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Chemoprevention Strategies: The Relevance of Premalignant and Malignant Lesions of the Upper Aerodigestive Tract

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Abstract Patients with premalignant and malignant lesions of the upper aerodigestive tract have historically been the focus of chemoprevention trials within the United States. Experience with this population has formed the basis for trials involving other environmentally induced cancers such as lung and bladder.

Given that head and neck cancer patients are at risk for second primary malignancies, prevention strategies can be directed towards decreasing mortality from these metachronous neoplasias. Validity of these strategies, including risk determination, intermediate endpoints, and preventive efficacy of single and combination agents, can be determined. Current limitations in chemoprevention trials involving these patients relate to the sporadic nature of the disease. In fact, the prevalence of oral premalignancy within the United States has not been clearly defined. Individual physician experience with this disease process is limited.

Organizational efforts should therefore be directed towards facilitating clinical trials involving dentists, oral surgeons, head and neck surgeons, and other primary health care providers in the community. Risk factors which identify clinically defined normal or premalignant tissue at risk for malignant progression need to be better defined.

Key words: chemoprevention, head and neck cancer

Historical perspectives regarding chemoprevention point to the usefulness of neoplasias of the upper aerodigestive tract for several reasons. First, the disease is readily accessible. The majority of premalignant lesions can be viewed without the need for invasive endoscopic procedures. Patient compliance and willingness to participate in therapeutic and/or screening trials is thereby enhanced. Second, recognized premalignant lesions with a well-studied natural history have been identified, *i.e.*, leukoplakia/erythroplakia. No definitive therapy currently exists for such lesions which occur in diffuse areas throughout the upper aerodigestive tract. Third, due to customary health habits in the United States, populations at risk can be readily identified. Patients are typically identified in a primary care setting, such as within the course of standard dental care. Asymptomatic patients are more likely to seek such care than submit to invasive and even non-invasive screening procedures in secondary or tertiary care centers. Furthermore, given the strong association between neoplasias of the upper aerodigestive tract and a known carcinogen, tobacco, a primary care setting can apply more targeted screening mechanisms. Finally, the use of tobacco, a

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common etiologic agent for neoplastic diseases of the upper aerodigestive tract, leads to a process termed "field cancerization." Field cancerization, a term initially coined by Slaughter [1], implies that all aerodigestive mucosa exposed to a carcinogen is at risk for malignant conversion. Such a term helps explain a meaningful endpoint for chemopreventive trials; namely, the propensity of patients with one malignancy of the upper aerodigestive tract to develop an additional malignancy when followed longitudinally. This risk has been shown to be constant with time and occurs at a rate approximating 4% per year [2,3]. The majority of these lesions occur in areas amenable to careful screening, *i.e.*, head and neck, lung, and esophagus. In common with diffuse premalignant lesions of the upper aerodigestive tract, no definitive therapy currently exists to prevent second malignancies. Current screening methods to detect multiple neoplasias are ineffective in reducing mortality rates.

Relevant factors such as those outlined above led to the involvement of patients with premalignant diseases of the aerodigestive tract in the earliest clinical chemoprevention trials. In 1958, Mulay and Urbach [4] applied topical vitamin A on oral leukoplakia in ten patients. Using dosages in the range of 300,000 to 450,000 units daily, seven patients responded; two patients showed complete response. Similar response rates were observed by others and led to trials using systemic vitamin A [5–7]. Today vitamin A and its derivatives have been tested as a preventive measure against neoplasias in multiple organ sites including lung, prostate, bladder, and breast. More recently various combinations of agents, such as β-carotene and α-tocopherol, have been used.

The use of vitamin A in these early trials involved head and neck cancer populations as well as patients with other neoplastic processes. Despite its biologic efficacy, vitamin A was limited due to its considerable toxicity. Silverman and others [6] noted persistent pruritus, rash, and elevated liver enzymes in patients receiving daily vitamin A. These observations led to efforts with synthetic retinoids [8,9]. These latter approaches have also been hindered by drug toxicity, but again, subsequent studies involving oral premalignancy have served as relevant models for the appropriate use of preventive agents in a less toxic capacity. Lippman *et al.* [10] induced regression of oral leukoplakia using short course, high dose 13-*cis*-retinoic acid (13-cRA). In their preliminary study, 55% of 66 patients responded with at least 50% regression. Patients were then randomized to receive either β-carotene or low dose 13-cRA. The latter regimen was found to be more effective in maintaining regression of oral leukoplakia and was more readily tolerated.

