

Head and neck cancer—Part 1: Epidemiology, presentation, and prevention

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Head and neck cancers include cancers of the upper aerodigestive tract (including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), the paranasal sinuses, and the salivary glands. Cancers at different sites have different courses and variable histopathological types, although squamous cell carcinoma is by far the most common. The anatomical sites affected are important for functions such as speech, swallowing, taste, and smell, so the cancers and their treatments may have considerable functional sequelae with subsequent impairment of quality of life. Decisions about treatment are usually complex, and they must balance efficacy of treatment and likelihood of survival, with potential functional and quality of life outcomes. Patients and their carers need considerable support during and after treatment.

In this first part of a two article series, we review the common presentations of head and neck cancer. We also discuss common investigations and new diagnostic techniques, as well as briefly touching on screening and prevention. In this review, we have used evidence from national

SOURCES AND SELECTION CRITERIA

We used the terms “head and neck”, “larynx”, “oral”, and “oropharynx”—with each limited by “cancer”, “diagnosis”, and “treatment” separately—to search the Medline, Embase, PubMed, Cochrane, CINAHL, and AMED databases. We also used them to cross check national guidelines, reference lists, textbooks, and personal reference lists. We assessed over 1000 identified abstracts for relevance.

guidelines, randomised trials, and level II-III studies. We have limited our discussions to squamous cell carcinoma of the head and neck, which constitutes more than 85% of head and neck cancers.

How common is head and neck cancer and who gets it?

Cancer of the mouth and oropharynx is the 10th most common cancer worldwide, but it is the seventh most common cause of cancer induced mortality.¹

In 2002, the World Health Organization estimated that there were 600 000 new cases of head and neck cancer and 300 000 deaths each year worldwide, with the most common sites being the oral cavity (389 000 cases a year), the larynx (160 000), and the pharynx (65 000).² The male to female ratio reported by large scale epidemiological studies and national cancer registries varies from 2:1 to 15:1 depending on the site of disease.^{w1} The incidence of cancers of the head and neck increases with age. In Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively.^{w2}

What regions have the highest incidence?

A high incidence of head and neck cancer is seen in the Indian subcontinent, Australia, France, Brazil, and Southern Africa (table). Nasopharyngeal cancer is largely restricted to southern China. The incidence of oral, laryngeal, and other smoking related cancers is declining in North America and western Europe, primarily because of decreased exposure to carcinogens, especially tobacco.² In contrast, because of the 40 year temporal gap between changes in population tobacco use and its epidemiological effects, the worst of the tobacco epidemic has yet to materialise in developing countries. WHO projections estimate worldwide mortality figures from mouth and oropharyngeal cancer in 2008 to be 371 000. This is projected to rise to 595 000 in 2030 because of a predicted rise in mortality in South East Asia (182 000 in 2008 to 324 000 in 2030).

SUMMARY POINTS

The incidence of head and neck cancer is relatively low in developed countries and highest in South East Asia

The main risk factors are smoking and heavy alcohol consumption

Incidence of human papillomavirus related oropharyngeal carcinoma is rising rapidly in developed countries and is easily missed. It has a different presentation and better prognosis than other head and neck cancers

Patients with head and neck cancer often present with hoarseness, throat pain, tongue ulcers, or a painless neck lump, and symptoms for longer than three weeks' duration should prompt urgent referral

No strong evidence supports visual examination or other screening methods in the general population

Box 1 | “Red flag” symptoms and signs of head and neck cancer¹²

Any of the following lasting for more than three weeks

Symptoms

Sore throat

Hoarseness

Stridor

Difficulty in swallowing

Lump in neck

Unilateral ear pain

Signs

Red or white patch in the mouth

Oral ulceration, swelling, or loose tooth

Lateral neck mass

Rapidly growing thyroid mass

Cranial nerve palsy

Orbital mass

Unilateral ear effusion

Data for head and neck cancers in 2004 in WHO regions*

	Africa	The Americas [†]	Eastern Mediterranean	Europe	South East Asia	Western Pacific
Population	737 536	874 380	519 688	883 311	1 671 904	1 738 457
Incidence	30	38	29	72	195	74
Mortality	22	25	22	51	158	56

*Numbers should be multiplied by 1000.

