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Mouth Cancer for Clinicians Part 5: Risk Factors (Other)

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 other cancer risk factors agents, such as human papilloma viruses (HPV) and irradiation.
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The main known definitive risk factors for mouth cancer are using tobacco and drinking alcohol: it is thought that about 3 out of 4 head and neck cancers (75%) are linked to tobacco or alcohol use (Articles 3 and 4). Other risk factors include radiation (eg sunlight, ionizing) which predisposes to lip cancer, and infections such as with the human papilloma viruses (HPV), which play a role mainly in oropharyngeal cancer. Immune defects or immunosuppression underlie some cases of mouth cancer.

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What are the other cancer risk factors?

The cause of cancer in most people is still unknown but risk depends on a combination of genes, environment and aspects of our lives (Article 1). It is impossible to control some mouth cancer risk factors, such as gender and age. However, many other factors can be controlled – modifiable risk factors – and many of these relate to the lifestyle chosen. Environmental and genetic factors may play a role but are generally less important than the modifiable lifestyle risk factors. Some risk factors are definitive and others are only possible risk factors.

There appear to be several distinct pathways to mouth cancer: most cancers are related to tobacco or alcohol or betel; some are related to HPV or other infections; others to irradiation; and some to other factors.

There are also protective factors: there is benefit from a healthy immune system and from diets rich in fruit and vegetables.

Infective agents

Among young people (under the age of 45 years) with mouth cancer, up to 25% appear not to have had any exposure to the major known risk factors, such as tobacco, alcohol or betel. Other factors known to be involved in OSCC include solar irradiation in lip cancers. Immunodeficient patients may also develop oral potentially malignant and malignant neoplasms. However, besides these factors, infections such as poor oral hygiene, periodontal disease, chronic candidosis and virus infections link statistically with mouth cancer. Human papillomavirus (HPV) infection is increasingly implicated, particularly in *oropharyngeal* cancer (Table 1). HPV-related tumours tend to be seen in younger patients, in the fauces, and usually have a better prognosis.

Bacteria

Many patients with OSCC have poor oral health, with carious teeth and

Micro-organisms	Potential Carcinogenic Mechanism
Dental plaque bacteria	Induce cell proliferation, inhibit apoptosis, interfere with cellular signalling. Mutagenic interaction with saliva
Periodontal disease bacteria	Acts on inflammatory reactions and proto-oncogenes
Viridans streptococci	Convert alcohol to acetaldehyde
Candida species	Convert alcohol to acetaldehyde
Herpes simplex virus	Activates proto-oncogenes, inactivates p53 tumour suppressor gene
Human papilloma viruses	Epithelial cell immortalization Interferes with tumour suppressor genes

Table 1. Microbial agents and possible mechanisms in oral carcinogenesis.

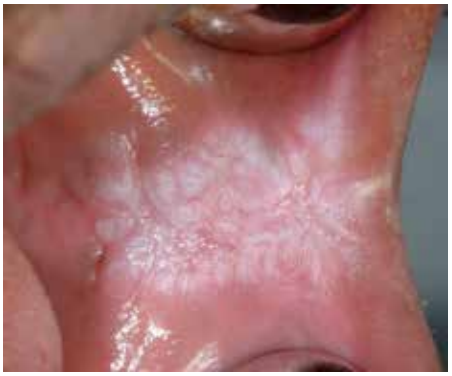

Figure 1. Candidal leukoplakia which proved to be carcinoma *in situ.*

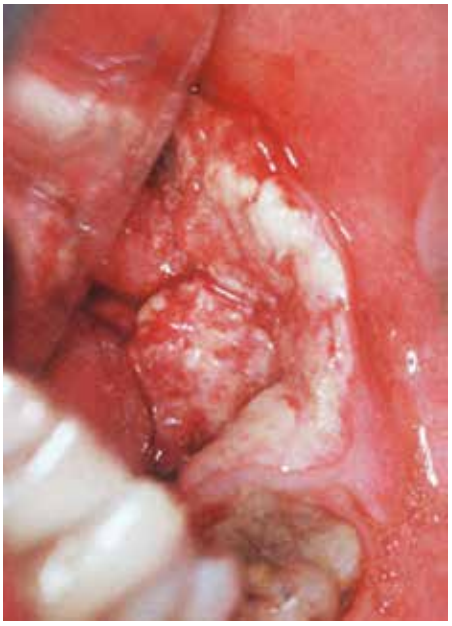

Figure 2. Oropharyngeal carcinoma.

