Abstract: Oral cancer incidence rates rose dramatically during the twentieth century in the United States and Europe, especially among individuals under the age of 60 years. Although influenced by age, sex, and country of origin, incidence trends were most strongly affected by elevated risk among individuals born after approximately 1915. This cohort effect was indicative of strong behavioral influences on oral cancer risk. In this article, associations between oral cancer risk and established behavioral risk factors including alcohol and tobacco use are reviewed. Additionally, possible associations between oral cancer risk and oral hygiene, diet, nutritional status, and sexual behavior as well as the influence of genetic factors on oral cancer risk are considered. Special emphasis is placed on evaluating possible risk differences in individuals above and below the age of 45 and in users and nonusers of alcohol and tobacco.

Keywords: oral cancer; risk; epidemiology; review

TRENDS IN INCIDENCE OF ORAL CAVITY AND OROPHARYNGEAL CANCERS

Oral squamous cell carcinomas arise from several anatomic sites within the oral cavity and oropharynx, but most commonly from the oral, mobile tongue. In the 1980s, 2 cancer centers in the United States (U.S.) reported an increase in the proportion of incident oral tongue cancers diagnosed in men younger 40 years. Although absolute numbers had increased, these reports provided no real evidence of rising incidence. Shortly thereafter, however, a significant 2-fold increase in oral tongue cancer mortality rates between 1950 and 1982 was reported in the U.S. for men younger than 30 years. This finding was corroborated by a study in Scotland. Further analysis of the Scottish data revealed that the increase in incidence was not restricted to those younger than 40 but extended to all age groups less than 65 years of age born after 1920—a strong “cohort effect.” The cohort effect was indicated by a strong effect of year of birth on oral cancer incidence rates. A flurry of research on global changes in oral cancer incidence was stimulated by these reports.
Similar cohort effects were observed for oral tongue cancer incidence rates in the U.S. and Scandinavia among men,6–8 and in some countries among women, born after 1915.7,9,10 Additional data provided by the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and country-specific tumor registries corroborated the increase in oral tongue cancer incidence and also indicated that the increase extended to other oral cavity and oropharyngeal sites as well.5,9,17 Furthermore, increased oral cancer mortality rates reported between 1955 and 1989 in several European countries among young adults (<44 years) were also observed for other smoking-related cancers (eg, lung and esophagus).18

Although incidence rates and trends over time varied substantially from country to country,1,19,20 regional trends in oral cavity incidence were largely mirrored by similar trends for oropharynx cancers.12 In addition to the strong effect of year of birth, incidence rates substantially increased with age13 and were consistently higher in men when compared with women.12

In the U.S., oral cancer incidence rates increased more sharply from 1935 through 1994 among women than men born after 1900.21 Incidence rates were higher among African American men when compared to white men, but similar for African American and white women.22 According to Surveillance, Epidemiology and End Results (SEER) data, incidence rates for the majority of oral cancer sites for the period 1973 to 2001 subsequently declined among white American men and women between ages 20 and 44. However, the incidence of oral tongue, base of tongue and tonsil cancers continued to increase by 1.7, 2.1, and 3.9% per year, respectively, in this age group during this time period.23 Additional analysis indicated that oral tongue cancer incidence in this age group grew more steeply at an annual rate of 6.7% (95% CI, 2.7–10.8) from 1973 to 1985 and then reached a plateau.24 However, tonsillar cancer incidence continued to increase annually by approximately 2% to 3% among African American and white men under the age of 60 through 1998.22,25

Data therefore indicate that age-standardized incidence rates for oral cancers are strongly influenced by age, sex, race, primary site, year of birth and geographic region. Although initial reports focused on oral tongue cancers, data indicate that in the U.S., Europe, the United Kingdom (UK), and Scandinavia, oral cancer incidence rates in general increased among men, and often among women, in all age groups under the age of 65 born after approximately 1915. In the U.S., despite a plateau in oral tongue cancer incidence rates in the late 1970s to early 1980s, the incidence of tonsil and base of tongue carcinomas continued to increase through 1998, predominantly among men younger than 60 years. In virtually all geographic regions studied, the rate of increase for oral cancers was more marked as age-group declined, as is observed for a strong cohort effect. Although young age at onset is a cardinal feature of genetic susceptibility to cancer, these strong cohort effects indicate that the trends in incidence are largely due to changes in environmental exposures that occurred after approximately 1900 to 1920. Rates that increase more dramatically with declining age categories are reflective of recent changes in patterns of exposure to carcinogens.18 Therefore, the heterogeneity of incidence trends by geographic region likely reflects regional differences in trends in exposure to carcinogens.

