Tobacco Use and Oral Cancer: A Global Perspective

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Abstract: For both genders, cancer of the mouth and pharynx ranks sixth overall in the world; it is also the third most common site among males in developing countries. In industrialized countries, men are affected two to three times as often as women, largely due to higher use of alcohol and tobacco. Ethnicity strongly influences prevalence due to social and cultural practices, as well as socioeconomic differences. In population terms, survival rates around the world show little improvement. In terms of etiology, the effects of tobacco use, heavy alcohol consumption, and poor diet together explain over 90 percent of cases of head and neck cancer. All forms of tobacco represent risk factors for oral cancer, but on present evidence, snuff habits as they exist in Scandinavia and probably in the United States carry lower risks of serious health hazards, including oral cancer. Alcohol synergizes with tobacco as a risk factor for all upper aerodigestive tract SCC: this is super-multiplicative for the mouth, additive for the larynx, and between additive and multiplicative for the esophagus. The increase in oral cancer in the Western world has been related to rising alcohol use.

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Key words: epidemiology, etiology, oral and pharyngeal cancer, tobacco, alcohol, diet

Most malignancies of the upper aerodigestive tract are squamous cell carcinomas (SCC) arising in the mucous membranes of the mouth, pharynx, and larynx and share common risk factors. Of all oropharyngeal malignancies reported to the SEER registries in the United States between 1973 and 1987, apart from lesions of salivary glands, gingivae, nasopharynx, nasal cavity, and sinuses, more than 95 percent were SCC.¹ Neoplasms of the major salivary glands have quite distinct natural histories and ill-understood etiologies compared to mucosal cancers. Similarly naso-pharyngeal malignancies are usually Epstein Barr virus-related carcinomas (NPC), distinctly different from the more widespread alcohol- and tobacco-related SCCs of the upper aerodigestive tract. Many datasets make a distinction between lip and intraoral cancer, and we have to be clear whether "oral cancer" is taken to include oropharynx and hypopharynx. Fortunately, data for the larynx are usually recorded separately.

For both genders combined, cancer of the mouth and pharynx ranks sixth overall in the world, behind lung, stomach, breast, colon and rectum, and cervix plus corpus uteri. Mouth and pharynx are the third most common site among males in developing countries and fourth among females. The highest rates in the world for oral cancer are found in France, the Indian subcontinent, Brazil, and central/eastern

Europe. In the United States in 1997 there were 20,900 new cases and 5,600 estimated deaths among males; for females there were 9,850 new cases and 2,840 deaths. This represents a death-registration ratio of 0.274. In other words, even in an advanced society like the United States, nearly one in three people with oral cancer in time die with or as a result of their disease.

Incidence increases with age in all countries. In the West, 98 percent of oral and pharyngeal cases are in patients over forty years of age. In high-prevalence areas, cases occur prior to the age of thirty-five due to heavy abuse of various forms of tobacco. Furthermore, a number of cases of oral mucosal SCC occur in both young and old patients often in the absence of traditional alcohol and tobacco risk factors and may pursue a particularly aggressive course.²

In industrialized countries, men are affected two to three times as often as women, largely due to their higher indulgence of alcohol and tobacco for intra-oral and laryngeal cancer and higher exposure to sunlight for lip cancer among those who work outdoors. However, the incidence of tongue and other intra-oral cancer for women can be greater than or equal to that for men in high incidence areas such as India, where chewing and sometimes smoking are also common among women. In the United States the annual death rate per 100,000 population in 1991-

93 for oral and pharyngeal cancer was 4.4 for males and 1.6 for females, down from 5.9 and 1.9 respectively in 1971-73. Note, however, that because the U.S. population has become larger and older, actual numbers of deaths have risen over the past twenty-five years, more so in women.

Ethnicity strongly influences prevalence due to social and cultural practices, as well as death rates due to socioeconomic differences. Where these represent risk factors, their continuation by emigrants from high-incidence regions to other parts of the world results in comparatively high rates in immigrant communities. Among Indians in the Malay Peninsular, for example, oral cancer has long been considerably more common than among Malays or Chinese.³ Similar trends are noted among Indian migrants from India to Natal.⁴ In the United States both the incidence and mortality rates for alcohol- and tobacco-related cancers in African-Americans are substantially higher than for whites. African-Americans are not enjoying the same downward trends in mortality rates, and the incidence for males is so high, at 20.4 per 100,000 per annum, that oral/pharyngeal cancer becomes the fourth most common site for malignant disease.