periodontitis. Although the use of tobacco, alcohol and betel may be confounding factors which are difficult to control in epidemiological studies, periodontal disease has been shown to increase the statistical risk for cancer. One study showed that practising no regular oral hygiene conferred a risk for *oesophageal* cancer when compared with those who undertook daily toothbrushing. Another large-scale case-control study involving 856 *upper aerodigestive tract* cancer cases and 2696 age- and sex-matched controls, showed that, compared with toothbrushing once per day, the adjusted odds ratio for brushing twice or more was 0.82 (95% confidence interval: 0.68, 0.99) but for not brushing was 1.79 (0.79, 4.05), suggesting toothbrushing might protect against cancer. Patients with periodontal disease appear to be at 2.6 times the risk of *head and neck cancers*, one meta-analysis has shown. People who lose six or more teeth have at least 60% increased risk of head and neck cancer, a meta-analysis showed; the risk increasing with the number of teeth lost (Article 3 discusses mouthwashes).

Specific mouth bacteria have been suggested to play a role in carcinogenesis. Several oral bacteria can metabolize alcohol to the carcinogenic product acetaldehyde, possibly explaining any association between poor oral hygiene, alcohol consumption and carcinogenesis. *Streptococcus anginosus* and *Treponema denticola* have been linked with various upper gastro-intestinal tract carcinomas. In the past, syphilis has been mentioned to be associated with cancer but there may have been confounding factors, such as other infections, tobacco and/or alcohol.

Fungi

Yeasts may be causally involved in oral leukoplakia and dysplastic changes (Figure 1): candidal leukoplakias have been estimated to develop into carcinomas in up to 40% of cases. *Candida albicans* is the common yeast but increasing numbers of non-albicans *Candida* are seen in OSCC patients. Nitrosamine compounds can be produced by *Candida*, and the yeast can also convert alcohol into acetaldehyde.

Patients with congenital chronic candidosis may also be predisposed to OSCC, but this might be because they are also immunocompromised.

Viruses

Epstein-Barr virus (EBV) is a herpesvirus associated with *nasopharyngeal* carcinomas, and lymphomas. EBV infection is found in 90% of nasopharyngeal cancer cases in the UK. IARC recognizes EBV as a cause of nasopharyngeal cancer. Studies in OSCC have generally not implicated EBV.

Herpes simplex viruses (HSV) have been associated with lip carcinoma, but interest in this virus has been submerged by that in HPV. These infections, the most common sexually shared infections, are now implicated mainly in oropharyngeal carcinoma (Figure 2). There are more than 100 different types of HPV. Some HPV types are called the wart virus, because they cause warts on the genital area or skin or mouth, most of which are benign.

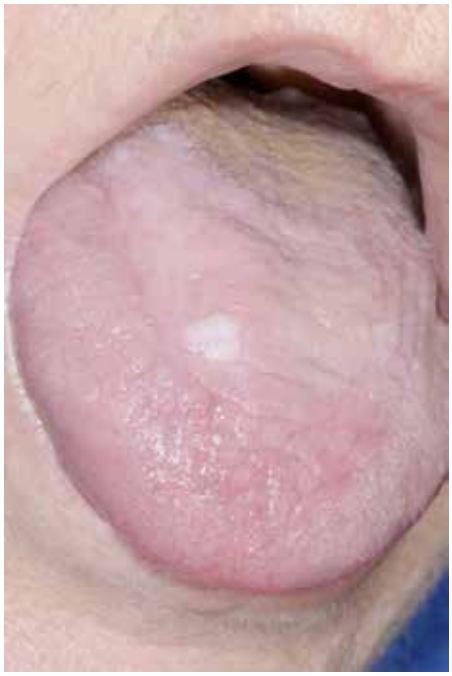

Figure 3. Leukoplakia in a boy with dyskeratosis congenita.

