

WJGP 5th Anniversary Special Issues (4): Barrett's**Barrett's oesophagus: Evidence from the current meta-analyses**

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Abstract

Guidelines have been published regarding the management of Barrett's oesophagus (columnar-lined oesophagus). These have examined the role of surveillance in an effort to detect dysplasia and early cancer. The guidelines have provided criteria for enrolment into surveillance and some risk stratification with regard to surveillance interval. The research basis for the decisions reached with regard to cancer risk is weak and this manuscript has examined the available data published from meta-analyses up to 25th April 2013 (much of which has been published since the guidelines and their most recent updates have been written). There were 9 meta-analyses comparing patients with Barrett's oesophagus to control populations. These have demonstrated that Barrett's oesophagus is

more common in males than females, in subjects who have ever smoked, in subjects with obesity, in subjects with prolonged symptoms of gastro-oesophageal reflux disease, in subjects who do not have infection with *Helicobacter pylori* and in subjects with hiatus hernia. These findings should inform public health measures in reducing the risk of Barrett's oesophagus and subsequent surveillance burden and cancer risk. There were 8 meta-analyses comparing different groups of patients with Barrett's oesophagus with regard to cancer risk. These have demonstrated that there was no statistically significant benefit of antireflux surgery over medical therapy, that endoscopic ablative therapy was effective in reducing cancer risk that there was similar cancer risk in patients with Barrett's oesophagus independent of geographic origin, that the adenocarcinoma incidence in males is twice the rate in females, that the cancer risk in long segment disease showed a trend to be higher than in short segment disease, that there was a trend for higher cancer risk in low-grade dysplasia over non-dysplastic Barrett's oesophagus, that there is a lower risk in patients with *Helicobacter pylori* infection and that there is a significant protective effect of aspirin and statins. There were no meta-analyses examining the role of intestinal metaplasia. These results demonstrate that guidance regarding surveillance based on the presence of intestinal metaplasia, segment length and the presence of low-grade dysplasia has a weak basis, and further consideration should be given to gender and helicobacter status, ablation of the metaplastic segment as well as the chemoprotective role of aspirin and statins.

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Key words: Barrett esophagus; Esophageal neoplasms; Meta-analysis; Review; Systematic

Core tip: The presence of intestinal metaplasia on biopsy has been regarded as a necessity for enrolment

in a surveillance programme for Barrett's oesophagus and surveillance intervals have been based on segment length and the presence or absence of dysplasia. Evidence from meta-analyses supports male gender and negative *Helicobacter pylori* infection status as important markers of cancer risk and of the role of aspirin, statins and ablation of the Barrett's segment to reduce cancer risk. The evidence from meta-analyses supporting segment length and dysplasia as markers of cancer risk is poor and for intestinal metaplasia has not been shown.

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INTRODUCTION

Barrett's columnar-lined oesophagus is a metaplastic change to the squamous mucosa of the oesophagus associated with gastro-oesophageal reflux disease^[1]. Guidelines concerning management of patients with Barrett's oesophagus have been published with recommendations on the control of pathological reflux and on periodic surveillance of this pre-malignant condition^[2-4]. There has been a rapid increase in the number of meta-analyses published, with over half published in the last 5 years and an increase in the focus of these on pharmacotherapy and reflux control to reduce cancer incidence, associations with smoking and obesity as well as new estimates on cancer incidence. In an attempt to examine the available best evidence since these guidelines were published/updated (in 2013^[2], 2011^[4] and 2008^[3]), this review has conducted a systematic review of the currently published meta-analyses to aid clinicians and patients in optimum decision making for the risk assessment and management of Barrett's oesophagus.

RESEARCH

A search was made of the Pubmed database for the search terms "Barrett's oesophagus" and "meta-analysis". The full search terms are listed in Table 1 with publication dates up to and including 25th April 2013 (including epublication). Papers were included in the analysis if the type of study was a meta-analysis of previously published data concerning Barrett's oesophagus in human subjects and published in English language. Studies were included if they compared subjects with Barrett's oesophagus to control groups or compared different groups of patients with Barrett's oesophagus with respect to cancer risk. Studies were then categorized into the following groups: (1) comparison of patients with Barrett's oesophagus to control groups; and (2) comparison of different groups of patients with Barrett's

oesophagus with regard to cancer risk. Where the papers retrieved did not contain meta-analyses, but useful observations were presented, these have been described in this manuscript, but not included in the results tables.