[†]North America, South America, and Canada.

Genetic factors

Most people who smoke and drink do not develop head and neck cancer, however, and a genetic predisposition has been shown to be important. The International Head And Neck Cancer Epidemiology Consortium (INHANCE) carried out pooled analyses of epidemiological studies that examined risks associated with the disease.⁷ This work confirmed the role of genetic predisposition that had been suggested by small studies. A family history of head and neck cancer in a first degree relative is associated with a 1.7-fold (1.2 to 2.3) increased risk of developing the disease.⁷ Genetic polymorphisms in genes encoding enzymes involved in the metabolism of tobacco and alcohol have been linked with an increased risk of the disease. For example, a meta-analysis of 30 studies showed that a polymorphism in *GSTM1*, which encodes a protein involved in the metabolism of xenobiotics (glutathione S transferase), was associated with a 1.23 (1.06 to 1.42) increased risk of developing head and neck cancer.^{w5}

Viral infection

Viral infection is a recognised risk factor for cancer of the head and neck. The association between Epstein-Barr virus infection and the development of nasopharyngeal cancer was first recognised in 1966.^{w6} More recently, HPV has attracted attention.⁴ Recent observational studies have found that this virus is a strong risk factor for the development of head and neck cancer, especially oropharyngeal cancer (63, 14 to 480), and they suggest that HPV infection—especially infection with HPV subtype 16 (HPV-16)—is an aetiological factor.^{10 w7} The disease is thought to be sexually transmitted. A pooled analysis of eight multinational observational studies that compared 5642 cases of head and neck cancer with 6069 controls found that the risk of developing oropharyngeal carcinoma was associated with a history of six or more lifetime sexual partners (1.25, 1.01 to 1.54), four or more lifetime oral sex partners (3.36, 1.32 to 8.53), and—for men—an earlier age at first sexual intercourse (2.36, 1.37 to 5.05).¹¹

HPV related oropharyngeal carcinoma is a distinct disease entity. Patients are younger (usually 40-50 years old), often do not report the usual risk factors of smoking or high alcohol intake, and often present with a small primary tumour and large neck nodes. This may lead to delayed diagnosis.

Other risk factors

Other risk factors identified from pooled analyses of case-control studies include sex (men are more likely to have head and neck cancer than women),⁷ a long duration of passive smoking (odds ratio for >15 years at home: 1.60, 1.12 to 2.28),⁷ low body mass index (odds ratio for body mass index 18: 2.13, 1.75 to 2.58),^{w8} and sexual behaviour (for example, odds ratio for cancer of the base of tongue in men with a history of same sex sexual contact: 8.89, 2.14 to 36.8).¹¹ Some evidence points to a role of occupational exposure, poor dental hygiene, and dietary factors, such as low fruit and vegetable intake.^{w9}

How does head and neck cancer present?

Patients with head and neck cancers present with a variety of symptoms, depending on the function of the site where

Box 2 | Presentations where cancer might easily be missed

Persistently enlarged neck nodes in younger patients (30-50 years)

These are often human papillomavirus related tumours. Patients often do not have the usual risk factors for head and neck cancer—they are often non-smokers and do not drink alcohol heavily. Tumours are often small or occult within normal looking tonsils. Because of the patient's young age, absence of risk factors, and unusual presentation, the problem might be confused with benign reactive nodal enlargement and the diagnosis delayed.

Persistent unilateral otalgia with no signs of ear infection in patients over 30

Patients with this problem should also be considered for early referral to a head and neck surgeon who can do a full examination of the upper aerodigestive tract with a flexible nasolaryngoscope to exclude pharyngeal and postnasal space tumours.

Recent onset wheeze in a patient over 40, usually a heavy smoker

The "wheeze" is in fact a mild biphasic stridor mistaken for wheeze and the patient, who may also have breathlessness, may be misdiagnosed as having sequelae of chronic obstructive airway disease or late onset asthma and may be treated as such. This presentation, however, may be that of a slow growing laryngeal carcinoma. Clinicians should consider this diagnosis in patients with late onset wheeze or asthma that does not respond to drugs in patients who smoke or give a history of heavy alcohol intake.