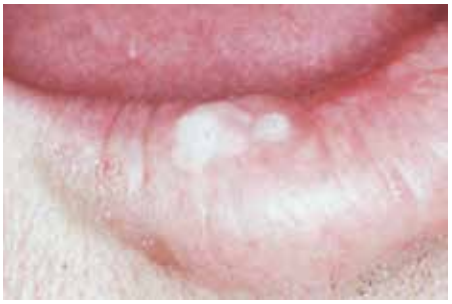

Figure 4. Early carcinoma on the lower lip in actinic cheilitis (solar cheilosis).

HPV-6, -11, -16, -18, -31, -33 and -42 have been isolated from the mouth and HPV infection may be latent in 12% of subjects with clinically healthy oral mucosa. HPVs-16, -18, -31, -33 and -42 are 'high- risk' (cancer-promoting or oncogenic) viruses, implicated also in anogenital cancers. HPVs can be transmitted by close contact between skin and/or mucosae, and risk factors for HPV infection include:

- Early onset of sexual activity;
- Multiple sexual partners;
- Unknown sexual partners;
- High-risk sexual behaviour;
- Lack of condom use.

Most sexually-active adults will be infected with at least one type of HPV at some time during their life. Tobacco and marijuana smoking also increase the risk of HPV infection in the mouth. HPV infection of the mouth is more common in men than in women.

Figure 5. Fruits may confer some cancer protection.

Most sexually active adults become infected with high-risk HPV types, such as HPV-16 and HPV-18 at some stage, but most patients (90%) clear the HPV infection spontaneously within 1–2 years. For example, in one study of 1626 males in Brazil, Mexico and USA, after 1 year:

- 4·4% had acquired incident oral HPV infection;
- 1·7% acquired oral oncogenic HPV infection.

However, new oral oncogenic HPV infections were rare and most cleared spontaneously (presumably via immune defences) within 1 year. Thus in many people HPV causes little or no harm and clears spontaneously without treatment and only a small percentage of people with HPV infection develop oropharyngeal cancer. HPVs may also play a role in some anogenital cancers, including cancers of the:

- Anus;
- Cervix;
- Penis;
- Vagina;
- Vulva.

HPV infection appears to cause all cervical cancers, most (~88%) anal cancers, and a subset of vaginal (70%), penile (50%), and vulvar (43%) cancers.

Mouth cancer is also increased in:

- Patients with anogenital cancer;
- Patients with cervical cancer;
- Partners of women with cervical cancer.

Anal, genital and skin cancers are also increased in patients with mouth cancer.

HPV of all types can thus be transmitted between the mouth and anogenital region, and there are associations demonstrated between oral and oropharyngeal, and anogenital cancers. The risk of HPV infection in the mouth and throat is linked to certain sexual behaviours, such as open mouth kissing and oral sex.

Risk factors for oropharyngeal cancer include a high lifetime number of oral-sex partners (6 or more) or vaginal-sex partners (26 +). People with a higher number of past sex partners (particularly oral sex partners), or who started having sex at a younger age, have an increased risk of oropharyngeal cancer (OPC), tonsil and base of tongue cancers.

The oropharyngeal cancer HPV prevalence rate appears to have increased over time, reaching over 70% in data from 2005 onwards. HPV-associated cancers are increasing in USA, Canada, several European countries, including Denmark and Sweden and Australia and now, 70% of OPCs are caused by HPV. It has been estimated that, by 2020, OPCs will exceed cervical cancer.

IARC now classifies HPV-16 as a cause of oral cavity, tonsil and pharynx cancers, and HPV-18 as a probable cause of oral cancer. HPV infection causes around 8% of mouth cancers and around 14% of oropharyngeal cancers in the UK. Around 4 in 10 (40%) oropharyngeal cancer cases in Europe are HPV-positive.

