

Editorial

Out of the Mouths of Babes: Oral Premalignant Lesions and Use of Alternative Tobacco Products

Commentary re: M. Hashibe, *et al.* Chewing Tobacco, Alcohol, and the Risk of Erythroplakia. *Cancer Epidemiol. Biomark. Prev.*, 9: 639–645, 2000

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Premalignant lesions of the oral cavity represent an important target for cancer prevention. The two most important lesions are leukoplakia and erythroplakia (both can occur in the same lesion, sometimes called erythroleukoplakia). These lesions represent clinical rather than histological diagnoses, but their importance derives from the high proportion of cases in which biopsy reveals dysplasia or even frank carcinoma. These lesions can be detected by visual inspection and are amenable for large-scale screening efforts. The strongest risk factors for these oral lesions are use of smokeless or inhaled tobacco, chewing substitutes that usually include tobacco such as pan masala or betel nut quid (common in some Middle and Far Eastern countries), and alcohol. Clinical management modalities include removal of exposures, chemoprevention, and ablative therapies. The treatment approach depends on a number of factors, including the size and clinical appearance of the lesion, histology, and presence of erythroplakia. Erythroleukoplakia and erythroplakia have a high rate of recurrence and a very high probability of malignant conversion, with more than 20% of cases progressing to cancer within 10 years, despite treatment (1, 2). However, erythroplakias are relatively uncommon, and research focusing on the lesion is even more so. A MedLine search revealed only 21 English-language publications in the last 5 years that included erythroplakia, and all of them primarily emphasized the more common leukoplakia.

In this issue of *Cancer Epidemiology, Biomarkers and Prevention*, the report by Hashibe *et al.* (3) demonstrates a dramatically increased risk of erythroplakia associated with chewing tobacco, primarily in the form of betel quid and pan masala, among adults in Kerala, India. This report is notable for being the largest series of erythroplakias described in the literature. As part of a randomized, population-based screening trial, 100 confirmed cases of erythroplakia were detected among 49,174 screenees (0.2%). The adjusted OR² associated with ever-use of chewing tobacco was 19.8 (95% confidence interval, 9.8–40.0), with a strong dose-response associated with increasing years of use (OR = 52.8) and daily frequency of use (OR = 130.8). Effects of smoking and alcohol were considerably smaller, but joint exposure to chewing and either smoking or alcohol conferred a greater risk than chewing alone. The pernicious nature of this lesion is suggested by the fact that past users of either chewing tobacco or alcohol had risks that were essentially the same as those of current users, although

the number of past users were small and could reflect effects in recent quitters. The seriousness of the problem is underscored by the fact that the oral cavity is the most common cancer site for males and the third most common site for females in Kerala, and oral cancer ranks among the top three cancers in most areas of India.

The risks observed by Hashibe *et al.* (3) are considerably higher than the risks for oral cancer observed in two previous studies conducted in the same region by one of the authors (4, 5). They are also much higher than those associated with chewing tobacco but are only slightly higher than those associated with snuff use in a recent United States survey (6). It is possible that detection bias could account for some overestimation of risk, a possibility discussed by the authors. This could have arisen because the health workers who conducted the screening did the oral exams after interviewing the subjects about tobacco use and other behaviors and thus may have searched less diligently for lesions in those who did not use tobacco or alcohol. However, even if the number of unexposed cases was actually twice the number reported (*i.e.* if 50% of unexposed cases had been misclassified as controls), the crude OR would still be 13.0, a very high risk level. This degree of risk is not surprising. Pan masala, the major form of chewing tobacco used in India, is a commercial mixture of tobacco, lime, spices, and areca nut. Its use in India has been growing steadily, and it is often used by teenagers and young adults. It has been shown to form high levels of carcinogenic *N*-nitroso compounds (7) and to induce cytogenetic damage in *in vitro* short-term mutagenicity assays (8).

Despite being conducted in a different population, the report by Hashibe *et al.* (3) is also highly relevant to risks among youth in the United States, who are increasingly exposed to the same or similar tobacco products associated with such strong risk in adults in India. In the last three decades, there has been a major shift in the use of smokeless tobacco in this country, with a decline among the traditional users, older adult males, and a dramatic increase among adolescent and young adult males. Since 1972, sales of chewing tobacco have decreased, but sales of moist snuff (the most common form of smokeless tobacco) have more than tripled (9). During that period, smokeless tobacco use among young males has increased to the point that 15.8% now admit to regular use (10). Moist snuff contains substantial amounts of carcinogenic tobacco-specific *N*-nitrosamines (11). A recent survey among 17,000 schoolchildren ages 12–17 years found oral premalignant lesions in 2.9% of males and 0.1% of females, a rate that projects to 300,000 affected children nationally in this age group. Risk of these lesions among white male students (who had the highest rate of use) was strongly associated with chewing tobacco and snuff with ORs of 2.5 and 18.4, respectively (6). Because oral premalignant lesions have a rate of conversion to oral cancer of 1–5% annually (1, 2, 12), this portends a

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² The abbreviation used is: OR, odds ratio.

potentially enormous increase in oral cancers in an age group traditionally at very low risk.

