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Mouth Cancer for Clinicians Part 4: Risk Factors (Traditional: Alcohol, Betel and Others)

Abstract: A MEDLINE search early in 2015 revealed more than 250,000 papers on head and neck cancer; over 100,000 on oral cancer; and over 60,000 on mouth cancer. Not all publications contain robust evidence. We endeavour to encapsulate the most important of the latest information and advances now employed in practice, in a form comprehensible to healthcare workers, patients and their carers. This series offers the primary care dental team, in particular, an overview of the aetiopathogenesis, prevention, diagnosis and multidisciplinary care of mouth cancer, the functional and psychosocial implications, and minimization of the impact on the quality of life of patient and family.
Clinical Relevance: This article offers the dental team an overview of the main cancer risk factors, namely tobacco and alcohol, betel and other chewing habits, and environmental factors.
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Mouth cancer arises out of DNA mutations (Article 1) which can affect various genes and are increased by various risk factors, which are mainly tobacco, alcohol and betel use. This article discusses alcohol, betel and similar habits, and occupational/environmental issues.

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Alcohol

Alcohol is a depressant. A small amount depresses anxiety and inhibitions and can make the user feel sociable and talkative; too much and a hangover may result, and the person may not even remember actions; and large doses of alcohol in a single session could produce coma or even death. In people drinking too much alcohol over a long period, a range of serious behavioural and health problems can arise (Table 1; Figure 1). Alcohol use is widespread in most communities worldwide, except Islamic communities and others such as Seventh Day Adventists, but there are wide cultural and gender differences in consumption. Alcohol use is increasing in many countries, especially in the young.

Alcoholic (ethanol or ethyl alcohol) beverages may also be carcinogenic as they may contain several other carcinogens or procarcinogens, including nitrosamine and urethane contaminants. An important additional mechanism is by alcohol oxidization to acetaldehyde (a carcinogen) by enzymes (alcohol dehydrogenases; ADHs). Acetaldehyde is cytotoxic and results in the production of free radicals and DNA hydroxylated bases. Acetaldehyde is then degraded to non-carcinogenic acetate by other enzymes – aldehyde dehydrogenases (ALDHs). Genetic variations in the activities of these (ADH and ALDH) alcohol-metabolizing enzymes may thus influence the outcome of exposure to alcohol, and thus its carcinogenicity (and other effects) in any individual. There are ethnic variations also in these enzymes. High ADH activity or low ALDH lead to high acetaldehyde levels with increased carcinogenic potential, though this may be balanced if the associated 'hangover' headache dissuades further alcohol

System	Possible Effects
Blood	Pancytopenia, folate deficiency, thiamine deficiency, immune defect
Central nervous system	Intoxication, dependency, dementia, Wernicke–Korsakoff syndrome
Heart	Arrhythmias, cardiomyopathy, hypertension
Intestine	Glucose and vitamin malabsorption
Liver	Hepatitis, fatty liver, cirrhosis, liver cancer
Mouth	Tooth erosion, cancer
Musculoskeletal	Myopathy, gout
Oesophagus	Gastro-oesophageal reflux, Mallory–Weiss syndrome, cancer
Pancreas	Pancreatitis
Reproductive system	Impotence, dysmenorrhoea, low birth-weight babies, foetal alcohol syndrome
Stomach	Gastritis, ulceration, carcinoma

Table 1. Possible systemic effects of chronic alcohol use. (Adapted from: Scully C. *Scully's Medical Problems in Dentistry* 7th edn. Oxford, Edinburgh, London: Elsevier, 2014.)

imbibition! Alcohol dehydrogenase type 3 genotypes appear predisposed to mouth cancer.

Acetaldehyde is also produced by:

- Oral and faecal bacteria from alcohol;
- Smoking;
- Poor oral hygiene;
- Cytochrome P 450 2 E1.

With alcohol there is for mouth cancer:

- A 20-fold risk with heavy alcohol drinkers (spirits are the worst);
- A strong dose-response relationship.