HPV-associated oropharyngeal cancers are associated with:

- HPV-16 (90%) but also HPVs -18, -31, -33. HPVs which are also associated with anogenital cancers;
- Marijuana use, but the tumours are not linked to alcohol, tobacco or betel use or poor oral health status. HPV-positive oropharyngeal cancers are associated with oral sex and marijuana use, while HPV-negative tumours are associated with tobacco use, alcohol use and poor dental status;
- HPV oncogenic genes E6/E7 mRNA and the cell cycle brake p16ink4a; P16 tumour suppressor gene overexpression (p16 is an inhibitor of cyclin-dependent kinases 4 and 6 which activate the negative cell cycle regulator protein pRB) (Article 1); specific alterations in FGFR3 and PIK3CA genes; these may also be present in a wider set of faults found in

smoking-related tumours and TGF beta genetic variations, especially T869C, in some (Article 1);
- Epidermal growth factor receptor (EGFR) gene defects rarely, despite these often being altered in HPV-negative tumours;
- Better prognosis than in HPV-negative cancers;
- Less risk of second primary tumours (SPTs).

Oropharyngeal cancer can thus be categorized as HPV-driven and non HPV-driven cancers. The former is a distinct type, with HPV DNA present in the tumour nuclei and fewer mutations compared to the latter, smoking and alcohol-related oropharyngeal cancer. High-risk (oncogenic) HPV subtypes, including HPV-16, -18, -31 and -33, have been identified in a significant fraction of oropharyngeal tumours.

HPV status has implications in the diagnosis and management of patients with oropharyngeal cancer, so the HPV status is determined routinely in patients in some centres. The most widely used methods for assessing HPV integration are *in situ* hybridization using specific primers (mainly for HPV-16) and immunostaining for p16ink4a (Article 1). Staining of tumour cells with some p16ink4a antibodies is a surrogate marker of HPV function. Polymerase chain reaction (PCR) testing combined with immunohistochemistry detection of p16 is frequently used diagnostically.

What are the other possible mouth cancer risk factors?

Other possible risk factors for mouth cancer for which there is often not enough evidence for them to be classed as definite risk factors include:
- Diseases:
  - -Chronic candidosis
  - -Diabetes
  - -Discoid lupus erythematosus
  - -HIV/AIDS
  - -Plummer-Vinson syndrome
  - -Primary carcinomas in the upper aerodigestive tract
  - -Scleroderma
  - -Some other cancers
- Genetic causes:
  - -Dyskeratosis congenita
  - -Fanconi anaemia
  - -Li Fraumeni syndrome
  - -Xeroderma pigmentosum
- Socioeconomic deprivation
- Iatrogenic causes:
  - -DXR (radiotherapy)
- Medications:
  - -Anti-hypertensives
  - -Immunosuppressives
  - -Marijuana
- Poor oral hygiene
- Dietary defects.

Diseases

Women have a higher risk of a second oral cancer than men. People who have had mouth or oropharyngeal cancer have an increased risk of getting a second primary tumour (SPT), mainly in the upper aerodigestive tract. People who have had some other types of cancer also have an increased risk of mouth cancer, including:
- Ano-rectal cancer in men;
- Cervical, anal or genital cancer in women;
- Lung cancer;
- Oesophageal cancer;
- Skin squamous cell cancer.

Oral potentially malignant disorders (Article 6) may develop into cancer over some years. Other conditions in which there may be increased mouth cancer include:
- Chronic candidosis;
- Diabetes;
- Discoid lupus erythematosus;
- HIV/AIDS;
- Plummer-Vinson syndrome;
- Scleroderma.

Genetic causes

There are a few familial cases, some of which may be inherited, others environmental or due to exposure to common risk factors. There may be a higher risk of developing a head and neck cancer if a close relative (a parent, brother, sister or child) has had head and neck cancer. A family history of oral and pharyngeal cancer and laryngeal cancer is a strong determinant of oral and pharyngeal cancer risk, independent of tobacco and alcohol use. One study found a 3.3-fold increased risk of developing oral and pharyngeal cancer among people who had a first-degree relative with cancer of the larynx, and a four-fold increased risk of oesophageal cancer where a first-degree relative had oral or pharyngeal cancer. A family history of head and neck cancer, particularly in a sibling, may be associated with almost doubling (70% increase) the risk of head and neck cancer.

Mechanisms are unclear (Article 1) but, for example, protective mechanisms that may fail and predispose to cancer include genes for enzymes that degrade carcinogens (cancer-causing chemicals); genes that repair DNA mutations; genes that repair damaged cells or kill cancerous cells by apoptosis or controlled cell death (tumour suppressor genes; TSGs); and genes for immune defences. Some other genes (oncogenes) also predispose to cancer. Tumour suppressor genes are now thought of as either gatekeeper or caretaker genes, according to whether they control cell growth directly by inhibiting cell proliferation and/or promoting cell death (gatekeepers) or whether, by DNA repair, they maintain genome integrity (caretakers).

