# Oesophageal cancer

## diagnostic, therapeutic and preventive strategies

**While the incidence of oesophageal squamous cell carcinoma has declined in western societies, that of oesophageal adenocarcinoma has been rising rapidly in the past 30 years. The prognosis is poor once the patient presents with symptoms. Prevention and early diagnosis and treatment are the best ways to improve outcome.**

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Worldwide, oesophageal carcinoma is the eighth most common cancer and ranks fifth in cancer mortality.[1] In developed countries, the overall incidence of oesophageal squamous cell carcinoma (SCC) has declined since the early 1970s, in contrast to the rising incidence of oesophageal adenocarcinoma.

A survey from 43 tumour registries in North America, Europe and Australia has shown an increase in adenocarcinoma incidence of 30% per year in white males in Southern Europe, 23.5% per year in Australia and 20.6% per year in the United States.[2] According to the same survey, the estimated incidence for oesophageal adenocarcinoma in Australia was 4.8 cases per 100,000 population in the year 2000.

Most symptomatic patients have advanced oesophageal cancer. To improve prognosis, much attention has been directed towards the identification of risk factors and the implementation of preventive strategies. General practitioners, being the primary health care providers, could play an important role in this aspect.

## Risk factors

### Oesophageal squamous cell carcinoma

Many risk factors are implicated in the development of SCC (Table 1). The best known factors are the use of tobacco and alcohol either alone or in combination. Both smoking and alcohol increase the risk of oesophageal carcinoma in a dose-dependent and synergistic manner.[3] Population based case–control studies in the USA found an increased risk of oesophageal SCC with smoking and alcohol, with odds ratios of 16.9 and 9.5, respectively.[4] Pipes and high tar cigarettes are

**IN SUMMARY**

- **The incidence of oesophageal adenocarcinoma has increased over the past three decades.**
- **Tobacco smoking and excessive alcohol are important risk factors for squamous cell carcinoma. Longstanding severe gastro-oesophageal reflux and obesity increase the risk of oesophageal adenocarcinoma.**
- **Identification of risk factors may lead to prevention or early diagnosis and treatment.**
- **Prognosis of both oesophageal squamous cell carcinoma and adenocarcinoma is poor because generally the cancer is advanced when found.**
- **Further studies are required to assess whether endoscopic screening and surveillance will lead to improved morbidity and mortality in patients with adenocarcinoma related to Barrett's oesophagus.**

## Table 1. Oesophageal squamous cell cancer – risk and protective factors

### Risk factors

Tobacco

Alcohol

Dietary:

- mouldy food
- pickled vegetables
- betel nut chewing
- very hot food and drinks

Other:

- achalasia
- oesophageal strictures
- squamous cell carcinoma of head and neck
- Plummer–Vinson syndrome
- tylosis