The World Cancer Research Fund/American Institute For Cancer Research (WCRF/AICR) and International Agency for Research against Cancer (IARC) classify alcohol as a cause of mouth, tonsil and pharynx cancers. A large Cancer Research UK (CRUK) study looking at lifestyle factors found about a third of cancers of the mouth and throat (30%) were caused by drinking alcohol (around 37% of mouth and pharyngeal cancers in men, and around 17% in women).

The more alcohol a person drinks, and the greater number of years they drink for, the higher the cancer risk. Overall, regular alcohol drinkers have around two-and-a-half times (155% increase) the risk of mouth and pharyngeal cancer, compared with non-drinkers and occasional drinkers. Heavy drinking (6 or more units per day) increases the risk of mouth and pharyngeal cancer more than five-fold (440%). Every 1.5 units of alcohol consumed per day increases the risk of mouth and pharyngeal cancer by 35% in men and 9% in women; every 6 units daily increases the risk more than three-fold (223% and 231% increase for men and women, respectively). Furthermore, the risk of a secondary primary tumour (SPT) in the upper aerodigestive tract (UADT) is increased by 9% for every 1.25 units of alcohol consumed per day.

Alcohol in mouthwashes

It has been speculated that frequent use of mouthwash could be a mouth cancer risk factor as a result of the ethanol (alcohol) it contains. Some studies have suggested that high alcohol content mouthwashes could increase the risk of mouth cancer but others have suggested that this is not the case. Others report that poor dental hygiene and excessive use of mouthwash containing alcohol could increase the risk of oral cancer (Article 4).

One meta-analysis showed that the use of mouthwashes containing alcohol is not associated with mouth cancer risk. A case control study of people diagnosed with cancer of the mouth, throat, larynx or oesophagus ('upper aerodigestive cancers') suggested that poorer dental and oral health may be associated with increased risk, independent of alcohol and smoking behaviour. One case control study adjusted for smoking and alcohol consumption, well-established risk factors for upper aerodigestive tract cancers that could otherwise influence the association between oral health and dental hygiene and these cancers, concluded that poor oral health and dental care seem to be independent risk factors for upper aerodigestive cancers (Article 5). After adjustment for all other measured health and lifestyle factors, the risk of upper aerodigestive cancers increased with poorer dental care. People with the worst dental care had the highest risk – more than double that for people with the best dental care. Looking at four gene variants, people with certain variants associated with faster ethanol metabolism, had a decreased risk of these cancers, while a variant associated with slower ethanol metabolism was associated with increased risk.

Any effect of the alcohol in mouthwash may be similar to that of alcohol used for drinking, although the contribution of mouthwash use to oral cancer must be small in terms of attributable risk. Whether mouthwash use may entail some risk through the alcohol content in most formulations on the market remains to be fully clarified. There is limited evidence of an increased risk associated with mouthwash containing alcohol.

