Novel Approaches to the Prevention of Head and Neck Cancer (44178)

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Abstract. **Head and neck cancer represents a paradigm for the prevention of environmentally induced diseases. Etiologic factors, including tobacco and alcohol, have been well established. Furthermore, disease development may depend not only upon such exposures but also upon a genetically defined susceptibility to exposure-induced DNA damage. As discussed in this review, the ability to identify etiologic factors, both external and host related, will lead to improved identification of individuals at risk. The development of novel strategies for cancer prevention will be promoted, among which lifestyle alteration will arguably play the most significant role. Therefore, this review places special emphasis on the translation of the understanding of disease into more effective behavioral modification strategies.**

[P.S.E.B.M. 1997, Vol 216]

Head and neck cancer represents a paradigm for the prevention of environmentally induced cancers. In the majority of circumstances, an acknowledged etiologic agent can be identified (e.g., tobacco) (1–4). Likewise, the ability to screen for disease should not be a limiting factor. In contrast to other organ sites, which may require specialized examination procedures, the mucosa of the head and neck can be readily evaluated in a variety of practical settings. Numerous health-care providers, such as dentists and primary-care physicians, are in a position to assess independently the same at-risk patient. Early detection is conceptually a very plausible goal. Finally, strategies that are designed to modulate risk, such as smoking cessation, have been greatly refined over the last decade. Yet, a review of recent head and neck cancer incidence and mortality has failed to demonstrate substantial change in head and neck cancer burden. Indeed, in certain segments of our society and elsewhere, the problem of head and neck cancer is actually increasing (5–9).

Health-care providers need to derive additional strategies if we are to succeed in reducing the presence of this disease. This edition of the *Proceedings of the Society for Experimental Biology and Medicine* has provided detailed summaries of several of these strategies, some of which will only be summarized briefly here. We will address in more detail elements that may be novel but are still unproven. We will also detail efforts that are intended to refine more currently proven strategies such as behavior modification.

This paper has been divided into two principal sections: primary prevention strategies and secondary prevention strategies. By primary prevention strategies, we refer to activities that alter susceptibility or reduce exposure. Such activities include (i) the use of epidemiological sciences (i.e., the identification of factors that may promote disease and their subsequent removal from the environment); (ii) the role of human genetics and genetic counseling; and (iii) strategies for modifying behavior, such as smoking cessation or dietary modification. By secondary prevention, we refer to the use of strategies that are applied early in disease (i.e., preclinical stages, such as premalignancy or in tissues at risk for multiple malignancy), strategies including chemoprevention and screening protocols.

Primary Prevention

Markers of Increased Risk. Perhaps the most significant step towards accomplishing decreased cancer mortality is the identification of those individuals at increased risk. Causative factors can then be modulated, and therapies more intensively directed. The epidemiology of head and neck cancer has greatly contributed to this goal. It has been well recognized that tobacco and alcohol are contributing factors to the development of the disease (10–16). Other contributing factors may include nutritional habits, various

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0037-9727/97/2162-0275$10.50/0

occupations including printers and asbestosis workers, substance abuse such as marijuana use, certain chronic infections, viral agents, as well as dental status (2–4). To detail the evidence for all these risk determinants is beyond the scope of this article. There are, however, disturbing trends in head and neck cancer incidence which demand attention, such as the increasing incidence of head and neck cancer among inner-city black males (5) and includes the increasing incidence of head and neck cancer among young adults that has been identified in the United States as well as other countries (7–9). We would conclude that two major areas of focus should be (i) a better understanding of socioeconomic determinants of disease and (ii) the role of inherent susceptibility traits that govern response to tobacco and alcohol carcinogenesis. We will address how strategies involving behavior modification, chemoprevention, and screening can be modulated to take these factors into account.

Socioeconomic indicators. Perhaps the studies that will contribute most to the identification of patients at increased risk will be those that assess socioeconomic indicators. However, the extent of information that addresses this perspective is limited (17–22). Socioeconomic factors to be considered include educational level, income, marital status, length of unemployment, and access to medical and dental care. The majority of these factors have been investigated in epidemiologic studies of head and neck cancer. Each of these studies have found a significant impact on head and neck cancer risk after adjusting for established risk factors such as tobacco and alcohol. Indeed, one can argue that such socioeconomic factors are a major contributor to the substance abuse that directly influences carcinogenesis.

