ORAL CANCER BACKGROUND PAPERS

Chapter III: Risk Factors

Working Draft

Introduction

Although oral cancer undoubtedly has a multifaceted etiology, tobacco use and alcohol consumption are widely considered to be its major risk factors.[1] Over the past 30 years, a series of authoritative reports issued by the U.S. government and various international health agencies have conclusively established that tobacco use, especially cigarette smoking, is causally related to at least 8 major cancer sites and increases the mortality rate for several others.[2-13] Although other lifestyle and environmental factors also have been identified as risk factors for oral cancer,[14] tobacco use remains the single most important and preventable cause of this disease.

A. State of the Science

Cigarettes

Reports by the U.S. Public Health Service have clearly established a direct causal relationship between cigarette smoking and cancer of the oral cavity.[4,5,15,16] A number of major prospective cohort mortality studies have been critical in both elucidating the causal nature of the association and estimating the magnitude of the disease burden. Two such studies, Cancer Prevention Study (CPS) I and II, sponsored by the American Cancer Society (ACS), are the largest epidemiological studies ever undertaken, each following more than 1 million men and women.[5] Evidence from these and other epidemiological studies has provided key documentation of the association between cigarette smoking and oral cancer.

The mortality risk for oral cancer in cigarette smokers is substantially greater than that observed among life long "never smokers."[4,5] Although estimates vary, most studies have reported mortality ratios for smokers versus never smokers of about 5-6:1, with several reporting ratios in excess of 10:1. Furthermore, the risk for death from oral cancer is consumption related; the more cigarettes consumed daily and the more years one has smoked, the greater the risk.[4,16]

In CPS II, which followed over 1.2 million individuals for 6 years beginning in 1982, male cigarette smokers had a relative risk for oral cancer 27.7 times greater than that of a male never smoker; the rates among women who smoked were nearly 6 times greater.[5] Estimates of the percentage of oral cancers attributable to cigarette smoking have been quite consistent, generally ranging from 75% to 90%.[4,5, 17-19]

A recent analysis conducted for the President's Cancer Panel on Avoidable Causes of Cancer estimated that 80% of all oral cancer deaths (International Classification of Disease Codes 140-149) expected to occur in 1995 would be directly attributable to cigarette smoking, 91% among men and almost 60% among women.[20] These estimates do not consider the possible interaction between smoking and other risk factors and, therefore, may overestimate the impact of smoking. Conversely,

however, these estimates do not include those oral cancers that result from non-cigarette tobacco use such as pipe and cigar smoking and the use of snuff and chewing tobacco.

Numerous studies examining the relative risk for oral cancer among former smokers have found that the risk for oral cancer was lower among former smokers after the first few years of abstinence than for those who continued to smoke. These studies have found that after 3 to 5 years of smoking abstinence, oral cancer risk decreased by about 50%.[5]

Cigars and Pipes

Although cigarette smoking is the form of tobacco use most often linked with increased incidence of oral cancer, regular use of pipes or cigars also increases the risk of disease.[3,4,11,21] Both prospective and retrospective studies have consistently documented that pipe and cigar smokers experience mortality rates for oral cancer either similar or higher than those risks observed among cigarette smokers.[4,5] A 1982 Surgeon General's Report, *The Health Consequences of Smoking: Cancer*, concluded:[16]

> **"Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker."**

Smokeless Tobacco (Snuff and Chewing Tobacco)

Only recently has the scientific and public health community turned its attention to the possible health implications of smokeless tobacco use.[10,22,23] In 1981, Winn and colleagues[24] published a seminal study involving 255 women living in rural North Carolina; they found a four fold increased risk of oral cancer among nonsmokers who dipped snuff. This association could not be explained by smoking or alcohol consumption, dentures, poor dentition, diet, or use of mouthwash. For long- term users there was a 50-fold increased risk for cancer of the gum and buccal mucosa. Even women who had used smokeless tobacco less than 25 years had a 14-fold greater risk for these cancers (Table 1). In 1982, the following statement was published in the *Report of the Surgeon General, the Health Consequences of Smoking: Cancer:*[16]