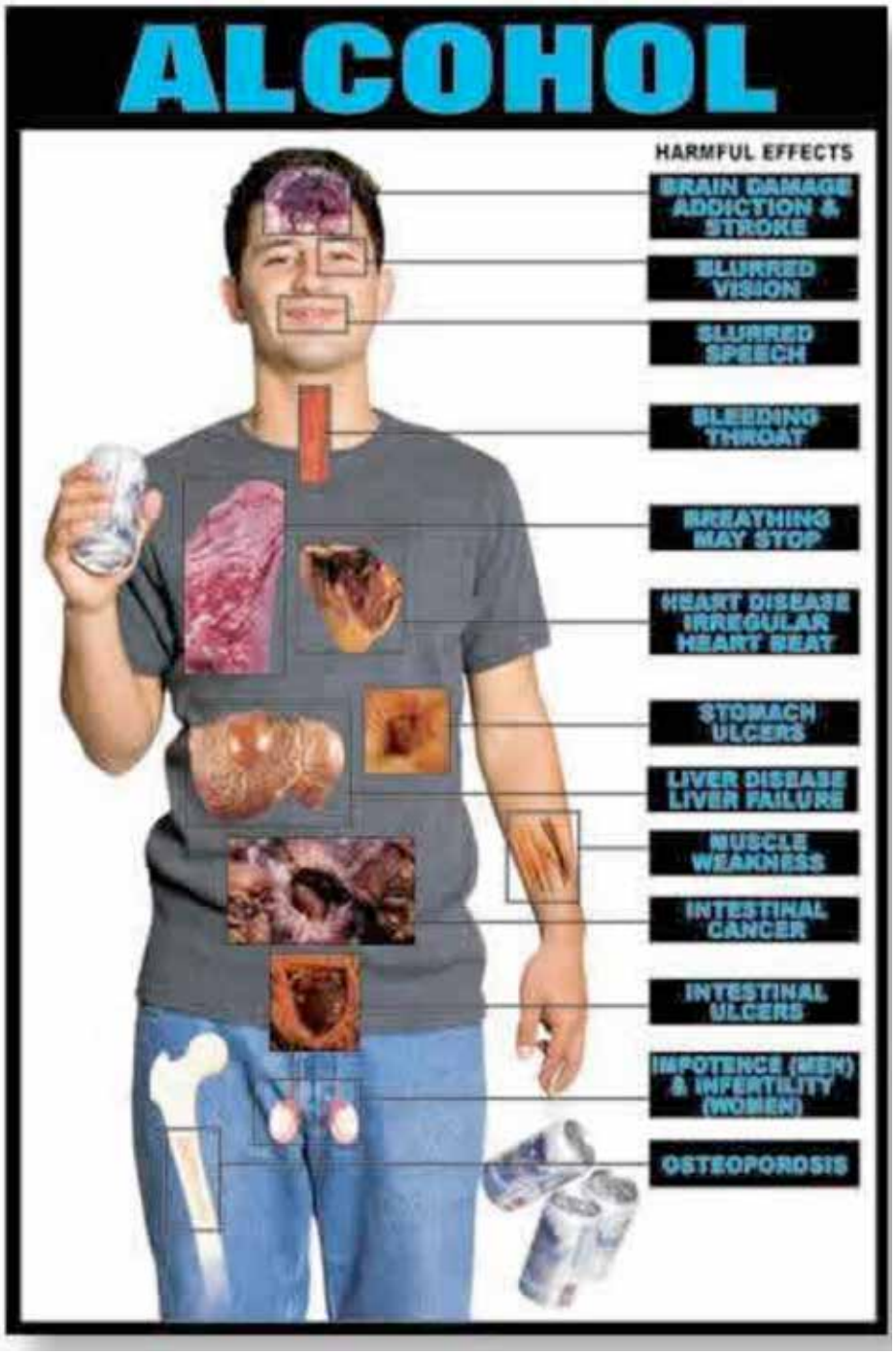

Figure 1. Alcohol abuse.

Figure 2. Tobacco in conjunction with alcohol increases the mouth cancer risk.

Nevertheless this controversy continues. If there is a link, it is currently unclear whether it could be related to the alcohol contained in mouthwash, or whether the link is caused by poor oral health rather than a direct mouthwash effect. It could be that poor oral health or hygiene increases risk of mouth cancer, and people with poorer oral health are more likely to use mouthwash.

Alcohol plus tobacco

People who both smoke and drink heavily over several years have the highest risk of developing head and neck cancers. Tobacco and alcohol use are independent risk factors for mouth cancer but these lifestyle habits often co-exist and they interact and contribute to a multiplicative carcinogenic effect (Figures 2, 3, 4). Heavy tobacco smokers have up to a 20-fold greater risk; heavy alcohol drinkers a 5 to 7-fold greater risk and those who do both have up to a 40 to 50-fold greater risk. Smokeless tobacco in conjunction with alcohol also increases the mouth cancer risk.

Alcohol has a more pronounced effect on current smokers (192% increased risk of mouth and pharyngeal cancers) than never/former smokers (32%). Heavy-drinking ever-smokers have an almost seven-fold (567%) higher risk than heavy-drinking never-smokers (153%).

