1 Epidemiology, risk factors and pathogenesis of squamous cell tumours

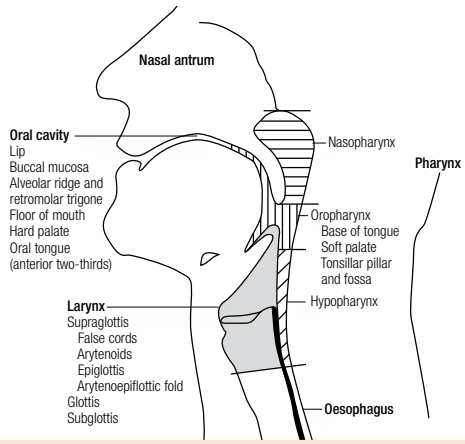
Epidemiology

Head and neck squamous cell carcinoma (HNSCC) encompasses a variety of tumours originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx.

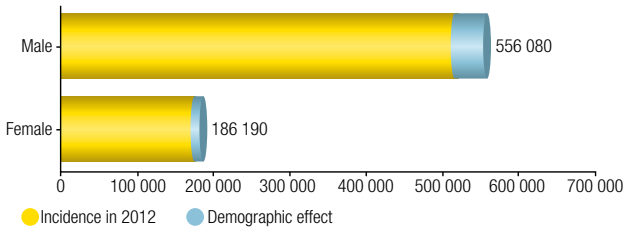
It is the sixth most common malignancy worldwide, accounting for approximately 6% of all cancer cases, responsible for an estimated 1%–2% of all cancer deaths.

Oral cavity and laryngeal cancers are the most common head and neck cancers globally (age-adjusted standardised incidence rate 3.9 and 2.3 per 100 000, respectively).

Anatomical sites and subsites of the head and neck. The approximate distribution of head and neck cancer is oral cavity, 44%; larynx, 31%; and pharynx, 25%



World
Lip, oral cavity, larynx, nasopharynx, other pharynx
Number of new cancers in 2015 (all ages)



HNSCC is predicted to account for 742 270 new cases and 407 037 deaths worldwide, for the year 2015. It is the most common cancer in Central Asia.

In the United States, more than 54 000 new cases were diagnosed in 2014, resulting in an annual incidence of 15 per 100 000, with 12 000 deaths attributed to the disease.

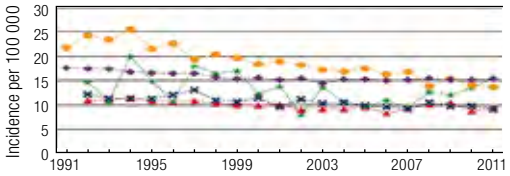
In Europe, HNSCC incidence and mortality rates are higher, with approximately 140 000 new cases diagnosed in 2014, corresponding to an annual incidence of 43/100 000.

HNSCC incidence trends have been strongly influenced by patterns of tobacco use over time and across countries.

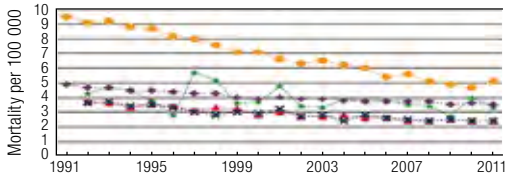
In the USA, overall incidence of oral cavity and pharyngeal cancers began decreasing 30 years ago and stabilised in 2003. Overall incidence of laryngeal cancer began declining in the 1990s.

In Eastern Europe and China (high tobacco consumption rates), a rise in HNSCC is anticipated. Infection with human papillomavirus (HPV) is responsible for a growing ratio of oropharyngeal tumours.

U.S. Head and neck cancer incidence



U.S. Head and neck cancer mortality



Whites · African Americans · Hispanics* · Asians/Pacific Islanders* · American Indians/Alaska Natives*

*Incidence and mortality data not available before 1992.

