Epidemiology and risk factors for Barrett's oesophagus

The highest incidence and prevalence of Barrett's oesophagus is in western countries. Risk factors include smoking, obesity, gastro-oesophageal reflux disease and hiatus hernia, increasing age and use of oral bisphosphonates. This article discusses the significance of these findings.

Sir Norman Barrett (1950) first described an abnormal lining of the oesophagus. Spechler (1994) has since defined it as a condition in which there is a metaplastic change of the lower oesophageal epithelium from an area of squamous to columnar epithelium. It is linked to gastro-oesophageal reflux disease and is a well-known precursor for adenocarcinoma of the oesophagus (Spechler and Goyal, 1996). Barrett's oesophagus has been reported throughout the world. However, certain areas may have a higher incidence of the condition, based on clinical observation. A literature review was conducted to examine the epidemiology of Barrett's oesophagus throughout various countries. Pubmed and Google scholar were searched, using the keywords Barrett's, oesophagus, epidemiology, incidence, and prevalence. Multiple searches were used but 'Barrett's' was used in every search. This review assesses current literature, and considers differences in incidence and prevalence rates as well as risk factors associated with the development of Barrett's oesophagus.

Epidemiology

Six studies in the USA have investigated the prevalence of Barrett's oesophagus. Conio et al (2001) conducted a study between 1965 and 1998, in Minnesota, which reviewed data on incidence and prevalence. Over this period there was a 22-fold increase in the number of endoscopies. However, there was a 28-fold increase in incidence from $0.4/10^5$ in 1965–69 to $11/10^5$ in 1995–97. During this period prevalence increased from $23/10^5$ in 1987 to $83/10^5$ in 1998. The results showed that both incidence and prevalence rates had increased parallel to increased use of endoscopy, suggesting that this had played an important role in more frequent diagnosis.

Gerson and Banerjee (2009) conducted a study in Stanford University, in California, which aimed to assess the role of endoscopy in diagnosing Barrett's oesophagus. One hundred and twenty six female patients, who were scheduled for routine colonoscopy, and those undergoing endoscopic examination before bariatric surgery, were recruited from an outpatient setting to undergo an endoscopy, after which eight patients were diagnosed with Barrett's oesophagus (prevalence 6%). This highlighted the increasing role of endoscopy in diagnosing Barrett's oesophagus. This is likely to have contributed to the apparent increase in incidence and prevalence of Barrett's oesophagus over the years. However, a recent cohort study conducted in the UK and the Netherlands between 2000 and 2012, by Masclee et al (2014), suggested that the incidence of Barrett's oesophagus increased between 2000 and 2003, after which it reached a plateau.

Studies conducted around the world have shown a variable prevalence for Barrett's oesophagus. In Brazil, Andreollo et al (1997) collected data from 15 976 endoscopies, and identified 110 (4.6%) cases with Barrett's oesophagus. The sample size was similar to studies conducted in Eastern Siberia (Butorin et al, 2013), Korea (Park et al, 2009) and China (Tseng et al, 2008), all of which produced much lower prevalence rates for the condition. A study from Korea aimed to record the prevalence of Barrett's oesophagus and compare it to western populations. Symptomatic patients aged between 18 and 75 years between April and July 2006 who were due to have a routine oesophago-gastro duodenoscopy were surveyed. Of 2048 patients, 21 had Barrett's oesophagus, a prevalence of 1%. There was a suggestion that the risk of developing Barrett's oesophagus was increased in those with gastro-oesophageal reflux disease or reflux oesophagitis (Lee et al, 2010). Another Korean study, by Kim et al (2007), which involved a retrospective analysis of 70 103 patients, found that 151 patients had Barrett's oesophagus, a prevalence of 0.22%. The two studies from Korea highlight the low prevalence of Barrett's oesophagus in this region of the world. Chinese studies reinforce the notion of low prevalence rates for Barrett's oesophagus in eastern parts of the world compared to the west, as reported by Peng et al (2009).

Risk factors

A number of studies have investigated potential risk factors associated with Barrett's oesophagus. In addition there are studies which have shown factors that reduce the risk, or are protective for Barrett's oesophagus (Vargas Cárdenas, 2010; Ibiebele et al, 2013; Jiao et al, 2013; Sharp et al, 2013).

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Smoking

Various studies have highlighted the involvement of cigarette smoking in the development of the condition, and its role enhancing the risk of adenocarcinoma. An investigation from Eastern Siberia, by Butorin et al (2013), reported that smoking more than 20 cigarettes per day for more than 10 years was associated with an increased risk. Although there were ethnic differences, with a lower prevalence of Barrett's oesophagus among Caucasoids (1.6%) compared to Mongoloids (3.1%), smoking cigarettes remained a common risk factor. This was further highlighted by a study from China (Huang et al, 2011), which found similar results.

