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Mouth Cancer for Clinicians Part 14: Cancer Prevention

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 cancer prevention.

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There is a huge effort searching for new and improved ways to prevent cancer, not only to avert suffering of patients and their families but also to control economic costs. Mouth cancer is rarely familial, when it may be genetic or environmental or due to risk factor exposure (eg diet or tobacco smoke exposure) but, for example, can be seen in Fanconi anaemia. Previous articles have discussed these risk factors (Articles 3, 4, 5). Mouth cancer is certainly related to modifiable risk factor (eg tobacco, alcohol) exposure.

In general, prevention includes activities – ‘interventions’ – aimed at reducing these risks. These are usually

grouped into primary, secondary and tertiary prevention and can be carried out by all members of the clinical healthcare team and others such as health trainers.

Primary prevention

The goal of primary prevention is to protect healthy people from developing cancer. Primary prevention is by far the most ideal approach; strategies include education of the public, high-risk individuals and healthcare practitioners and, for example:

- Health lifestyle education;
- Avoidance of known cancer risk factors;
- Legislation against known risk factors;
- Regular examinations and screening tests;
- Immunizations against relevant infectious disease, such as HPV.

Secondary prevention

The goal of secondary prevention is to slow or halt disease progression (if possible) in its earliest stages. For example:

- Educating people about risk factors;
- Recommending regular examinations and monitoring.

Tertiary prevention

The goal of tertiary prevention is to help people manage the long-term health problems faced in cancer, to prevent further issues and to optimize the quality of life (QoL; Article 13) for example, via:

- Pain management;
- Speech rehabilitation;
- Psychological support;
- Patient support groups;
- Financial support.

What is primary prevention?

DNA mutations can occur spontaneously, but the rate of mutations is increased by the various ‘cancer risk factors’ (Articles 3, 4, 5). The mainly modifiable lifestyle risk factors, most of which are used because they are addictive, are tobacco and alcohol. In some cases, betel use and similar habits, infections (eg human papillomaviruses [HPV], other microbes), radiation (eg sunlight, ionizing), or other risk factors may be responsible. There is protective benefit from a healthy immune system and from diets rich in fruit and vegetables.

There are a number of strategies which, in theory, may reduce exposure to

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the risk factors, which include:

- Avoiding tobacco in any form – smoked, chewed, or smokeless;
- Avoiding betel nut, even without tobacco;
- Reducing alcohol consumption;
- Reducing the chances of HPV infection (via safe sex and HPV immunization);
- Protecting lips from sun UV rays;
- Eating at least five fruit and vegetables a day;
- Exercising 30 minutes daily.

Such a healthy lifestyle should not only reduce the risk of mouth cancer, but also has a wide range of other health benefits. Further detail follows below.

What measures are available for primary prevention?

It has been estimated that perhaps 75% of mouth cancers could be prevented by eliminating tobacco use and reducing alcohol consumption (Figure 1).

Tobacco

Tobacco is frequently smoked in cigarettes but there are several other forms used in different cultures (Tables 1 and 2: Article 3). Tobacco in any form, smoked, chewed, or smokeless, should be avoided.

Unfortunately, tobacco use is widespread worldwide and increasing in the young and in resource-poor communities. Tobacco use may be recognized from the history, or odour, or staining of fingers, teeth and even lips, but a fuller smoking history should be taken (Table 3).

Smoking cessation reduces the increased cancer risk by 35% within 1–4 years and by 80% after 20 years of quitting.

Treatment of tobacco dependence can be addressed in primary care (including dentists), and smoking cessation clinics. Smoking cessation should be gradual, because withdrawal symptoms are then less severe.

Evidence from NICE suggests that the following brief interventions for smoking cessation work and should be used:

- Ask smokers how interested they are in quitting;
- If they wish to stop, refer them to an intensive support service such as NHS Stop Smoking Services;
- If they are unwilling or unable to accept

African	Arabic	South Asian	Western
Cigarettes	Cigarettes, hookah (shisha – water pipe)	Cigarettes, bidi (cheerot), chuta (reverse smoking) kreteks, hookah	Cigarettes, cigars, pipe

Table 1. The main types of tobacco smoking in different cultures. (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 4th edn. Oxford: Elsevier, 2014.)