REVISION QUESTIONS

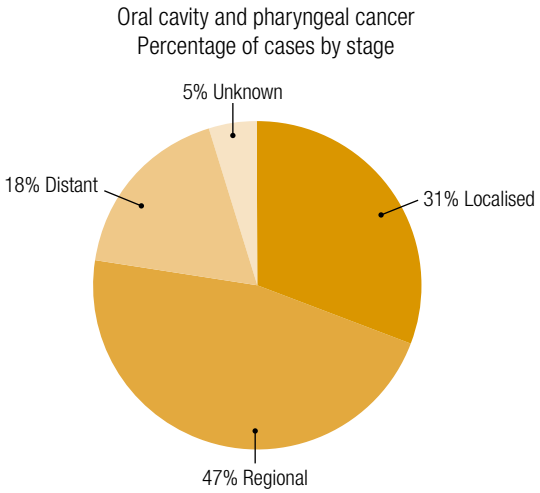
1. Which is the most common head and neck cancer globally?
2. What is the trend of HNSCC incidence in the USA and Europe in the last 20 years?
3. What is the percentage of deaths due to head and neck cancer among all cancer-related deaths?

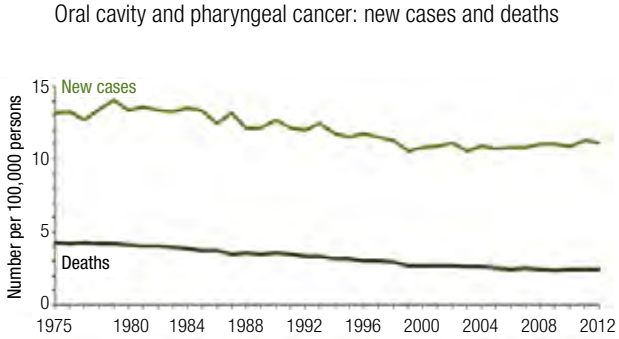
Clinical features and survival rates

Survival in HNSCC is predicted primarily by anatomical site, stage and HPV status, with other pathological and clinical factors influencing prognosis to a lesser degree.

In the recent EUROCARE population-based study, five-year relative survival was poorest for hypopharyngeal cancer (25%) and highest for laryngeal cancer (59%).

For oral cavity and pharyngeal cancer, 31% of cases are localised at the time of diagnosis. For laryngeal cancer, 55% of patients are diagnosed with localised disease.





For oral cavity and pharyngeal cancer, 5-year survival rates have increased from 57% in 1992 to 65.1% in 2003. Death rates have not changed over 2003–2012.

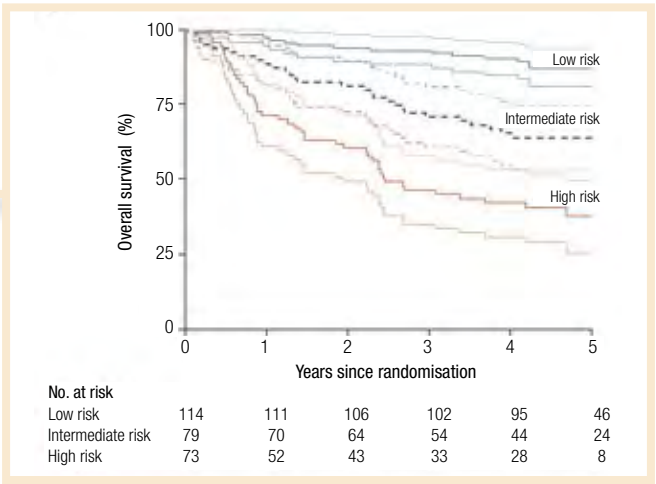
For cancer of the larynx, 5-year survival rates have not changed significantly over the past 30 years.

The survival improvement is greatest for tonsil cancer (39.7% to 69.8%). This trend is attributed to HPV-positive tumour status, which is a strong predictor for survival.

High cure rates are reported for localised and locoregional disease. However, the 3-year survival rate does not exceed 40% in a subset of patients with localised HNSCC.