> **"Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum."**

Table 1: Estimated Relative Risk of Oropharyngeal Cancer According to Duration of Snuff Use and Site[24]

Anatomic Site	Duration of Snuff Use (yrs)	Relative Risk
Gum and Buccal Mucosa	0	1.0
	1-24	13.8
	25-49	12.6
	≥50	48.0
Other Mouth and Pharynx	0	1.0
	1-24	1.7
	25-49	3.8
	≥50	1.3

The Winn study was one of the first to provide strong evidence for a causal relationship between smokeless tobacco use and oral cancer. As results from other studies began to emerge, the National Cancer Advisory Board (NCAB) of the National Cancer Institute issued a resolution on smokeless tobacco in 1985, which stated that the NCAB "considers the use of smokeless tobacco to pose a serious and increasing health risk." In September 1985, the International Agency for Research on Cancer (IARC) issued its own report on smokeless tobacco, which concluded:[10]

> **"In aggregate, there is sufficient evidence that oral use of smokeless tobacco is carcinogenic to humans."**

In April of the following year, the Surgeon General released a report during Congressional testimony on new legislation for labeling smokeless tobacco.[22] The overall conclusion of this comprehensive review clearly established the use of smokeless tobacco as a health risk:

> **"After a careful examination of the relevant epidemiologic, experimental, and clinical data, the committee concludes that the oral use of smokeless tobacco represents a significant health risk. It is not a safe substitute for smoking cigarettes. It can cause cancer and a number of noncancerous oral conditions and can lead to nicotine addiction and dependence.**"

The report also reached a number of conclusions regarding smokeless tobacco use and oral cancer that parallel those reached by the IARC review.

> **"The scientific evidence is strong that the use of snuff can cause cancer in humans. The evidence for causality is strongest for cancer of the oral cavity, wherein cancer may occur several times more frequently in snuff dippers**

compared to nontobacco users."

Since the publication of both the IARC's and the Surgeon General's reports, additional studies have appeared in the scientific literature that strongly support the conclusion that smokeless tobacco use, particularly use of snuff, is causally related to oral cancer.[23]

Chemistry, Pharmacology, and Toxicology of Tobacco and Tobacco Smoke

Because the majority of carcinogens in tobacco smoke are the byproduct of pyrolysis, they are also found in pipe and cigar smoke, often in much higher concentrations.[3] The International Agency for Research on Cancer has generated a significant body of research demonstrating the biological activity of these agents in both laboratory animals and humans.[10,11] Chemical analysis reveals that smoke from a single cigarette is composed of over 4,000 different constituents, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic.[3,25]

Smokeless tobacco also contains carcinogens, some at extremely high levels.[10,22,23,26] It is especially significant that the preparation of smokeless tobacco products, which entails curing, fermentation, and aging, occurs under conditions favoring the formation of tobacco-specific N-nitrosamines (TSNAs) from nicotine and other tobacco alkaloids such as nornicotine, anatabine, and anabasine. During tobacco chewing and snuff dipping, it is likely that additional amounts of carcinogenic TSNAs are also formed endogenously in the oral cavity.[27]

Two of the six TSNAs identified in smokeless tobacco, N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1 3-pyridyl-1-butanone (NNK), are strong carcinogens in mice, rats, and hamsters, capable of inducing both benign and malignant tumors of the oral and nasal cavity as well as of the lung, esophagus, and pancreas.[27-29] Polynuclear aromatic hydrocarbons (PAHs) in tobacco smoke have been implicated extensively in oral carcinogenesis, and NNK and NNN, which are found in both tobacco and tobacco smoke, likely play a major etiological role in cancers of the oral cavity as well.

In summary, in light of the vast number of toxic and carcinogenic compounds that exist in tobacco and tobacco smoke and the level of exposure to these agents among tobacco users, it is not surprising that tobacco use is so profoundly implicated in the causation of human cancer. A number of these compounds have been directly implicated in the production of oral carcinomas and exist in both cigarette smoke and in smokeless tobacco in concentrations that have induced oral malignancies in laboratory animals.