African	Arabic	South Asian	Western
Toombak	Shama/shammaah Nass/naswar Zarda	Pan (paan; betel quid) ingredients can be used alone (eg mishri, zarda and kiwan) Khaini Gutkah Oral cleaning products (eg gudakha) Bajar and creamy snuff	Chewing tobacco (plug, loose leaf and twist) Snuff Snuss

Table 2. Non-smoking tobacco use in different cultures. (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 7th edn. Oxford: Elsevier, 2014.)

Smoking and binge drinking blamed for rise in mouth cancer

As deaths increase, study shows that young women are at risk

Figure 1. Newspaper article on mouth cancer.

a referral, offer a stop smoking aid. The five steps in advising people to stop smoking are the 'five As':

1. Ask;
2. Assess;
3. Advise;
4. Assist;
5. Arrange.

Ask

Tobacco use (type, frequency and how long used) should be noted on clinic records and information kept as up to date as possible.

Assess

Assess how keen is the person

to quit, and whether the patient has ever tried to give up; aids used, previous failures at cessation.

Advise

Give plain, precise and personalized advice of the benefits of cessation and hazards of not stopping smoking (Figure 2). Other reasons for quitting tobacco (eg benefits in preventing heart disease; Table 4) should be included.

Assist

Assist with directions to use cessation aids. These include counselling, nicotine replacement therapy (NRT), pharmacotherapy and electronic cigarettes.

Questions	SMOKER		
	Current	Former	Never
What smoked?			
How many per day?			
Age starting?			
How many years?			
Quit attempt?			
Quit success?			
Exposed to passive smoke?			

Table 3. Smoking history questionnaire. (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 4th edn. Oxford: Elsevier, 2014.)

System	Diseases
Cardiovascular	Ischaemic heart disease Peripheral vascular disease Buerger disease
Respiratory	Sinusitis Chronic obstructive pulmonary disease
Carcinomas	Oropharyngeal and oral Bronchial Bladder Breast Colorectal Laryngeal Pancreatic
Foetus	Higher prevalence of abortion Low birthweight Higher risk of perinatal and sudden infant deaths
Gastrointestinal	Periodontal disease Peptic ulcer
Central nervous system	Alcoholism Cerebrovascular disease Dementia

Table 4. Diseases associated with tobacco smoking. (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 4th edn. Oxford: Elsevier, 2014.)

Arrange

Pharmacological treatments combined with psychological treatment result in some of the best long-term abstinence rates.

Nicotine replacement therapy (NRT)

Nicotine replacement therapy is well-established and includes skin patches, nasal and mouth sprays, chewing gum, inhalators and tablets. NICE guidance from June 2013 recommends the use of licensed nicotine-containing products (NCPs) but

does not currently include E-cigarettes. There is little difference in effect of the different types of NRT (Table 5).

Drugs

Two main agents are available.

Bupropion (amfebutamone)

This is an antidepressant, an aminoketone, that appears to affect brain neurotransmitters, but is also used for nicotine withdrawal. Treatment usually lasts for 7–12 weeks, with the patient stopping tobacco use at about 10 days



Figure 2. Controversy exists as to cigarette pack labelling.

into the course. Bupropion approximately doubles the chance of quitting smoking successfully after three months. One year after treatment, the chances of sustaining smoking cessation are still 1.5 times higher with bupropion than a placebo. Bupropion seems as effective as NRT. However, it can cause dry mouth, headache and gastrointestinal symptoms, and is contra-indicated in the under-18s, pregnancy, epilepsy, people on epileptogenic medications, eating disorders, people with a CNS tumour, and the very old.

Varenicline

This is a nicotine receptor partial agonist. It is not statistically superior to NRT but has better efficacy and fewer adverse effects than bupropion. It may cause nausea, depression and can interfere with driving. A Cochrane systematic review concluded that varenicline improved the likelihood of successfully quitting smoking by 2–3-fold relative to pharmacologically unassisted attempts.