The literature search yielded 50 papers. Of these papers, 10 were excluded after retrieving the abstracts and 6 after retrieving the full papers (2 were letters concerning meta analyses, 1 examined cell culture lines rather than studying human subjects, 4 were in foreign language-3 German and 1 Spanish, 1 was a systematic review without a meta-analysis, 1 was an economic review without a meta-analysis, 2 were reviews only, 3 did not contain a meta-analysis comparing any different groups and 2 were single studies). There were 34 remaining studies and the full manuscript of each was obtained. Eleven studies were excluded as they examined oesophageal cancer compared to control groups without an examination of a comparative risk in Barrett's oesophagus. Three examined diagnostic techniques only and have been excluded. Two examined the risk of adenocarcinoma development within high-grade dysplasia and were excluded. One examined the association of Barrett's oesophagus with colonic tumours (which demonstrated the increased risk of colonic tumours and colorectal cancer in subjects with Barrett's oesophagus^[5]).

There were no studies comparing cancer risk in patients with Barrett's oesophagus to control groups. The remaining 17 studies are examined below.

The retrieved studies spanned the last 10 years. As would be anticipated with the growing popularity of meta-analyses, over half of the eligible studies were published since the beginning of 2010. The United States and United Kingdom guidelines were most recently updated in 2013^[2], 2011^[4] and 2008^[3]. With the time required for preparation of these guidelines, this indicates that only a handful of the meta-analyses had been published sufficiently early for their results to be incorporated in the compilation of the American College of Gastroenterology guidelines and a limited number into the American Gastroenterological Association guidelines. In general, the guidelines have not examined differences in cancer risk between individuals beyond segment length, presence of intestinal metaplasia and dysplasia.

Comparison of patients with Barrett's oesophagus to control groups

There were 11 papers comparing patients with Barrett's oesophagus to control groups, usually taken from the general population, but also other endoscopic populations including those with reflux disease but no Barrett's oesophagus. These studies examined gender, smoking habits, obesity, symptom association, presence of *Helicobacter pylori* (*H. pylori*), presence of hiatus hernia and pattern of proton pump inhibitor usage. Of these, 9 were meta-analyses (Table 2).

Gender: The association between male gender and Barrett's oesophagus was demonstrated by Cook *et al*^[6]. They

Table 1 Search terms

{“barrett’s oesophagus” (All Fields) OR “barrett esophagus” (MeSH Terms) OR [“barrett” (All Fields) AND “esophagus” (All Fields)] OR “barrett esophagus”(All Fields) OR [“barrett’s” (All Fields) AND “esophagus” (All Fields)] OR “barrett’s esophagus” (All Fields)} OR {“barrett’s oesophagus” (All Fields) OR “barrett esophagus” (MeSH Terms) OR [“barrett”(All Fields) AND “esophagus” (All Fields)] OR “barrett esophagus”(All Fields) OR [“barrett’s” (All Fields) AND “esophagus” (All Fields)] OR “barrett’s esophagus”(All Fields)}	AND	[“meta-analysis” (Publication type) OR “meta-analysis as topic” (MeSH Terms) OR “meta-analysis” (All Fields)]
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Search strategy: “Barrett’s esophagus” or “Barrett’s oesophagus”.

Table 2 Meta-analyses comparing patients with Barrett’s oesophagus to control groups