Steevens et al (2011) conducted a large prospective Dutch cohort study, which collected data over a 16-year period from 1986 to 2002, and studied 120 852 men and women aged 55–69 years. It found former cigarette smokers were at increased risk of Barrett's oesophagus, with an incidence rate ratio of 1.33 and 95% confidence interval 1.00–1.77. The duration of smoking also showed a positive association (P trend = 0.03). Kiciński et al (2009) conducted a case control study in Poland, which looked at 36 individuals with a diagnosis of Barrett's oesophagus who were admitted into hospital between 2005 and 2007. Sixteen (45%) patients smoked cigarettes and, among other risk factors, this increased the risk of developing Barrett's oesophagus. Although nine studies have highlighted the involvement of cigarette smoking, there are some which suggest smoking is not directly linked to Barrett's oesophagus, but does increase the risk of oesophageal adenocarcinoma. In a study by Thrift et al (2014) of 258 cases, 77% were either current or ex-smokers. There was no link to age at initiation, duration, pack-years, age of cessation or Barrett's oesophagus. However, it highlighted that smoking cigarettes was associated with development of oesophageal adenocarcinoma.

This notion of cigarette smoking being associated with oesophageal adenocarcinoma and the unclear association with Barrett's oesophagus was investigated using data from five case-control studies included in the international Barrett's and Oesophageal Adenocarcinoma Consortium (Cook et al, 2012). Results showed patients with Barrett's oesophagus were more likely to have smoked cigarettes than population-based controls (odds ratio=1.67, 95%=confidence interval 1.04–2.67). It concluded that increasing pack-years, up to a peak of 20 pack-years, did in fact increase the risk of Barrett's oesophagus, after which the risk began to plateau. Furthermore smoking has synergistic effects with heartburn and regurgitation. Cook et al (2012) concluded that there appeared multiple ways in which smoking can increase the risk of Barrett's oesophagus.

Obesity

Nine studies have investigated a potential association between increasing visceral abdominal obesity and the development of Barrett's oesophagus. One particular case control study by El-Serag et al (2014) compared the risk of visceral adipose tissue and subcutaneous adipose tissue. One hundred and seventy three patients with Barrett's oesophagus and a random sample of 515 controls undergoing endoscopy and colonoscopy underwent mid-abdominal non-contrast computed tomography scans to assess the role of visceral adipose tissue and subcutaneous adipose tissue. Patients with Barrett's oesophagus had a higher ratio of visceral adipose tissue to subcutaneous adipose tissue (odds ratio=2.42; 95% confidence interval=1.51–3.88). This highlighted the association between increasing visceral adipose tissue and the development of Barrett's oesophagus.

Some studies have suggested that a larger waist-to-hip ratio, as opposed to a raised body mass index, contributes to the development of Barrett's oesophagus (Nelsen et al, 2012; Kramer et al, 2013). In their case control study Kramer et al (2013) found that of 237 patients with Barrett's oesophagus, 92% had a high waist-to-hip ratio, suggesting a relationship to the condition. They suggested that a high body mass index appears to contribute to the development of gastro-oesophageal reflux disease, or the development of a hiatus hernia, which in turn could lead to Barrett's oesophagus, and this appears to be the mechanism rather than a high body mass index itself.

Alcohol

The role of alcohol in the development of Barrett's oesophagus has been investigated, with studies suggesting no apparent association. Two hundred and fifty eight patients with Barrett's oesophagus were compared with two separate control groups; 453 colonoscopy controls and 1145 patients from an elective endoscopy group. Of study participants 91% were current or ex-alcohol drinkers. Results suggested that alcohol consumption was not associated with Barrett's oesophagus, rather that moderate intake may lower the risk (14 to <28 drinks/week, odds ratio=0.39, 95% confidence interval=0.15–1.00) (Thrift et al, 2014). Similar results were found in other studies (Steevens et al, 2011), in particular from a population-based case-control study which collected information on lifetime alcohol consumption. Total lifetime alcohol consumption was inversely associated with dysplasia (7–20 drinks/week odds ratio=0.52, 95% confidence interval=0.19–1.43; 21–41 drinks/week odds ratio=0.22, 95% confidence interval=0.07–0.73) and non-dysplasia (7–20 drinks/week odds ratio=0.53, 95% confidence interval =0.31–0.91 and 21–41 drinks/week odds ratio=0.37, 95% confidence interval =0.19–0.73). These results were observed for both beer and wine, suggesting that alcohol consumption does not increase the risk of Barrett's oesophagus as suggested by Thrift et al (2011).

Gastro-oesophageal reflux disease and hiatus hernia

Patients with gastro-oesophageal reflux disease or hiatus hernia are at increased risk of developing Barrett's oesophagus. Watari et al (2013) highlighted this in a

Japanese cross-sectional study. It suggested that reflux oesophagitis was an independent risk factor for Barrett's oesophagus (odds ratio=3.48, 95% confidence interval=1.89–6.41), but obesity was not. This was reinforced by Sanchís Blanco et al (2013) who conducted a Spanish study among children. This case control study, conducted over a 10-year period, found six patients with a histological diagnosis of Barrett's oesophagus, and who also had gastro-oesophageal reflux, but without proton pump inhibitor treatment. Exposure time to acid reflux without use of proton pump inhibitor treatment was the only independent risk factor (odds ratio=1.046). These results suggest that exposure to acid reflux, and factors that increase this risk such as gastro-oesophageal reflux disease, hiatus hernia and obesity, increase the risk of patients developing Barrett's oesophagus.