There is much geographical variation regarding mortality rates, with several European countries, France, Hungary, and the Czech Republic ranking especially high. This pattern has historically been linked to heavy alcohol and tobacco use in these communities; see the article by Dr. Banoczy in this issue for further data.

Mortality rates show major changes over time. Recently the SEER program reported an overall fall in the mortality rate of oral cancer between 1973 and 1993 of 22.6 percent (Table 1). However, there is a considerable rise in mortality among African-American males (10.3 percent), more so in those aged sixty-

five and over (16.4 percent), an even larger rise in older African-American females (19.1 percent), and a smaller but significant rise among older white females (3.4 percent). Furthermore, for males of all races there is a decline in five-year survival rates from 53.5 percent in 1974 to 47.5 percent in 1988: rates range from a high of 72.1 percent for white females in Utah to a low of 24.8 percent for black males in metropolitan Atlanta. These are striking differences likely to be explained by socioeconomic condition, age, stage at diagnosis, continued presence or absence of environmental risk factors, and access to hospital and community care.

Within the continental United States, there is a greater than fivefold regional variation by state in mortality rates due to ethnic differences, socioeconomic status, and differences in risk factors, including the use of oral smokeless tobacco in the South. Striking variations are also seen across the European Union (EU).⁶ There is likely to be a doubling in deaths from oral cancer in the EU between 1970 and 2020, fueled by younger age groups and therefore continuing well into the next century. The highest mortality rates in the world for laryngeal cancer in men are in Hungary, Poland, Slovakia, and Romania.⁷

In population terms, survival rates around the world show little improvement. Cure and survival rates are better in highly specialized, high-volume treatment institutions. But such expert management is not uniformly available. The major determinants of survival, discussed elsewhere,⁸ include:

- Patient factors at diagnosis: age, gender, socioeconomic status, nutritional status, intercurrent disease, and continuing presence of risk factors⁹
- Tumor factors: site, size, differentiation, and biological behavior of the neoplasm, including host immune response, extent of regional, and distant metastases

Table 1. Mortality trends for oral and pharyngeal cancer in the United States between 1973 and 1993, by race and sex⁵

	All races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages									
Percent change	-22.6	-26.2	-16.3	-26.7	-31.6	-17.5	2.9	10.3	-8.8
Est. ann percent	-1.4*	-1.7*	-1.0*	-1.7*	-2.1*	-1.1*	-0.1	0.2	-0.3
Under 65									
Percent change	-26.7	-24.5	-34.0	-33.2	-32.3	-37.5	-1.6	7.3	-21.5
Est ann percent	-1.8*	-1.6*	-2.3*	-2.2*	-2.1*	-2.6*	-0.4	0.0	-1.2*
65 and over									
Percent change	-18.2	-26.8	3.7	-20.4	-31.1	3.4	12.6	16.4	19.1
Est ann percent	-1.1*	-1.8*	0.2	-1.3*	-2.1*	0.1	0.6*	0.7*	1.4*

*Indicates that the estimated annual percentage change in rate is statistically significantly different from zero

- Management factors: treatment modality and thoroughness, with smaller components derived from the quality and extent of supportive care and after care and treatment institution facilities.

Etiology and Risk Factors

Familial and Genetic Predisposition

Lip cancer is among the sites that show the strongest cancer clustering within families in the genealogical records of the Utah (Mormon church) database; the others are leukemia, lobular breast cancer, early melanoma, and adenocarcinomas of the lung in females.¹⁰ Studies from Kerala, South India, revealed a familial association in only 0.94 percent of the total oral cancers accrued January to July 1995, consistent with autosomal inheritance.¹¹ In the Netherlands, Copper et al.¹² took 617 first-degree relatives of 105 patients with head and neck cancer and found among them thirty-one cases of cancer of the respiratory and upper digestive tract versus ten cases in the control group composed of first-degree relatives of the index patient's spouses (n=617). This produced a relative risk (RR) of 3.5 (p=0.0002) for first-degree relatives, and of 14.6 (p=0.0001) for siblings. There was no relation to smoking and drinking histories, implying a constitutional factor affecting the way genotoxic compounds are dealt with.