### Protective factors

Vegetables, fruits

Carotenoids

Vitamin C

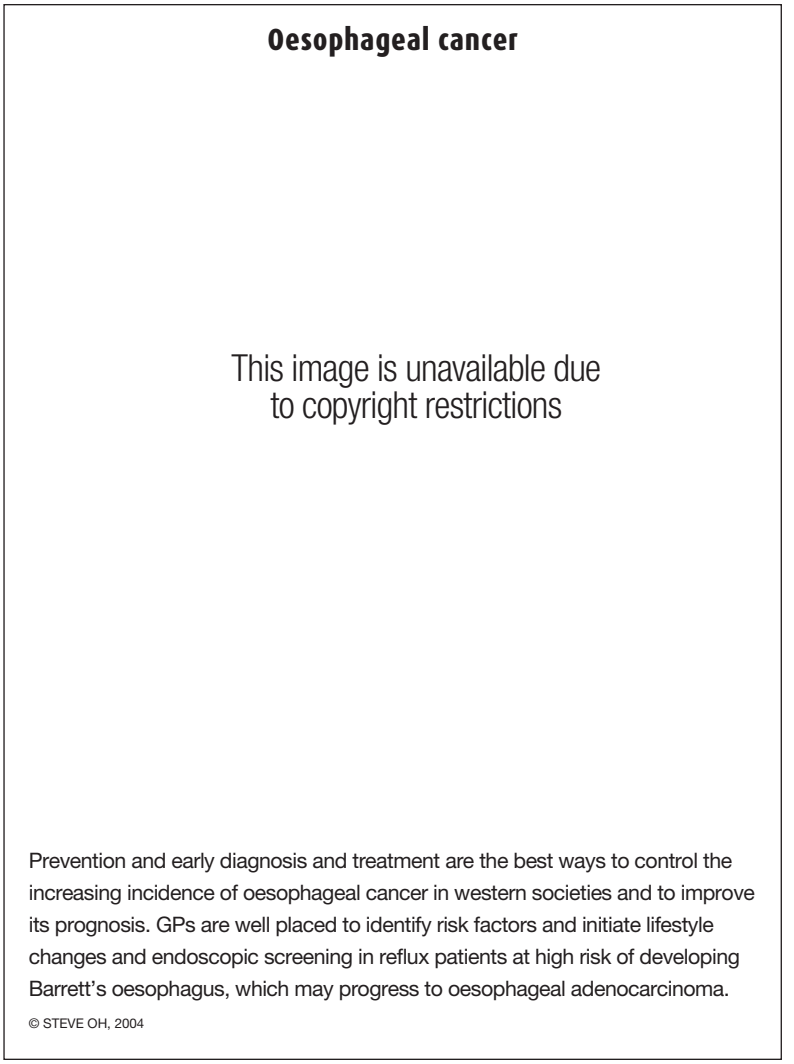
associated with the greatest risk among smokers.[3] Distilled spirits pose the highest risk among alcohol drinkers,[5] although the quantity of alcohol is probably more significant than the type of alcohol consumed.

Food that has gone mouldy and certain pickled vegetables containing nitrosamines are associated with an increased risk of oesophageal SCC. Some studies have shown a two- to four-fold increase in oesophageal SCC by drinking very hot coffee and tea.[1]

Prolonged contact of oesophageal epithelium with noxious substances is the postulated cause of oesophageal SCC in longstanding achalasia and oesophageal strictures. Plummer–Vinson syndrome (a syndrome linking iron deficiency anaemia and oesophageal webs) and tylosis (an autosomal dominant disease characterised by hyperkeratosis of palms and soles) are rare diseases that carry an increased risk.

A population based case–control Swedish study reported that subjects with a high fruit and vegetable consumption had a 40% lower risk of oesophageal SCC.[6] No specific vitamin or mineral deficiency has been linked to the development of SCC.

**Oesophageal cancer**




Prevention and early diagnosis and treatment are the best ways to control the increasing incidence of oesophageal cancer in western societies and to improve its prognosis. GPs are well placed to identify risk factors and initiate lifestyle changes and endoscopic screening in reflux patients at high risk of developing Barrett's oesophagus, which may progress to oesophageal adenocarcinoma.



### Oesophageal adenocarcinoma

Multiple risk factors are associated with oesophageal adenocarcinoma (Table 2).

A strong association between gastro-oesophageal reflux disease (GORD) and oesophageal adenocarcinoma has been reported. The strength of association appears to increase with the duration, frequency and severity of reflux symptoms. A large population based case–control study from Sweden found that longstanding severe reflux symptoms significantly increased the risk of oesophageal adenocarcinoma (odds ratio 43.5).[7]

Obesity is increasingly recognised as a strong and consistent risk factor for oesophageal adenocarcinoma. In one large population based study,

obese persons, defined as those with a body mass index (BMI) of over 30 kg/m$^2$, had a 16-fold increased risk compared with persons having a BMI of less than 22 kg/m$^2$.[8] Several case–control studies have demonstrated that diets high in total fat, saturated fat and cholesterol were associated with an increased risk of adenocarcinoma.