ALCOHOL AND TOBACCO SMOKING

It is clear that oral cancer risk is related to both intensity and duration of alcohol and tobacco consumption. Furthermore, there is a strong dose-response relationship between alcohol and tobacco use and combined use increases risk above that expected with either exposure alone.26–28 As an example of this synergistic effect, the risk of oral cancer with joint consumption of high amounts of alcohol (>5 drinks per day) and cigarettes (>20 per day) was 13-fold greater than expected based upon the independent effects of the same amount of alcohol or tobacco alone.29 In this case-control study in Spain, heavy smokers and drinkers were estimated to have an approximately 50-fold greater risk of oral cancer (odd ratio [OR] 50.65, 95% CI, 19–134) than the never smoker and never drinker.29 The most significant risk factors for oral cancers among the current nonsmoker and nondrinker are previous use of alcohol and tobacco. Additionally, environmental tobacco smoke exposure may be an important risk factor for oral cancer in both individuals with a history of tobacco smoking and among never smokers.30,31 Data support the conclusion that at least 80% of oral cancers are attributable to alcohol and tobacco exposure.32 Therefore, the greater part of the rise in oral cancer incidence after 1915 in the U.S. and other regions of the world is likely attributable to dramatic increases in the per capita consumption of alcohol and tobacco that occurred around this time.33,34
Tobacco exposure is unquestionably a risk factor for oral cancers, however, only a minority of those exposed develops a malignancy. Tobacco contains as many as 50 known carcinogens, for example, polycyclic aromatic hydrocarbons and nitrosamines. To date, investigations have focused on whether genetic polymorphisms in enzymes that activate or detoxify tobacco-related carcinogens modify the risk of oral cancer in tobacco-exposed individuals. Genetic polymorphisms of interest include those that alter the expression or function of enzymes that both convert tobacco-related carcinogens to reactive intermediates capable of forming adducts with DNA and those that subsequently detoxify these intermediates. Examples of the former include cytochrome p450 enzymes (eg, CYP1A1, CYP2D6, CYP2E1) and of the latter include glutathione S-transferase, UDP-glucuronosyltransferases and N-acetyl transferases. As detailed in several reviews, there is inconsistent evidence that these enzymes modify risk for oral cancers. Many studies simply compare frequency distributions of polymorphism without consideration of alcohol and tobacco use and are inadequately powered or inappropriately designed to evaluate hypothesized gene–environment interactions. Evidence for a gene–environment interaction would include: statistically significant associations between genotype and oral cancer risk after adjustment for potential confounders (eg, age, sex, alcohol use); distinct trends in risk for oral cancer at different strata of tobacco exposure for individuals with different genotypes; and formal statistical evidence of interaction. For example, Zheng et al reported significant associations between oral and laryngeal cancer and predicted activity of a tobacco-carcinogen detoxifying enzyme (UDP-glucuronosyltransferase) among smokers, but not among nonsmokers. Although heavy smokers with genotypes predicted to have low enzyme activity had higher risk (OR 44, 95% CI, 5.3–373) for cancer than those with high activity genotypes (OR 5.3, 95% CI, 1.9–15), a formal test for interaction was not significant. Similarly, Olshan et al reported that heavy smokers (more than 40 pack years) with a gene polymorphism in which a detoxifying enzyme is not expressed (glutathione S-transferase, GSTTI null) appeared to have a higher risk of oral cancer (OR 13.5, 95% CI, 3.6–50.4) than those with the gene present (OR 5.4, 95% CI, 2.1–14.2), but the formal test of interaction was not significant. By contrast, Chen et al found no association between oral cancer risk and polymorphisms in another enzyme (N-acetyl transferase) involved in detoxification of tobacco-carcinogens. This research is complicated by the fact that many of these enzymes are inducible by their substrate, may be redundant in their activity, and that gene–gene interactions are likely to be important. Risk may be related to an overall “balance” between activation, detoxification, and repair of DNA damage due to tobacco-related carcinogens. There is no data to suggest that polymorphisms in tobacco-metabolizing enzymes account for development of oral cancer at a lower dose of exposure or at a younger age. Very large, population-based studies with appropriate exposure measures would be needed to formally evaluate potential gene-environment and gene–gene interactions.