Modest rises are predicted in Africa, the Americas, and the Middle East, whereas mortality in Europe is expected to remain stable.³

Several retrospective analyses of samples collected from patients recruited in randomised trials, as well as retrospective patient series, have shown recent changes in epidemiology and pathogenesis of head and neck cancers related to the human papillomavirus (HPV), especially oropharyngeal carcinoma. A rapid rise in HPV related oropharyngeal cancers in particular has been shown in epidemiological studies from the developed world.⁴ For example, the United Kingdom has seen a doubling in the incidence of oropharyngeal cancer (from 1/100 000 population to 2.3/100 000) in just over a decade.⁵ A recent retrospective study showed a progressive proportional increase in the detection of HPV in oropharyngeal squamous cell carcinomas in Stockholm over the past three decades: 23% in the 1970s, 29% in 1980s, 57% in 1990s, 68% between 2000 and 2002, 77% between 2003 and 2005, and 93% between 2006 and 2007.⁶ Other prospective studies, such as ones from the United States, have also reported proportional increases.

What are the risk factors for head and neck cancer?

Tobacco and alcohol

The major risk factors are tobacco (smoking and smokeless products such as betel quid) and alcohol. They account for about 75% of cases, and their effects are multiplicative when combined.^{7 w3} Smoking is more strongly associated with laryngeal cancer and alcohol consumption with cancers of the pharynx and oral cavity.^{w4} Pooled analyses of 15 case-control studies showed that non-smokers who have three or more alcoholic drinks (beer or spirits) a day have double the risk of developing the disease compared with non-drinkers (odds ratio 2.04, 95% confidence interval 1.29 to 3.21).^{8 9}

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Previous articles in this series

- ▶ Diagnosis and management of Barrett's oesophagus (BMJ 2010;341:c4551)
- ▶ Managing anaemia in critically ill adults (BMJ 2010;341:c4551)
- ▶ Managing gastro-oesophageal reflux in infants (BMJ 2010;341:c4420)
- ▶ Evaluating the child who presents with an acute limp (BMJ 2010;341:c4250)
- ▶ A guide to imaging for common neurological problems (BMJ 2010;341:c4113)

Box 3 | Investigations used for head and neck cancer**Imaging**

Computed tomography scanning from the skull base to the diaphragm is the first line investigation to assess nodal metastasis and identify the primary tumour site and tumour size

Magnetic resonance imaging is indicated for:

- Oral cavity and oropharyngeal tumours; it provides better information than because of the absence of interference from dental amalgam and the better delineation of soft tissue extension
- Cases where extension through the laryngeal cartilage is suspected but cannot be conclusively determined on computed tomography

Ultrasound guided fine needle aspiration performed by experienced practitioners is highly accurate and used by some centres to diagnose nodal metastasis and determine its distribution¹⁴

Positron emission tomography-computed tomography scanning is used to investigate occult primary and distant metastases in some cases

Sentinel node biopsy is used to detect nodal metastases in cases with a high risk of occult metastasis. A radioactive tracer with blue dye is injected into the lesion, often a mouth cancer, and under general anaesthesia a Geiger counter locates the node with highest radioactivity, which is removed. If the node contains tumour, the patient undergoes neck dissection

Histological confirmation of diagnosis

Examination under anaesthetic and biopsy allows assessment of the size and extent of the primary tumour

Fine needle aspiration or core biopsy, often under ultrasound guidance, can provide cytological evidence of nodal metastasis¹⁴

2 describes unusual clinical scenarios in which clinicians may miss a diagnosis of cancer.

How are suspicious lesions investigated?