Understanding the biological and toxic effects of chemopreventive agents is facilitated through trials on patients with premalignant lesions. It would be highly inefficient to launch a study in which the goal is to prevent malignancy without such baseline studies. Any target population would require lengthy treatment and follow-up in order to reach significant numbers of observed endpoints, *i.e.*, cancer development. To conclude that one test agent or a combination of agents is no more effective than another would require a large number of patients. Considerable time and resources may be spent in studies which prove to be inconclusive.

Clinically identifiable oral premalignancy is not, however, the only relevant process in chemoprevention trials. Hong *et al.* [3] have made considerable strides towards cancer prevention by addressing field cancerization within the upper aerodigestive mucosa. Head and neck patients (n = 103) were randomized to receive either 13-cRA or a placebo. The endpoint of this study was the development of second primary malignancies. Trial results were significant. Only one-fourth the number of second malignancies developed in the cRA-treated population compared with placebo. The resources required to demonstrate positive results are relevant to efforts in cancer chemoprevention. One hundred patients were evaluated, and the majority of second cancers observed occurred within three years of the initiation of the trial. Demonstration of cancer prevention in the general population or even in high risk populations such as smokers would require considerably more patients, time, and resources. The use of chemopreventive agents in the head and neck cancer population provides an intermediate step between biologic efficacy testing and trials on larger high risk populations. The end result is the prevention of the most common malignancies observed worldwide.

THE PROBLEM OF NEOPLASIA OF THE UPPER AERODIGESTIVE TRACT

Given that the prevention of this disease carries implications that impact the majority of environmentally induced cancers, it is important to understand the magnitude of head and neck cancer and precancer both within the United States and throughout the world. Within the United States, carcinoma of the upper aerodigestive tract occurs in approximately 43,000 individuals annually [11]. The problem of head and neck cancer is considerably greater worldwide. Indeed, cancer of the oral cavity and pharynx constitute the fourth most frequently observed cancer among males and the eighth most common cancer among females worldwide [12, 13]. Compared to the United States with an incidence rate of head and neck cancer of approximately 11 individuals per 100,000, incidence rates in Hong Kong, Bombay (India), Bas-Rhin (France), and Newfoundland (Canada) are 39, 34, 49, and 21 per 100,000, respectively.

Studies from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, as well as other population registries documenting head and neck cancer incidence, have identified several important trends. First, the male predominance in disease development is less apparent today than several decades ago. A recent summary utilizing the Connecticut tumor registry showed that the male:female ratio in 1930 was 9.8:1 [14]; by the 1960s, this ratio had shifted to 4.1:1. By the late 1980s, the ratio stood at 2.6:1. The increase of disease among women has been attributed to an increase in tobacco consumption beginning in the early part of the century. Since the prevalence of smoking among women today is equivalent to that of males, this trend of an increasing incidence of head and neck cancer is likely to continue.

Head and neck cancer among young adults is also increasing, although this trend has not been clearly established. The young adult head and neck cancer population is generally described as patients less than 40 years of age. The problem was first brought to the forefront by Shemen *et al.* [15], who reported an increase in young adults with head and neck cancer evaluated at Memorial Sloan-Kettering Cancer Center. A similar increasing incidence was identified within the SEER registry [15]. This trend has subsequently been identified in other registries [16,17]. Data from the Connecticut registry, however, point out that although an increase has been observed, young adults still represent only a minor proportion of all head and neck cancer patients [14]. The etiology of this increase is uncertain. Some have attributed the trend to an increase in smokeless tobacco consumption among young adults [17]. The experience of most head and neck oncologists suggests that tobacco consumption patterns are not the determinants. In fact, the majority of young adults are not tobacco users [16]. Critical to chemoprevention studies which are designed to prevent second malignancies is an awareness that the natural history of disease in the young adult population appears to differ from the older cohort. The young adults who deny tobacco usage infrequently develop second primary tumors [18]. Until the benefit of chemopreventive agents has been clearly established, committing these individuals to a lifetime use of therapies which also carry significant toxicity cannot be justified.

Perhaps the most significant incidence trend in head and neck cancer development has been observed among black males [19]. The SEER data base registry shows that the overall incidence of oral cavity and pharyngeal cancer has decreased 1.7% annually since 1973. This is principally due to a 4% decrease in cancer of the lip. However, among black males the problem of head and neck cancer appears to be increasing. Specifically, pharyngeal cancer in the latter population is developing at an increased rate approximating 6% per year [19]. To date no epidemiologic studies have addressed this important trend. Why should the increase be restricted to males and not females? Why should disease development be restricted to pharynx and not other sites within the upper aerodigestive tract? Focusing on this issue may provide additional insight into cancer prevention strategies, including the choice of chemopreventive agents.