**ALCOHOL CONSUMPTION AND METABOLISM**

The major risk factor for oral cancers among non-drinkers is tobacco use and among nonsmokers is alcohol use. Oral cancer risk significantly increased with both intensity (drinks per day) and duration of alcohol use and declined with cessation of use. Alcohol consumption increased risk of oral cancer among never, ever, former, and current smokers. Risk may increase directly with alcohol concentration (eg, consumption of spirits vs beer or wine), even after adjustment for total alcohol consumed. It is currently unclear whether the type of alcohol used affects oral cancer risk after adjustment for total amount consumed and alcohol concentration. In several studies, risk varied by anatomic site with equivalent levels of alcohol consumption, but no site was consistently at greatest risk. It is currently unclear whether the risk of oral cancer associated with alcohol consumption is influenced by sex.

Alcohol may act as a solvent to enhance mucosal exposure to carcinogens, but is not itself a direct carcinogen. However, acetaldehyde, a metabolite of alcohol, can form DNA adducts that interfere with DNA synthesis and repair. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH) and subsequently to acetate. Genotoxic levels of salivary acetaldehyde have been measured after consumption of alcohol and are likely due to combined effects of mucosal or bacterial ADH. ADH sequence polymorphisms affect enzyme activity and may modulate local concentrations of acetaldehyde. Individuals homozygous for the “fast metabolizing” enzymes ADH1C*1 and ADH1B*2 have higher salivary ac-
et aldehyde levels.\textsuperscript{55} Approximately 30\% to 40\% of whites/Europeans are homozygous for ADH1C*1, whereas the ADH1B*2 allele common in Asians is rare among whites.\textsuperscript{57}

Several case-control studies have investigated whether ADH polymorphisms modify risk of oral cancer in association with alcohol exposure. A single study in Brazil demonstrated elevated odds (OR 3.7, 95\% CI, 1.5–9.7) of all head and neck squamous cell carcinomas (HNSCC; inclusive of oral cavity, oropharynx, larynx, and hypopharynx) for the homozygous ADH1C*1-1 genotype at low levels of alcohol consumption compared with the ADH1C*1-2 and ADH1C*2-2 genotypes.\textsuperscript{58} Elevated odds (OR 5.3, 95\% CI, 1.0–28.8) of oral cancer in association with the ADH1C*1-1 genotype were observed only among heavy alcohol users (≥57 drinks per week) in Puerto Rico\textsuperscript{59} and among alcoholics in Germany\textsuperscript{60} and France.\textsuperscript{61} However, contradictory conclusions were reported in studies conducted in the U.S.\textsuperscript{62,63} and Greece.\textsuperscript{64} in which the “slow metabolizing” ADH1C*2-2 genotype was associated with increased risk for HNSCC among heavy drinkers. Other studies reported no associations between ADH genotype and risk of HNSCC.\textsuperscript{65–67} A recent pooled analysis reported no evidence of interaction between alcohol intake, ADH genotype and risk of HNSCC after adjustment for age, sex, study, and alcohol drinking status (never, former, current).\textsuperscript{57}

It is therefore currently unclear whether genotype modifies the risk of oral cancer associated with alcohol exposure. The heterogeneity of findings by geographic region may be due to combined effects of polymorphisms in other alcohol-metabolizing enzymes (eg, aldehyde dehydrogenase, alcohol-inducible cytochrome CYP2E1) that differ significantly by race and ethnicity.\textsuperscript{57} Differences may also exist for downstream genes, such as those for excision and repair of acetaldehyde-induced DNA adducts. It may be necessary, therefore, to examine combined effects of several genes concurrently, and to expand investigations to identify as yet undefined genetic associations by use of haplotype blocks or single nucleotide polymorphism data or both. Although the majority of the studies adjusted for age, sex, race and tobacco exposure, none of the studies adjusted for oral hygiene, which may have significant effects on local concentrations of acetaldehyde (see below). The solvent effects of alcohol may also be more important to its carcinogenicity than the genotoxic effects of acetaldehyde, depending of local customs (eg, dietary influences, smokeless tobacco products).