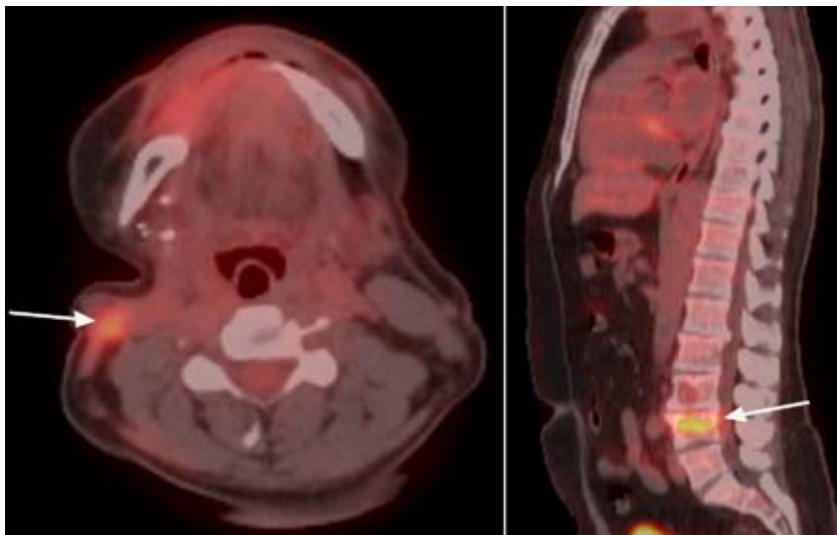
A recent *BMJ* clinical review discussed the investigation of oral lesions in detail.¹³ Examination of any lesion of the head or neck should include palpation of the entire neck for lymph nodes, and examination of the scalp and the whole oral cavity, including tongue, floor of mouth, buccal mucosa, and tonsils. Dentures should be removed before examination. The nose and ears should also be examined, especially if no other abnormalities are found. Flexible nasolaryngoscopy allows proper examination of the nasal cavities, postnasal space, base of the tongue, larynx, and hypopharynx. Box 3 summarises the investigations that are performed in specialist care.

Diagnosis of the cancer is confirmed on histology of the biopsy from the primary site. The new technique of fusion positron emission tomography-computerised tomography has become one of the most important diagnostic tools for head and neck cancers. It combines normal computed tomography scanning with functional imaging using 18F-fluorodeoxyglucose (18F-FDG), which is taken up preferentially by cells with high metabolic activity, especially cancer cells (fig). This technique can therefore help identify occult primary tumours, which are relatively common and not detected by examination and conventional imaging. The technique may also have a role in the assessment of persistent nodal disease after treatment, and in the monitoring and follow-up of patients with head and neck cancer in the longer term, but sufficient evidence to support this is not yet available.¹⁵

To prove that a tumour is caused by HPV, virus specific DNA must be identified within the tumour and it must be shown that it has undergone transcription. HPV DNA can be demonstrated by polymerase chain reaction or in situ hybridisation. Transcription can be demonstrated by using immunohistochemistry to identify expression of p16, a downstream product of HPV DNA transcription.¹⁶

Can we screen for head and neck cancer?

Data are available for oral cancer screening only. It is unclear whether treating premalignant lesions can prevent the occurrence of invasive cancer.^{w11} A Cochrane review of randomised controlled trials of screening for oral cancer or precursor oral lesions found no strong evidence to support visual examination or other methods of screening for oral cancer in the general population.¹⁷ The sensitivity of visual examination of the mouth for detecting oral precancerous and cancerous lesions varies from 58% to 94% and the specificity from 76% to 98%. These figures may be even lower for areas affected by HPV related oropharyngeal cancer, such as the tonsil and base of tongue, which are less accessible. Randomised studies in areas of high incidence have suggested that opportunistic visual screening of high risk groups may reduce mortality.¹⁸ In special groups such as patients with Fanconi's anaemia, who have a higher lifetime risk of developing head and neck cancer, it is recommended that everyone over the age of 10 is screened every four months.¹⁹



Positron emission tomography-computed tomography scans showing: left, recurrence in neck (arrow) in a patient who had previously undergone a neck dissection and chemoradiotherapy; and right, 53 year old man with adenoid cystic carcinoma of the parotid gland showing spinal metastases in the fourth lumbar vertebra

they originate. Laryngeal cancers commonly present with hoarseness, whereas pharyngeal cancers often present late with dysphagia or sore throat. Many often present with a painless neck node. Patients with head and neck cancer can present with non-specific symptoms or symptoms commonly associated with benign conditions, however, such as sore throat or ear pain.^{w10} Box 1 lists “red flag symptoms” that practice guidelines consider to warrant urgent referral and consultation with a specialist head and neck clinician. UK guidelines specify that urgent referral should mean that patients are seen within two weeks.¹² Head and neck centres often run a dedicated clinic—a neck lump clinic—to diagnose such patients. Box