It is important to control for environmental factors in such studies. This research was done in a large case/control study of oral and pharyngeal cancer in the United States.¹³ The strongest elevated risk was of oral/pharynx cancer among those whose sisters developed other cancers, but here the odds ratios (ORs) were only 1.6 (95 percent Confidence Interval 1.1-2.2). There are likely to be important familial clusters of individuals with more or less adequate genetic polymorphisms for carcinogen metabolising and detoxifying enzymes. Jefferies et al.¹⁴ and Llewellyn et al.² have critically reviewed the evidence in this growing field.

Occupational Risks

Outdoor workers like farmers, fishermen, foresters, and postal delivery workers are at risk of lip cancer from ultraviolet light in two venues: first, in

countries at high latitudes with clean air through which UV penetrates easily, albeit for only part of the year, such as Finland,¹⁵ and, second, in countries closer to the equator with regular long hours of sunshine, such as rural Greece, where lip can account for 60 percent of oral cancers.¹⁶ A study from California shows that the risk of lip cancer for women is strongly related to lifetime solar radiation exposure, but that lipstick and other sunscreens are protective.¹⁷ Well-differentiated SCCs arise out of long-standing solar keratoses.

The effects of early life exposure are long-standing. New Zealanders, for example, have four or more times the RR of developing cutaneous melanoma and lip cancer than of residents of England and Wales, while migrants in both directions retain intermediate risks.¹⁸

Part of the urban/rural difference in incidence of head and neck cancer also relates to atmospheric pollution. Mean sulphur dioxide and smoke concentrations in the atmosphere are positively correlated with SCC of the larynx and, to a lesser extent, the pharynx in parts of England.¹⁹ The importance of fossil fuel combustion at work is confirmed in a large study in four areas in the United States (1,114 cases, 1,268 controls), with ORs of approximately 2.0 for pharyngeal sites.²⁰ Asbestos, pesticide exposures, and mists from strong inorganic acids (OR 95 percent CI 1.1-2.9 for the latter) were shown for laryngeal cancer in Uruguay.²¹ The risk of laryngeal cancer from acid mists in the steel industry is confirmed in a United States study of 1,031 exposed men.²²

Tobacco Use

Taken together, the effects of tobacco use, heavy alcohol consumption, and poor diet probably explain over 90 percent of cases of head and neck cancer. Among men in industrialized countries, smoking is estimated to be the cause of 40-45 percent of all cancer deaths, 90-95 percent of lung cancer deaths, over 85 percent of oral cancer deaths, 75 percent of chronic obstructive lung disease deaths, and 35 percent of cardiovascular disease deaths in those aged thirty-five to sixty-nine years. Thus, although upper aerodigestive tract cancers are prominently represented, lung cancer and other pulmonary and cardiovascular diseases should be the starting point for anti-tobacco counselling. Alcohol synergizes with tobacco as a risk factor for all upper aerodigestive tract SCC:

this is super-multiplicative for the mouth, additive for the larynx, and between additive and multiplicative for the esophagus.²³

Types of Tobacco Use: A Global Perspective

Smoking of tobacco as factory-made cigarettes, cigars and cheroots, and loose tobacco in pipes or hand-made cigarettes is familiar to all. Tar, nicotine, and nitrosamine content varies greatly, depending on species, curing additives, and method of combustion. Such smoking habits are the predominant form of tobacco use in the West and among increasing millions in developing countries. With government regulation of tobacco advertising, restrictions on smoking in public transport and public places, and the awarding of damages to individuals and health authorities, manufacturers are increasingly targeting developing countries for sales, especially of their higher tar varieties.

Smokeless Tobacco

Much of the tobacco in the world is consumed without combustion. Rather, it is placed in contact with mucous membranes, through which nicotine is absorbed to provide the pharmacological effect. Use of nasal stuff, popular in the last century, is returning. Other forms of snuff, loose or packeted and placed in the oral vestibule, are common in Scandinavia and the United States. Tobacco is also prepared in blocks or flakes for chewing. In developing countries, tobacco is mostly consumed mixed with other ingredients (Table 2). The very extensive

evidence for carcinogenicity of these mixtures is covered exhaustively in Daftary et al.²⁴ and Gupta et al.²⁵ Toombak, the form used in Sudan, contains very high levels of tobacco specific nitrosamines (TSNs), and users show significantly increased risks of oral squamous cell carcinoma.²⁶

Betel Quids

The recommended terminology is that of Zain et al.²⁷ Quids are prepared from areca nut, cured or sun-dried, and chopped, then usually placed on a leaf of the Piper betel vine, although the inflorescence is used by some, for example, in Papua New Guinea. Slaked lime is an essential ingredient. It lowers pH and accelerates release of alkaloids from both tobacco and nut, with enhanced pharmacological effect. Daftary et al.²⁸ set out the evidence for the carcinogenicity of betel quid and the important role of tobacco in considerable detail.