**SMOKELESS TOBACCO**

The relationship between use of smokeless tobacco products and oral cancers is complicated by significant heterogeneity in smokeless tobacco products by region, culture, and time period.\textsuperscript{68,69} The content of tobacco specific nitrosamines (TSNA) in smokeless tobacco has also varied by type and over time.\textsuperscript{69} In the U.S., air-cured, chewing tobacco tends to be low in TSNA, whereas fermented moist snuff and fire-cured dry snuff tend to have high levels of TSNA.\textsuperscript{69} In a study conducted among women in North Carolina who used predominantly fire-cured dry snuff, a strong dose-response relationship was observed between duration of smokeless tobacco use and risk of buccal and gingival sulcus cancer among nonsmokers, with an OR 47.5 (95\% CI, 9.1–249.5) for 50 years or more of use.\textsuperscript{70} A similar dose-response was not observed at other anatomic sites. The large number of exclusive users of smokeless tobacco combined with long durations of use likely contributed to the study’s strong findings. This strong association (OR 11.2, 95\% CI, 4.1–30.7) was confirmed in a population-based study in Florida,\textsuperscript{71} but not in other studies.\textsuperscript{72,73} In Sweden, several large, population-based, case-control studies reported no association between intensity or duration of moist snuff use (pasteurized and low in TSNA) and oral cancer.\textsuperscript{69,74–76} In India, where smokeless tobacco is often mixed with other carcinogenic substances (betel, areca nut, and lime), very strong dose-response relationships were observed with increased intensity and duration of smokeless tobacco use and risk of premalignant\textsuperscript{77,78} and malignant\textsuperscript{44,79,80} lesions of the oral cavity. These conflicting findings can be explained by type of smokeless tobacco use, variability in qualitative and quantitative measures of use, and the number of cases and their anatomic site distribution.

Although the increase in oral tongue cancer incidence rates reported among young men in the U.S. were thought to be due to smokeless tobacco use, there is little U.S.-based data to support this hypothesis. Three case-control studies conducted in Italy and England among young adults with oral cancer neither measured smokeless tobacco use\textsuperscript{81} nor found associations because of uncommon use among cases (see later).\textsuperscript{82,83}

**MARIJUANA USE**

The prevalence of marijuana use increased by 8-fold among individuals under the age of 35 between 1930 and 1955 in the U.S.\textsuperscript{84} Therefore
ecological data were consistent with a role for marijuana in the increase in oral cancer incidence that occurred after 1910. However, epidemiological studies performed to date have not indicated that marijuana use increased risk for HNSCC. No association of marijuana use with oral cancers was observed in a California cohort study, in a case-control study restricted to those under the age of 45, or in a population-based study in the U.S. A single study in New York State reported elevated odds of oral cancer (OR 2.6, 95% CI, 1.1–6.6) among ever users of marijuana, after adjustment for age, sex, race, education, alcohol use and pack-years of tobacco use. Risk also increased directly with duration and frequency of use. These odds were likely inflated by the use of a control population of blood donors with half the expected frequency of marijuana use than reported in the general population. In the majority of studies, assessment of risk was limited to ever versus never use of marijuana, and therefore risks associated with heavy use would likely be attenuated by the occasional user. Study power was also limited by small numbers of marijuana users, such that small elevations in risk that nevertheless may be important because of the high prevalence of marijuana use may not be measured. Under-reporting of use due to social stigma may also attenuate the association. However, reporting of marijuana use may be differential among patients and controls, resulting in a bias away from the null: cases may recall and report exposures to a greater extent than controls. Therefore, further research is needed before it can be concluded that marijuana use carries no risk for oral cancer.