There is limited evidence that a decline in *Helicobacter pylori* infection, particularly the *cagA*+ strains, may contribute to an increased incidence of oesophageal adenocarcinoma.[9]

Cigarette smoking is a less significant risk factor for oesophageal adenocarcinoma (odds ratio, 3.4) than for SCC (odds ratio, 16.9).[4] In contrast to SCC, the development of adenocarcinoma of the oesophagus has not been shown to be related to alcohol consumption.[5,10]

It is estimated that 8 to 14% of chronic GORD patients develop Barrett's oesophagus, in which stratified squamous epithelium of the distal oesophagus has been transformed into columnar type epithelium with specialised intestinal metaplasia.[11] Current data suggest that the rate of progression of known Barrett's oesophagus to oesophageal adenocarcinoma is 0.5% per year.[12] It is not known whether long segment Barrett's oesophagus (intestinal metaplasia in the distal oesophagus greater than 3 cm in length) carries a greater risk for oesophageal adenocarcinoma than short zsegment Barrett's oesophagus.[12]

Increased consumption of plant foods rich in fibre, vitamin C, β-carotene and folate have been found to be associated with a reduced risk of oesophageal adenocarcinoma.[10] People with a high fruit and vegetable intake were reported in a Swedish study to have a 50% lower risk of this adenocarcinoma compared to those with a low intake.[6]

Interestingly, some of the risk factors for oesophageal adenocarcinoma, such as GORD, obesity and smoking, are also risk factors for adenocarcinoma of the gastric cardia.[3,10] High intakes of dietary fibre, β-carotene, vitamin C and folate have been shown to be protective factors for gastric adenocarcinoma also.[10]

**Table 2. Oesophageal adenocarcinoma – risk and protective factors**

| Risk factors | Protective factors |
|---|---|
| Gastro-oesophageal reflux | Dietary fibre |
| Barrett's oesophagus | Beta-carotene |
| Obesity | Vitamin C |
| Dietary fat and cholesterol | Folate |
| Tobacco smoking | |

**Table 3. Clinical presentations of oesophageal carcinoma**

| |
|---|
| Dysphagia and odynophagia |
| Anorexia and weight loss |
| Anaemia and haematemesis |
| Chest pain |
| Cough and pneumonia |
| Hoarseness |
| Other features due to metastasis to lungs, liver, bone or brain |

## Clinical presentation

Oesophageal SCC is most commonly found among Asians (especially from China), Africans and Iranians, and has a higher incidence in men than women. In the USA, SCC affects black males five times more often than white males. Patients are usually in their sixth or seventh decade of life. In contrast, oesophageal adenocarcinoma affects predominantly white males in western societies, usually between the ages of 45 and 65 years.

Although SCC occurs predominantly in the upper and middle thirds of the oesophagus and adenocarcinoma in the distal third, both types of tumours have similar clinical features (Table 3). SCC is often associated with more aggressive local invasion.

Early oesophageal cancer is often asymptomatic and discovered during endoscopy for other indications. When a patient presents with symptoms, the cancer is usually advanced.

Dysphagia is the most common symptom, occurring in about 90% of patients. Initially it may appear as 'sticking' of solid food, with the food being able to be swallowed after careful chewing. Progressive dysphagia to include semisolids and liquids occurs as the oesophageal diameter progressively diminishes. Odynophagia (pain on swallowing) is seen in about 50% of patients, indicating an ulcerated tumour. Anorexia and weight loss are common.

Patients may be anaemic due to chronic gastrointestinal bleeding. Mild haematemesis is due to tumour ulceration. Massive haematemesis is rare and occurs with erosion of pulmonary or bronchial arteries or development of aorto-oesophageal fistula. Chest pain may begin as retrosternal discomfort, and is an ominous sign that usually indicates mediastinal invasion. Cough and frequent pneumonia may be caused by aspiration due to oesophageal obstruction or oesophagorespiratory fistula. Hoarseness appears when the recurrent laryngeal nerve is invaded. There may be other clinical features due to metastases to the lungs, liver, bone or brain.