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

WHO. The global burden of disease: 2004 update. 2008. www.who.int/evidence/bod
 National Cancer Comprehensive Network (www.nccn.org/index.asp)—Guidelines on treatment of cancers including head and neck in US
 Scottish Intercollegiate Guidelines Network. Diagnosis and management of head and neck cancer guidelines. Guideline no 90. 2006. www.sign.ac.uk/guidelines/fulltext/90/index.html
 National Institute for Health and Clinical Excellence. Improving outcomes in head and neck cancers—the manual. 2004. <http://guidance.nice.org.uk/csgn/guidance/pdf/English>
 Fanconi Anaemia Clinical Network. Clinical standards of care in the UK. www.fanconi.org.uk/clinical-network/standards-of-care/

Resources for patients and carers

Cancer Research UK (www.cancerresearchuk.org)—National site that covers all cancers; very easy to navigate with lots of information
 Macmillan (www.macmillan.org.uk)—National site that covers all cancers; easy to navigate; need to type larynx into the search engine
 Merseyside Head and Neck Cancer Centre (www.headandneckcancer.co.uk)—Suitable for patients and carers in any part of the country, easy to navigate, very clear language and format
 Get A-Head (<http://www.getahead.org.uk>)—Easy to navigate, suitable for patients and carers in any part of the country, very informative; click on “patient info” then “helpful information”
 National Association of Laryngectomy Clubs (www.laryngectomy.org.uk)—Patient organised site with a wide selection of information for patients and professionals; hard copies are free on request
 Guidelines and Audit Implementation Network (<http://www.gain-ni.org>)—Informal learning course of six modules



This week's cover image of Henry reproduced with permission of the charity Saving Faces.

Henry underwent several operations culminating in the removal of all his right upper jaw and maxillary sinus for what was thought to be a benign tumour. In fact it was a malignant bone tumour (osteosarcoma). He sought treatment from Iain Hutchison, chief executive of Saving Faces, but was advised that because of the position of the tumour an unacceptable amount of his face would need to be excised to achieve its total removal. The affected area was built up using rib to reconstruct the underlying facial architecture, latissimus dorsi muscle from the back to seal the space between the brain and the mouth, and skin from the back to replace lost skin. The tumour recurred five years later on the left side of his upper jaw, and Henry's left upper jaw, sinus and nasal support were removed. No surgical reconstruction was carried out, but he wore a large denture (obturator) to fill the space.

Can head and neck cancer be prevented?

Prevention of head and neck cancer is closely linked to the success of tobacco control programmes. After pooling more than 50 000 sets of individual level data from case-control studies, INHANCE estimated that quitting tobacco smoking for one to four years reduces the risk of developing head and neck cancer (0.70, 0.61 to 0.81 compared with current smoking), with further risk reduction at 20 years or more (0.23, 0.18 to 0.31), at which time risk is similar to that of never smokers.⁵ For alcohol use, a beneficial effect was seen only after 20 years or more of quitting (0.60, 0.40 to 0.89 compared with current drinking).²⁰

HPV related oropharyngeal cancer may theoretically be prevented by vaccination against HPV-16, although no strong evidence is available to support this. Currently, most national HPV vaccination programmes include only girls, because several health economics assessments did not support the cost effectiveness of including boys.²¹ However the rapid increase in HPV related oropharyngeal cancer has led some health professionals to call for a reassessment of the cost effectiveness of including boys in such programmes.⁴

TIPS FOR NON-SPECIALISTS

- Refer any patient with hoarseness, stridor, swallowing problem, unilateral ear pain, lump in the neck, red or white patch or ulceration in the mouth, cranial nerve palsy, or orbital masses, to a specialist urgently
- Patterns of presentation of head and neck cancer are changing, possibly because of a rise in human papillomavirus related cancers. Patients may present at younger age—30–50—with an isolated neck lump and may not give a history of smoking or heavy alcohol consumption

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