Subject	Ref.	Comparison	Group	Studies	Results	Outcome
Gender	Cook <i>et al</i> ^[6] , 2005	Gender	Barrett’s	32	M:F Ratio 1.96:1 (95%CI: 1.77, 2.77)	Higher M:F ratio in Barrett’s oesophagus and reflux oesophagitis than in non-erosive reflux disease
			Erosive reflux disease	28	1.57 (95%CI: 1.40, 1.76)	
			Non-erosive reflux disease	14	0.72 (95%CI: 0.62, 0.84)	
Smoking	Andrici <i>et al</i> ^[7] , 2013	Ever smoking	Barrett’s <i>vs</i> GORD	20	OR, 1.18 (95%CI: 0.75, 1.86)	Cigarette smoking associated with increased risk of Barrett’s oesophagus
			Barrett’s <i>vs</i> non-GORD	27	OR, 1.44 (95%CI: 1.20, 1.74)	
Obesity	Cook <i>et al</i> ^[8] , 2008	BMI	Barrett’s <i>vs</i> GORD	9	OR, 0.99/kg per m ² (95%CI: 0.97, 1.01)	Barrett’s oesophagus associated with higher BMI than control but not GORD
			Barrett’s <i>vs</i> general population	3	OR, 1.02/kg per m ² (95%CI: 1.01, 1.04)	
	Kamat <i>et al</i> ^[9] , 2009	Obesity (BMI ≥ 30 <i>vs</i> BMI < 30) Overweight (BMI ≥ 25 <i>vs</i> BMI < 25)	Barrett’s <i>vs</i> control (BMI ≥ 30 <i>vs</i> BMI < 30)	9	OR, 1.35 (95%CI: 1.15, 1.59)	Barrett’s oesophagus associated with being overweight and obese
			Barrett’s <i>vs</i> control	8	OR, 1.49 (95%CI: 1.24, 1.80)	
Symptoms of gastro-oesophageal reflux	Taylor <i>et al</i> ^[11] , 2010	Symptoms of GORD	All Barrett’s <i>vs</i> controls Short segment Barrett’s <i>vs</i> controls Long segment Barrett’s <i>vs</i> controls	4	Males OR, 2.24 (95%CI: 1.08, 4.65) Females OR, 3.75 (95%CI: 1.47, 9.56) No significant association	Symptoms of GORD associated with all Barrett’s oesophagus, more strongly with long segment Barrett’s oesophagus than with short segment Barrett’s oesophagus
				26	OR, 2.90 (95%CI: 1.86, 4.54)	
				12	OR, 1.59 (95%CI: 1.07, 2.38)	
Helicobacter pylori	Wang <i>et al</i> ^[12]	Helicobacter pylori infection rate	Barrett’s oesophagus <i>vs</i> all controls	12	OR, 0.74 (95%CI: 0.40, 1.37)	Similar helicobacter pylori infection rate in Barrett’s oesophagus to all controls but lower than in endoscopically normal controls
			Barrett’s oesophagus <i>vs</i> endoscopically normal	9	OR, 0.50 (95%CI: 0.27, 0.93)	
	Fischbach <i>et al</i> ^[13] , 2012	Helicobacter pylori infection rate Cag A Helicobacter pylori infection rate	Barrett’s oesophagus <i>vs</i> all controls	49 7	RR, 0.46 (9%CI: 0.35, 0.60) RR, 0.38 (95%CI: 0.19, 0.78)	Lower helicobacter infection rate in patients with Barrett’s oesophagus compared to controls
Hiatus hernia	Andrici <i>et al</i> ^[14] , 2012	Hiatus hernia presence	Barrett’s oesophagus <i>vs</i> all controls	31	OR, 3.94 (95%CI: 3.02, 5.13)	Hiatus hernia associated with Barrett’s oesophagus and more strongly associated with long-segment Barrett’s oesophagus

OR: Odds ratio; BMI: Body mass index; CI: Confidence interval.

examined data from studies on Barrett’s oesophagus, erosive reflux disease and non-erosive reflux disease. The

overall male: female ratio in Barrett’s oesophagus was 1.96 and was similar in erosive reflux disease, but higher than

in non-erosive reflux disease.

Cigarette smoking: The association between cigarette smoking and diagnosis of Barrett's oesophagus was examined by Andrici *et al*⁷¹. They included a variety of different study designs and control subjects. They demonstrated that having ever smoked was associated with Barrett's oesophagus compared to control subjects who did not have gastro-oesophageal reflux disease or to population-based controls. There was no significant association when compared to controls with gastro-oesophageal reflux disease. There was a dose-related relationship with a higher number of pack-years smoked associated with increased risk of Barrett's oesophagus. The relationships were similar for current, former and ever smokers.

Obesity: Three studies examined the association between obesity and Barrett's oesophagus. Cook *et al*⁸¹ examined studies which compared Barrett's oesophagus to those with reflux disease (those with unknown histology and those with histologically-proven oesophagitis) in 9 studies and to the general population in one study. Their results were similar for all comparison groups with no association noted with obesity and Barrett's oesophagus compared to gastro-oesophageal reflux disease, but in 3 studies comparing Barrett's oesophagus to control subjects there was a small statistically significant association between Barrett's oesophagus and higher body mass index. Kamat *et al*⁹¹ showed that obesity was associated with Barrett's oesophagus and comparing patients who were either overweight or obese showed similar results. More recently, Kubo *et al*¹⁰¹ showed that from 4 case-control studies that there was no clear association between BMI and Barrett's oesophagus, but that there was an increased risk of Barrett's oesophagus with higher waist circumference.