## Diagnosis and staging

### Diagnosis

Diagnosis begins with history taking, looking for suspicious clinical features (Table 3) and enquiring about risk factors (Tables 1 and 2). Physical findings depend on the stage of the disease. There are usually no specific physical findings. Hepatomegaly

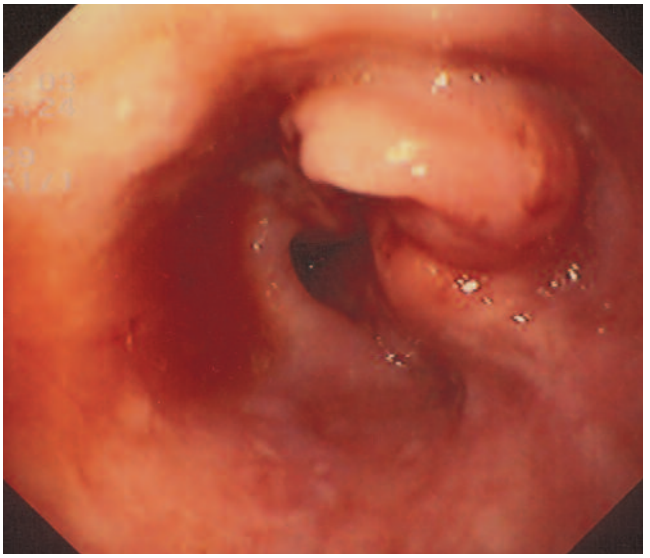


Figure 1. Distal oesophageal carcinoma.

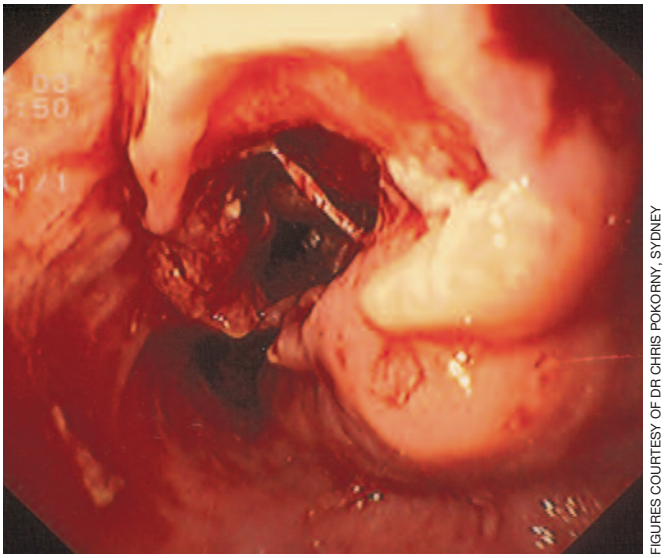


Figure 2. The same lesion as in Figure 1 after a few biopsies.

FIGURES COURTESY OF DR CHRIS POKORNY, SYDNEY

may be present if there are multiple liver metastases. A study involving 838 patients found that 18% of newly diagnosed oesophageal carcinoma patients had metastases at presentation, and 35% of these were hepatic.[13]

Endoscopy with biopsy is the gold standard diagnostic test. Endoscopy allows direct visualisation of the tumour as well as histopathological confirmation of the diagnosis by biopsy (Figures 1 and 2). Several biopsies are usually taken to increase diagnostic accuracy. Oesophageal carcinoma may be seen as a superficial plaque, an ulcerated mass or a stricture. Endoscopic ultrasound-guided fine-needle aspiration biopsy is occasionally used to detect submucosal cancer that eludes detection by standard forceps biopsy.

Barium swallow has been superseded by endoscopy for diagnosis. However, it may be used prior to endoscopy to localise any lesion so as to prevent potential complications of endoscopy such as oesophageal perforation. It may also be used to confirm or refute suspected oesophagorespiratory fistula.

Diagnosis and staging are summarised in Table 4.

## Staging

The stage of oesophageal carcinoma determines the management options and prognosis. Staging is designated by the tumour, node, metastasis (TNM) classification.

CT of the chest and abdomen is performed to detect distant metastatic disease, and has an accuracy of up to 94% in detecting liver metastases.[5]

If the CT does not show metastases, endoscopic ultrasound is performed to evaluate the extent of locoregional disease.