Smoking increases the acetaldehyde burden following alcohol consumption and alcohol-drinking enhances the activation of pro-carcinogens present in tobacco, as well as permeation through the oral epithelium.

Betel and similar chewing habits

The term quid (or paan) means a substance or mixture of substances put in the mouth and chewed, usually for long periods. The betel quid contains various ingredients, areca nut (supari; from the areca catechu tree) and also tobacco, either on its own or mixed with slaked lime and sometimes spices in a leaf called a betel leaf. Some people prefer paan and others chew the nut only.

Chewing betel is common in parts of Asia and in some immigrant groups in Europe, North America and Australia.

Use is very popular, especially in Hindu and Buddhist people from the Indian sub-continent, Taiwan and parts of Southern China and causes an orange-brown staining in the mouth of users (Figure 5). Indeed, betel quid use is a habit of something like 20% of the world's population. Studies from the UK and US have reported persistence of areca nut chewing among immigrants from South Asia, resulting in increased rates of mouth cancer in these new settlements. Chewing of these products usually begins at an early age (at approximately 13 to 15 years) and, by adulthood, most users are addicted.

There are three main products all called 'Betel', but they are not the same plant though all contain the stimulant arecoline (Figure 6) which has muscarinic and nicotinic agonist properties.

Arecoline is the primary active ingredient responsible for the effects of the areca nut, betel and paan. Arecoline has effects comparable to nicotine. It is a mild stimulant and mood enhancer. It also causes slight pupillary constriction and bronchial constriction. It may improve the learning ability of healthy volunteers and therefore has been suggested as a trial for Alzheimer's disease.

Betel leaves of the Piper betel plant

This popular recreational drug in Indonesia and southern Asia should not be mistaken for betel nut. The leaves of the plant are consumed/chewed (Figure 7). The main active ingredient is *arecoline*.

Betel nut – the nut of the areca catechu (betel) palm

This can be consumed fresh, roasted or dried (Figure 8). Betel nuts contain arecoline, which is mildly addictive and is widely used in south-east Asian ethnic communities, such as people of Indian and Sri Lankan origin.

Paan: the most often consumed betel product

This is a mixture of betel nuts, betel leaves and slaked lime popular in India and Indonesia and throughout the Middle East. Sometimes tobacco is added (mostly in India). Paan produces the strongest psycho-active effects. Betel leaves and paan (betel + areca nut) need to be freshly prepared and the prepared product's shelf life is short. Therefore, betel consumption is restricted to regions where betel is cultivated (southern Asia and Indonesia). In Thailand, paan is called betel quid. Gutka is a manufactured preparation of betel nuts and tobacco, plus an extract of acacia called catechu and slaked lime, designed to be chewed. It originated in the Indian Subcontinent, where its consumption is widespread today, and spread from there to areas with a large Indian population. Classically, gutka comes in the form of a loose powder that is inserted into the mouth, chewed leaving a characteristic reddish to orange stain on the lips, tongue and teeth (Figure 9), and is eventually spat out. According to traditional Ayurvedic medicine, chewing areca nut and betel leaf is a bad breath remedy.

Betel quid substitutes contain both carcinogens and genotoxic agents which have a role in multistage progression of mouth cancer. In the last few years, small attractive and inexpensive sachets of betel quid substitutes have become widely available, and are aggressively advertised and marketed, despite having higher genotoxic and carcinogenic potential compared with conventional quids. The IARC recognized that betel (which contains the stimulant arecoline) chewed as quid (with or without tobacco) is carcinogenic; arecoline N-oxide is mutagenic. The IARC classifies betel