Genetics occasionally has a proven notable role in cancer predisposition. In rare inherited disorders, such as ataxia telangiectasia, Bloom syndrome, dyskeratosis congenita, Fanconi anaemia and xeroderma pigmentosum, caretaker genes are defective, and there is an increase in primary malignancies, including mouth cancer. The relevant rare inherited syndromes include mainly:
- *Dyskeratosis congenita* – a genetic syndrome of aplastic anaemia, rashes, abnormal nails and a high risk of developing oral leukoplakia (Figure 3), and cancer of the mouth and throat when young. In about half of those with dyskeratosis congenita, mutations are found in genes (TERT, TERC, DKC1 or TINF2) that make proteins that help maintain telomeres (Article 1). Telomeres protect chromosomes from abnormally sticking together or degrading; telomeres become progressively shorter as the cell divides and, after a number of cell divisions, telomeres usually become so short that they trigger the cell to stop dividing or cause it to self-destruct (undergo apoptosis).
- *Fanconi anaemia* – a genetic disorder that can cause short stature and bone changes, and increase the risk

of developing cancers, leukaemia and aplastic anaemia.
- *Xeroderma pigmentosum* – a genetic disorder of DNA repair which predisposes mainly to skin and lip cancer on exposure to the sun.

By contrast, with the exception of Li Fraumeni syndrome, abnormalities of many gatekeeper genes (p53 mutation, MDM2 over-expression, CDKN2A deletion) appear rarely to predispose to mouth cancer. People with mouth cancer also have an increase of gene polymorphism expression related to inflammation (NFKB1-294-ATTG, TNFα308-A2A2/A2A1 and TNFβ252- B2B2/B2B1) or carcinogen metabolism (GSTM1 null and CYP1A1 m1/m1). Furthermore, the increased expression of genes associated with the stabilization and repair of the cellular damage, and genes associated with the regulation of proliferation, apoptosis or tumour survival (miRNA499-CT/CC, CRYABC802G-CG/GG) are considered as risk factors.

Socio-economic deprivation

Socio-economic deprivation has been linked to an increased risk of mouth cancer, but many other explanations (eg habits, oral health, diet, nutrition) should be excluded. As the definitive risk factors for mouth cancer in the UK are tobacco smoking and excessive alcohol consumption and, in some cultures, betel chewing, plus there may be dietary and other influences, it is not surprising that cancer incidence is associated with socio-economic deprivation when these habits are commonplace.

England-wide data for 2000–2004 showed European AS incidence rates for head and neck cancer (ICD-10 C00-C14, C30-C32) around 130% higher (more than double) for men from more deprived areas compared with the least deprived, and more than 74% higher for women. Similar results have been shown for Northern Ireland, Wales and Scotland. A study in Scotland for 2005–2009 showed a slightly larger deprivation gap.

Iatrogenic causes

Irradiation

There is an increased risk of mouth cancer following a previous cancer diagnosis. This is possibly due to a combination of shared aetiological factors (eg smoking or HPV) and the effect of radiotherapy for the first cancer. People with a previous head and neck cancer (including tongue, mouth, pharynx and larynx) have between a 12- and 16-fold increased risk of subsequent head and neck cancer. Survivors of oesophageal squamous cell carcinoma have an almost seven-fold increase in risk of mouth and pharynx cancers. People with a previous lung cancer have between 1.5 and 5.7 times the general population risk of developing head and neck cancer.

Lip cancer is seen largely on the lower lip in male Caucasians chronically exposed to actinic radiation from sun exposure, especially smokers (Article 3 and Figure 4). This group is also predisposed to basal cell carcinomas (rodent ulcers) on the face, head and neck, and other chronically sun-exposed areas.

Medications

Anti-hypertensives

The role of antihypertensive drugs in new cancer occurrence and cancer-related death has been raised since a meta-analysis raised the possibility that angiotensin receptor blockers (ARBs) might be implicated, but two further meta-analyses failed to demonstrate any increased risk of new cancer occurrence or cancer-related deaths from ARBs.