In one of the third studies related to socioeconomic factors, Ernster *et al.* utilized the Third National Cancer Survey, conducted in the United States from 1969 to 1971 (21). Ernster *et al.* noted the risk to be nearly twice as high for those in the lowest income bracket as for those the highest income category. The significance of the income grouping in predicting head and neck cancer risk persisted after adjustment for tobacco and alcohol use. Elmwood *et al.* explored the significance of employment level in a hospital-based study in Canada (22). The risk of head and neck cancer was elevated 2.2-fold in individuals described as unskilled workers. Several additional studies have suggested that social stability factors rather than income and employment level are greater determinants of head and neck cancer risk. Increased risk of the disease is associated with marital status (i.e., single, separated, or divorced) (17, 20). The type of employment may be less important than the number of years employed, unemployment during midlife being the most significant contributor.

The degree to which social instability contributes to substance abuse becomes a critical question when viewed in the context of head and neck cancer prevention. In light of the increasing incidence of head and neck cancer among black males, who are more frequently identified as single, poor, and unemployed, we must address this issue in order to design effective prevention strategies.

Genetic susceptibility factors. It is intuitive that factors other hand simply tobacco and alcohol contribute to head and neck cancer. Though 25 million individuals smoke in this country, only a fraction of that tobacco-exposed population develop head and neck cancer annually. Considerable emphasis has been placed the role of inborn genetic factors as a potential explanation. The development of head and neck cancer depends not only on the exposure to environmental carcinogens but an abnormal sensitivity to those carcinogens. This undoubtably involves a polygenic phenomenon. Relevant determinants include genes that metabolize tobacco compounds to more carcinogenic intermediates (23–25) and genes that eliminate carcinogens from the cell. Likewise, relevant genes can be related to characteristics defined by gender, ethnicity, aging, and host response. Reviews of studies addressing genetic susceptibility to head and neck cancer have recently been provided (26, 27).

Perhaps the most extensive data regarding genetic susceptibility to head and neck cancer has involved the so-called mutagen-sensitivity assay (26, 27). This assay makes use of peripheral blood lymphocytes from an individual patient. Lymphocytes are exposed to free radical oxygen (FRO)–producing compounds (bleomycin) following short-term culture. The lymphocytes are then arrested in metaphase, and the number of chromosomal breaks induced by bleomycin are then quantitated. It has been shown that the number of chromosomal breaks per cell can be related to DNA repair capacity (26). Results of several studies show that head and neck cancer patients are more likely to express mutagen sensitivity than are healthy controls (27–32).

Furthermore, the existence of mutagen sensitivity remains a significant risk factor after controlling for tobacco and alcohol exposures. The combination of mutagen sensitivity and tobacco exposure have typically shown a multiplicative effect in risk estimates; both measures together provide more information than either one alone. It should be emphasized that the mutagen-sensitivity assay reflects only one mechanism of tobacco carcinogenesis (i.e., the generation of free radical oxygen). There are numerous carcinogenic compounds within tobacco that may induce DNA damage by a variety of means independent of the generation and repair of FRO damage. This is evident given that not all head and neck cancer patients express mutagen sensitivity as quantitated by this assay.

Strategies in Behavior Modification. Although there has been some reduction in the prevalence of cigarette smoking since the first report by the Surgeon General on smoking and health (33), smoking remains the single most important preventable cause of cancer (34). Tobacco use is the major cause of oral cancers, with 85% of these cancers associated with a history of smoking (35). Despite the clear adverse health consequences associated with smoking, as well as the intensive public-health focus on smoking pre-

vention and cessation during the past decade, about 26% of Americans ages 17 and older continue to smoke (36). Prevention of smoking initiation among youth and the reduction of tobacco use among those who already smoke remain primary goals for cancer prevention.

In recognition of the clear health hazards of smoking, there has been much attention given to the development and refinement of innovative smoking cessation techniques. Some of the most valuable recent advances have involved targeting of specific interventions for unique groups of smokers, or have identified unique opportunities where smokers may be most receptive to smoking cessation messages. While a thorough review of the voluminous literature on smoking cessation techniques is beyond the scope of this paper, the interested reader is referred to several excellent articles highlighting recent accomplishments in this growing field (37–39). Here, we will review some of the most important innovations in smoking cessation treatment.

Tailoring interventions for special populations. One of the most important recent observations in the area of tobacco control and smoking cessation has been the differential impact of interventions on different populations. In fact, smokers do not represent a homogeneous group and do not necessarily smoke in the same way or for the same reasons. Burgeoning knowledge of specific characteristics of smokers has underscored the importance of matching smoking cessation treatment to the smoker's level of motivation to quit, as well as to the age, gender, or race of the smoker. Here, we will highlight issues germane to the choice, delivery, and efficacy of smoking cessation interventions recognizing diverse characteristics of smokers.