SEXUAL BEHAVIOR AND HUMAN PAPILLOMAVIRUS INFECTION

Human papillomavirus (HPV) infection is a newly appreciated etiologic factor for a subset of HNSCC that arise predominantly from the lingual and palatine tonsils within the oropharynx. A vast cervical literature has indicated that anogenital HPV infection in adults is largely sexually transmitted. Analogously, oral HPV infection has recently been associated with sexual behavior, in particular with number of oral sex partners. Young age at first intercourse, number of lifetime sexual partners, a history of genital warts and ever performing oral sex were associated with oral cancer risk in men. Risk among women was associated with number of lifetime sexual partners. By contrast, several case-control studies observed no significant associations between risk of oral cancer and number of sex partners, frequency of oral sex, sex with prostitutes, or a history of genital herpes or gonorrhea. Because only a fraction of oropharyngeal cancers are likely attributable to HPV, risk estimates may be attenuated if the majority of oral or oropharyngeal cancer cases are not etiologically associated with HPV. For example, case-control studies that observed no associations with sexual behaviors in the entire study population found that number of sexual partners, oral sex, and oral-anal contact were significantly associated with HPV-positive cases. Patients under the age of 55 years, who were found to have higher-risk sexual behaviors, were also more likely to have an HPV-associated tumor.

Direct measures of HPV exposure and infection have also been associated with risk of oral cancers. HPV16 seropositivity conferred a 2- to 3-fold and oncogenic, oral HPV infection a 6-fold increase in risk for oral cancer. Stronger associations were observed when data were restricted to oropharyngeal cancer risk. For example, oral infection by oncogenic HPV types strongly elevated risk for oropharyngeal cancer (OR 230, 95% CI, 44–1200), after adjustment for alcohol and tobacco in a study conducted in Sweden. Furthermore, HPV16 seropositivity conferred an estimated 14-fold increase in risk for subsequent oropharyngeal cancer in a nested, case-control study that provided important evidence that exposure preceded development of disease. Although evidence suggests that HPV is associated with cancers in nonsmokers and non-drinkers, the degree to which oral HPV infection may combine with tobacco use or alcohol use or both to increase risk of oral cancer is currently unclear, with some studies suggesting a synergistic effect with tobacco or alcohol while others have found no such synergy.

A role for HPV in the pathogenesis of non-oropharyngeal cancers remains unclear. Although a recent meta-analysis reported an HPV prevalence of 23.5% in oral cavity carcinomas, the IARC multicenter study reported a prevalence of 3.9% (95% CI, 2.5–5.3). Although seropositivity for HPV16 independently elevated odds of oral cavity carcinoma (OR 1.5, 95% CI, 1.1–2.1) in the IARC study, this has not been observed in other studies. In contrast to data for oropharyngeal cancers, there is a lack of strength, consistency, and limited molecular data to indicate a role for HPV in
the development of oral cavity cancers. Misclassification of oropharyngeal cancers as oral cavity primaries (e.g., base of tongue as oral tongue) may explain these associations.

HPV infection may recently have altered the demographic of the patient with head and neck cancer. As noted above, tonsillar and base of tongue cancer incidence significantly rose in the U.S. between 1973 and 1998. The increase is unlikely to be entirely explained by the corresponding decline in tonsillectomy rates between 1970 and 1990, because this would not be expected to affect the incidence of base of tongue primaries. Therefore, it remains tempting to attribute this increase to HPV. Although sexual behavior trends were rarely studied prior to 1970, the frequency of premarital sex did increase from 12.3% to 62.9% among women and from 61% to 89.5% among men between 1910 and 1949. Increased exposure to HPV16 over time was observed in population-based studies in rural Finland. In Sweden, HPV16 seroprevalence significantly increased from 1969 to 1983 among pregnant women. Herpes simplex 2 seroprevalence, a validated marker for high-risk sexual behaviors, increased in the U.S. by 30% between the periods 1976 to 1980 and 1988 to 1994, and the relative increase rose with declining age category, suggestive of a cohort effect. It is therefore possible that changes in sexual behaviors over time have increased exposure to HPV16 and have resulted in the increased incidence of tonsillar cancer, particularly in young, nonsmokers and nondrinkers. Additional studies in this patient population are needed to further clarify risks associated with oral cancers (see below).