### Table 4. Diagnosis and staging of oesophageal carcinoma

**Diagnosis**

History and physical examination

Endoscopy and biopsy

Barium swallow

**Staging**

CT chest and abdomen

Endoscopic ultrasound, with or without guided fine-needle aspiration

Endoscopic ultrasound has been shown to have an accuracy of 84% for T-staging and 77% for N-staging.[14] The accuracy of lymph node staging can be further improved by endoscopic ultrasound-guided fine-needle aspiration biopsy .

### Table 5. Therapy of oesophageal carcinoma

**Primary therapy (potentially curative therapy)**

Surgical monotherapy

Multimodality therapy

Endoscopic mucosectomy/endoscopic mucosal resection

**Palliative therapy**

Palliative surgery

Palliative radiotherapy (with or without chemotherapy)

Dilatation

Stenting

Laser therapy

Photodynamic therapy

Chemical ablation (absolute alcohol injection; cisplatin/adrenaline injection)

MedicineToday **PATIENT HANDOUT**

## Patient information

### What are the symptoms of oesophageal cancer?

There are often no symptoms in the early stage. Later, there may be difficulty and pain on swallowing as well as loss of appetite and weight. Other symptoms appear as the cancer becomes more widespread. Difficult and painful swallowing is more commonly due to other diseases such as reflux and oesophageal thrush.

### What can I do to reduce the risk of getting oesophageal cancer?

You can live a healthy lifestyle, stop smoking and drink alcohol in moderation, eat plenty of fruits and vegetables, and avoid food high in fat and cholesterol. You should also maintain a normal body weight. If you have chronic or frequent heartburn, you should discuss this with your doctor.

### Can any test be done to diagnose oesophageal cancer early?

Many tests can be done to detect oesophageal cancer, but the most useful is endoscopy. In this procedure, a special tube is swallowed to look for abnormal growths and take tissue samples from the oesophagus.

### What are the treatments for oesophageal cancer?

Early oesophageal cancer can be treated by surgical removal of the diseased oesophagus. This may be combined with chemotherapy and/or radiotherapy. Sometimes, early cancer tissues are removed endoscopically. Several methods are available for relief of swallowing difficulty and other symptoms when the cancer is advanced.

### Is oesophageal cancer curable?

Oesophageal cancer is potentially curable if diagnosed early. However, the outcome is poor if diagnosis and treatment are delayed.

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## Therapy

Primary therapy of oesophageal SCC and adenocarcinoma is reserved for the minority (approximately 25%) of patients with early, potentially curable cancer (Table 5). Most patients present at an advanced stage requiring palliation, with their median survival being between six and nine months.

### Primary therapy

Oesophagectomy is the treatment of choice for early superficial oesophageal cancer. The five-year survival rate after surgical resection of early stage SCC and adenocarcinoma is over 80% for cancer limited to the mucosa, and 50 to 80% if there is submucosal involvement.[3] Operative morbidity includes anastomotic leakage, anastomotic strictures and cardiopulmonary complications. The operative mortality rate is 3 to 10%.[5]

Numerous studies have been done concerning the role of pre- or postoperative chemotherapy or radiotherapy for localised oesophageal cancer. As results are conflicting, it is impossible to conclude whether multimodality therapy (combined surgery and chemoradiotherapy) provides better outcomes than surgical monotherapy.[15]

Endoscopic mucosal resection is used for superficial oesophageal cancer when patients are medically unfit for surgery or unwilling to undergo oesophagectomy. It has been shown to be effective for both oesophageal SCC and adenocarcinoma.[16,17] The procedure may be complicated by bleeding and perforation.

### Table 6. Prevention of oesophageal carcinoma

- Lifestyle changes:
  - stop smoking
  - reduce alcohol intake
  - eat a healthy diet: increase fresh fruits and vegetables, decrease dietary fat
  - reduce weight to ideal
- Screening and surveillance for Barrett's oesophagus
- Treatment of Barrett's oesophagus:
  - antireflux therapy, e.g. proton pump inhibitors
  - endoscopic therapy
  - oesophageal resection
  - chemoprevention

### Palliative therapy

Optimal palliation of oesophageal cancer usually requires a combination of available methods. Palliative surgical excision is an option for large tumours with or without extensive regional nodal metastases. It can result in prolonged relief of dysphagia.