Stage of readiness to change. A major obstacle in many efforts to change smoking behavior has been the failure to address smokers' level of smoking cessation readiness. The transtheoretical model (40) postulates that smokers can be classified according to one of the following stages of readiness to quit: precontemplation (not thinking about quitting within the next 6 months), contemplation (seriously thinking about quitting within the next 6 months), preparation (seriously thinking about quitting within the next 6 months and have made a recent quit attempt), action (having quit within the past 1 to 6 months), and maintenance (having quit for more than 6 months). Intervention efficacy is greatly increased when the treatment is maximally matched to the individual smoker's motivation or readiness to quit (41). For instance, personalized counseling to increase a smoker's appreciation of the benefits of quitting are appropriate for someone in the contemplation stage, whereas guidance in setting a quit date and providing instructions regarding the use of nicotine replacement would be most suited to a smoker in the preparation stage of readiness to quit.

Youth-focused interventions. Interventions to address the smoking behavior of young people generally focus on averting the initiation of smoking, or on preventing teenagers who experiment with tobacco from becoming regular smokers. Indeed, by the early 1990s smoking initiation had been identified as a uniquely adolescent behavior, with very few adults commencing tobacco use after the age of 18 (42). Important factors in heightened teenage smoking initiation include lower socioeconomic status, greater acceptance and approval of smoking within the child's social peer group, an inability to refuse cigarettes when offered, reduced self-esteem, as well as the absence of a firm decision *not* to smoke. Some personality factors, such as rebelliousness and aggressiveness, also are consistently related to smoking initiation (43). School-based smoking prevention programs attempt to solidify nonsmoking norms, utilize peer models for avoiding smoking, as well as instituting methods of identifying teenagers who, because of low self-esteem, disruptive behavior, or difficulties with socialization might be most susceptible to initiating many risky health behaviors such as smoking or the use of other drugs.

Interventions for women smokers. Up until the middle of the 20th century, tobacco use was predominantly a male habit; as such, early smoking cessation efforts made little distinction between the male and female smoker. Male smoking rates were already beginning to decline by 1964, when the surgeon's general report was published (33). In contrast, smoking rates among women increased steadily until 1977. Although smoking rates among women have slowly declined since then, it is projected that by the year 2000, a larger proportion of women than men will be smokers in the United States (43). Clearly, gender-specific research and interventions remain a uniquely important public health challenge.

Specific strategies targeting the female smoker must include methods to help women, who are often responsible for multiple work and family role demands, to prioritize their efforts to quit smoking over the competing demands of their lives, to include stress management techniques, as well as methods to deal with the weight gain that is often associated with smoking cessation (44). Pregnancy, childbirth, or the initiation of oral contraceptive use can serve as important motivators for women to quit smoking; primary-care physicians and obstetricians can play a unique role in stressing the vital importance of smoking cessation on their female patients' health, as well as the health of their families, and in providing them with smoking cessation services.

Tailoring for diverse ethnicities. Smoking prevalence rates of the last three decades have been consistently higher among ethnic minorities, particularly African-Americans (45). In addition, the quit ratio for African-American smokers has increased at a much slower rate than that of Caucasians (46). The most significant increase in oral cancer has occurred among males of African descent, with the incidence of squamous-cell cancer of the pharynx having increased 6% per year in this population since 1973 (1). Yet, traditional smoking cessation efforts have been particularly ineffective with ethnic minority smokers. Despite high motivation for cessation, ethnic minorities' quit attempts and smoking relapse are complicated by poverty and corre-

sponding neglect of health concerns, limited access to health resources, stress and multiple lifestyle hardships, as well as aggressive and successful targeting of ethnic minorities by tobacco company advertising (47). Tailored interventions attempt to transcent barriers of cost and access, bringing minimal impact techniques to health clinics and community centers. It is also very important not to assume homogeneity of norms among ethnic groups. Health workers who are well known in specific communities are often more successful than outside professionals in addressing the specific attitudes and cultural meanings of smoking, and can act as healthy nonsmoking models for those attempting to quit.

Marshaling unique opportunities for smoking cessation intervention. In addition to the described interventions for unique groups of smokers, recent innovations attempt to create powerful opportunities where smokers may be most receptive to quit-smoking messages. In the remainder of this section, we will describe some specific ways in which clinicians are creating unique opportunities for successful smoking cessation.