Electronic cigarettes (E-cigarettes)

Electronic cigarettes

(E-cigarettes) include electronic vaping devices, personal vaporizers or VPs, and electronic nicotine delivery systems (ENDS). E-cigarettes are battery-powered devices that simulate conventional cigarettes that deliver nicotine in many instances, plus diluents like propylene glycol and glycerine and flavourings. They contain a heating element and thereby provide an aerosol of vaporized chemicals to the user (Figure 3). Glycerine helps produce the vapour and can add sweetness. Propylene glycol makes up 90% of the solution and contributes to the 'smoke'. Other flavours added may include tiramisu, pomegranate or pina colada. Other added substances with claimed benefits may include: rimonabant for weight loss or tadalafil to heighten sexual activity.

There is little firm evidence of health benefits or hazards of E-cigarette use. Rates of relapse are highest in the first few weeks and months, and diminish considerably after 3 months. An advantage over conventional smoking would appear to be a significant reduction in carcinogen exposure, though some studies have detected traces of tobacco specific N-nitrosamines. Very low levels of a carcinogen, diethylene glycol, have been detected in some E-cigarettes, as have lead, nickel and chromium.

The overall effect of E-cigarette use on public health is still unclear and there are some concerns about the effect on the developing brain, an increased risk for addiction, and the potential for E-cigarettes to lead to conventional tobacco use. Minor side-effects may include mouth and throat irritation, headache, vertigo, and/or nausea. More serious effects reported include aspiration pneumonia, cardiac arrhythmias and facial burns following explosion of a device.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has expressed concerns 'about the quality and inaccurate labelling of electronic cigarettes'. E-cigarettes are regulated by the EU Tobacco Products Directive (TPD) and relations have just changed (www.cigelectric.co.uk/e-cig-uk-regulation-2016/) and now stipulate some core requirements concerning, for example, limiting the strength and size of the nicotine-containing 'e-liquid', incorporating safety features to packaging and including warnings about the addictive

nature of nicotine. In the USA, the Food and Drug Administration (FDA) has expressed concerns with manufacturing practices and the presence of carcinogens in products tested. Public Health England (PHE) summarized a report (2014) as follows; 'The emergence of electronic cigarettes and the likely arrival of more effective nicotine-containing devices currently in development provides a radical alternative to tobacco, and evidence to date suggests that smokers are willing to use these products in substantial numbers. Electronic cigarettes, and other nicotine devices, therefore offer vast potential health benefits, but maximising those benefits while minimising harms and risks to society

requires appropriate regulation, careful monitoring, and risk management. However the opportunity to harness this potential into public health policy, complementing existing comprehensive tobacco control policies, should not be missed.'

E-cigarettes are not regulated under current smoke-free legislation in the UK.

Alcohol

Alcohol use should be minimized: aim to drink no more than 1 standard drink a day (2–3 units) for women, or 2 standard drinks a day (3–4 units) for men. Screen all patients for excessive

How an electronic cigarette works

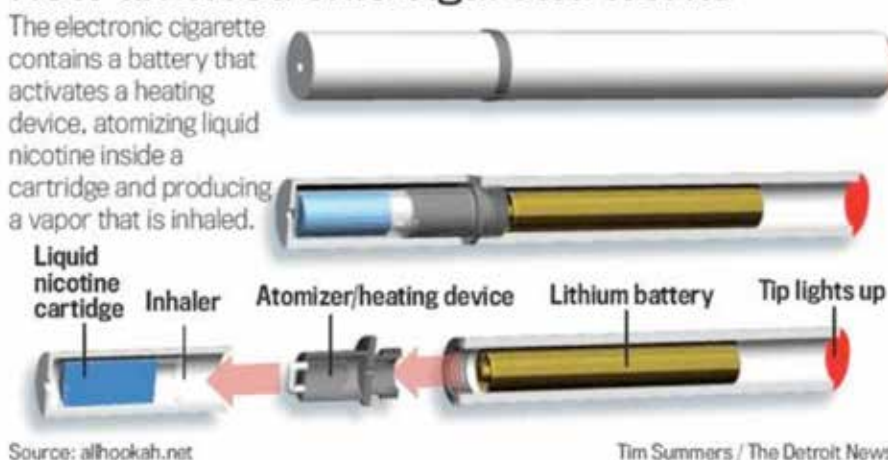


Figure 3. E-cigarettes are battery-powered devices which include electronic vaping devices, personal vaporizers or VPs, and electronic nicotine delivery systems (ENDS).