For palliation, external beam radiation may be combined with chemotherapy. It may also be used in conjunction with brachytherapy, which involves the placement of a radioactive source within the oesophagus. Good palliation of dysphagia is possible but is often delayed for several weeks. Radiotherapy may be complicated by oesophageal strictures and oesophagorespiratory fistulas.

Palliative methods involving the use of endoscopes are collectively referred to as endoscopic palliative therapy. These

methods include dilatation, stenting, laser therapy, photodynamic therapy and chemical ablation. The choice of method is determined by available expertise, patient preferences and the anatomical features of the tumour.

Dilatation of the oesophagus provides temporary relief of dysphagia until palliative radiotherapy takes effect or until other more definitive therapy can be instituted. It may be repeated every three to four weeks. It is simple and inexpensive but carries a small risk of perforation and bleeding.

Stenting of the oesophagus using self-expanding metal stents produces relief of dysphagia in up to 95% of patients. It is also effective for the management of oesophagorespiratory fistula. Possible complications are stent migration, tumour ingrowth or overgrowth, dysphagia, fistulisation, bleeding and perforation.

Standard laser therapy relieves dysphagia by fulgurating tumour tissue and restoring the patency of the oesophageal lumen. Dysphagia is relieved in 70 to 85% of patients.[5] It requires frequent treatment sessions and the cost is high, and it may produce chest pain and odynophagia as well as perforation, bleeding and fistulas.

Photodynamic therapy combines the use of a photosensitising agent and low power laser exposure. Significant palliation of dysphagia is achieved and maintained in about 75% of patients for at least one month.[18] Compared with standard laser therapy, photodynamic therapy is equally expensive but is easier to perform, better tolerated by patients and can treat a wider area in a single session. Side effects include skin photosensitivity, chest pain, odynophagia and oesophageal stricture.

Chemical ablation using intratumour injection of absolute alcohol is an inexpensive endoscopic palliative procedure.[19] Potential complications include mediastinitis, oesophagorespiratory fistulas and perforation. The procedure needs to be repeated between 28 and 50 days because of recurrent dysphagia.[3] Cisplatin plus adrenaline gel and other injectates have also been used, but these are still experimental treatments.

## Prevention

### Lifestyle changes

The prevention of oesophageal cancer should begin with lifestyle changes including cessation of tobacco use, reduction of alcohol consumption, reduction of dietary intake of fat and cholesterol, increased consumption of fruits and vegetables, and weight reduction in overweight and obese persons (Table 6; see also the Patient information sheet on page 20).

### Screening and surveillance for Barrett's oesophagus

It has been suggested that endoscopic screening of reflux patients should be confined to patients at high risk of developing Barrett's oesophagus, such as white males aged over 50 years of age who have had reflux symptoms for more than five years.[20] However, there is little evidence that screening for Barrett's prevents death from oesophageal adenocarcinoma.

Despite the high cost of endoscopic surveillance for Barrett's oesophagus and the lack of definitive evidence that it reduces death from oesophageal cancer, the American College of Gastroenterology has recommended endoscopic surveillance at intervals determined by the presence or absence as well as the grade of dysplasia.[21] (The USA recommendations are followed in Australia.) In the absence of dysplasia, surveillance every two to three years is recommended. A finding of dysplasia requires confirmation by another expert pathologist. When low grade dysplasia is detected, surveillance should be done half-yearly for the first year, and then yearly thereafter. Patients with high grade dysplasia can have either intensive surveillance every three months or oesophagectomy.

### Treatment of Barrett's oesophagus

When gastro-oesophageal reflux is present in patients with Barrett's oesophagus, one suggestion is to suppress acid secretion aggressively with high doses of proton pump inhibitors. This suggestion is based on the finding that adequate acid suppression by omeprazole caused partial regression of Barrett's oesophagus.[22] However, neither aggressive antireflux medical therapy or antireflux surgery has been shown to reduce the risk of oesophageal adenocarcinoma.[23]

In addition to the management strategies mentioned above, high-grade dysplasia may be treated by standard laser therapy, photodynamic therapy or endoscopic mucosectomy. Oesophagectomy is recommended by some specialists, but not by others because of associated morbidity and mortality.

