PERSISTENT HEARTBURN, BARRETT'S OESOPHAGUS AND OESOPHAGEAL CANCER

Action Against Heartburn – Before it's too late

Charities promoting earlier diagnosis of oesophageal cancer.

A joint awareness campaign supported by:

Association of Upper GI Surgeons (AUGIS)
Barrett's Oesophagus Campaign (BOC)
Barrett's Wessex
British Society of Gastroenterology (BSG)
Campaign Against Reflux Disease (CARD)
Cancer Research UK
CORE charity – Fighting Gut and Liver Disease
Fighting Oesophageal Reflux Together (FORT)
Gutsy Group
Heartburn Cancer UK
Humberside Oesophageal Support Group
Michael Blake Foundation
OCHRE (Scotland)
Oesophageal Patients Association (OPA)
Oesophagoose – Oesophageal and Gastric Cancer Awareness Campaign
Oxfordshire Oesophageal and Stomach Organisation (OOSO)
Primary Care Society for Gastroenterology

www.actionagainstheartburn.org.uk

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The size of the problem of oesophageal cancer

Oesophageal (or gullet) cancer is the sixth most common cause of cancer death in the United Kingdom (2013). Each year in the UK around 8,800 people are diagnosed with oesophageal cancer, and around 7,700 die from it[1]. Only 15% of adult oesophageal cancer patients survive their cancer for five years or more.[2] Oesophageal cancer mortality rates have increased in the UK since the 1970s, but in Europe, age-standardised mortality rates have fallen, by 5% for males and 13% for females, reflecting the pattern of incidence for the disease.[3]

In some areas of the country, over a quarter of cases are diagnosed in patients admitted to hospital as an emergency, with a corresponding tendency for them to be too late for curative treatment. Diagnosis at an early stage by endoscopy is particularly important, as it has been shown to improve treatment outcomes compared to late stage cancers.

The UK has the second highest incidence of oesophageal cancer in Europe for men and the highest for women.[4] Within the UK there is a north-south divide, with incidence rates highest in the North West of England, and parts of Scotland and Wales.[5] In 2007, the Chief Medical Officer drew attention to a rise, over the previous two decades, in the incidence of oesophageal cancer (87% for men).[6] The age-standardised rate of incidence of oesophageal cancer has risen 5.7%, from 14.47 to 15.31 per 100,000 population from 1993-95 to 2011-13[7]. One prediction concludes that the 2007 figures for oesophageal cancer in men in the UK will rise by 40% by 2020.[8] All such projections need to be treated with care, however, not least because of a growing and ageing population.

It has been estimated that 950 UK lives could be saved each year if the rate of early diagnosis and outcomes of oesophago-gastric cancer matched the best in Europe.[9]

Gender differences

Around two-thirds of oesophageal cancer cases in the UK are in men. For adenocarcinoma (see below) in England the male:female ratio is even higher at 4:1.[10]

Types of oesophageal cancer

There are two main types of oesophageal cancer: squamous cell carcinoma (OSCC) and adenocarcinoma (OAC). OSCC (more than a quarter (28%) of oesophageal cancers in the UK) tends to occur in the upper two thirds of the oesophagus and is associated with smoking and alcohol consumption. The age-standardised rate of OSCC is rising in England alone[11]. OAC (about 70%[12]) occurs mainly at the lower end of the oesophagus near the junction with the stomach, is not generally related to alcohol consumption but is associated with a pre-cancerous condition called Barrett's Oesophagus (BO), persistent acid reflux and obesity.[13] [14] [15] OAC tends to occur in younger patients than OSCC, and its incidence is rising rapidly. The UK is reported as having the highest incidence of OAC in the world.[16] The average annual

age-standardised incidence rates for oesophageal adenocarcinoma in England alone has increased by around 18.7% from 7.3 per 100,000 people between 2003-2005 to 8.6 per 100,000 between 2011-2013[17].

Age Profile

Around 95% of oesophageal cancer cases are diagnosed in patients aged 50 years or more, more than eight of ten cases in the UK are in people aged 60 and over, and incidence increases with age. The profile plateaus in the eighth decade. Barrett's Oesophagus (BO), the only known precursor lesion for oesophageal adenocarcinoma, occurs earlier; 18% of those diagnosed with BO are under 50 years of age.[18] The age profile for BO diagnosis is becoming progressively younger, and there are some reported cases progressing to adenocarcinoma in their 30s and 40s.