Gender

Various studies have found a link between gender, and risk of Barrett's oesophagus. Some suggest that male sex is a risk factor. This notion has been echoed in different parts of the world including the Netherlands, Japan and Spain (Watari et al, 2013; Masclee et al, 2014; Rodríguez-D'Jesús et al, 2014). Others have found that being female is protective (Ibiebele et al, 2013). A large community-based study, by Corley et al (2009), of 4205 patients in Northern California, found a higher annual incidence among men (31 *vs* 17/105 respectively; $P<0.01$). Similar results were found by Fan and Snyder (2009) in Texas, USA, where Barrett's oesophagus was a male-predominant condition. However, no studies offer an explanation for this gender difference.

Age

Age has been investigated as a possible risk factor for Barrett's oesophagus. This was highlighted in a study conducted in both China and Russia (Butorin et al, 2013), which showed that age greater than 40 years was associated with the condition. This was reinforced in a large analysis in Korea, which found increasing age to be a risk factor for Barrett's oesophagus, with a mean age at diagnosis of 54±11 years (Kim et al, 2007). More recently, a cohort study conducted across the UK and the Netherlands found that the incidence of Barrett's oesophagus increased with age; $16/10^5$ (UK) and $24/10^5$ (Netherlands) for patients aged 40–44 years, increasing to $86/10^5$ (UK) and $87/10^5$ (Netherlands) for patients aged 70–74 years (Masclee et al, 2014).

Other risk factors

Use of oral bisphosphonates is known to cause oesophagitis. A case control analysis by Lin et al (2013) of American military veterans compared their use in patients with Barrett's oesophagus and a group of controls. The study adjusted for age, sex, race, smoking status, gastro-oesophageal reflux disease symptoms, proton pump inhibitor use, *Helicobacter pylori* infection, waist-to-hip ratio and hiatal hernia. The proportion of Barrett's oesophagus cases who filled prescriptions for oral bisphosphonates (4.6%) was greater than controls (1.6%). The adjusted analysis showed odds ratio of 2.33, 95% confidence interval=1.11–4.88. These results suggest that use of oral bisphosphonates may be linked to the development of Barrett's oesophagus, but there is a wide confidence interval with the lower end only marginally above 1. Furthermore the study also concluded that patients with definite Barrett's oesophagus were more likely to be male (97.2% *vs* 91.5%, $P<0.001$) and white (86.3% *vs* 61.1%, $P<0.001$) and were on average 1.2 years older than controls ($P=0.009$).

Recent research

Gatenby and Soon (2014) examined data published from meta-analyses up to 2013 about guidelines for managing Barrett's oesophagus. The results of nine meta-analyses comparing patients with Barrett's oesophagus to controls showed that Barrett's oesophagus was more common in males compared to females, in those with a smoking history, obese patients, patients with prolonged gastro-oesophageal reflux disease symptoms and in those with a hiatus hernia. Furthermore data collected in relation to cancer risk in patients with Barrett's oesophagus suggested that there was a similar cancer risk in patients with Barrett's oesophagus irrespective of geographical origin and that the adenocarcinoma incidence in males is twice that of females. In addition, it highlighted that there was no statistical benefit of anti-reflux surgery compared to medical therapy and that endoscopic ablative therapy was effective in reducing the cancer risk. These findings will help influence the role of surveillance of dysplasia and cancer and provide guidance on the management of such cases.

Similar epidemiological results were elicited by Spechler and Souza (2014) who suggested that the frequency of oesophageal adenocarcinoma in the USA had increased more than seven-fold in the last four decades and further by Al Dulaimi (2014) who analysed different review articles and meta-analyses and found that the risk factors for Barrett's oesophagus remained the same between eastern and western countries but with a lower prevalence in Asia compared to the west and a greater proportion of the short segment type. Furthermore infection with *H. pylori*, an infection more prevalent in Asia than the west, had a protective effect for Barrett's oesophagus. The analysis also reinforced the notion of lower rates of oesophageal adenocarcinoma in Asia (incidence of 1.418 per 1000 person-years) compared to western countries.

Conclusions

There are a number of risk factors associated with the development of Barrett's oesophagus. Some of these directly increase the risk of developing Barrett's oesophagus, while others increase the risk of complications such as development of adenocarcinoma of the oesophagus. There are differences in incidence and prevalence rates

for Barrett's oesophagus throughout the world, and this is partly as a result of different lifestyles around the world, with higher incidence and prevalence in places where smoking, and obesity are commonplace (Vargas Cárdenas, 2010). To date, there have been no studies to look at interventions which will reduce the risk of developing Barrett's oesophagus or indeed to assess the impact of surveillance programmes. **BJHM**

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KEY POINTS

- There are a number of risk factors associated with the development of Barrett's oesophagus, such as smoking, obesity, gastro-oesophageal disease, increasing age and the use of oral bisphosphonates.
- Incidence and prevalence rates for Barrett's oesophagus vary throughout the world with the highest rates being in Western countries.
- Western culture and lifestyle has contributed to the higher incidence and prevalence rates for Barrett's oesophagus.