There is evidence that COX-2 expression is increased in intestinal metaplasia, dysplasia and adenocarcinoma associated with Barrett's oesophagus.[24] The administration of COX-2 inhibitors should theoretically reduce a patient's risk of oesophageal adenocarcinoma. However, the role of chemoprevention needs further study.

## Conclusion

Oesophageal cancer often becomes symptomatic only at an advanced stage and the outcome of treatment then is poor. Of particular concern is the rapid increase in the incidence of oesophageal adenocarcinoma in western societies over the past three decades. The hope of controlling this rise and improving prognosis lies in the identification and treatment of risk factors and the endoscopic detection of precancerous and early cancerous lesions, as well as prompt therapeutic intervention. MT

*A list of references is available on request to the editorial office.*

DECLARATION OF INTEREST: None.

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## References

1. American Institute for Cancer Research. Oesophagus. In: Food, nutrition and the prevention of cancer: a global perspective. Washington: The Institute; 1997. p. 118-129.
2. Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92: 549-555.
3. Allum WH, Griffin SM, Watson A, et. al. Guidelines for the management of oesophageal and gastric cancer. Gut 2002; 50(Suppl 5): vl-v23.
4. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995; 4: 85-92.
5. Ginsberg GG, Fleischer DE. Esophageal tumors. In: Feldman M, Friedman LS, Sleisenger MH, Scharschmidt BF (eds.). Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management, 7th ed. WB Saunders, 2002: 647-671.
6. Terry P, Lagegren J, Hansen H, Wolk A, Nyren O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. Eur J Cancer Prev 2001; 10: 365-369.
7. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 240: 825-831.
8. Lagergren J, Bergstrom R, Nyren 0. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999; 130: 883-890.
9. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 1998; 58: 588-590.
10. Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. J Nutr 2002; 132 (11, Suppl): 3467S-3470S.
11. Kim R, Weissfeld JL, Reynolds JC, Kuller LH. Etiology of Barrett's metaplasia and esophageal adenocarcinoma Cancer Epidemiol Biomarkers Prev 1997; 6: 369-377.
12. Spechler SJ. Managing Barrett's oesophagus. BMJ 2003; 326: 892-894.
13. Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. Cancer 1995; 76: 1120-1125.
14. Rosch T: Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin N Am 1995; 5: 537-547.
15. Law S, Wong J. Esophageal cancer. Curr Opin Gastroenterol 2001; 17: 393-399.
16. Narahara H, Iishi H, Tatsuta M, et al. Effectiveness of endoscopic mucosal resection with submucosal saline injection technique for superficial squamous carcinoma of the esophagus. Gastrointest Endosc 2000; 52: 730-734.
17. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000; 118: 670-677.
18. Saidi RF, Marcon NE: Nonthermal ablation of malignant esophageal strictures. Photodynamic therapy, endoscopic intratumoral injections, and novel modalities. Gastrointest Endosc Clin N Am 1998; 8(2): 465-491.
19. Chung SC, Leong HT, Choi CY, Leung JW, Li AK. Palliation of malignant oesphageal obstruction by endoscopic alcohol injection. Endoscopy 1994; 26: 275-277.
20. Spechler SJ. Clinical practice. Barrett's esophagus. N Engl J Med 2002; 346: 836-842.
21. Sampliner RE, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 1998; 93: 1028-1032.
22. Peters FT, Ganesh S, Kuipers EJ, et al. Endoscopic regression of Barrett's oesophagus during omeprazole treatment; a randomised double blind study. Gut 1999; 45: 489-494.
23. Ye W, Chow WH, Lagergren J, Yin L, Nyren 0. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology 2001; 121: 1286-1293.
24. Morris CD, Armstrong GR, Bigley G, Green H, Attwood SE. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. Am J Gastroenterol 2001; 96: 990-996.