HPV-positive oropharyngeal cancer (OPC) patients show better response to treatment, and survival is improved by approximately 50%. Improvement in survival is reduced in smokers.

Despite advances in multimodality treatment, survival rates for recurrent/metastatic disease remain dismal.



REVISION QUESTIONS

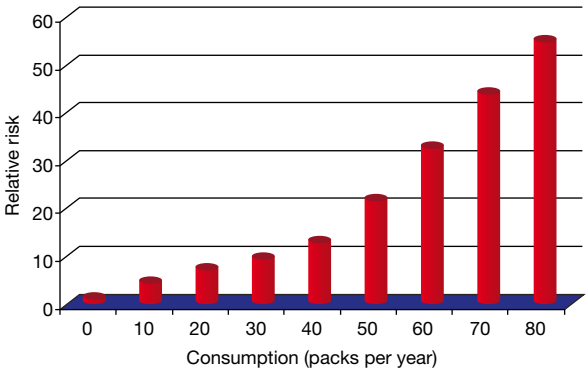
1. What is the 5-year survival rate of head and neck cancer in Europe by anatomical site?
2. What is the trend of survival rates for oral cavity and pharyngeal cancer and cancer of the larynx in the past 20 years?
3. What is the 3-year survival rate of head and neck cancer according to stage?

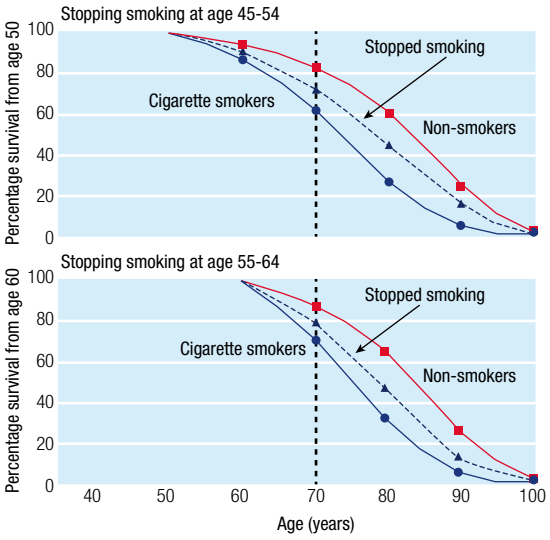
Risk factors

Tobacco: Approximately 90% of patients with HNSCC have a history of tobacco use.

Compared to non-smokers, tobacco users have a 4–5-fold increased risk for cancer in the oral cavity, oropharynx and hypopharynx and a 10-fold increased risk of laryngeal cancer.

Risk of HNSCC is related to the frequency, intensity and duration of tobacco consumption; association is dose-dependent.





Smoking cessation may reduce risk of HNSCC. Risk decreases with time since smoking cessation.

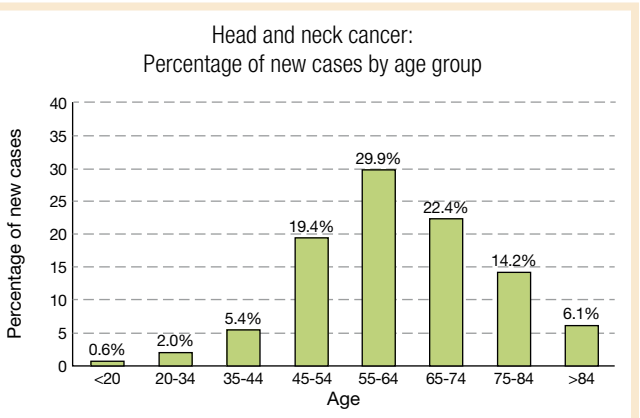
Smokeless (chewing) tobacco increases the risk of cancer of the oral cavity. In India and Sudan, 50%–60% of oral cavity cancers are attributed to smokeless tobacco.

It is estimated that tobacco smoking increases the risk of HPV infection and persistence; therefore it may contribute to development of HPV-positive OPC.