Biological markers of tobacco carcinogenesis and personalized cancer risk counseling. Recent advances in the molecular epidemiology of tobacco carcinogenesis offer unprecedented opportunities for identifying subgroups of smokers who are most likely to develop tobacco-related cancers. Although most smokers are aware of the dangers of smoking, they tend to maintain an optimistic bias about their potential risk. Providing asymptomatic smokers biological feedback about their risk of developing oral cancer, particularly if they are identified as at higher risk, may serve to heighten motivation to quit smoking (48). Knowledge of one's personal oral cancer risk may represent a "teachable moment" that is likely to raise perceived vulnerability to smoking-related health hazards and receptivity to health-care provider advice and assistance to quit. Integrating personalized risk feedback based on biological markers of oral cancer susceptibility with smoking cessation advice and counseling represents a compelling multidisciplinary initiative to cancer prevention and control (49). However, further studies examining the behavioral and psychosocial impact of cancer risk notification are critically important to cancer prevention efforts. Clinical guidelines for how best to communicate genetic risk information, who should receive this information, and whether or not the benefits (e.g., maximizing smoking cessation adherence) of distributing this information outweigh the costs (e.g., increasing illness-related distress) are the focus of ongoing studies (48). As such, the collaboration of behavioral scientists, oral health-care providers, and molecular epidemiologists provides unique translational opportunities for the prevention of oral and other tobacco-related cancers.

Physician-assisted smoking cessation. Regular health-care appointments with physicians and other health-care providers represent ideal opportunities for delivering cost-effective smoking cessation interventions. Primary-care physicians have multiple, excellent opportunities to encourage their patients to quit, and to promote smoking prevention among youth. According to patients, physician advice conveys an authoritative message about the risks of smoking and the benefits of quitting. Abstinence rates following physician advice to quit smoking have varied from 10% in the general population (50–52), 15%–25% among hospitalized, general medical patients (53, 54), and 60%–70% for medical patients hospitalized for serious, life-threatening conditions (55, 56).

As summarized in the recently published clinical practice guidelines for smoking cessation (46), it is strongly recommended that health-care providers include the following in their routine patient care: (i) ask about tobacco use and systematically identify all tobacco users at every visit; (ii) strongly advise all smokers to quit; (iii) identify smokers willing to make a quit attempt; (iv) assist the patient in quitting, and (v) arrange follow-up contact to encourage maintenance of smoking cessation efforts. Nicotine replacement *via* transdermal patches, nasal sprays, or gum is strongly recommended and has been shown effective in assisting the nicotine-dependent patient in quitting and maintaining cessation.

Prevention of second primary cancers and tobacco-related comorbidity: Smoking cessation following diagnosis of head and neck cancers. The majority of head and neck cancer patients have a history of heavy tobacco and alcohol use (57). Furthermore, continued tobacco and alcohol use among patients diagnosed with tobacco-related malignancies is associated with increased risk of secondary primary cancers; disease recurrence; complications of surgery, radiation, and chemotherapy; and developing or exacerbating other noncancer smoking-related diseases (34, 58–62). Cancer diagnosis can be utilized as a catalyst to quit smoking, as patients are confronted with strong incentives to quit smoking and to abstain from alcohol use through physician advice to quit, hospital restrictions, and physical discomfort. While these barriers may provide the added motivation needed for those who have been contemplating and preparing to change their smoking and drinking habits, they may raise distress in others who feel forced into abstaining prior to being ready to make that commitment.

Approximately one-third of patients will continue to smoke and drink excessively following diagnosis and treatment (63). Given the deleterious impact of tobacco and alcohol use in patients with head and neck cancer, specific interventions should be directed towards smoking and alcohol cessation with these patients. The stepped-care approach (64) to treating nicotine dependence on medical settings provides a useful and comprehensive model with which to address nicotine and alcohol addiction in medical settings. This approach emphasizes a facilitative, tobacco-free office environment, a patient-matched intervention plan, educational materials, and follow-up treatment to encourage sustained abstinence. Smoking cessation intervention should begin at diagnosis, with strategies based on the patient's tobacco and alcohol history, and motivation to quit. Tailor-

ing interventions to the patient's illness-related concerns and readiness to change will facilitate health-behavior change (40). In addition, there are a number of specific ways to assist patients in quitting. For highly nicotine-dependent patients, nicotine replacement can be effective in managing withdrawal symptoms. Education and personalized counseling about the deleterious effects of these addictive substances on the course of their disease and the benefits of quitting are essential components of enhancing motivation. Helping patients find alternative means of coping with their stress, other than smoking and drinking, is important. Setting a quit date, encouraging family support, providing written material on smoking/drinking cessation, nicotine replacement, and providing follow-up sessions with the patient should be included in rehabilitation of patients who smoke and drink alcohol. The diagnosis of a tobacco-related cancer in the family also provides a critical opportunity to encourage and assist family members to quit smoking (65). Therefore, a hospital-based, smoking cessation program is likely to be effective in providing services to patients and their families during a critical period of heightened attention to the restoration and maintenance of physical health.

