Editorial

Is There any Role of Oral Inflammation and Infection in Oral Cancer?

Rudolf Virchow (1821-1902)

The association between oral cancer and risk factors has very well been documented in the literature.[1] Tobacco—either smoked or chewed—plays a major role in oral carcinogenesis. Alcohol leads to increased permeability of the oral mucosa giving access of tobacco-specific nitrosamines to the epithelial basal cell layer, where gene methylation takes place. Dose-related effects of smoking and alcohol intake for oral cancer have clearly been shown. Another possible factor, namely lack of oral hygiene has been discussed controversially during the last many years. Generally, cancer-related infections and long-standing inflammation are characterized by high prevalence in most population, persistence and extended periods of time before onset of cancer.

Rudolf Virchow (1821-1902), one of the most outstanding pathologists—even founder of pathology—was probably the first—who suggested that chronic persistent infection/inflammation may have a role in pathogenesis of cancer, in general. Infection by *Helicobacter pylori* and gastric cancer is one of the most well known examples of such association.[2] These days as it is well known that eradication of *H. pylori* may markedly reduce the risk of gastric cancer.

Oral infections are extremely prevalent in general population worldwide. Since, there is a wide spectrum of oral microbiota, it is difficult to show that specific viruses, bacteria or fungi are involved in diseases, such as cancer. The association, however, between oral cancer and some viral infections has been demonstrated in recent years. In particular, human papilloma virus (HPV) type 16 infections have been shown to be involved in about 24% of oral cancer patients in one case series.[3] There is increasing evidence that patients with oral cancer associated with HPV 16 are younger and have a better prognosis as patients with oral cancer caused by tobacco and alcohol. However, HPV is also found in healthy oral mucosa by polymerase chain reaction (PCR). Therefore, its role in carcinogenesis is still controversial and further research is needed. DNA of herpes simplex type 1 and 2 has been detected in oral cancer tissues, but the possible role of herpes viruses for malignant potential has as yet not clearly been demonstrated.[4]

Of interest is that periodontal disease may increase the risk for head and neck cancer and that periodontitis has been associated with poorly differentiated oral squamous carcinoma.[5] Thus, lack of oral hygiene—much discussed as a relevant factor in the pathogenesis of oral cancer in recent years—may in fact play a certain additional role in oral carcinogenesis. However, more research in this particular field is needed. Due to the high number of confounding factors involved (tobacco, alcohol, betel, quid, etc.), it may become a difficult task, even using prospective case-controlled studies.

Finally, yeast infections—in particular *Candida* species—have been shown to be of importance in pathogenesis of oral cancer. Oral epithelium may be invaded by *Candida albicans* and has been shown to be implicated in oral leukoplakia (so-called *candidal* leukoplakia) and oral epithelial dysplasia. In this type of leukoplakia, malignant transformation may occur in 9 to 40%.[6] Recently, non-*Candida albicans* strains in oral cancer have also been demonstrated.[7]

In summary, there is some evidence that, besides the classical risk factors for oral cancer, oral infections may play a role in oral carcinogenesis. To draw final conclusions, however, seems to be too early. While some epidemiological data seem to support an association between oral infection/inflammation and oral cancer, a true causal relationship has not clearly been demonstrated to date. Rudolf Virchow was the first to draw attention to a possible relationship between cancer and infections, more than 150 years ago. Since then, medical and dental science has led to enormous progress but still more basic and clinical research is urgently needed.

REFERENCES

1. Reichart PA. Identification of risk groups for oral precancer and cancer and preventive measures. Clin Oral Invest 2001;5:207-13.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118:3030-44.
3. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systemic review. Cancer Epidemiol Biomarkers Prev 2005;14:467-75.
4. Shillitoe EJ. The role of viruses in squamous cell carcinoma of the oropharyngeal mucosa. Oral Oncol 2009;45:351-55.
5. Tezal M, Sullivan MA, Hyland A, et al. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2009;18:2406-12.
6. Hooper SJ, Wilson MJ, Crean SJ. Exploring the link between microorganisms and oral cancer: A systematic review of the literature. Head Neck 2009;31:122-239.
7. Davies AN, Brailsford S, Broadley K, Beighton D. Oral yeast carriage in patients with advanced cancer. Oral Microbiol Immunol 2002;17:79-84.

Peter A Reichart
Professor (Emeritus), Charité Berlin, Berlin, Germany;
Visiting Professor, Department of Oral Surgery and Stomatology,
Head and Chairman Prof D Buser,
University of Bern, Bern, Switzerland