Chemoprevention of Oral Cancer

Risk Assessment, Plausible Intervention, and Monitoring

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1. INTRODUCTION TO ORAL CANCER AND PRECANCER

Oral squamous cell carcinoma (OSCC) afflicts an estimated 500,000 patients annually worldwide (1,2). Oral carcinoma incidence is increasing in developing countries (1,3), substantially among younger people (4–6). Of note, patients with oral cavity cancer have an increased risk of acquiring a second primary cancer in other parts of the upper aerodigestive tract, such as the bronchial tree and esophagus (7).

In developing countries with limited public health system resources, head and neck cancer may account for as much as 50% of all cancers (5). Treating patients who have oral precancers with cancer-preventive agents is a possible low-cost approach to an important global health problem that, in Western countries, has proven difficult to control by cost-intensive surgery, radiotherapy, and chemotherapy (8). Current treatments and chemoprevention have not significantly improved the poor 5-yr survival rate of patients with OSCC, perhaps because intervention comes too late (2). Increasing incidence of head and neck cancers even among the young (9,10) emphasizes the importance of early identification of oral leukoplakia, white patches that will develop into carcinomas (11–17).

2. FIELD CANCERIZATION

The concept of multiclonal “field cancerization” is supported by patients with oral cancers who present with multiple primary tumors or secondary tumors (18–20). Multifocal dysplastic lesions could arise from
a single site as a result of lateral intraepithelial migration or intraoral dispersion and, with additional genetic changes, acquire a growth advantage (21–23). The clonal origin of multiple premalignant or malignant lesions in the same patient is supported by recent cytogenetic findings (24). Either a polyclonal or a monoclonal hypothesized origin of multiple oral cancers is consistent with the finding that aneuploidy in only one of several biopsy specimens obtained simultaneously or successively from the same patient can be used to predict subsequent carcinoma occurrence (25,26).

3. RISK FACTORS

Leukoplakia of the oral cavity is frequently encountered, and has a well-documented potential to develop into OSCC (27–29) with a poor 5-yr survival rate (30,31). Tobacco and alcohol are recognized as principal etiological factors in development of OSCC (14) and possible carcinogenic mechanisms have been proposed (32). Ogden and Wight found that tobacco use does not seem to have a confounding effect on the observation that DNA content is a significant prognostic marker in oral leukoplakia. Reliable data on alcohol consumption are difficult to establish (33); for almost half the patients in this retrospective study, such information was not available. A confounding effect of alcohol consumption on our results can therefore not be ruled out, although we demonstrate that DNA content is a significant prognostic factor independent of tobacco use. Carcinoma development in response to environmental factors may also be modified by the presence of susceptibility-confering genotypes (34–36) with a relation to sporadic cancers that is, however, incompletely understood (37). In addition, genetic events may not be limited to rare, highly penetrant mutations that confer increased cancer risk, but could include more prevalent polymorphisms carrying a much lower risk for acquiring cancer (38). Accordingly, of the large number of risk-factor-exposed patients presenting with oral leukoplakia, only some will progress to carcinoma. Knowledge of patient exposure to risk factors still leaves the clinician challenged to identify those in particular need of preventive counseling or active treatment.

4. INSUFFICIENCY OF CONVENTIONAL TYPING AND GRADING IN DIAGNOSTIC HISTOPATHOLOGY

Adequate reproducibility in description of tissue architecture is still a challenge to diagnostic pathology, because systems for typing and grading cancerous and precancerous lesions can be clinically useful only if they are reproducible between separate observers (39). In addition, parameters considered in histological assessment should be biologically meaningful, i.e., should reflect the malignant potential of lesions (40–42).

Leukoplakia of the oral mucous membrane has well-documented potential to develop into OSCC. In this respect, the histological finding of dysplasia is of particular prognostic importance (27–29,41). Approximately one of 10 leukoplakias is histologically classified as dysplasia. However, no current marker exists that reliably predicts the clinical outcome of dysplastic leukoplakia (43). With current therapeutic options, it is too late for cure in the majority of patients with clinical manifestation of OSCC. The challenge therefore is to identify those leukoplakias with the potential to develop into OSCC, which accordingly demand particular attention.

Several published studies demonstrate a low intra- and interobserver agreement in subjective grading of oral preneoplastic lesions. Approaches to improve the prognostic value of histological grading have been investigated, e.g., by simplifying grading systems that have proved superior to the Broders’ grading, WHO, and UICC classification (Fig. 1) (44,45). Studies on the prognostic impact of grading generally have included a standard tutorial and prediagnostic calibration of participating pathologists. This, however, is most likely an exception in most situations of diagnostic pathology, particularly in routine settings. The consequence of these diagnostic shortcomings is to make reliable prognostication of oral preneoplastic lesions difficult, which not only makes treatment planning inefficient but also has implications on testing chemopreventive agents in trials (46). It is significant that even in lesions regarded as nonmalignant (e.g., hyperplasia, edema, or hyperkeratosis), we found gross quantitative aberrations in DNA content, and predicted subsequent carcinoma occurrence (47). This is in keeping with previous findings by Califano and coworkers (48), who used microsatellite analysis to identify possible sites of origin of unknown primary head and neck SCC.

5. IMPROVING PROGNOSTIC IMPACT BY ASSESSING GROSS GENOMIC ABERRATIONS

Genetic instability (aneuploidy) was one of the first characteristics postulated to underlie neoplasia (49).