Alcohol

Most patients with oropharyngeal cancer drink alcohol. One study found rates as high as 94% in men and 82% in women.[1] However, one problem with identifying alcohol as an independent risk factor for oral cancer is that heavy drinkers are usually heavy users of tobacco products. Another problem is that consumption of alcohol and a poor diet might affect the risk for oral cancer. Furthermore,

assessment of alcohol intake is inherently imprecise because of a bias toward underreporting and the often episodic nature of usage. Thus, it is hard for a patient to estimate "average" use.

All three forms of alcohol (beer, hard liquor, and wine) have been associated with oral cancer, although hard liquor and beer have a higher associated risk.[29-34] Studies that have found alcohol use to be a factor for oral carcinogenesis have usually concluded that the level of consumption was important; one study found elevated risk only if 56 or more glasses of wine per week were consumed.[34] Another study showed a significant increase only if the average *daily* consumption of alcohol exceeded 120 grams.[30] That evidence is contradictory about the role of alcohol in oral cancer may relate to the difficulty in measuring intake or to alcohol's effect on other variables (or both), but it is reasonable to assume that any form of alcohol taken in excess may promote oral cancer.

Cigarettes and Alcohol

A combination of "heavy" smoking and "heavy" drinking results in odds ratios (ORs) for oral cancer of up to 38 for men and 100 for women.[1] (An *odds ratio* is a measure of association that quantifies the relationship between an exposure and health outcome.) An OR of 38 in men indicates a multiplicative effect, because the OR for "heavy" smoking alone among men is 5.8; for "heavy" drinking alone it is 7.4. Another study of smoking and drinking showed these factors to have a greater than additive but less than multiplicative effect.[35] In this study, the risk of oral cancer attributed to smoking (76%) was higher than the risk attributed to alcohol consumption (55%).[35] Similarly, Brunneman et al. found the oral cancer risk attributable to tobacco to be higher (72%) than for alcohol (23%).[29] It is apparent that, used in combination, alcohol and tobacco exert a synergistic effect that substantially increases the risk for oral cancer. Blot et al. estimated that tobacco smoking and alcohol drinking combine to account for approximately three-fourths of all oral and pharyngeal cancers in the United States.[1] Research on pigs has shown that applying 5% or 15% ethanol enhances the permeability of tobacco carcinogens in porcine mucosa, especially in the floor of the mouth.[36,37]

Mouthwash

There is some concern that mouthwashes might cause oral cancer because they have high alcohol content (as great as 26%) and are used frequently. However, Elmore and Horwitz, who combined the data from seven case control studies that evaluated mouthwash use and oral cancer, found that ORs ranged from 0.82, which suggested a protective effect, to 2.5 at the highest mouthwash exposures. They concluded that there is insufficient evidence to establish a causal relationship between the use of mouthwash and oral cancer.[38]

Diet

Although dietary factors have been identified as having a possible association with oral cancer, accumulated scientific evidence that use of tobacco and alcohol increases oral cancer risk far outweighs any evidence linking a deficient diet to increased risk.

Low beta-carotene intake has been associated with an increased risk of lung, laryngeal, gastric, ovarian, breast, cervical, and oral cancers.[39-44] Several studies have shown that a low intake of fruits and vegetables, which are the primary sources of beta-carotene, is also related to a generalized increased cancer risk and mortality.[45-51] Conversely, an increased consumption of fruits and/or vegetables has been associated with a decreased risk of oral or oropharyngeal cancer when compared with low intake levels.[46,52-54] Garewal[55] summarized the findings of 54 studies that evaluated fruit and vegetable intake in the development of cancers in the upper aerodigestive tract; he found that 52 of the studies demonstrated a protective effect.