Type of NRT	Delivery System	Possible Adverse Effects
Chewing gum	Gum is chewed gently to release nicotine	Jaw ache Gastric irritation Unsuitable for denture wearers
Inhalor/inhalator	Puff steadily for about 20 min/h	—
Lozenges	Suck until dissolution	—
Nasal spray	1–2 doses per hour for 2 months	Irritation of nasal mucosa
Sublingual tablets	4 mg hourly for 3 months	—
Transdermal patches	Worn during waking hours	Local skin irritation

Table 5. Nicotine replacement therapies (NRTs). (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 7th edn. Oxford: Elsevier, 2014.)

Organization	Contacts	Remit
Addiction	www.addiction.org.uk	A UK wide treatment agency, helping individuals, families and communities to manage the effects of drug and alcohol misuse
ADFAM	020 7553 7640 or www.adfam.org.uk	Information and advice for families of alcohol and drug users
Al-Anon	Helpline 0207 40 30 888 open 10 am–10 pm or www.al-anonuk.org.uk	Offers support and understanding to families and friends of problem drinkers
Alcoholics Anonymous Great Britain	www.alcoholics-anonymous.org.uk	AA is an organization of men and women who share their experience with each other hoping to solve their problems and help others to recover from alcoholism
Alcohol Concern	020 7928 7377 or www.alcoholconcern.org.uk	General information about alcohol, and can help put you in touch with nearest alcohol advice centre
Alcohol Focus Scotland	0141 572 6700 or www.alcohol-focus-scotland.org.uk	Information and advice on responsible drinking
Drinkline	Helpline: 0800 917 8282	Drinkline runs a free, confidential helpline for people who are concerned about their drinking, or someone else's
National Association for Children of Alcoholics (NACOA)	0800 358 3456 helpline@nacoa.org.uk www.nacoa.org.uk	Advice and support to children of alcohol-dependent parents and people
NHS Choices	www.nhs.uk/Livewell/alcohol/Pages/Alcoholsupport.aspx	Advice and information on alcohol and offers a database of support and treatment services
Samaritans	08457 90 90 90 or Email jo@samaritans.org or www.samaritans.org	Confidential non-judgemental emotional support, 24 hours a day for people who are experiencing feelings of distress, despair or suicide
Talk to Frank	www.talktofrank.com	Drugs awareness site for young people and parents/carers

Table 6. UK alcohol support.

alcohol consumption with a validated questionnaire such as the Fast Alcohol Screening Test (FAST).

- Brief interventions are effective for hazardous and harmful drinking;
- Specialist interventions are effective in people with alcohol dependence;
- Most people with alcohol dependence can undergo medically-assisted withdrawal safely at home, after risk assessment.

Some UK alcohol support services are shown in Table 6.

Betel and khat

Betel nut (or areca nut) chewing, even without tobacco, should be avoided. In the UK, knowledge about the betel risks and about mouth cancer are lacking in many high-risk south Asian populations where control could be achieved by implementation of policies to reduce betel quid chewing and improve public awareness of the dangers of use (Table 6). Khat use should also be discouraged (Figure 4).

Diet

Fruit and vegetables appear to protect, mediated via folate, antioxidants (carotene, carotenoids, flavanones, flavonoids, phytosterols, vitamins A, C and E, riboflavin), iron and magnesium. Eat at least 5 servings of fruit and vegetables daily; cereals, dairy products and olive oil may also be protective. No single dietary factor alone appears responsible: antioxidants may be anti-carcinogenic, eg in green tea, but a Cochrane review concluded that the

evidence is insufficient and conflicting. Similarly, any role of polyphenols, abundant in vegetarian diets, and recent reports of a protective effect of coffee and of non-

steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, call for more investigation. One study found a significant protective association of aspirin use.