Symptoms: One study by Taylor *et al*¹¹¹ examined the association of Barrett's oesophagus with symptoms of gastro-oesophageal reflux. This analysis included 26 published studies (the majority of which were case-control) and demonstrated that symptoms of gastro-oesophageal reflux were associated with the diagnosis of Barrett's oesophagus, strongly with long segment Barrett's oesophagus and that there was a weaker association with short-segment Barrett's oesophagus.

Helicobacter pylori: Wang *et al*¹²¹ showed that there was no overall difference in *H. pylori* infection between patients with Barrett's oesophagus and control subjects (taken from blood donating populations and subjects with normal findings on endoscopy). When patients with Barrett's oesophagus were compared to those with normal endoscopy only, Barrett's oesophagus was associated with lower rate of *H. pylori* infection. With further data available, Fischbach *et al*¹³¹ found that there was a strong negative association between the presence of *H. pylori*

and Barrett's oesophagus. There were a smaller number of studies which examined the effect of virulent Cag A positive *H. pylori* with similar results.

Hiatus hernia: Andrici *et al*¹⁴¹ examined the relationship between Barrett's oesophagus and hiatus hernia. Barrett's oesophagus was strongly associated with the presence of hiatus hernia compared to all controls, a significant association when compared to the control group of patients with gastro-oesophageal reflux disease and stronger association compared to control subjects without gastro-oesophageal reflux disease. The relationship was stronger for long segment Barrett's oesophagus than for short segment Barrett's oesophagus.

Pattern of proton pump inhibitor usage: There were 2 studies reported in the analysis of Hungin *et al*¹⁵¹, but this was not undertaken as a meta-analysis. They analysed medication possession rates in patient with Barrett's oesophagus to those with gastro-oesophageal reflux disease and demonstrated higher adherence in those with Barrett's oesophagus. The self-reported adherence was also higher in patients with Barrett's oesophagus than subjects with gastro-oesophageal reflux disease in one of the included studies.

Comparison of different groups of patients with Barrett's oesophagus with regard to cancer risk

There were 12 studies which examined for differences in adenocarcinoma incidence in different groups of patients with Barrett's oesophagus. These studies looked at treatment for control of gastro-oesophageal reflux, endoscopic ablation of the metaplastic segment, demographic factors, segment length, dysplasia, enzyme polymorphisms, infection with *H. pylori* and drugs taken for other conditions. Eight of these studies contained meta-analyses (Table 3).

Treatment of gastro-oesophageal reflux and endoscopic ablation

Corey *et al*¹⁶¹ examined the question of whether a surgical antireflux procedure was of benefit in reducing cancer risk in patients with Barrett's oesophagus. The cancer incidence was not significantly different between medical and surgical therapy and when the earlier medical cohorts were excluded (those prior to the proton-pump era), the cancer incidence in the medical group remained similar (0.43% per annum) to patients treated with anti-reflux surgery.

Li *et al*¹⁷¹ examined randomized controlled trials of medical, surgical and endoscopic therapy for Barrett's oesophagus. There was one study of medical *vs* surgical therapy¹⁸¹ which showed no significant difference in cancer incidence between patients treated by medical and surgical therapy (5% and 3% respectively), however there was a significantly lower risk of dysplasia development in the surgical arm (2%) compared to the medical arm (20%). There were three studies included of endo-

Table 3 Meta-analyses comparing cancer risk in different groups of patients with Barrett's oesophagus