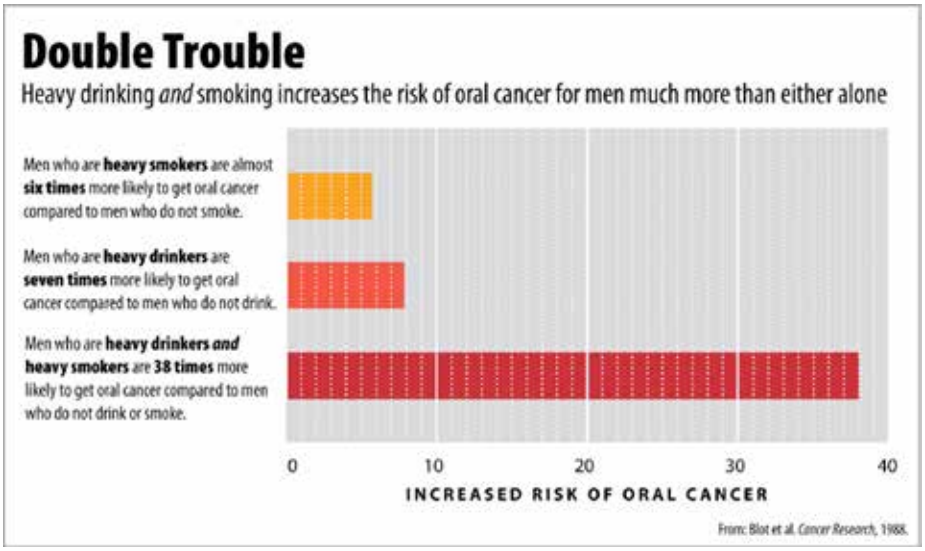

Figure 3. Tobacco in conjunction with alcohol increases the mouth cancer risk.

Figure 4. Newspaper article on tobacco/alcohol additive risk.

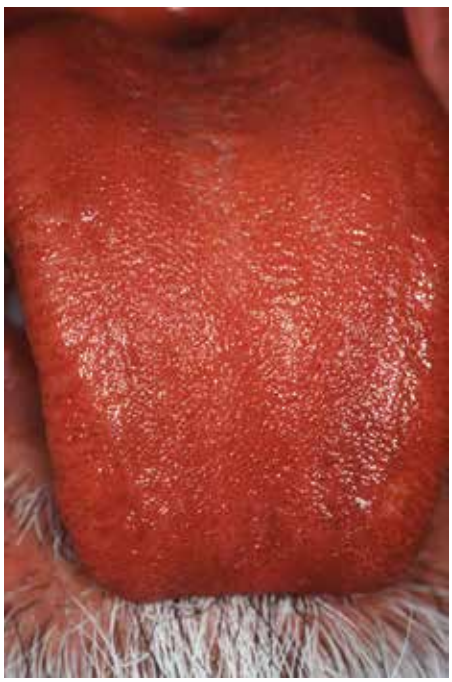

Figure 5. Betel staining in a patient of Bangladeshi origin.

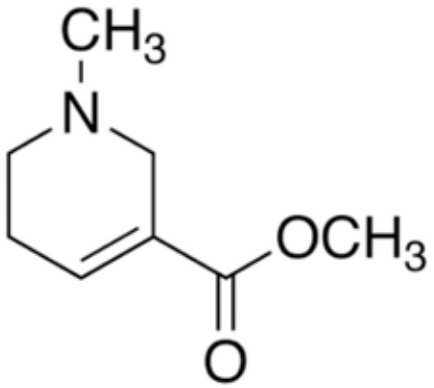

Figure 6. Arecoline formula.

Figure 7. Betel leaf.

quid *with* tobacco as a cause of mouth, tonsil and pharynx cancers, and betel quid *without* tobacco as a cause of mouth cancer. Smokeless tobacco contains nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; areca nut contains arecoline and 3-(methylnitrosamino) propionitrile, while lime provides reactive oxygen radicals, each of which has a role in oral carcinogenesis.

Chewing betel quid without tobacco is an independent risk factor for developing mouth cancer, increasing the risk of mouth cancer in tobacco non-smokers by around three-and-a-half times, and in those who neither smoke nor drink alcohol by around 15 times. Betel quid *with* tobacco increases the risk of mouth cancer in those who neither smoke nor drink by around 7 times. When betel quid with tobacco is consumed with alcohol and smoking the relative risk for mouth cancer increases 10 to 30-fold. The risk of such interactions may be underestimated in some South Asian communities. For example, Sikhism and Punjabi religious beliefs prohibit alcohol and tobacco use; however, there are reports of alcohol and tobacco consumption among them.