A US cohort study showed Caucasians who were taking the anti-hypertensive hydrochlorothiazide for five or more years had a four-fold increased risk of lip cancer. IARC classifies hydrochlorothiazide as a probable cause of lip cancer but further evidence is awaited. Hydrochlorothiazide is a photosensitizing drug that enhances UVA-induced DNA damage, so should be used with caution in xeroderma pigmentosum.

Immunosuppressives

Research has found that people have an increased risk of mouth cancer if they have a reduced immunity due to taking agents to suppress immunity. Several large cohort studies and a meta-analysis have shown that organ transplant patients have a 17–46 times increased risk of lip cancer and 2–5 times increased risk of mouth and pharyngeal cancers, compared with the general population. Lip cancer risk is particularly raised in kidney, heart or lung transplants, possibly due to persistent HPV infection and increased sensitivity to UV radiation.

Marijuana (Article 3).

Oral hygiene (see 'Bacteria' earlier in this article)

Diet (see also below)

A diet high in animal fats and low in fresh fruit and vegetables may increase the risk of head and neck cancer. This may be due to a lack of zinc, or other vitamins and minerals. Vitamin A deficiency increases the risk of developing cancer of the mouth and oropharynx. Poor diets and eating patterns are common in people who drink excess alcohol, which may help explain why alcohol increases the risk of some cancers.

Some types of salted fish that may be eaten as part of a Chinese diet can increase the risk of *nasopharyngeal* cancer.

Immune defects

HIV/AIDS

Since the onset of the HIV epidemic, there have been many case reports of mouth cancer in people with HIV/AIDS. Meta-analyses have shown that people with HIV/AIDS have around double the risk of mouth, oropharyngeal and pharyngeal cancers, compared with the general population. There is a positive association between HIV and HPV infection, which might be relevant.

What factors may reduce mouth cancer risk?

Diet

People with the highest fruit intake have around half the risk of head and neck cancer and each portion of fruit consumed per day approximately halves the risk of oral cancer, as does each portion of vegetables (Figure 5). One study from the USA showed an inverse association between total fruit and vegetable intake and incidence of head and neck cancer. The Mediterranean diet has been shown to be particularly associated with a reduced oral and pharyngeal cancer risk.

A significant protective effect of diet against mouth cancer has generally been shown in people who consume beta-carotene–rich vegetables and citric fruits: this may be because these foods contain antioxidants, vitamins and other substances. People who have ever used vitamin C supplements have a 24% reduced risk of head and neck cancer, and ever users of calcium supplements have a 36% reduced risk, but a Cochrane review concluded the evidence to be conflicting and insufficient. World Cancer Research Fund/American Institute For Cancer Research (WCRF/AICR) classifies the consumption of non-starchy vegetables and fruits (not salted or pickled), and foods containing carotenoids, as possibly protective against mouth, pharynx and larynx cancers.

There is an inverse association between caffeinated coffee drinking and risk of mouth and pharynx cancer: people who drink one cup of caffeinated coffee each day have a 4% lower risk compared with non-drinkers, and those who drink more than four cups daily have a 39% risk decrease.

Tea and decaffeinated coffee do not appear to be associated with oral cancer risk. A systematic review on green tea consumption of all prospective, controlled interventional studies to date and observational studies showed insufficient and conflicting evidence on any possible cancer prevention by tea.

Drugs

There is interest in possible cancer protection by aspirin and other Cyclo-OXygenase (COX) enzyme inhibitors; so evidence is awaited.

Exercise, height and body weight

Recreational physical activity appears associated with a 26–47% reduction in mouth cancer risk, and a 33–42% reduction in pharyngeal cancer risk. The beneficial effects of recreational physical activity seems most in males, people aged 45 or younger, and ever-smokers and ever-drinkers.

Head and neck cancer risk is 9% lower per 10 cm increase in height for men, and 14% lower per 10 cm height for women.

A meta-analysis of case-control studies found that overweight and obese people had under half the risk of mouth cancer, compared with healthy-weight people, and underweight people had more than double the risk but a prospective cohort study found no association between body mass index and risk of mouth, oropharynx or hypopharynx cancers.

Further reading

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