A low intake of vitamin C has been associated with an increased risk of cancers of the stomach, esophagus, oral cavity, larynx, and cervix.[56,57] Patients who ingest high levels of vitamin C and fiber have half the risk of oral cancer as those with the lowest level of consumption.[55]

One study found that patients with low serum levels of vitamin E had more than double the general risk of gastrointestinal cancers.[57] In another study, which evaluated more than 2,000 cases, the use of vitamin E supplements correlated with a diminished risk for oral and pharyngeal cancer.[59] The most consistent dietary findings across multiple cultural settings are that high fruit consumption has a protective effect and that high alcohol consumption has a carcinogenic effect.[43]

Actinic Radiation

Sunlight, through actinic radiation, helps to produce cancer along the vermilion border of the lip. Because these "sunlight" induced cancers are much more common in fair-skinned individuals exposed to the outdoor life than in individuals with darker pigmentation, it appears that darker pigment protects against actinic radiation damage.[60, 61] (The wavelengths of the light thought to be responsible for the actinic damage are in the 2900-3200 Å range.)

Dental Factors

There is little evidence to suggest that poor oral hygiene, improperly fitting dental prostheses, defective dental restorations, or misaligned or sharp teeth promotes oral cancer.[62] Gorsky and Silverman[63] evaluated 400 patients with oral cancer to determine whether dentures were a risk factor and found no correlation between the wearing of dentures and the patient's cancer.

Viruses and Their Interactions with Oncogenes

Alterations of cellular oncogenes, which lead to altered expression of their products, have been implicated in human cancers.[64] Cellular oncogenes, also known as proto-oncogenes, acquire their transforming properties or become activated by gene amplification, point mutations, and gene rearrangements. Oncogenes can encode growth factors and growth factor receptors, act on internal signaling molecules, and regulate DNA transcription factors.[65-68] Other genes encode proteins that inhibit the cell cycle or promote programmed cell death (apoptosis). Tumor suppressor genes may become inactivated or mutated with consequential loss of control over cell division.[68,69] The

retinoblast and p53 gene products are examples.

Consideration of risk factors should recognize that many molecular events governing control of cell cycles are influenced by viruses. Those most commonly implicated in oral cancer transformation have been the human papillomavirus (HPV),[70,71] herpes group viruses,[72] and the adenoviruses.[73] Of these, HPV and herpes have been the most thoroughly studied and are now considered to be the most likely "synergistic viruses" involved in human oral cancer. The herpes viruses most often linked to oral cancer are the Epstein-Barr virus (EBV) and cytomegalovirus (CMV); both EBV DNA and CMV DNA have been demonstrated in oral carcinomas.[72] The hamster cheek pouch model has been used to evaluate the role of herpes simplex virus (HSV),[74] and reports indicate that HSV can act synergistically with chemical carcinogens to initiate oncogenic transformation in this animal model.[75] However, there is still debate as to whether the presence of HSV in such tissues shows a cause-and-effect association between virus and cancer.

More than 100 different HPV types have been isolated from benign and malignant neoplasms. HPV antigens and gene products have been detected in biopsies of oral cancer and precancer;[76-79] HPV has also been identified in nodal metastases from oral, head, and neck cancers. The genotypes most often found in oral carcinoma are HPV 16 and 18, but HPV can also be found in normal oral mucosa. Whether or not HPV plays an active role in the initiation of oral malignancy, whether it is simply a passenger virus, and whether the virus acts in synergy with exogenous agents such as tobacco or alcohol to promote neoplasia are all questions that still await answers.

Some viruses, particularly HPV and herpes, interact with oncogenes and tumor suppressors. Recent evidence suggests that the HPV 16/E5 gene can induce malignant transformation in epithelial cells, possibly acting by enhancing growth-factor-mediated intercellular signal transduction.[79] The E6 and E7 HPV 16 and 18 gene products act as oncoproteins by interacting with host cell p53 apoptotic protein, promoting its elimination.[80] Loss of p53, in turn, removes inhibition of cell-cycling influences. Still, there are substantial gaps in our knowledge about how oncogenes, tumor suppressor genes, and viruses promote oral cancer.