DIET AND BODY MASS INDEX

The relationship between diet and risk of oral cancer is among the strongest for any malignancy. Strong and consistent inverse associations between risk of oral cancer and consumption of fruits and vegetables have been observed, after controlling for the effects of alcohol and tobacco. Oral cancer risk declined significantly as intake of raw vegetables, citrus and noncitrus fruits increased in the majority of studies. In the IARC multinational case-control study of 1670 oral cancer cases, adjustments were made for age, sex, country, education, tobacco smoking and chewing, alcohol drinking, body mass index, and caloric intake. Patients with the highest quartile of intake of fruit and vegetables had significantly lower oral cancer risk (OR 0.4, 95% CI, 0.4–0.8) than those in the lowest quartile of intake. Elevated but inconsistent oral cancer risks were observed for diets high in eggs and butter, and for certain types of meats. Specific micronutrients correlated with a diet high in fruits and vegetables, such as the antioxidant Vitamins C and E and carotenoids, were associated with decreased risk. Importantly, risk of subsequent oral cancer increased as serum carotenoid levels declined in a nested, case-control study. Associations with folic acid intake are less consistent.

The effect of diet on oral cancer risk may be modified by other risk factors. The benefits of a diet high in fruits and vegetables was independent of primary site of the tumor, age (stratified at 60 years), and sex. Benefit was more pronounced in association with a family history of upper aerodigestive malignancy or mutagen sensitivity (not adjusted for tobacco and alcohol). However, in the IARC multinational case-control study, the protective effect of a diet high in fruits and vegetables was restricted to ever-smokers and ever-drinkers. Other studies that claimed the protective effect of diet extended to the non-smoker nondrinker, included former smokers and light to moderate drinkers (1–6 drinks per day) in the analysis with never-smokers and non-drinkers. Therefore, there is currently no data to suggest that diet is associated with risk of oral cancer in the absence of alcohol and tobacco consumption.

Chronic nutritional deficiency may contribute to oral cancer risk. The risk of oral cancer increased as body mass index (BMI) declined both at diagnosis and two years prior to diagnosis. However, the influence of decreasing BMI on risk was observed predominantly among current and former smokers and drinkers. Furthermore, low BMI several years before diagnosis was associated only with risk among smokers. These data suggest that low BMI may be a biomarker of chronic nutritional deficiencies secondary to chronic alcohol and tobacco use, at least in developed countries. In the IARC Multinational case-control study, risk of oral cancer increased with declining tertiles of BMI in never-smokers and ever-smokers as well as in never-drinkers and ever-drinkers. In comparison to the studies noted above, a large proportion of the
IARC study population was enrolled from developing countries where chronic nutritional deficiency states may be independent of alcohol and tobacco consumption. In support of this, a study conducted in India observed elevated risks with decreasing BMI in nonsmokers and in nondrinkers.79

**ORAL HYGIENE**

There is sufficient evidence in the literature to conclude that poor oral health is associated with risk of oral cancer. Oral cancer risk was inversely associated with several measures of oral hygiene, including frequency of tooth brushing and visits to a dental care provider.28,94,95,131,132 Clinical findings consistent with poor oral hygiene on examination (eg, mucosal irritation, dental caries, tartar) were associated with a 2- to 4-fold increase in risk after adjustment for sex, age, diet, alcohol, and tobacco habits.93,133 The strongest and most consistent indicator of risk in the literature was tooth loss, likely indicative of chronic poor oral health. Several studies reported elevated risk associated with any tooth loss,90,93,129,134–136 and also increased risk with increased number of lost teeth.95,137

Both smoking and alcohol drinking have significant direct effects on oral health and are strongly correlated with poor oral hygiene. Smoking and alcohol consumption increased risk for chronic inflammatory conditions caused by pathogenic oral microflora that predispose to tooth loss, for example, gingivitis and periodontitis. Therefore, it may be difficult to determine the degree to which tobacco and alcohol account for the association between oral hygiene and oral cancers. However, an independent role for oral hygiene was supported by significant elevations in oral cancer risk (approximate OR 3–9) among nonsmokers and nondrinkers with poor oral hygiene in case-control studies.136,137 Additive and multiplicative risk (in which combined exposures act synergistically to either add to or multiply, respectively, the risk associated with either exposure alone) between poor oral hygiene and alcohol and tobacco use have also been observed. Quantitative and qualitative differences were found between the oral microflora of smokers, patients with oral cancer, and controls.86,140 High microflora counts can affect local, salivary levels of carcinogens, such as acetaldehyde.141 Chronic infection and chronic inflammatory states are increasingly recognized as important in the pathogenesis of several cancers.142,143 Data therefore suggest that poor oral hygiene is an independent risk factor for oral cancer, likely due to a chronic inflammatory state for which tooth loss is a surrogate marker.