Subject	Ref.	Comparison	Group	Studies	Results	Outcome			
Medical <i>vs</i> surgical treatment of reflux	Corey <i>et al</i> ^[16]	Antireflux surgery <i>vs</i> medical treatment	Antireflux surgery	34	18 cancers/4678 patient-years (0.38% per annum)	No significant difference in cancer risk between medical and surgical antireflux therapy			
			Medical therapy		26 cancers/4906 patient-years (0.53% per annum)				
Endoscopic ablative therapy <i>vs</i> surveillance	Wani <i>et al</i> ^[25]	Non-dysplastic Barrett's oesophagus	Surveillance	45	5.98/1000 patient-years	Endoscopic ablative therapy is effective in reducing adenocarcinoma risk in patients with non-dysplastic Barrett's oesophagus, low-grade dysplasia and high-grade dysplasia compared to surveillance alone			
			Endoscopic ablative therapy	49	1.63/1000 patient-years				
			Low-grade dysplasia	16	16.98/1000 patient-years				
			Endoscopic ablative therapy	21	1.58/1000 patient-years				
			High-grade dysplasia	4	65.8/1000 patient-years				
Demographic factors	Thomas <i>et al</i> ^[26]	Location	United Kingdom	13	7/1000 patient-years	Cancer incidence similar in all geographic areas			
			United States	16	7/1000 patient-years				
			Europe	10	8/1000 patient-years				
			Australia and New-Zealand	2	5/1000 patient-years				
	Yousef <i>et al</i> ^[27]	Gender	Males	6	10.2/1000 patient-years	Cancer incidence in males is double the rate in females			
			Females	5	4.5/1000 patient-years				
Segment length	Thomas <i>et al</i> ^[26]	Segment length	Short segment	6	2.8/1000 patient-years	Trend for lower risk in short segment Barrett's oesophagus (<i>P</i> = 0.25)			
			Long segment	6	7.8/1000 patient-years				
	Yousef <i>et al</i> ^[27]	Segment length	Short segment	6	6.1/1000 patient-years	Similar risk in short and long segment disease			
			Long segment	26	6.7/1000 patient-years				
Dysplasia	Thomas <i>et al</i> ^[26]	Low-grade dysplasia as a confounding factor	Presence of low-grade dysplasia at index endoscopy	15	<i>P</i> = 0.23	No significant confounding effect on cancer incidence in meta-regression analysis			
<i>Helicobacter pylori</i>	Rokkas <i>et al</i> ^[30]	All <i>Helicobacter pylori</i>	Cases	10	253/757 (34.3%)	<i>Helicobacter pylori</i> associated with lower rate of oesophageal cancer OR, 0.52; (95% CI: 0.37, 0.73)			
			Controls	10	1398/2788 (50.1%)				
			Cag A <i>Helicobacter pylori</i>	Cases	6	120/462 (26%)	Cag A <i>Helicobacter pylori</i> associated with lower rate of oesophageal cancer OR, 0.51; (95% CI: 0.31, 0.82)		
			Controls	6	774/1936 (40%)				
Non-steroidal Anti-inflammatory drugs	Wang <i>et al</i> ^[31]	Aspirin and NSAIDs <i>vs</i> controls		3	RR 0.64 (95% CI: 0.42, 0.96)	Lower risk of adenocarcinoma in patients taking aspirin or NSAIDs			
			Statins	Statins <i>vs</i> controls	Alexandre <i>et al</i> ^[33]		2	RR, 0.53 (95% CI: 0.36, 0.78)	Protective effect of statins <i>vs</i> controls
					Singh <i>et al</i> ^[36]		5	RR, 0.57; (95% CI: 0.44, 0.75)	
Statins and NSAIDs	Singh <i>et al</i> ^[36]	Combined statins and NSAIDs <i>vs</i> neither		2	0.28; (95% CI: 0.14, 0.56)	Protective effect of NSAIDs and statins higher than either individually			

NSAIDs: Nonsteroidal antiinflammatory drugs; OR: Odds ratio; CI: Confidence interval.

scopic ablative therapy *vs* medical therapy for patients with dysplasia. The studies were heterogenous in their designs and outcome measures. Photodynamic therapy was superior to PPI in reducing the area of Barrett's epithelium^[19] and eradication of dysplasia in patients with low-grade dysplasia^[20] and high-grade dysplasia^[20]. Over-

holt *et al*^[20,21] also showed a lower rate of progression of high-grade dysplasia to cancer in the PDT group. There was one study^[22] comparing endoscopic ablation of the metaplastic mucosa (with argon plasma coagulation) after antireflux surgery and showed a trend for superior endoscopic regression of the Barrett's segment after the

ablation, but no difference in cancer incidence^[20]. In ablation of the metaplastic mucosa, 3 studies demonstrated that overall argon plasma coagulation was superior to photodynamic therapy with ablation rates of 59.0% and 27.5% respectively [odds ratio (OR), 3.46, 95% confidence interval (CI): 1.67, 7.81]. These studies did not examine long-term cancer incidences. There were 2 studies comparing argon plasma coagulation to multipolar electrocoagulation which demonstrated similar rates of successful ablation of the metaplastic segment (78.6% in patients treated with multipolar electrocoagulation and 64.4% treated with argon plasma coagulation) and again no long-term data on cancer incidence.