Areca Nut Alone

Although the IARC²⁹ concluded that there was insufficient evidence that the chewing of betel quid without tobacco was carcinogenic to man, this is a probability. Areca nut is certainly the main aetiological agent in oral submucous fibrosis,³⁰ but in this case-control study twelve of the fourteen concurrent oral cancer and submucous fibrosis patients also used tobacco.

In Guam, where areca nut is chewed alone or with leaf only, there is apparently no increase in oral cancer.³¹ Conversely in Taiwan, most heavy chewers of betel quids do not include tobacco, yet oral can-

Table 2. Some common forms of oral smokeless tobacco

Habit	Ingredients	Population
Pan/paan/betel quid	Areca nut, betel leaf/inflorescence, slaked lime, catechu, condiments, with or without tobacco	Indian subcontinent, Southeast Asia, Papua New Guinea, part of South America
Khaini	Tobacco and lime	Bihar (India)
Mishri	Burned tobacco	Maharashtra (India)
Zarda	Boiled tobacco	India and Arab countries
Gadakhu	Tobacco and molasses	Central India
Mawa	Tobacco, lime and areca	Bhavnagar (India)
Nass	Tobacco, ash, cotton or sesame oil	Central Asia, Iran, Afghanistan, Pakistan
Naswar/niswar	Tobacco, lime, indigo, cardamom, oil, menthol, etc.	Central Asia, Iran, Afghanistan, Pakistan
Shammah	Tobacco, ash, and lime	Saudi Arabia
Toombak	Tobacco and sodium bicarbonate	Sudan

cer is clearly associated.³² Importantly, the synergistic role of alcohol has not been evaluated in these studies.³³ As we evaluate the dangers of these complex mixtures, it is important to remember that betel leaf is protective,³⁴ and at least two compounds have been identified: carotene and hydroxychavicol, an astringent antiseptic.

Oral Snuff in Scandinavia and North America

Brown et al.³⁵ described “snuff-dipper’s cancer” in the southeastern United States due to the habit of placing snuff in the labial sulcus—the basis of the classic description of verrucous carcinoma by Ackermann,³⁶ confirmed later by McCoy and Waldron.³⁷ Females in the textile industry in this area have a high prevalence of snuff dipping and elevated death rates from oral cancer.³⁸

There is also concern regarding use of factory-produced portion-packed snuff and the oral cancers it might cause, particularly among adolescents in the United States.³⁹ The U.S. Department of Health and Human Services⁴⁰ concluded that such use constituted a significant risk to health from oral cancer and other oral lesions and that it could lead to nicotine addiction and dependence. Congress banned the advertising of smokeless tobacco on radio and television in 1986 and required health warnings on packages and printed advertisements. The EU banned the sale of portion and loose snuff in all of its member states in 1992: when Sweden joined the EU in 1995, it was exempted from the ban on sales, but exports were banned.⁴¹ The IARC²⁹ stated that there was sufficient evidence that snuff causes cancer, and the Swedish government requires warning labels on such products.

Hatsukami and Severson⁴² comprehensively reviewed the North American scene (see also the article by Dr. Winn in this issue). This habit is addictive and can produce hyperkeratotic lesions in the area of habitual contact.⁴³ Overall, there is limited evidence that malignancies follow, though there may be a long latent period. A paper⁴⁴ based on combined data of the 1986 U.S. National Mortality Followback Survey (n=16,598) and the coincident National Health Interview Survey (1987), with correction for confounders, concluded that use of smokeless tobacco, either as snuff or chewing tobacco, does not increase the risk of oral or other digestive cancers. There is a considerable margin for error here, how-

