegner, Adelheid Munz, Peter Teriete, Wiebke Kraut and Siegmar Reinert. Association of cancer metabolism-related proteins with oral carcinogenesis – indications for chemoprevention and metabolic sensitizing of oral squamous cell carcinoma? Journal of Translational Medicine 2014, 12:208 doi:10.1186/1479-5876-12-208*

3. *Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya KA (2003). Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol 2003; 39:106–114.*
4. *Ragin CCR, Modugno F, Gollin SM. The Epidemiology and Risk Factors of Head and Neck Cancer: a Focus on Human Papillomavirus. J DENT RES February 2007 86: 104-114*
5. *Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. Cancer 1994;74:1933-8.*
6. *http://www.oralcancerfoundation.org/facts/metastasis.php*
7. *Hong WK, Lippman SM, Itri LM, et al. Prevention of secondary primary tumors with isotretinoin in squamous cell carcinoma of the head and neck. N Engl J Med 1990;323:795-801, 8257.*
8. *R. Mehrotra, M. Hullmann, R. Smeets, T. E. Reichert, and O. Driemel, "Oral cytology revisited," Journal of Oral Pathology and Medicine, vol. 38, no. 2, pp. 161–166, 2009.*
9. *Retham MP, Carpenter W, et al. Evidence Based Clinical Recommendations Regarding Screening for Oral Squamous Cell Carcinomas. J Am Dent Assoc 2010; 141: 509-520.*
10. *Wong DT. Salivary diagnostics powered by nanotechnologies, proteomics and genomics. J Am Dent Assoc 2006; 137: 313-321.*
11. *Ponta H, Sherman L, Herrlich PA. CD44: from adhesion molecules to signaling regulators. Nature Rev Mol Cell Biol. 2003;4:33-45.*
12. *Perez A, Neskey DM, Wen J, et al. CD44 interacts with EGFR and promotes head and neck squamous cell carcinoma initiation and progression. Oral Oncol. 2013;59(4):306-313.*
13. *Prince ME, Sivanandan R, Kacsorowski A, et al. Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma.Proc Natl Acad Sci USA. 2007;104:973-978*
14. *Hirvikoski P, Tammi R, Kumpulainen E, et al. Irregular expression of hyaluronan and its CD44 receptor is associated with metastatic phenotype in laryngeal squamous cell carcinoma. Virchows Arch. 1999;434(1):37-44.*
15. *Ioachim E, Assimakopoulos D, Goussia AC, et al. Glycoprotein CD44 expression in benign, premalignant and malignant epithelial lesions of the larynx: an immunohistochemical study including correlation with Rb, p53, Ki-67 and PCNA.Histol Histopathol. 1999;14:1113-1118.*
16. *Dasari S, Rajendra W, Valluru L. Evaluation of soluble CD44 protein marker to distinguish the premalignant and malignant carcinoma cases in cervical cancer patients. Med Oncol. 2014 2014;31(9):139.*
17. *Kajita M, Itoh Y, Chiba T, et al. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. J. Cell Biol. 2001;153(5):893-904.*
18. *Franzmann EJ, Reategui EP, Carraway KL, et al. Salivary soluble CD44: a potential molecular marker for head and neck cancer. Cancer Epidemiol Biomarkers PrevMarch 2005;14;735.*
19. *Franzmann EJ, Reategui EP, Pereira LH, et al. Salivary protein and solCD44 levels as a potential screening tool for early detection of head and neck squamous cell carcinoma. Head Neck. 2012;34(5): 687–695.*
20. *Pereira LH, Adebisi IN, Perez A, et al. Salivary markers and risk factor data: a multivariate modeling approach for head and neck squamous cell carcinoma detection. Cancer Biomark. 2011;10(5):241-249.*

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