UV irradiation

UV rays from the sun are damaging. Protection against solar irradiation would reduce the incidence of lip

System	Tobacco	Alcohol	Betel
Bladder	Cancer	Control loss, Ataxia, Infections, Cancer	Cancer?
Cardiovascular	Coronary heart disease	Arrhythmias, Cardiomyopathy, Hypertension,	Hypertension, Metabolic syndrome
CNS	Alzheimer disease, Stroke	Intoxication, Dependency, Dementia, Wernicke-Korsakoff syndrome	Dependency
Gastrointestinal	Oesophageal cancer	Gastro-oesophageal reflux, Mallory-Weiss syndrome, Oesophageal carcinoma Gastritis, Gastric ulceration, Gastric carcinoma, Glucose and vitamin malabsorption	Oesophageal cancer, Submucous fibrosis
Haematological	Malignancies	Pancytopenia, Folate deficiency, Thiamine deficiency, Immune defect	?
Hepatic	Abnormal liver function, Cancer?	Hepatitis, Fatty liver, Cirrhosis, Liver cancer	Cirrhosis, Cancer
Oral	Carcinoma, Potentially malignant disorders, Candidosis, Dry mouth (xerostomia), Dry socket, Halitosis, Implant failure, Keratosis, Necrotizing gingivitis, Chronic periodontal disease, Teeth staining	Tooth erosion, Potentially malignant disorders, Carcinoma	Cancer, Potentially malignant disorders, Periodontitis, Submucous fibrosis
Musculoskeletal	Musculoskeletal ailments, Osteoporosis	Myopathy, Gout, Osteoporosis	?
Pancreatic	Cancer	Pancreatitis	Cancer
Renal	Cancer	Renal tubular dysfunction	Chronic kidney disease, Urinary calculi (related to calcium hydroxide 'chuna' in betel quid)
Reproductive	Infants with low birthweight, premature or stillborn, Earlier menopause	Impotence, dysmenorrhoea, Low birthweight babies, Foetal alcohol syndrome	Lower birth weight babies, Lower male to female sex ratio
Respiratory	Cancer, Chronic obstructive pulmonary disease	Respiratory distress, Infections	Breathing problems

Table 7. Possible systemic effects of main lifestyle cancer risk factors. (Adapted from Scully C. *Scully's Medical Problems in Dentistry* 7th edn. Oxford: Elsevier, 2014.)

Here are some facts about Khat that you should know

- You can get addicted to Khat
- Khat can stay in your blood for 24 hours
- Khat was used on social and religious occasions 'back home'. This is no longer the case in many cities.
- Many young people are mixing this with illegal drugs and using it on the streets
- An increasing number of women are using Khat
- Khat is a stimulant and after use you can test positive for amphetamine which is an illegal drug

Health Risks

- You can get depression after prolonged use of Khat
- Frequent Khat use leads to decreased productivity because it tends to reduce the user's motivation
- Repeated use can cause manic behaviour with grandiose delusions, paranoia, and hallucination
- Repeated use can also cause sleeplessness, nervousness, impotence and nightmares
- Gastro-intestinal tract problems such as anorexia and constipation are linked to Khat use
- There is an increase in Tuberculosis amongst Khat users
- Khat use is also associated with low birth weight in infants, and infant survival rates
- Long-term use of Khat is found to be linked to neck cancer

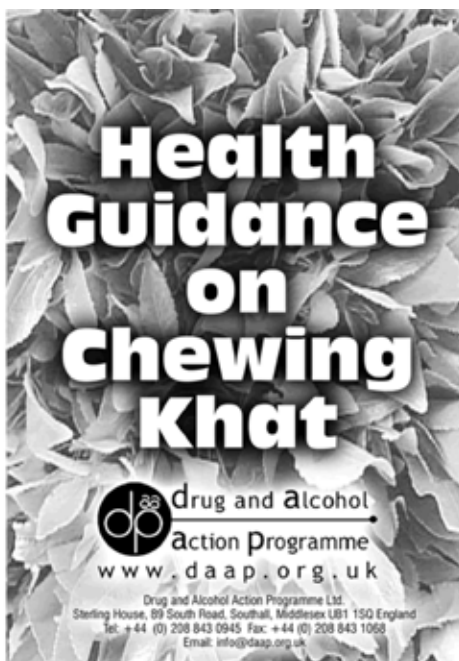


Figure 4. Warning about khat.

cancers among white-skinned populations. Protect the lips with sunscreen and a wide-brimmed hat, and when the sun is strong, spend time in the shade.