Secondary Prevention Strategies

Chemoprevention. The chemoprevention of tobacco carcinogenesis has been addressed thoroughly in other articles within this issue and will not be developed here. Suffice it to say that these strategies will not be successful if chemoprevention is viewed in isolation. Rather, such therapy must be used in combination with other preventive strategies, including strategies that identify and reach high-risk individuals, as well as behavior modification strategies as described above. Perhaps the most illustrative example of this need is the well-known Physician's Health Study. Begun in the early 1980s, this 2 × 2 factorial design study assessed the role of aspirin and β-carotene in the modulation of risk of coronary artery disease and cancer. Over 20,000 physicians were entered. It was noted early in the course of the trial that aspirin was successful in reducing coronary artery disease, and that portion of the trial was closed. In contrast, the results of the β-carotene portion of the trial were only recently reported and noted to be negative. β-Carotene at a dose of 50 mg every other day failed to lower cancer incidence. However, significant alterations in cancer risk were noted in this prospective study based on certain lifestyles. Namely, physicians who either had never smoked or had quit using tobacco were at significantly decreased risk of developing lung cancer. Results demonstrate that lifestyle choices rather than relatively short-term chemopreventive therapy had the greatest impact on cancer risk. Future chemoprevention studies must build upon these observations.

Screening. It is intuitive that detection of disease at its earliest stages would improve cancer mortality. Given the degree to which the oral cavity, and upper aerodigestive tract can be easily examined, it also seems that screening for head and neck cancers would be a readily accomplishable goal. Diminished mortality rates would be readily achievable. The significance of screening as a potentially significant modality is emphasized by a review by Smart, who reported that 94% of head and neck cancer patients had seen a physician at least 1 year prior to diagnosis (66). Each patient reported an average of 11 physician visits within a 3-year period prior to diagnosis. Smart's review emphasizes that, with appropriate training and practice of systematic screening habits by examining physicians, head and neck cancer may be diagnosed considerably earlier. In that regard, a study by Prout *et al.* assessed the value of educational programs for health-care providers in the Boston area and provided information reinforcing that notion (67). The latter authors noted that health-care providers schooled in the oral-cancer educational program were significantly more likely to perform systematic oral screening in subsequent years. These studies emphasize the important role of the physician in the early detection of head and neck cancer, and that such individuals, if properly motivated, are more likely to perform such screening than those less aware of the significance of oral cancer.

Despite the intuitive benefit that would come with more effective screening, confounding factors may limit success. First, head and neck cancer is a relatively sporadic disease. Mass-screening procedures would detect cancer in only limited instances. Second, individuals at risk tend to be less health conscious. Compliance with health-care advice such as avoidance of substance abuse, good nutritional habits, and regular physical evaluation is not readily achieved in this population. Third, neck and head cancer patients can be characterized by diminished social support systems. Access to medical care is hindered, making routine follow-up by a health-care provider difficult. Finally, though it is often stated that a readily identifiable premalignant condition exists (i.e., leukoplakia/erythroplakia), few head and neck cancer cases can be shown to progress through this premalignant clinical stage. Though head and neck cancers tend to occur late in life, these same cancers can occur at any time within a 20-year interval. Knowing which patient and when that patient will develop disease remains a conundrum. Furthermore, whether or not the identification of disease will change its natural history is not clear. We cannot state with certainty the interval required for a tumor to achieve its initially diagnosed stage. We do not know whether the biologic potential of a head and neck cancer follows the same time course within every individual. Ultimate tumor aggressiveness may be determined very early in its natural history. The window of opportunity to detect the most lethal cancers may be small. No studies have yet demonstrated that systematic screening will diminish head and neck cancer mortality. Indeed, the Task Force for the Guide to Preventive Services has concluded that routine screening for oral cancer cannot be recommended (68).