The prevalence of premalignant lesions of the upper aerodigestive tract is less well understood. Indeed, epidemiologic studies which define the problem within U.S. populations have not been reported. Undoubtedly, this reflects its relative infrequency as well as patterns of

health care related to the disease. Prevalence of leukoplakia varies worldwide among various ethnic and racial groups. It is as high as 41% among rural Hungarian gypsies [20], but in urban India, Silverman *et al.* [21] noted the prevalence to be 11.7%, and 0.4% prevalence has been reported in Guam [22].

BIOMARKERS AND RISK OF MALIGNANT TRANSFORMATION

As discussed earlier, leukoplakia and erythroplakia are relevant to the study of chemoprevention. The malignant potential of these lesions has been reported to vary from 6% to 30% [23–25]. Such variation in transformation rates provides a significant confounding factor in clinical trials. Additionally, from the earliest chemoprevention trials it is apparent that various premalignant lesions will differ in their responsiveness to treatment [6,26]. More accurate analyses will be provided by identifying more specific markers of malignant transformation.

The predominant marker of transformation risk has been histopathologically defined mucosal dysplasia. Maerker and Burkhardt [24] noted a rate of transformation of 2% for those leukoplakic lesions which histopathologically demonstrated only hyperplasia. This rate increased to 4% with evidence of early dysplasia. As the degree of dysplasia within the intraepithelial lesion increased, so did the likelihood for subsequent invasive disease. For severe dysplasia or carcinoma *in situ*, this risk approached 40% in Maerker and Burkhardt's analysis [24]. Clearly, histopathologic descriptives of premalignant lesions must be established in any study. In addition to providing relevant information about risk of invasive disease, such descriptives may impact observed response rates. Most studies have revealed that hyperplasia is more responsive than various intraepithelial neoplasias to chemopreventive agents [6,26].

There are other factors related to the risk of malignant transformation. For instance, the site of leukoplakia within the oral cavity will influence the risk of transformation. Lesions within the floor of the mouth are far more likely to progress to invasive disease than leukoplakia within the buccal mucosa [25,27–29]. Shafer *et al.* [28] noted that tongue lesions have a 27% chance of progressing to invasive disease. Two percent of buccal mucosal lesions will progress. Other factors associated with probability of malignant risk include sex, number of lesions within the oral cavity, and the duration of time a particular lesion has been present. Multiple lesions are far more likely to progress to malignancy than single lesions. Lesions which have been present for more than six months will have a malignant potential three times as great as lesions which have been present for less than six months [30]. Females have a greater risk of malignant transformation than males [25]. Finally, several studies have revealed that the risk of malignant conversion is greater in patients with no history of tobacco use as compared to smokers [31].

The incidence of malignant transformation of leukoplakia may change with age. Einhorn [34] showed a 2.4% risk of transformation at 10 years which increased to 4% at 20 years. For patients younger than age 50, malignant transformation occurred in 1%. In contrast, 7.5% occurred in individuals between the ages of 70 and 89 years old.

Another critical factor in interpreting trial results involving premalignant lesions is the approximately 15% rate of spontaneous regression [25]. Furthermore, changes in tobacco consumption patterns may alter disease course. A study from India suggested that for those patients who stopped smoking for at least one year, 60% of leukoplakia lesions disappeared [32]. Silverman *et al.* [33], however, failed to demonstrate this effect. Forty-four percent of lesions regressed to varying degrees in those individuals who stopped smoking as compared to a 37% regression rate in those who continued to use tobacco. The malignant transformation in the latter group was 16% as compared to 12% in patients who ceased tobacco use [33].

Leukoplakia and erythroplakia are not the only lesions with malignant potential. Oral submucous fibrosis (OSMF) has been reported to lead to malignancy in approximately 32% of patients [29]. OSMF is a chronic progressive disease characterized by increasing fibrosis and associated oral functional impairment. It is seen almost exclusively in Asian populations, principally India. OSMF has also been noted in China, Nepal, Thailand, and South Vietnam. The

etiology of this process is uncertain but is commonly associated with betel quid use. Collagenases within the quid may lead to breakdown of submucosal elastic fibers [31].