ever, as the number of users of oral smokeless tobacco was small and the assessment of use was both reliant on individual recollection and grouped into large and insensitive categories. Importantly, alcohol emerged as a major risk factor for oral cancer with a strong dose-response relationship, as it did to a lesser extent with other digestive cancers. Smoking was associated with risk of oral but not other digestive cancers. Bouquot and Meckstroth⁴⁵ have pointed out that West Virginia, a state with the highest consumption of chewing tobacco in the United States, has below average oral cancer incidence rates. Chewing tobaccos are distinctly different from snuff, and snuff as manufactured and used in Europe and North America is very different from snuff-like products used in the Middle East, which are made locally in a variety of small-scale industries, by individual vendors, or directly by the users. In Scandinavia it is clear that local snuff is not a major risk factor: two recent case-control studies of oral cancer cases in Sweden have failed to show an association.⁴⁶ This is because Swedish snus is not fermented and contains much lower nitrosamine levels than fermented tobaccos.

The view that smokeless tobacco use may be associated with a lower risk of oral cancer in the United States has led to a movement to advocate the practice as a less dangerous alternative to smoking and an aid to nicotine withdrawal in those addicted to smoking.^{47,48} This approach has been condemned on the grounds that it can lead to nicotine addiction and it ignores both the potential role of snuff in other cancers and cardiovascular diseases and the fact that other ethically accepted forms of nicotine replacement therapy (such as chewing gums, skin patches, inhalators, and nasal sprays) are widely available. It is of interest, therefore, to consider two recent Swedish studies: one showed a RR for myocardial infarction of 0.89 (95 percent CI 0.62-1.29) in snuff users, compared to 1.87 (95 percent CI 1.40-2.48) in smokers.⁴⁹ Another study from health screenings of 135,036 construction workers showed that the RR for death due to cardiovascular disease was 1.4 (1.2-1.6) for this group, compared to 1.9 (1.7-2.2) for smokers.⁵⁰ No increased risk among snuff users who had never smoked was found among men with Crohn’s disease and ulcerative colitis in a case-control study.⁵¹ The possibility of increased risk of cancer at other sites has not yet been fully addressed. Nevertheless, on present evidence, snuff habits as they exist in Scandinavia and, probably in the United

States, carry low risks of serious health hazards, including oral cancer. As Axell^{52,53} points out, however, this does not mean that oral snuff should be encouraged: it almost always produces mucosal lesions, often affects salivary flow, causes gingival recession, and creates nicotine dependence and addiction.

Smoking and Head and Neck Cancer

The most comprehensive source of evidence for the carcinogenicity of tobacco smoke remains the IARC publication of 1986.⁵⁴ This evidence is summarized by the U.S. Surgeon General's Report of 1989: upper aerodigestive sites have the highest ARs in males, of all the many sites influenced by smoking. A major difficulty in accurately quantifying smoking risks for aerodigestive tract cancer is its strong synergism with alcohol.

Pipe smoking has long been associated with lip cancer, where the nature of the stem and its permeability and, maybe, temperature are cofactors. Some literature suggests that pipe and cigars are less risky for oral cancer than cigarettes,⁵⁵ but a study from North Italy²³ shows higher risks associated with these practices for cancer of the mouth and esophagus than cigarettes.

The relationship between smoke and the anatomical site of oral cancer is less clear-cut than with smokeless tobacco. Pooling of carcinogens in saliva gives cancers in the "gutter" area—floor of the mouth and ventral and lateral tongue. Mashberg and Meyers⁵⁶ reported in a U.S. population that 201 of 207 asymptomatic, primarily erythroplastic carcinomas were in three locations: floor of mouth (101 carcinomas), ventral or lateral tongue (36 carcinomas), and soft palate (64 carcinomas). In the Amsterdam series,⁵⁷ the floor of mouth and retromolar area were significantly more related to tobacco use than cancers or the tongue and cheek. However, in another series of 359 male cases among U.S. veterans, smoking was more strongly associated with soft palate cancers than anterior sites, and alcohol was associated with floor of mouth lesions.⁵⁸ This is interesting because the long-recognized lesions of stomatitis nicotina ("smokers palate") have a low malignant potential (except in reverse smokers). These predominantly affect the hard palate, producing hyperkeratosis without significant epithelial dysplasia, with plugging of the orifices of minor salivary glands and associated inflammation. Stomatitis nicotina, in the

West, is most commonly associated with pipe smoking, and both hard and soft palate are relatively uncommon sites of oral cancer.