Immunocompetence

Studies suggest that HPV 16 transfectants play a significant role in oral cancer development by altering intercellular immune surveillance mechanisms.[74] The most common interpretation of surveillance mechanism data is that specific cellular defense mechanisms acting against cancer development, such as anti-oncogenes, can be mutated by viruses. This theory is supported by the fact that HPV 16 E6 and E7 gene products may be able to bind various human gene products, particularly the p53 gene, thereby deregulating control of cell proliferation and differentiation. There are also studies demonstrating that HPV-related lesions can mediate protection against certain tumor cells.[76]

Oral cancer does not appear to be a common consequence of systemic immunosuppression even

though, among HIV-positive immunocompromised individuals, HIV-associated oral malignancies have been reported.[81] The most common are Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas. KS is a malignant reactive lesion that stems from factors (cytokines) that induce the formation of tumors in a number of tissues and organs. The most prominent feature of Kaposi's is produced by an angiogenesis factor, which leads to the characteristic appearance of a vascular lesion. Skin is the most common site for KS, but about half of all patients will have oral manifestations. In many of these individuals, the disease will manifest itself first in the oral cavity; sometimes, other sites will not be affected. KS can afflict any oral mucosal site, the palate being the most frequent and the gingiva second.

The occurrence of non-Hodgkin's lymphoma (NHL) continues to increase as the number of HIV-infected individuals grows and their longevity extends. Inappropriate B-lymphocyte stimulation and the presence of Epstein-Barr virus play a role in this disease, but the co-factors are poorly understood.[82] Frequently, these lymphomas are extranodal and can involve the mouth. In some cases, oral NHL has been either the first or only evidence of NHL tumor.

B. Emerging Trends

Tobacco

Estimates from the most recent data available (1993) indicate that 46 million adults in the United States are current smokers, or 25% of persons aged 18 years or older (27.7% of men and 22.5% of women).[83] The annual prevalence of cigarette smoking among adults in the United States declined 40% during 1965-1990 (from 42.4% to 25.5%) but was virtually unchanged from 1990 to 1992.[84]

Newspaper and other media sources have suggested a renewed interest in cigar smoking; recent consumption figures from the US Department of Agriculture lend some support to this trend.[85] Last year, 2.29 billion large cigars (including cigarillos) were consumed in the U.S., an increase of almost 7% from the previous year, and the first reported increase in several decades. However, regular cigar smoking remains almost exclusively an older male behavior. In 1991, only 3.5% of all adult males reported they had used cigars, whereas in 1970 16% had reported themselves to be regular users of cigars.[84]

Pipe tobacco consumption dropped below 10 million pounds for the first time in U.S. history in 1994.[85] Consistent with this drop in consumption, prevalence has also declined. Two percent of all adult males report they currently smoke pipes, the lowest figure ever recorded on national surveys.[84]

Although these smoking trends among adults are encouraging, the trends among our children are not. It is estimated that 3,000 young people become *regular* smokers every day.[86] Data for 1995 from the University of Michigan's 1995 Monitoring the Future Study indicate that 32.5% of the nation's

high school seniors are current smokers and 21.6% smoke daily.[87]

The consumption of smokeless tobacco, especially snuff, continues to increase, having tripled between 1972 and 1991. In 1991, the prevalence of smokeless tobacco use among adults was 2.9%, 5.6% among men and 0.6% among women. Among 18- to 24-year old men, the rate was 8.2%.[88] More recent data on the prevalence of use in 1995 among secondary school students is particularly disturbing. In 1995, the 30-day prevalence of use among eighth, tenth, and twelfth grade males was 11.8%, 17.2%, and 23.6%, respectively.[87]

Unless these current trends are reversed, the nation will fall short of meeting two key Year 2000 Health Objectives—a reduction to a 15% prevalence of regular smoking among adults, and a reduction of smokeless tobacco use by males ages 12-24 to a prevalence of no more than 4%.[89]

Viruses and Oncogenes

Increased knowledge and techniques have developed a data base to better understand the cause, progression, and treatment of viral infections, which will allow better understanding of risks and their control.

Immunocompetence

The utility of cell markers as predictors of malignant transformation or disease progression is discussed in Chapter II. As more scientific data emerge on the molecular events that take place in oral cancer and the interaction of viral products with oncogenes, interventions may be engineered. Vaccines, antivirals, and gene transfer techniques may prove beneficial in targeted high-risk patients.