Alcohol: Alcohol use independently increases the risk of HNSCC, with 1%–4% of cases attributed to alcohol alone. It specifically increases the risk of hypopharyngeal cancer.

It acts synergistically with tobacco, resulting in an approximately 35-fold increase in HNSCC risk in heavy smokers (>2 packs/day) and drinkers (>4 drinks/day).

Gender, age: Men have a 2- to 5-fold greater risk of HNSCC than women. HNSCC risk also increases with age, with a median age of diagnosis in the late 60s and 70s.



REVISION QUESTIONS

1. What percentage of patients with HNSCC have a history of tobacco use?
2. Which type of head and neck cancer has the strongest association with tobacco?
3. How much is the risk of HNSCC increased by the combined effect of tobacco and alcohol?

Risk factors (continued)

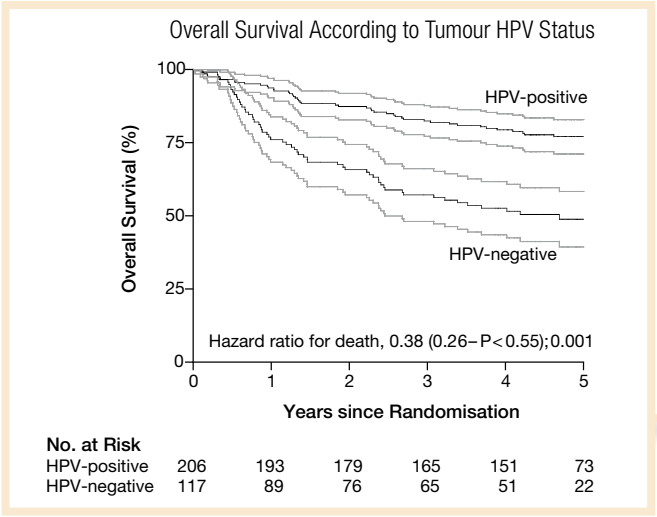
HPV infection: It is the cause of a distinct subset of HNSCCs that occur primarily in the oropharynx. The proportion of HPV-positive (HPV+) OPCs is growing.

HPV Type 16 (HPV16) is responsible for more than 90% of HPV+ OPCs. The time from first oral HPV infection to the development of cancer is estimated to be more than a decade.

Measures of sexual behaviour (number of vaginal and oral partners, history of genital warts) have been associated with HPV+ OPC.

Parameter	HPV-	HPV+
Gender	2-3 fold more common in men	4-5 fold more common in men
Age at diagnosis	Median age late 60s and 70s	Median age early 50s
Race		More common in Whites
Smoking	90% smoking history	50%-65% smoking history
Sexual behaviour	Not a significant risk factor	Number or oral and vaginal sex partners is an important risk factor
Site	Oral cavity and larynx most commonly	Oropharynx HPV+ <20% at other sites
Clinical picture	Varies	Early T stage, enlarged nodes
Incidence trends	Decreasing	Increasing
Survival rates	All sites: 65% 5-year survival Oropharynx: 25% 5-year survival	60%-80% 5-year survival

HPV-, Human papillomavirus negative; HPV+, human papillomavirus positive.



HPV, Human papillomavirus.

Patients with HPV+ OPC are less likely to be smokers than HPV-negative (HPV-) patients. However, approximately 50% of patients with HPV+ OPC have a history of tobacco use.

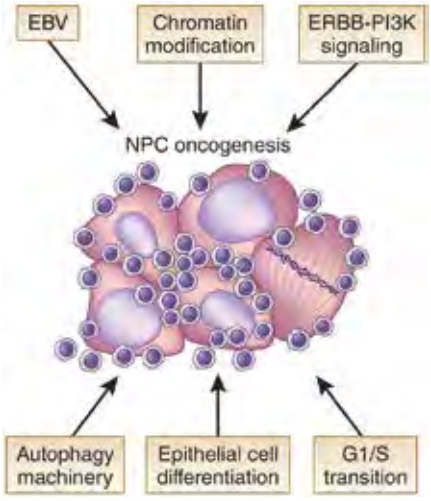
Individuals with HPV+ OPC tend to be male and white, although these characteristics do not predict HPV positivity. In addition, they present at a younger age at diagnosis.