Exercise

High recreational physical activity significantly reduces head and neck cancer risks among subjects ≥45 years-old, quite apart from the wider health benefits.

HPV

HPV infection can be minimized by practising safer sex, and by HPV vaccination. HPV vaccines have been available for some years, and are administered to young people in an effort to prevent cervical cancer. The 2007 Australian HPV vaccination for women programme had, by 2011, already shown significant declines in the proportion of young women with genital warts, an absence of genital warts in vaccinated women, and large declines in genital warts in heterosexual men.

The effect of an HPV vaccine tested on 5,840 sexually active women in Costa Rica (ages 18–25 years) showed that, after 4 years, mouthwash samples in 15 women after a placebo vaccine were

infected, but only 1 woman who had received the HPV vaccine was infected with HPV.

The vaccines appear to afford protection against other HPV-related lesions, including oral lesions, but there is no hard evidence yet as to a *significant* protective effect against mouth cancer. Research is active in this area as are efforts to promote male vaccination.

There are always safety concerns about vaccines: one study of the safety and immunologic responses to an immunomodulatory HPV peptide vaccine GL-0810 (against HPV-16) showed it to be well tolerated in patients with recurrent HNSCC, with T cell and antibody responses seen in most patients.

What is secondary prevention of mouth cancer?

The treatment of early stage mouth cancers achieves higher survival rates with reduced attendant morbidity, however, many patients present with late stage disease and there is still the difficulty of reaching high-risk patient groups. Therefore, screening for potentially malignant disorders or early stage oral cancers is worth considering. However, the UK Working Group on Screening for

Oral Cancer and Precancer concluded that there was insufficient evidence to support population screening because of the relative rarity of the cancer, a lack of knowledge of the natural history, disagreement over management and the lack of evidence on the efficacy of different screening methods. Others have reached similar conclusions. An alternative strategy would be to encourage opportunistic screening of high-risk groups attending primary care services. Screening thus remains a controversial issue.

Potentially Malignant Disorders (PMD) should be monitored; NICE guidelines clearly state that patients with oral lichen planus should be monitored for oral cancer as part of the routine dental examination (*Referral Guidelines for Suspected Cancer*. Clinical Guideline 27 NICE June 2005). NICE guidelines are under consideration at present.

What is tertiary prevention of mouth cancer?

Lifestyle changes might improve survival and QoL among treated cancer patients. Smoking during radiotherapy is likely to aggravate adverse effects, and it reduces the effect of radiotherapy. Smoking cessation even after a mouth cancer diagnosis improves prognostic outcomes: cancer patients who continue to smoke during their radiotherapy have a poorer response and survival than those who claim to quit smoking prior to cancer treatment. The risk for multiple primary cancers is higher in those who continue to smoke and drink alcohol after therapy. Among patients treated for head and neck cancer, about 50% continued to smoke after one year of treatment and 30% developed a second primary tumour (compared with 13% who quit). Alcohol, especially spirits, will irritate the areas affected by treatment.

Who is responsible for health promotion for mouth cancer prevention?

Health promotion for mouth cancer prevention is the remit of the whole healthcare team, and there are a number of national (eg Mouth Cancer Week) and international initiatives (eg www.ncbi.nlm.nih.gov/pubmed/18691457), some of which have been brought

together under the umbrella of the International Consortium on Head and Neck Cancer Awareness (ICOHANCA; [www.oraloncology.com/article/S1368-8375\(07\)00174-1/abstract](http://www.oraloncology.com/article/S1368-8375(07)00174-1/abstract)) and, more recently, the Global Cancer Forum (www.globaloralcancerforum.org/) whose object is to increase cancer awareness, and lead to prevention and earlier diagnosis.

What is the wider importance of health promotion?

A healthy lifestyle is theoretically possible, involves lifestyle decisions and protects not only against many cancers, but also against several other conditions, many of which are also life-threatening (Table 7). Mouth cancer prevention strategies thus have potential for much wider health benefits.

Further reading

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