Figure 8. Betel nuts.

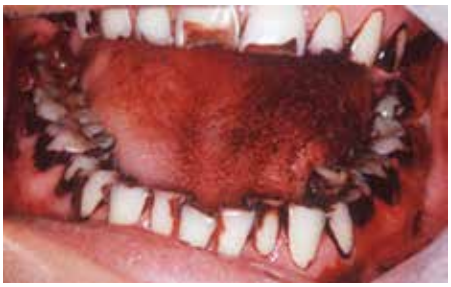

Figure 9. Betel staining and tooth damage from nut chewing.

Regular chewers of betel leaf and areca (betel) nut as in 'pan' or 'paan' have a higher risk of oral disease such as:

- Teeth discoloration;
- Oral submucous fibrosis (Figure 10);
- Leukoplakia (Figure 11) and increased risk of oral cancer (if consumed with tobacco the risk is even higher);
- Various systemic issues (Table 2).

Betel may also cause the following:

- Oesophageal, pancreatic, and hepatocellular cancers;
- Adverse birth outcomes;
- Chronic kidney disease;
- Contact dermatitis;
- Liver cirrhosis;
- Hypertension;
- Metabolic syndrome.

Spitting out the chewed material in public areas also poses a health risk.

Kava, another legal high, is a close relative of betel. Various other chewing habits, usually combinations that contain tobacco, are used in different cultures (eg khat, shammah, toombak).

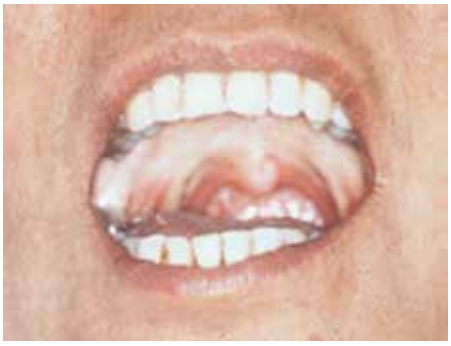

Figure 10. Oral submucous fibrosis.

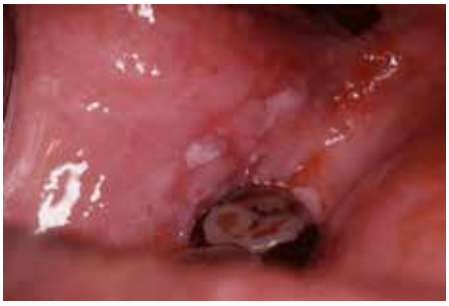

Figure 11. Leukoplakia and mucosal and tooth staining in a betel user.

Figure 12. Khat.

Khat (qat)

Khat (*Catha edulis*) is a plant (Figure 12) that contains the stimulant cathinone and is commonly used, especially by young males in and from South Arabia/Eastern Africa. Often tobacco is also smoked.

Khat appears possibly to be carcinogenic via free radicals and mitochondrial damage, and also may

System	Possible Effects
Heart	Hypertension, metabolic syndrome, diabetes, coronary heart disease, obesity
Kidneys	Chronic kidney disease, urinary stones
Liver	Cirrhosis, cancer
Mouth	Periodontitis, leukoplakia, submucous fibrosis, cancer
Oesophagus	Cancer, submucous fibrosis
Pancreas	Cancer
Reproductive system	Lower birth weight infants, prematurity
Respiratory	Asthma

Table 2. Possible systemic effects of chronic betel use.

produce:
- Neuro-psychiatric effects;
- Periodontitis;
- Teratogenicity.

http://www.daap.org.uk/educational-resources.php

Marijuana

The carcinogenicity of other psychotropic products, such as marijuana, is controversial. The incidence of oropharyngeal and tongue cancers has increased over the last 20 years and this parallels an increased use of marijuana among individuals born after 1950, but may be related to HPV infection. A pooled analysis comprising individual-level data from nine case-control studies showed that, compared with never marijuana smokers, ever marijuana smokers had a raised risk of oropharyngeal but a reduced risk of tongue cancer. The risk of oropharyngeal cancer remained raised among never tobacco and alcohol users. The risk of tongue cancer was reduced among never users of tobacco and alcohol. The results suggested that the association of marijuana use with head and neck carcinoma may differ according to tumour site. However, there are possible sources of bias, including confounding by HPV infection and misclassification of marijuana exposure.