Certain oral mucosal diseases which carry a risk for malignant conversion can be identified by broadly stated histopathologic similarities. Sideropenic dysphagia is also known as Plummer-Vinson Syndrome or Patterson-Kelly Syndrome [35]. Malignant transformation of upper aerodigestive mucosa in these patients is frequently observed. Histomorphologic assessment reveals characteristic atrophic mucosa, which is more susceptible to carcinogen damage [31]. Other disease processes which have been characterized by atrophic changes and malignant potential include erosive lichen planus, syphilitic glossitis, and dyskeratosis congenita [31,36, 37]. Chronic hyperplastic candidiasis carries a risk of malignant transformation approaching 30% [38].

In reviewing variables associated with the malignant potential of upper aerodigestive mucosa, three significant features become apparent. First, the clinically defined premalignant syndromes such as leukoplakia, chronic hyperplastic candidiasis, or erosive lichen planus are highly variable in their malignant potential. Second, histomorphologic assessment of these lesions better characterizes risk than gross clinical descriptives. Third, individuals with the known highest rate of transformation, namely, patients with a previous history of upper aerodigestive cancers, characteristically have no identifiable clinically or histomorphologically defined lesions. Such features point to the need for better genotypic and/or phenotypic markers of malignant potential. It is beyond the scope of this review to fully detail recent results in biomarker investigations; however, it is evident that progress is being made. Markers of abnormal proliferation and differentiation have been identified both within premalignant lesions as well as within normal mucosa of patients with known head and neck cancers. To date, the most extensively investigated marker has been altered blood group antigen expression [39–41].

The mistake in biomarker research may be to focus simply on abnormalities within mucosa. For instance, stromal abnormalities as observed in OSMF and syphilitic glossitis may precede epithelial changes and may contribute to abnormal epithelial proliferation and differentiation [42,43]. Additional factors include genetic defects such as inherent DNA repair deficiencies [44]. Risk of transformation may occur at a higher rate in mucosa, regardless of its clinical state, in individuals genetically predisposed to DNA damage or instability. The probability of transformation will depend not only on exposure to carcinogens but an abnormal sensitivity to relevant carcinogens. In addition to DNA repair abnormalities, studies have assessed the varying capacity of individuals to metabolize carcinogens. Highly inducible metabolizing enzyme systems within various sites of the upper aerodigestive tract will convert carcinogens to their active form and thus lead to genetic damage [45,46]. Carcinogen exposure in one individual may be far more damaging than a similar exposure in another, depending upon a particular cytochrome P-450 enzyme phenotype and/or genotype.

The problem of second malignancies within the upper aerodigestive tract provides the opportunity to validate the significance of these markers. A potentially prototypical example of this process is a marker for mutagen sensitivity. It has been proposed that within the general population there exists a differential susceptibility to environmental carcinogens [44]. This can be determined through the quantitation of chromosomal breaks in freshly cultured peripheral blood lymphocytes. Hsu *et al.* [44] have proposed that differences in such chromosomal fragility between individuals will not be evident from spontaneous breakage but only after exposure to clastogens. It is those individuals who express the greatest sensitivity to clastogens who are likely to develop environmentally induced cancers. This trait would be relevant to diseases such as colon, lung, and head and neck cancer, in which exposures play an etiologic role. It would not be relevant to such diseases as breast cancer and central nervous system cancers. The initial studies by Hsu and colleagues [44,47,48] have confirmed this hypothesis. Lymphocytes from patients with aerodigestive tumors are more sensitive to clastogen-induced chromosomal damage than non-cancer bearing controls. The most clastogen-resistant populations were individuals with a long history of tobacco exposure who failed to develop cancer.

Validation of this marker of susceptibility to environmentally induced cancers is being performed with the head and neck cancer population. It is suggested that patients who are most sensitive to clastogens *in vitro* would be most likely to express field cancerization, *i.e.*, develop second primary malignancies. Initial results support that hypothesis. Head and neck cancer patients who were hypersensitive to clastogens as determined *in vitro* through the use of peripheral blood lymphocytes had a 4.4-fold higher risk of developing an additional cancer when followed longitudinally [49]. The significance of using the head and neck cancer population to validate genetic markers is evident. Results can be achieved in the relatively short period of less than five years. The number of patients needed for such studies is also considerably smaller than that needed for general population studies.

New markers will be similarly validated. These may include capacities for DNA repair, enzyme detoxification, or carcinogen metabolism. They will also provide a background for determining the choice and effectiveness of various chemopreventive agents. For instance, the variable inducibility of glutathione-*S*-transferase, which is critical for cellular detoxification, may govern the choice of chemopreventive agents which act upon that enzyme.