HPV+ OPC is characterised by an earlier T stage at presentation but with extensive nodal involvement. However, prognosis is better compared with tobacco-related HNSCC.

Incidence patterns by ethnic origin have changed over time. Incidence of HNSCC in Black people has been declining since the 1990s and is currently lower than in White people.

Other risk factors for HNSCC include immunosuppression (organ transplant recipients, human immunodeficiency virus), systemic diseases (lichen) and genetic diseases (Fanconi anaemia).

Nasopharyngeal and paranasal sinus cancers are associated with the Epstein-Barr virus (EBV). Nasopharyngeal cancer is common in endemic areas (Southern China, Northern Africa).



EBV, Epstein-Barr virus; NPC, nasopharyngeal cancer.

REVISION QUESTIONS

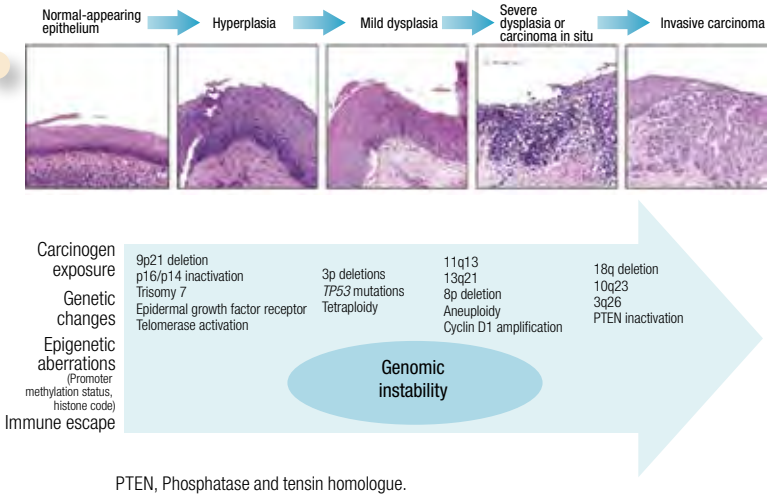
1. Which type of HPV is associated with the majority of HPV+ OPCs?
2. What are the clinical features of HPV+ OPC?
3. Which virus is associated with nasopharyngeal cancer?

Pathogenesis

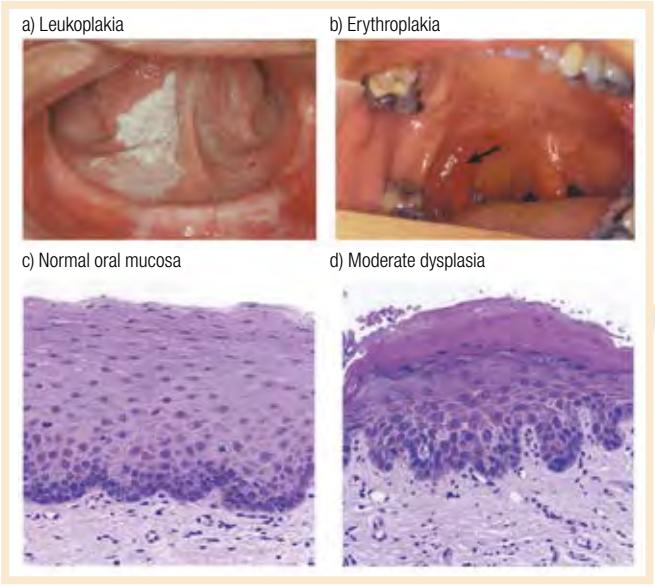
Transformation of normal mucosa into invasive HNSCC follows a molecular progression model of multistep carcinogenesis.