The Mechanisms of Tobacco Carcinogenesis

More than 300 carcinogens have been identified in tobacco smoke or in its water-soluble components that will leach into saliva.⁵⁴ The major and most studied of these are the aromatic hydrocarbon benz-pyrene and the tobacco specific nitrosamines (TSNs), nitroso-nor-nicotine (NNN), nitrosopyrrolidine (NPYR), nitrosodimethylamine (NDMA), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

We have known since the 1920s that polycyclic aromatic hydrocarbons were the carcinogens present in tars, thus the interest in "low-tar" smoking materials. Benz-pyrene is a powerful carcinogen, with twenty to forty nanograms per cigarette.⁵⁹ Hoffman and Hecht⁶⁰ reviewed the role of N-nitrosamines. Mainstream cigarette smoke can contain NNN and NNK. These are generated primarily during pyrolysis, but also endogenously from some smokeless tobacco. They act locally, on keratinocyte stem cells, and are absorbed and act in many other tissues in the body. They produce DNA adducts, principally O6 methyl Guanine, which interfere with DNA replication. There is damage to all replicating cells, including those of the immune response.

Metabolism of these carcinogens usually involves oxygenation by p450 enzymes in cytochromes, and then conjugation, in which the enzyme glutathione S transferase (GST) is involved. Polymorphisms of the p450 and GST genes are currently under active study in the search for genetic markers of susceptibility to head and neck cancer, and indeed to tobacco-related cancers at many other body sites.⁶¹ Not all results are consistent, however.

Marijuana Use and Head and Neck Cancer

Reports of aerodigestive tract cancer in marijuana users have been reviewed.⁶² Recreational users of marijuana often also enjoy alcohol and tobacco, and tobacco usually forms part of the marijuana smoking mix. It is thus impossible at present to discern an independent risk for the smoking of cannabis

products themselves though, because of their composition, a theoretical risk certainly exists.

Little evidence exists regarding the risk of marijuana smoking for the development of potentially malignant oral lesions. However, as with more conventional tobacco smokers, leukoedema, nicotinic stomatitis, denture-related stomatitis, angular cheilitis, and median rhomboid glossitis are more common.⁶²

Alcohol and Head and Neck Cancer

Pure ethanol has never been shown to be carcinogenic in vitro or in animal studies.⁶⁴ It is presumed to act in concert with other, more direct, carcinogens in the beverage—so-called congeners—and with other environmental carcinogens, especially from tobacco. Nevertheless, an increased risk of upper aerodigestive tract cancer associated with alcohol drinking in nonsmokers has been demonstrated.⁶⁵

The increase in oral cancer in the Western world has been related to rising alcohol use. In England and Wales, alcohol consumption per capita fell from the turn of the century to the 1930s, but has more than doubled since. Using mortality from liver cirrhosis as a surrogate measure of damage to health from alcohol, Hindle⁶⁶ has plotted trends over this

century and shown how they closely match the trends in oral cancer mortality. Taking deaths from lung cancer as a measure of tobacco damage, it is striking how the trends for oral cancer move, both down and up this century, in opposite directions: strong circumstantial evidence that alcohol rather than tobacco is the major factor in the observed trends in oral cancer mortality and, by inference, incidence.

All forms of alcoholic drink are dangerous if heavily consumed, the most dangerous reflecting the predominant habit in the population under study. Thus there is evidence for the role of beer,^{67,68} wine,^{69,23} and spirits⁷⁰ which some⁷¹ have taken to implicate ethanol itself. Good evidence for the very significant role of alcohol comes from Northern Italy (Table 3). It is notable that the 95 percent confidence intervals for the odds ratio for all beverages do not cross unity until the total consumption is really quite high—above fifty-five drinks per week. This is consistent with other data.⁷² When the tobacco effect is adjusted for, heavy alcohol consumption itself produces considerable risks, with ORs or RRs of 17, 23, 33, and 70 appearing for oral cancer in the different studies. For these high rates of alcohol use/abuse, the risks are greater than for tobacco, adjusted for alcohol. Self-reported alcohol consumption tends to be underestimated, implying that alcohol may be even more important.