Acid reflux is common in the UK

Gastro-oesophageal reflux (GOR) occurs when stomach contents (mainly acid but also bile) rise up into the oesophagus due to impaired function of the valve (lower oesophageal sphincter – LOS) between the oesophagus and the stomach. This may lead to a burning sensation known as heartburn, since the normal lining of the oesophagus is not designed to withstand acid and bile. Gastro-oesophageal reflux disease (GORD) is a very common condition, with 30-40% of the UK population experiencing regular heartburn[19]. In 2010, the number of prescriptions for heartburn / dyspepsia totalled 58 million at a cost of £336 million.[20] There were approximately 50m prescriptions for PPI (proton pump inhibitor) medication (eg Omeprazole, Esomeprazole, Lansoprazole, Losec) to reduce stomach acid in 2013-14[21]. These figures exclude the additional thousands of over-the-counter purchases.[22]

Heartburn is sometimes combined with dyspepsia as an indigestion issue.

Smoking and alcohol can relax the LOS and thereby contribute to GORD. Chocolate might have a similar effect. A hiatus hernia can also be relevant because the LOS comes to lie above the diaphragm where it is unable to function properly. Obesity, and indeed some postural issues such as sitting on very low chairs after a meal, can lead to upward pressure that pushes stomach acid into the oesophagus. Stress can also increase GORD, as can a diet high in fatty food that takes longer to digest.

There is a high rate of reflux and obesity in the UK compared with Sweden, which may explain the UK's rate of OAC being five times higher than that of Sweden.[23] Most people who suffer from acid reflux, for a variety of reasons, will not develop complications, but there are estimated to be between 375,000 and one million people in the UK who have Barrett's Oesophagus, that carries a cancer risk.[24]

Acid reflux and Barrett's Oesophagus as cancer risk factors

Barrett's Oesophagus (also called *Columnar Lined Oesophagus*) is thought to be an acquired condition, though the cause remains unclear. An association between reflux of stomach acid (which is necessary for digestion and should normally be

prevented from rising into the oesophagus by the LOS) and BO has been demonstrated by a landmark study.[25]

It is thought that prolonged exposure to stomach acid and bile can lead to the cells lining the oesophagus being replaced by columns of cells that are similar to those of the stomach or intestine. These columnar cells are thought to protect people against the pain of heartburn as the cells can withstand acid: this may explain the phenomena of the heartburn stopping after a number of years; and of patients presenting with BO who report only mild or no heartburn. As a result of not being adequately treated, the BO continues to be assaulted by refluxate, and the cells may start to develop in a disorderly pattern called *dysplasia*, a condition that increases the risk of adenocarcinoma.

A sustained period of acid reflux in the past is therefore also a risk factor, notwithstanding that symptoms can resolve with PPI medication.

It is prudent for doctors to review and properly examine patients who have taken PPI medication for a significant period to clarify the diagnosis of the underlying condition. This may often involve an endoscopy. It is important to investigate for potential BO because of the risk of adenocarcinoma. The British Society of Gastroenterology (BSG) Guidelines on the Management of Barrett's Oesophagus recommend endoscopic screening be considered in patients with chronic GORD symptoms and multiple risk factors (at least three of: aged 50 years or older; white race; male gender; obesity) but that the threshold of risk factors should be lowered in the presence of family history including at least one first degree relative with BO or OAC.[26] National Institute of Clinical Excellence (NICE) Guidelines on Dyspepsia and GORD provide for patients with persistent, unexplained dyspepsia or reflux symptoms to have a discussion with their GP about referral to a specialist service.[27]

Complications of Barrett's Oesophagus and the risk of cancer

The changed cells in the Barrett's Oesophagus columns may resemble those of the stomach or intestine. If the latter, this is referred to as intestinal metaplasia (IM). In the USA, absence of a finding of IM has led to cases not being defined as Barrett's; in the UK it has been shown that IM is not as relevant as was once thought since the malignant risk is similar whether IM is present or not. DNA abnormalities (which may be present with or without IM) are better predictors of malignant risk than IM[28]. Recent research in America has suggested significant genetic links.[29] There is evidence that Barrett's patients with a rhesus negative blood group are at a higher risk of progression to cancer.[30] BO cases can cluster in families.

The length of the BO segments can be significant, with a higher risk of cancer in Barrett's segments over 7cms in length[31].