Loss of genetic material from chromosome region *9p21* and inactivation of *p16* tumour suppression gene are the earliest alterations identified at transition to hyperplastic mucosa.

Subsequent transition to dysplasia is characterised by loss of *3p* and *17p* and by *p53* inactivation. Loss of *11q, 13q* and *14q* precedes transition to carcinoma *in situ*.



PTEN, Phosphatase and tensin homologue.



Loss of *6p*, *8p* and *4q* is identified during transformation to invasive HNSCC. Tobacco-related HNSCC is associated with mutation of *p53* and downregulation of p16 protein.

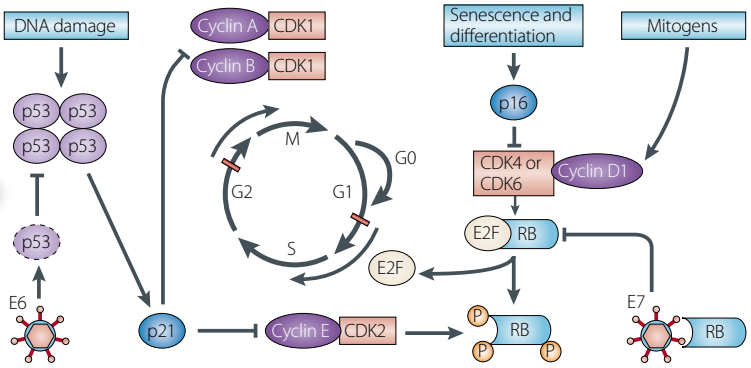
Leukoplakia and erythroplakia are the precursors of invasive HNSCC in the oral mucosa. Leukoplakia appears as white plaques and erythroplakia as a red zone of mucosa.

Field carcinogenesis refers to carcinogen distribution over large areas in upper aerodigestive tracts, due to continuous exposure, rendering mucosa a potential site for cancer.

HPV infection carcinogenesis: The integration of HPV DNA into the host genome disrupts the expression of factor E2, the transcriptional repressor of E6 and E7 viral proteins.

E6 and E7 encode oncoproteins that bind and degrade p53 and retinoblastoma (Rb) tumour suppressors, respectively. Degradation of Rb induces expression of p16^{INK4A}.

Rb is a negative regulator of p16 protein; low Rb levels lead to p16 upregulation. HPV+ OPC is typically *p53* and *Rb1* wild-type and demonstrates high p16 protein levels.



REVISION QUESTIONS

1. Which molecular abnormalities are associated with tobacco-related HNSCC?
2. What are the molecular features of HPV+ OPC?
3. What are the premalignant lesions of invasive squamous cancer in the oral mucosa?

Summary: Epidemiology, risk factors and pathogenesis of squamous cell tumours

- HNSCC encompasses a heterogeneous group of upper aerodigestive malignancies originating in the lip, oral cavity, pharynx and larynx
- It is the sixth most common cancer worldwide, accounting for 1%–2% of all cancer-related deaths
- Historically, HNSCC has been associated with tobacco smoking and alcohol use
- Globally, the incidence of tobacco-related HNSCC is associated with patterns of tobacco use and is decreasing in countries with declining rates of tobacco consumption
- In the past decade, infection with high-risk HPV and especially with HPV16 has been implicated in the pathogenesis of a growing subset of HNSCCs, mainly those arising from the oropharynx
- HPV-related OPC represents a distinct entity in terms of biology and clinical behaviour
- Five-year survival rates for all stages of HNSCC is approximately 65%. High cure rates are reported with localised and locoregional disease, but prognosis is dismal for recurrent or metastatic disease
- For HNSCC, malignant transformation of normal mucosa to invasive carcinoma follows a molecular progression model of multistep carcinogenesis
- Tobacco-related HNSCC demonstrates mutation of the *p53* gene and downregulation of the p16 protein
- On the contrary, HPV-associated OPC is typically characterised by wild-type *p53* and *Rb* genes and upregulation of p53 protein levels

Further Reading

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