Alcohol is also high in calories, which suppresses appetite. Those with a serious drinking problem become socially fractured, and many choose to spend available cash on drink rather than food. All of this contributes to inadequate diet. Metabolism is further damaged by liver disease. As a result, nutritional deficiencies are common.⁷⁴

Risk of Oral Cancer from Mouthwash

Winn et al.⁷⁵ found increased risks associated with regular use of mouthwash, of 40 percent for men and 60 percent for women, after adjusting for alcohol drinking and tobacco use. Risks generally increased in proportion to frequency and duration of mouthwash use, and were only apparent when the alcohol content of the mouthwash exceeded 25 percent. Several published reviews⁷⁶⁻⁷⁷ have helped the British, Canadian, and American dental associations to endorse products of this type for control of dental plaque and gingivitis.

Table 3. Odds ratios for oral and pharyngeal cancer in males, according to alcohol habits: Northern Italy, 1984-1989, adjusted for age, area of residence, education, occupation, and smoking⁷²

	Oral cavity (n=157)	Pharynx (n=134)
WINE (drinks/week)		
<=20	1	1
21-34	1.1 (0.5-2.3*)	0.7 (0.3-1.6)
35-55	1.9 (0.9-3.7)	1.9 (0.9-3.7)
56-83	4.9 (2.6-9.5)	3.1 (1.6-6.1)
84+	8.5 (3.6-20.2)	10.9 (4.7-25.3)
BEER (drinks/week)		
0	1	1
1-13	1.0 (0.6-1.8)	0.5 (0.3-1.0)
14+	0.8 (0.5-1.4)	0.9 (0.5-1.5)
SPIRITS (drinks/week)		
0	1	1
1-6	0.7 (0.4-1.3)	0.4 (0.2-0.9)
7+	0.9 (0.6-1.3)	1.2 (0.8-1.8)
TOTAL (drinks/week)		
<=19	1	1
20-34	1.1 (0.5-2.5)	0.9 (0.4-2.0)
35-59	3.2 (1.6-6.2)	1.5 (0.8-3.1)
60+	3.4 (1.7-7.1)	3.6 (1.8-7.2)

*(95 percent confidence intervals)

Head and Neck Cancer in Non-Users of Tobacco and/or Alcohol

A minority of patients develop a cancer in the apparent absence of one or both of these risk factors. Rich and Radden⁷⁸ found that Australian patients with oral cancer who had never used tobacco or alcohol developed their carcinomas particularly on the buccal mucosa and upper alveolar ridge; the Amsterdam data⁵⁷ are consistent with this finding. Hodge et al.,⁷⁹ in a Kentucky population, described thirty-three of 945 cases (3.4 percent) of head and neck cancers in non-users of tobacco. The non-users of both tobacco and alcohol had a definite majority of women, especially older women, and comparatively few cancers of the floor of the mouth. Other findings⁸⁰ with oral cancer in non-user American cohorts are:

- a low incidence of second primaries,
- a higher level of differentiation of the primary lesions,
- a lower frequency of associated oral candidiasis, and
- importantly; no better overall survival.

None of these studies on the rare cases that occur in non-users of tobacco and/or alcohol dilutes the evidence that these are far and away the major risk factors. Viral infections and nutritional inadequacies, which are addressed next, are the main hypothetical factors in this group of patients.

Viruses and Head and Neck Cancer

About 15 percent of all human cancers may have an etiological relationship to viruses.

Papilloma Viruses

HPV 16 is the most common type associated with cervical and oral cancers.⁸¹ In vitro studies show that primary human oral epithelial cells can be immortalized by high-risk HPV types.^{82,83} However, exposure to tobacco-related chemicals was required for these cells to progress to a fully malignant phenotype.⁸⁴

That infection with high-risk HPV, and even demonstrable integration of known viral oncogenes, is neither necessary nor sufficient for the development of head and neck cancer is supported by our observations that p53 mutations (but not over-expression) correlate with the absence of HPV 16 E6.⁸⁵ This finding is consistent with data from Riethdorf et al.,⁸⁶ who showed that only about 40 percent of head and neck squamous carcinomas carrying p53 mutations also carried high-risk HPV, and only about 40 percent of HPV positive tumours showed p53 mutations.

The question of the predictive value of HPV infection in at-risk individuals with or without a detectable potentially malignant lesion is important. High-risk HPVs have frequently been detected in benign oral lesions and in clinically and histologically normal mucosa.^{87,88} Whether or not detecting them adds to the utility of oral screening is unknown and requires substantial further work.