CHEMOPREVENTION DEVELOPMENT

Given the importance of neoplasias of the upper aerodigestive tract to our understanding of cancer prevention, mechanisms to enhance patient and physician participation in cancer prevention are required. As discussed above, the sporadic nature of the disease is a major problem. Indeed, our understanding of the prevalence of upper aerodigestive premalignancy within the United States is extremely limited. Very few medical centers in the United States evaluate more than twenty patients with intraepithelial neoplasias of the upper aerodigestive tract yearly. Secondly, a recent study by Benner *et al.* [50] has identified handicaps in conducting chemopreventive trials. Patient referral to treatment centers is limited, and contribution by various community oncology programs is inconsistent.

Surveys of the dental community and primary medical care centers are needed to establish several perspectives. The practice standard of dental professionals needs to be known by the oncologic community. It is likely that the community dentist evaluates only one or two patients with leukoplakia yearly. Are patients in such a setting commonly referred to surgeons or are they simply observed? If referred to a surgeon, what are the standards of the secondary care professional, *i.e.*, oral surgeon, head and neck surgeon, otolaryngologist, or general surgeon? Are these latter individuals likely to practice in a community hospital or a major medical center?

What are the attitudes and limitations of health care professionals in conducting clinical trials involving oral premalignancy? To a large extent, this latter question is itself a reflection of patient attitude. Though malignant conversion is always a possibility, impending mortality from premalignant lesions is not a concern to the patients or to the health care provider. The implication of current therapies is not one of significant morbidity which impacts quality of life. Most lesions of the upper aerodigestive tract can simply be removed without the need for radical resections involving functionally important structures such as the mandible, tongue, or larynx. Speech and swallowing should not be significantly affected. In the absence of a real threat, patient motivation to seek a specialized care center or second opinion is limited.

Tangrea *et al.* [51] have recently documented patient attitudes about participating in chemoprevention trials. Factors which precluded patient involvement revolved around perceived inconveniences—distance from treating medical center, patient waiting time, and number of visits to a treatment facility. Indeed, the above were reported more frequently as mitigating factors than the perceived risk of therapy, trial expense, or drug toxicity. All these attitudes will influence the willingness of the primary health care community to stress patient participation.

Patient attitudes about health care delivery involving premalignancy are justifiable. However, given the significant implications of upper aerodigestive premalignancy to the broad field of cancer prevention, efforts to identify the appropriate infrastructure required to conduct clinical trials should be made. Clinical trial infrastructure should also reflect attitudes not

only of the patients but of the primary health care provider, as well as the experienced clinical trial investigator. A recent survey of head and neck surgeons was conducted to define their interest in participating in clinical trials [51]. Over 50% of the surgeons surveyed practiced in a private community setting, and this had no significant impact on reported attitudes concerning clinical trials. Furthermore, the percentage or absolute numbers of patients with upper aerodigestive neoplasias in a physician's practice was not a factor in reported attitudes. Of the 312 active physician members surveyed, responses were obtained from 30% regarding their willingness to participate in clinical trials as well as clinical trial priorities. Apparent from these interviews was support among head and neck surgeons for clinical trial activities. Nearly 80% of the respondents expressed a desire to participate in such activity. Seventy-seven percent were willing to provide office support for trial conduct. Of the clinical trial priorities, approximately 68% of the physicians identified chemoprevention as a critical area of investigation. Similar surveys should involve other disciplines, including general dentistry and oral surgery. The willingness of the community health care provider to participate in the conduct of upper aerodigestive chemoprevention trials is apparent.

The quality standards of multiple investigators who contribute a limited number of patients to trials remain a concern. This concern may be more perceived than real. The capacity to document disease process and therapeutic response is greatly facilitated by the accessibility of upper aerodigestive mucosa to clinical assessment. The majority of professionals in the community who deal with diseases of the upper aerodigestive mucosa are highly experienced in recognizing mucosal abnormalities, frequently more experienced than those currently conducting chemoprevention trials. With appropriate clinical trial guidelines, the maintenance of high standards of chemoprevention studies will not be a limiting factor.

The relative sporadic nature of oral premalignancy as well as the attitudes of both health care providers and patient populations must be taken into consideration when developing chemoprevention trials in the United States. The capacity to develop the science of chemoprevention will also be served by developing a clinical trial infrastructure on a multinational basis. Upper aerodigestive mucosal malignancy is relevant to the greater issue of cancer prevention. Advances in treating oral premalignancy can become standards for treating the most common neoplasias within the United States, including those of the lung and digestive tract.

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