Equally of concern are trends in the use of other tobacco products among adolescents and young adults. Bidis are a type of cigarette from India that contain tobacco laced with sweet flavor additives designed to enhance their appeal to youngsters in the United States (the flavorings are not added to bidis sold in India). Bidis are sold in tobacco shops, "head" shops, and some health food stores, and the majority do not display the Surgeon General's warning about health hazards (13). Kreteks are another alternative cigarette featuring tobacco mixed with clove, targeted at a similar market. A recent nationwide survey of tobacco use in middle school and high school by the Centers for Disease Control and Prevention found that bidis are used regularly (*i.e.*, within the last 30 days) by 5.0% of children in high school and 2.4% of those in middle school, whereas kreteks are used by 5.8% and 1.9% of children in high school and middle school, respectively (14). Use may be much higher in some urban areas; a recent survey in urban Massachusetts found that 16% of students in seventh through twelfth grade claimed to be regular users (15). Perhaps not surprisingly, it is likely that pan masala will also be marketed in the United States in the near future, with advertising directed at a youth market (13).

These alternative tobacco products are often advertised as being safer than conventional cigarettes, a claim that many young users believe to be true. In fact, the converse is likely to be true. Bidis contain much higher levels of phenol, hydrogen cyanide, and benzo(a)pyrene than conventional cigarettes (16). Bidis and kreteks may in fact produce carcinogens other than those commonly found in tobacco. Flavoring agents added to bidis are not rigidly controlled, so the composition may be variable. Mutagenicity testing of flavoring agents is commonly done using aqueous or organic extracts. However, testing of the parent compound in this way may not identify potentially hazardous pyrolysis products formed during combustion of the flavoring agent. Combustion of virtually all organic matter produces polycyclic aromatic hydrocarbons, some of which may be metabolized to form carcinogenic epoxides. Clove cigarettes contain the genotoxic phenylpropenes safrole, eugenol and methyleugenol which are established or suspected carcinogens in animal models (17). Furthermore, some spices that are not mutagenic based on an Ames assay of conventional extracts become mutagenic when treated first with nitrite (18). Nitrite is abundant in tobacco, where it is the primary nitrosating agent (11).

Adolescents and young adults may be particularly susceptible to exposures to oral carcinogens. Epidemiological studies (19) and mathematical carcinogenesis models (20) implicate young age at initiation of smoking as an independent risk factor for lung cancer. A recent study also showed that, at least in former smokers, young age was associated with higher levels of DNA adducts (21). It is possible that the oral cavity may also show age-related susceptibility. Before puberty, children are not very susceptible to inflammatory conditions of the oral cavity such as gingivitis and periodontitis. However, puberty brings changes in oral mucosal cell proliferation rates, bacterial populations, and hormonal stimulation (22, 23). All of these can potentially contribute to altered sensitivity to carcinogens.

What are the implications for prevention of oral cancer in young adults? Studies are necessary to clarify some of the issues above, such as the carcinogenicity of alternative tobacco products and the mechanisms of age-related susceptibility to carcinogenesis in the oral cavity. Greater understanding is needed of the factors influencing progression from leukoplakia or erythroplakia to oral cancer. The unpredictable nature of these lesions is reflected in the persistence of genetic abnormalities, *i.e.*, loss of heterozygosity of 9p, in premalignant lesions that exhibited complete clinical and histological regression after chemopreventive therapy (24). Lee *et al.* (2) recently described a risk assessment model to predict

progression of premalignant lesions that included histology and a score combining chromosomal polysomy, p53 expression, and loss of heterozygosity in 3p or 9p. Efforts should be made to include children and young adults with premalignant lesions in studies to determine the utility of chemopreventive treatments and biomarkers of progression. Clearly, additional education efforts are needed, particularly to target youngsters' misconceptions about the safety of alternative tobacco products. Education should especially include the short-term health consequences (tooth loss, destructive oral lesions, and so forth) as well as the disfiguring consequences of surgery because long-term health consequences are often not a strong motivator for adolescents and young adults (9). Teachers, athletic coaches, and others who work with children should also be instructed to be alert for use of smokeless tobacco products, which can be more readily concealed during use.

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