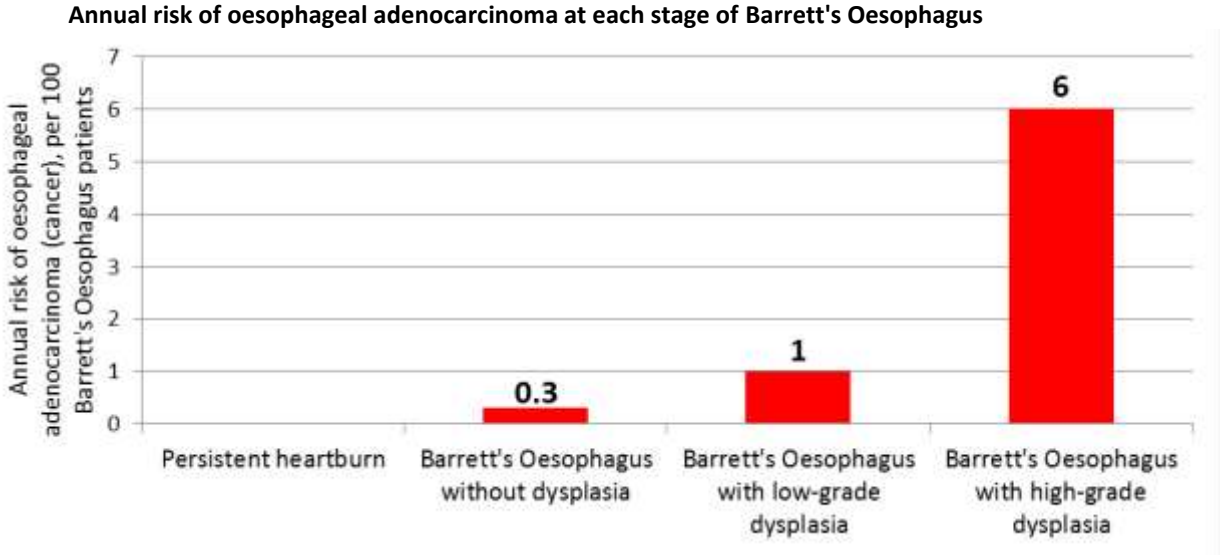
The chance of developing cancer is often expressed as a risk for any one year (ie per patient year). Studies expressing the risk of BO patients developing adenocarcinoma have variously quantified this risk as low, between 0.22% and 0.5% per patient year.[32 33 34 35] If this annual risk were progressive in a linear way, it would imply that a 30-year-old patient would have a risk of cancer of between 11% and 25% before

reaching the age of 80 years. There are many variables involved, however, and this projection should be treated with caution. It must also be noted that 90% of patients with non-dysplastic BO will have a constant cell type that will not progress to cancer, and are more likely to die from an unrelated disease.[36]

Dysplasia is at present the most robust routinely used clinical marker of cancer progression in Barrett's oesophagus. Currently, these cell changes can only be assessed after endoscopy with biopsy, where small pieces of tissue are removed and then looked at under the microscope. Histology (microscopy) reports may refer to 'gastric type mucosa' or 'glandular epithelium of the gastric type' rather than the more accurate 'columnar-lined oesophagus'. Risk of cancer progression varies between grades of dysplasia:

a) Indefinite for dysplasia, or 'atypia' (unknown risk)
b) Low grade dysplasia (5.3% risk of adenocarcinoma in 1-8 years)
c) High grade dysplasia (50% risk of adenocarcinoma in 1-8 years)[37]

Annual risk of oesophageal adenocarcinoma at each stage of Barrett's Oesophagus



Barrett's Oesophagus is present in the majority of all OAC cases but will not be seen if the tumour has arisen from a non-Barrett's source or if a large tumour has over-grown the original Barrett's[38]. The mortality rate for all oesophageal cancer in a group of patients already known to have Barrett's Oesophagus was found to be 11-fold higher than would otherwise be expected in a comparable group without Barrett's, and in relation to OAC it was 25 times higher.[39]

Surveillance Endoscopy

Patients diagnosed with BO are checked at intervals by surveillance endoscopy, in order to identify dysplasia and treat it with endoscopic therapy when the disease is potentially curable. BSG guidelines recommend surveillance every 2-5 years depending on the length of Barrett's segment. The use of high-resolution endoscopy is recommended, to be carried out in a structured way for standardised measurement of the Barrett's segment (the Prague classification). Biopsies are recommended of nodular lesions if present, and random biopsies every 2cm from four quadrants. Advanced imaging modalities, such as chromoendoscopy or 'virtual chromoendoscopy' (i.e Narrow Band Imaging (Olympus), I-scan (Pentax) or FICE

(Fuji)) are not recommended for routine use but may have a role for patients at higher risk of progression. The finding of dysplasia in BO needs a confirmatory repeat endoscopy with appropriate treatment at a specialist oesophageal cancer centre.