C. Opportunities and Barriers to Progress

Significant progress in prevention depends upon research breakthroughs in the biologic factors related to cancer development and in innovative techniques to reduce their negative consequences. In the absence of scientific breakthroughs, however, some risks of cancer are best controlled currently through behavior modification (also discussed in Chapter IX).

Tobacco

Efforts to prevent tobacco use, particularly efforts targeted to youth, hold the most promise for preventing tobacco-related diseases, including oral cancer. Additionally, advice on tobacco use cessation provided by physicians, dentists, and other primary care clinicians can significantly affect individual decisions to discontinue a type of tobacco use. The National Cancer Institute has published two manuals, one for physicians and one for the oral health team, to facilitate the delivery of one-on-one smoking cessation advice in medical and dental offices.[90,91]

Community- or office-based programs in smoking or smokeless tobacco cessation take a variety of forms. Many individuals receive office-based assistance from their family physician or dentist. A monograph published by the National Cancer Institute (NCI) of the National Institutes of Health, entitled *Tobacco and the Clinician: Interventions for Medical and Dental Practice*, summarizes the lessons learned from a number of physician- or dentist-administered office-based smoking cessation programs.[92] The monograph also evaluates the effectiveness of various worksite, school, and community-based smoking control efforts. Because 70% of smokers see a physician each year and 52.6% visit a dentist, the potential for the health care community to affect smoking prevalence in the United States is very large; unfortunately, it is substantially underutilized.[93]

Local hospital-based or worksite programs that offer tobacco cessation are frequently developed through research projects funded by organizations such as the American Cancer Society, the American Lung Association, the National Cancer Institute, and the Centers for Disease Control and Prevention (CDC). One such project is supported by CDC as part of their National Tobacco Prevention and Control Program's Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT). Through cooperative agreements to state health departments, comprehensive tobacco prevention and control programs are being developed with participation by diverse community groups, coalitions, and leaders.

It is evident from our experiences thus far that a multi-pronged initiative that involves office-based clinician assistance and community-based interventions, such as restricting advertising and limiting the access of youth to tobacco products, is the best approach to prevent tobacco initiation and encourage cessation among current users. Strategies for discouraging initiation among young people should include using the popular media to promote abstinence from tobacco, offering school-based educational programs, enforcing state and local restrictions on the sale and advertising of tobacco products,[94] and encouraging in-office counseling by primary care clinicians.

Intervention programs to help individuals stop using smokeless tobacco are less widely available and have been less successful than smoking cessation programs. Additional research to identify effective interventions for smokeless tobacco is needed, particularly in light of recent increased use among young adult males.

Alcohol

Minimal use of alcohol does not appear to be associated with a significantly elevated oral cancer risk. However, all patients diagnosed with either a premalignant or malignant oral lesion should refrain from any use of alcohol. There should be more health education about how using both tobacco and alcohol increases the risk of oral cancer; health promotion efforts should emphasize the danger of combining the two substances.

Mouthwash

Although there is no certain link between oral cancer and mouthwash, its excessive use should be

discouraged.

Diet

Although there is evidence that certain dietary deficiencies may be linked to oral cancer, at present it is not possible to recommend useful guidelines for prevention, other than the current general recommendation to consume five servings of fruits or vegetables per day.[95] A recent comprehensive review of epidemiological investigations in this area identified high fruit consumption as a protective factor in preventing oral and pharyngeal cancers across a variety of cultural settings.[43] Additional research is necessary.

Actinic Radiation

Sunscreens and sunblocks are effective in protecting the lip from the damaging effects of ultraviolet light. These products can and should be promoted to the public as part of an overall skin cancer prevention message.

Dental Factors

Reassuring patients that dental appliances, restorative materials, and routine trauma do not appear to increase the probability of oral cancer is an important health message. Additionally, patients should be encouraged to consult their dentist or physician if they observe any unusual growths or lumps in their mouths.

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