It is not surprising, therefore, that various mass-

screening programs for head and neck cancer have demonstrated mostly negative results. Jullien *et al.* and others have made it apparent that the identification of head and neck cancer is only one part of the process (69–72). Once the disease has been identified, patients must still comply with referrals for therapy. In the assessment of nearly 1000 patients as reported by Jullien *et al.*, only 67% of the 12 patients noted to have potentially malignant disease were compliant with follow-up recommendations (69). The experience in Cuba likewise showed similar discouraging results (70). Annual oral examination had been considered mandatory for all individuals over 15 years of age in Cuba since 1984. The proportion of early-stage disease was noted to increase during this period of more intensive screening. However, overall oral-cancer mortality was not altered. As in the Jullien *et al.* study, a major problem was patient compliance in follow-up examinations once the disease has been diagnosed. The investigators of these large population based studies conclude that systematic mass screening for head and neck cancer is not a cost-effective process and makes little impact on overall cancer mortality.

Perhaps more significant than the screening process itself and in light of the development of more effective behavioral modification approaches, Cowan *et al.* have demonstrated that screening strategies are valuable in identifying the health-care beliefs of the provider (72). Primary-care dentists participating in this study were noted to assess routinely the oral cavity for evidence of disease (72). However, a minority of dentists routinely recorded information about tobacco and alcohol abuse. The implication of Cowan's study was that screening was already adopted. What needs to be developed in the primary-care setting is a clearer understanding of the benefits of health promotion involving substance abuse modification.

There are novel strategies under development that may enhance screening effectiveness (73–79). We have previously noted in this brief review that epidemiologic investigations continue to refine risk estimates. Current computer technology may allow for translating previous risk-factor assessments into clinical strategies that enhance screening efforts. An example involves the use of neural networks. The Oral Cancer Screening Group in England has demonstrated its potential utility (73). The performance of the network to identify individuals at increased risk was compared with the results of oral screening by health-care specialists. Over 2000 adults were entered into the study and were asked to fill out a questionnaire that identified 10 input variables. The overall sensitivity and specificity of the screeners compared to the neural network were comparable. The use of neural networks could, however, be performed at a fraction of the cost.

Other screening techniques under investigation include the use of genetic markers of increased risk, molecular cytology, the use of serum tumor markers, as well as newer technologies involving optical engineering and the computer sciences (73–79). To detail fully each of these strategies is beyond the scope of this review. We will, however, emphasize one such strategy, namely native cellular fluorescence.

Native cellular fluorescence. Native cellular fluorescence (NCF) represents the innate capacity of tissues to absorb and transmit light. It is determined by the qualitative and quantitative state of cellular fluorophores consisting of various proteins, nucleic acids, coenzymes, as well as diverse micronutrients. Each of these fluorophores can be characterized by its capacity to absorb and emit light as specified wavelengths. For instance, the fluorescence profile of collagen with differ from deoxyribonucleic acid (DNA) in that the former will absorb and emit at 330 nm and 390 nm, respectively, while DNA absorbs at 260 and emits at 290 nm. Thus, when measuring the spectral characteristics of tissues, the degree to which these two fluorophores contribute to the spectral characteristics of a particular tissue will contribute to differences in measurable spectral profiles. For instance, when considering the above two fluorophores, the spectral characteristics of relatively acellular deposits of collagen may differ from other highly cellular tissues in which there is an increased nuclear to cytoplasmic ratio. The number of known fluorophores is extensive (79). It is likely that the overall NCF pattern of a particular tissue represents a highly complex process. The ability to understand this process will depend upon the sophistication of the optical instrumentation, the capacity of computer technology to record measured output, and the knowledge of the clinician involved in measuring NCF characteristics of specific tissues within an individual patient.

Though NCF characteristics of other organ sites have been explored for the last 5 years, only recently have studies on upper aerodigestive mucosa been reported. We have recently analyzed NCF characteristics of both normal as well as diseased mucosa (80). Our studies have differed from other studies in that we utilized a xenon lamp–based spectrometer as the excitation light source. The instrumentation allows the opportunity to generate excitation and emission wavelengths over the entire spectral range. Pulsed laser sources, in contrast, though a more powerful energy source, are restricted by their emission wavelengths. Relatively fewer fluorophores can be excited. The xenon lamp facilitates the development of a more composite picture of the various fluorophores within aerodigestive mucosa. It should consequently have the capacity to provide more sensitive and specific diagnostic information. Indeed, within the initial study normal mucosa of the head and neck cancer patient will differ from that of tumorous tissue of the same site (80). These studies are in their infancy but ultimately may be used to identify individuals at increased risk.

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