Treatment

Barrett's oesophagus with high risk features can now be treated in many cases by either destroying or removing the affected cells by endoscopy, without the need for surgery[40]. In the UK, endoscopic therapy is now the standard care for Barrett's oesophagus demonstrating high grade dysplasia (HGD) and early cancer. Recently the BSG and NICE have approved these techniques for the treatment of persistent or confirmed Low grade dysplasia. Techniques include Endoscopic Mucosal Resection (EMR), Radiofrequency Ablation (RFA) and, for small 'islands', Argon Plasma Coagulation (APC). Photodynamic Therapy (PDT) has been superseded by RFA and is seldom used now. These techniques should be performed at centres where endoscopic and surgical options can be offered to patients. All patients with dysplasia or early cancer, for whom therapy is considered, should be discussed at the specialist Multi-Disciplinary Team meeting for oesophago-gastric cancer. The 2014 National Oesophago-Gastric Cancer Audit reflected the recent trend towards endoscopic therapy, finding that 39.6% of treatments for HGD were EMR, 14.4% were RFA and 5.6% were surgery. Surveillance was offered as a management option in 35% of HGD cases despite the apparently high cancer risk.

Other symptoms of oesophageal cancer

Late symptoms of oesophageal cancer are difficulty or pain in swallowing food, food sticking in the gullet, and unexplained weight loss. In the presence of these symptoms, the cancer has often progressed to a stage when the opportunities for curative treatment are greatly reduced.

Better diagnosis of Barrett's Oesophagus is an opportunity for making an impact on earlier diagnosis of oesophageal adenocarcinoma that is not available for many other types of cancer.

'Action Against Heartburn' - The Awareness Campaign's messages

The key messages of this awareness campaign are:

- Consult your GP if you have
  - persistent heartburn, particularly at night, for three weeks or more.
  - persistent indigestion, for three weeks or more.
  - persistent hiccups or regurgitation of food
  - difficulty or pain in swallowing food
  - unexplained weight loss.

- Do not keep taking over-the-counter digestion remedies week after week without seeing your GP to investigate underlying causes (which most frequently will be less serious than cancer)

- GPs should consider a review of patients taking prescription remedies for reducing stomach acid after an appropriate period.

- An endoscopic examination is the only sure way of detecting Barrett's oesophagus or oesophageal cancer. This may need to include those at a younger age than the current profile for diagnosis.

- Diet, obesity, stress, tobacco and alcohol may contribute to heartburn. There are good reasons for us to address these issues, even if they do not contribute to us developing cancer.

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[2] Cancer Research UK (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Four)

[3] Cancer Research UK and GLOBOCAN: http://globocan.iarc.fr/Default.aspx

[4] European Age-Standardised rates calculated by Cancer Research UK Statistical Information Team, 2011, using data from GLOBOSCAN 2008 v1.2 IARC, version 1.2 http://globoscan.iarc.fr

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[11] Cancer Research UK. The annual average squamous cell carcinoma incidence rates (defined specifically as ICD-O3 M805-M808, considering behaviour code 3 only) are based on cases diagnosed in England between 2003 and 2013. Please note that the recording quality of this data is quite low and there are difficulties in defining the exact morphology each cancer site, meaning that there are likely to be further cases that have not been classified with the appropriate morphology coding within this dataset.

[12] Victoria Coupland of Thames Cancer Registry quotes 58.5% OAC for England for 2008 with 12% unknown morphology, and 64.2% lower oesophageal cancer (8.5% not known). Cancer Research UK give the proportion of OADC as just over half (from Devita et al, *Cancer - Principles & Practice of Oncology 8th edition 2008*, p.1000; PMID:19513070.
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[17] Cancer Research UK. The annual average adenocarcinoma incidence rates (defined specifically as ICD-O3 M814-M838, considering behaviour code 3 only) are based on cases diagnosed in England between 2003 and 2013. Please note that the recording quality of this data is quite low and there are difficulties in defining the exact morphology each cancer site, meaning that there are likely to be

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