**GENETIC PREDISPOSITION TO HEAD AND NECK CANCER**

Young age at onset is a cardinal feature of an inherited predisposition to malignancy. Only a few known heritable disorders have been associated with an increased risk of oral cancers. Fanconi anemia (FA) is a rare autosomal recessive syndrome caused by defects in at least 11 genes involved in the recognition and repair of DNA intrastrand crosslinks.144 Individuals with FA are at high risk for bone marrow failure, leukemia and solid tumors and have an estimated 500- to 700-fold increase in risk of HNSCC.145,146 Approximately 14% of individuals with FA develop HNSCC by the age of 40, and the majority occur in the absence of alcohol and tobacco exposure.145 Recently, high-risk HPV was detected in the majority (84%) of oral cancers from patients with FA,147 suggesting the FA gene defects may increase sensitivity to HPV-mediated tumorigenesis.148,149 Although oral cancers have been reported among individuals affected by other inherited cancer syndromes (eg, xeroderma pigmentosum and dyskeratosis congenital, Blooms Syndrome), these associations are less well studied.150,151 Oral cancer at a young age has also been reported in families with functionally inactivated germine mutations in p16.152–154 Somatic inactivation of p16, an important regulator of the G1-S transition of the cell cycle, is also a common event in the genetic progression of sporadic oral cancers.155 Although oral cancer is rarely associated with specific known inherited cancer syndromes, studies of the impact of family history on risk of oral cancer are consistent with a genetic component to sporadic cancers. Because only a fraction of exposed (eg, tobacco and alcohol) individuals develop cancer, risk may depend upon an individual’s intrinsic cancer susceptibility. These likely complex and as yet undefined hereditary factors may be reflected in a family history of cancer. In the majority of studies, risk of all HNSCC is increased by 2- to 4-fold among individuals with a positive family history (PFH), after adjustment for the age, sex, alcohol and tobacco exposure of the index case.124,156–160 A PFH was usually defined as 1 or more first degree relatives with a history of HNSCC. Risk was greater if the affected family member was a sibling (approximately 8- to 14-fold),124,157,161 and elevations in risk were more con-
sistent for pharyngeal cancers. A PFH was also associated with an approximate 4- to 8-fold increase in risk for a second primary tumor among individuals with HNSCC. There was no evidence in any of these case-control studies to suggest a younger age at onset in patients with a PFH.

Although these studies suggest a consistent association of family history with HNSCC risk, several aspects of study design could limit inferences. In all but 1 of the studies, the cancer diagnosis was not confirmed in relatives of patients or controls, and therefore recall bias may overestimate the influence of family history due to heightened awareness of familial malignancies among cases. Furthermore, while the majority of the studies adjust for the smoking of the index case, the majority of the studies did not account for alcohol and tobacco use among family members. The alcohol and tobacco behaviors of parents and siblings significantly affect risk of smoking, and there are strong genetic influence on smoking initiation, persistence, and quantity as well as on nicotine dependence.

However, in a study conducted in Canada, risk of HNSCC was associated with a PFH (OR 3.79, 95% CI, 1.1–13), after adjustment for age, sex, ethnicity, and the alcohol and tobacco use of both index cases and relatives. No increase in risk for cancer before the age of 60 was observed in individuals with a PFH.

Several findings in these studies suggest that the influence of a PFH is due to an increased sensitivity to mutagens in alcohol and tobacco. Significant increases in risk for HNSCC were restricted to individuals with a PFH for smoking-related cancers and not non–smoking-related cancers. In a population-based study in Puerto Rico, a PFH did not increase risk for HNSCC among nonsmokers and nondrinkers, but did substantially increase the magnitude of the risk associated with smoking and drinking. Heavy smokers and drinkers with and without a PFH had a 60-fold and 12-fold increase in risk of HNSCC, respectively, when compared with nonsmokers and nondrinkers without a PFH.