Herpes Simplex Viruses

Animal studies show that HSV can act as a co-carcinogen with tobacco or other chemical carcinogens⁸⁹ and that immunization against HSV can inhibit the co-carcinogenic effect with dimethyl benzantracene.⁹⁰

Serum IgA antibodies to HSV I are higher in smokers and higher again in smokers with head and neck cancers, suggesting that prolonged exposure to HSV may sensitize the mucosa to tobacco carcinogens. A more likely explanation, however, is that the generalized immunosuppression, particularly of natural killer-cell (NK) activity, which is induced by smoking favors the acquisition or chronicity of HSV infections/carriage, with consequent raised antibody titres.⁹¹

Fungal Infections

A proportion of leukoplakias are superficially invaded by fungal hyphae,⁹² particularly nodular leukoplakias, and these have a higher risk of malignant transformation. There is also a clear association between smoking and the risk of candidal infection in the mouth⁹³; this also applies to HIV positive individuals, compounding the risk.⁹⁴ Patients with iron deficiency, clearly at increased risk for oral cancer, are also more prone to oral candidiasis, indicat-

ing an interactive, multifactorial process in oral carcinogenesis.

It remains uncertain as to whether candida invades oral potentially malignant lesions as a secondary event or it is causal in the lesion and/or subsequent cancer. However, a mechanism clearly exists, as these organisms have the necessary enzymes to promote the nitrosation of dietary substrates.⁹⁵

Diet and Nutrition in the Etiology of Oral Cancer

Interest here relates to the roles of iron, of the anti-oxidant or free-radical scavenging vitamins A, C, and E and to trace elements such as Zinc and Selenium, for which there is evidence of a protective effect. There is a high incidence of upper gastrointestinal tract cancer in middle-aged women with chronic anaemia, with dysphagia, glossitis, and atrophy of associated mucosae—the Plummer-Vinson or Patterson-Brown-Kelly syndrome. In animals rendered experimentally iron-deficient by venesection and a low iron diet, there is epithelial atrophy⁹⁶ and increased cancer risk, clearly shown when such animals are challenged with chemical carcinogens.⁹⁷

Food Groups

Of thirteen case-control studies that have examined the association between fruit and vegetable consumption and oral/pharyngeal cancer, eleven report a meaningful inverse association.⁹⁸⁻¹⁰⁰ The reduction in risk with fruits, from the highest to the lowest intake, varies from 80 percent to 20 percent¹⁰¹ and is evident for tongue, mouth, and pharynx.¹⁰² There is similar protection from vegetables rich in carotenes.^{23,103,104} A strong protective effect is evident for carotenoids and vitamin C from vegetables and fruit and of fiber intake in oral cancer risk in an important study in Beijing, China.¹⁰⁵

La Vecchia et al.⁹⁸ estimate that approximately 15 percent of oral and pharyngeal cancers in Europe can be attributed to dietary deficiencies or imbalances, perhaps accounting for 5,000 avoidable deaths per year. Similar conclusions can be drawn from studies of laryngeal cancer.¹⁰⁶ In the presence of tobacco and/or alcohol, low intake of fruit and vegetables has been estimated to account for 25-50 percent of cases among men.¹⁰⁷

Dental Factors in the Etiology of Head and Neck Cancer

Clinicians have long noticed an association between poor oral hygiene, poor dental status, and oral cancer; in addition, “dentition” (recorded as number of natural teeth, appliances, sharp or fractured teeth) appears as a correlate in several studies.⁷⁰ As these are certain to be confounded by socioeconomic, tobacco, alcohol abuse, nutritional, and other correlates of cancer risk, it requires carefully designed and large case series and case control studies to evaluate the importance of dental factors. Furthermore, it is well known that, in chemical carcinogenesis experiments in animals, repeated traumatizing of mucosa localizes the site at which the tumor appears, increases the yield, and reduces the latent period. Many human cases are described of an oral cancer at the site of chronic trauma arising from a broken tooth, a denture clasp, or an ill-fitting denture flange or excrescence.

Three recent studies indicate that denture wearing per se is not a risk factor, but that chronic ulceration from an unsatisfactory appliance may promote a neoplasm in the presence of other risk factors.¹⁰⁸ Data from a northern Sweden study⁴⁶ and from a smaller study in the United States¹⁰⁹ show no increased risk associated with fillings, dentures, or fixed prostheses nor, importantly, in the Swedish study, with experience of dental x-rays.

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