What are the environmental factors on mouth cancer?

The effects of environmental factors, such as ionizing radiation, ultraviolet light or air pollution (wood stoves; fossil fuels; volatile carcinogenic compounds formed during cooking) are ill-defined but they may act via the production of free radicals that elicit DNA mutations.

What are the known occupational risk factors?

Radiation

Ultraviolet light

Skin cancers are relatively common on the face and neck, and *lip cancer* is an issue mainly in older men exposed over long periods to sunlight, as these areas are often exposed to ultraviolet light (UV). More than 1 in 3 people with lip cancer have worked outdoors and been exposed to the sun for long periods. Both the sun and tanning beds give off UV rays which can cause skin cancers in unprotected skin.

X-radiation and gamma radiation

X-radiation and gamma radiation are causes of *salivary gland* cancer. Early evidence on the effects of ionizing radiation came from atomic bomb survivors, but studies of people exposed to diagnostic or therapeutic medical radiation show an increased risk of salivary gland cancer. Treatment of thyroid cancer with radioiodines increases the risk of salivary gland cancer (and hyposalivation).

Chemicals and dusts

Occupations with an increased risk of mouth cancer mostly involve blue collar workers, and they may include:
- Benzene exposure;
- Blacksmithing;
- Building industry;
- Carpet installation;
- Construction work;
- Driving;
- Electricity working;
- Fossil fuel exposure;
- Furniture industry;
- Grain production;
- Machinery operations;
- Masonery;
- Metal working;
- Painting;
- Pesticide exposure;
- Petroleum industry;
- Plumbers;
- Railway working;
- Textile industry;
- Woodworkers.

People exposed to asbestos have a 25% increased risk of *oral* and *pharyngeal* cancers. The IARC classifies asbestos and exposure to printing processes (which may entail exposure to polycyclic aromatic hydrocarbons and mineral oils) as probable causes of *pharynx* cancer. Exposure to polycyclic aromatic hydrocarbons is associated with a 14% increased risk. The IARC and WCRF/AICR classify drinking hot maté, a South American infused drink, as a cause of pharyngeal cancer; maté users have around double the risk of mouth and oropharyngeal cancer.

Primary cancers of the *nasopharynx* are distinct among head and neck cancers in aetiology and in racial and geographic distribution, being endemic to southern China, south-east Asia and northern Africa, and having only a weak association with tobacco and alcohol.

Their pathogenesis is thought to involve exposure to unrelated carcinogens, such as nitrosamines from consumption of salted fish in endemic areas and a very strong association with Epstein-Barr Virus (EBV). Prolonged exposure to some types of dust and certain chemicals increases the risk of developing cancers of the *nasopharynx* and *sinuses*. Hardwood dust, leather dust and formaldehyde (found in dust *from medium-density fibreboard [MDF]* an engineered wood product made by breaking down hardwood or softwood residuals into wood fibres) and formaldehyde are linked to some cancers of the nasopharynx and paranasal sinuses. Workers heavily exposed to formaldehyde (including embalmers and funeral directors) have around double the risk of dying from nasopharyngeal cancer and woodworkers (specifically furniture and plywood workers) have a 140% increased risk of dying from nasopharyngeal cancer.

Conclusion

A variety of agents can increase cancer risks, notably tobacco and alcohol.

Further reading

1. **http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/riskfactors/**
2. **http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/riskfactors/oral-cancer-risk-factors#Previous**
3. **http://www.who.int/mediacentre/factsheets/fs339/en/**
4. **http://www.ons.gov.uk/ons/dcp171776_302558.pdf**
5. **http://www.cancerresearchuk.org/cancer---help/type/lung---cancer/**
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