A PFH may therefore represent an inherited sensitivity to the genotoxic effects of mutagens in tobacco smoke and metabolites of alcohol. Hsu and colleagues developed an in vitro mutagen sensitivity assay that may be a biomarker of this likely complex genetic defect in DNA repair capability. This assay measures the mean number of chromatid breaks observed in metaphase spreads of cultured lymphocytes after exposure to bleomy-

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**EPIDEMIOLOGY OF ORAL CANCERS IN YOUNG PATIENTS**

The majority of the literature on risk factors for oral cancer in young patients, variably defined as less than 40 or 45 years of age, are retrospective, single institution medical record reviews with limited quality of exposure data. Three prospective case-control studies indicated that young patients with HNSCC have the same risk factors as do older patients. A hospital-based, case-control study conducted in Italy and Switzerland compared risk factors for oral and pharyngeal cancers among 137 patients under the age of 45 to age-, sex- and hospital-matched controls. Smoking, alcohol consumption, diet, BMI and coffee consumption were each independently associated with risk of oral cancers in young patients. A strong dose-response relationship was observed with increased intensity (dose per day) for alcohol and with intensity and duration of tobacco con-
High intensity use of both alcohol and tobacco led to an odds of 48 (95% CI, 17.6–131). Risk was inversely related to consumption of green vegetables and carotenoids as well as BMI and coffee consumption. Fourteen (approximately 10%) and 13 (approximately 9%) of 137 patients were never-smokers or did not currently drink alcohol, but the proportion of never-smokers/never-drinkers was not reported. The influence of second hand smoke, smokeless tobacco use, oral hygiene, marijuana use, sexual behavior, and family history was not accounted for in this study. Nevertheless, 85% of cases could be attributed to alcohol, tobacco, and diet, a proportion quite similar to that for all patients with HNSCC.

Risk factors for lip, oral cavity, and oropharyngeal cancers among patients under age 45 were evaluated in 2 sequential case-control studies in England.82,83 Significantly elevated odds ratios for alcohol consumption (OR 5.5, 95% CI, 2.0–15.3) and smoking prior to the age of 16 (OR 19.5, 95% CI, 1.3–287) were reported, predominantly among men. Risk was elevated among individuals with more than 20 pack-years of smoking, and risk was highest among those with combined alcohol and tobacco exposure. Risk was inversely associated with fruit and vegetable consumption, predominantly among women. In these studies, approximately 26% of patients were never users of tobacco who did not consume “excessive amounts of alcohol,” defined as more than 21 or more than 14 drinks per week in men and women, respectively. Although no effect was observed for smokeless tobacco or marijuana use, secondary tobacco smoke, BMI, oral hygiene, sexual behavior and family history were not evaluated.

The rarity of oral cancers in individuals under the age of 45 substantially limits sample size, power, and the ability to carefully consider the influence of multiple factors on risk. Despite these limitations, the existing data suggest that the risk factors in young adults largely mirror those for individuals over the age of 45.

CONCLUSIONS

The strong cohort effect that accounted for the increased incidence of oral cancers after 1915 indicates that oral cancer is a disease largely attributable to behaviors that expose an individual to environmental carcinogens. The majority of oral cancers in individuals above and below the age of 45 can be attributed to the combined effects of alcohol and tobacco smoking. Other risk factors for oral cancers in both age groups include diet, BMI, oral hygiene, and HPV infection. However, further research is needed to clarify the risks associated with diet, BMI, and family history in the never user of alcohol and tobacco. Certain types of smokeless tobacco increase risk for oral cancers, but there is insufficient evidence to conclude that observed trends in oral cancers in young individuals are due to smokeless tobacco use. HPV infection may account for a greater proportion of oropharyngeal cancers in young versus older age groups as well as the annual increase in tonsillar cancer incidence in the U.S. in individuals under the age of 60. There is currently insufficient evidence to implicate or exonerate marijuana use in development of oral cancers at any age. Although a family history and mutagen sensitivity are associated with increased risk of oral cancer, there is no evidence that either predisposes to early onset of disease. However, rare syndromes such as Fanconi anemia and inherited mutations in p16 are associated with a positive family history and young age at onset. There is currently insufficient data to conclude that the proportion of cancers in young individuals that remain unexplained by known risks is substantially different from older individuals. Case-control studies restricted to the never-smoker and never-drinker regardless of age184 and to individuals younger than 40 years old are uniquely suited to identify risk factors for the small proportion of oral cancers that cannot be attributed to known risk factors.

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REFERENCES


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177. Schantz SP, Hsu TC, Ainslie N, Moser RP. Young adults with head and neck cancer express increased susceptibility to mutagen-induced chromosome damage. JAMA 1989;262:3313–3315.