Fayter *et al*^[23] examined the evidence from 11 randomised controlled trials of photodynamic therapy for Barrett's oesophagus. The trials were heterogeneous in their design, the protocol of therapy used, the patients studied (most studies examined patients with high-grade dysplasia, but some had low-grade dysplasia, non-dysplastic epithelium or a combination of histological findings) and outcome measures. The conclusions drawn from this systematic review were: (1) it was not possible to determine whether there was a significant clinical difference between photodynamic therapy and argon plasma coagulation and which would be the most appropriate treatment; (2) photodynamic therapy was more effective than omeprazole alone in producing long-term ablation of high-grade dysplasia and slowing/preventing progression to cancer; (3) Photodynamic therapy with 5-ALA as the photosensitising agent was more effective than placebo in producing regression of dysplasia and reduction in the area of Barrett's epithelium in patients with low-grade dysplasia; (4) photodynamic therapy with 5-ALA may be more effective than with Photofrin; (5) optimal treatment for patients without dysplasia had yet to be determined; and (6) side effects were similar between 5-ALA and Photofrin with higher levels of photosensitivity with Photofrin.

Rees *et al*^[24] examined randomized controlled studies only. They demonstrated that in the 3 studies which examined H₂ receptor antagonists to proton pump inhibitors: cancer risk, eradication of dysplasia or complete regression of the metaplastic segment were not reported. There was a trend towards a reduction in the areas of metaplastic mucosa (but not the length of the Barretts' segment) with PPI. There were no new studies available on antireflux surgery *vs* medical therapy, argon plasma ablation, argon plasma coagulation *vs* multipolar electrocoagulation or argon plasma coagulation *vs* photodynamic therapy since Li *et al*^[17].

Wani *et al*^[25] compared the rate of development of adenocarcinoma in published series of patients with non-dysplastic Barrett's oesophagus, low-grade dysplasia and high-grade dysplasia comparing cohorts treated with endoscopic ablative therapy to those in surveillance programmes without ablation of the mucosa. They found that there were significantly lower rates of adenocarcinoma incidence in the cohorts treated with ablative ther-

apies compared to the control cohorts. The differences were significant for examinations of non-dysplastic Barrett's oesophagus, low-grade dysplasia and high-grade dysplasia.

Demographic factors: Thomas *et al*^[26] showed that age did not influence cancer risk from 41 studies of 9469 patients undergoing surveillance (36635 patient-years follow-up). There was also no significant difference in cancer incidence depending on geographic origin of the included studies. Yousef *et al*^[27] showed that the incidence of adenocarcinoma in males was double the rate in females.

Segment length: Thomas *et al*^[26] showed that from 6 studies including 960 patients with long-segment Barrett's oesophagus (4130 patient-years of follow-up) and 258 patients (1074 patient-years of follow up) that 32 of the 35 cancers which developed were in long segment Barrett's oesophagus (but this did not reach statistical significance). Yousef *et al*^[27] reported a cancer incidence of 0.67% per annum in long segment Barrett's oesophagus and a similar incidence (0.61%) in short segment Barrett's oesophagus in 30 studies.

Dysplasia: Thomas *et al*^[26] did not demonstrate an increased cancer risk associated with dysplasia over non-dysplastic Barrett's oesophagus. Desai *et al*^[28] examined specifically patients without dysplasia at baseline, but there was no comparison cohort in this study and it has subsequently been excluded from this review.

Intestinal metaplasia: The question of the importance of intestinal metaplasia for cancer risk was not specifically examined by any of the meta-analyses.

Enzyme polymorphisms: Bull *et al*^[29] examined enzyme polymorphisms in case-control studies and found an association between Barrett's oesophagus and GSTP1 homozygotes for the Ile105 variant (OR, 1.50, 95%CI: 1.16, 1.95). This genetic variant results in increased IgE and immune-mediated inflammation. There was no other significant association with Barrett's oesophagus and a variety of metabolic gene polymorphisms^[29].

Helicobacter pylori: Rokkas *et al*^[30] showed similar results in studies of oesophageal cancer to those of Barrett's oesophagus with a negative association between the presence of *H. pylori* and oesophageal cancer. The results were similar in studies of *Cag A H. pylori*.

Other medications

The reduction in cancer risk with aspirin and non-steroidal anti-inflammatory drugs was examined in 3 cohort studies by Wang *et al*^[31]. They demonstrated that there was a trend towards lower cancer risk in patients taking aspirin and non-steroidal anti-inflammatory drugs, however 2 case-control studies were excluded for unclear

reasons.

Rees *et al.*^[24] reported one study^[32] comparing celecoxib to placebo and found no difference in cancer risk at 2 years (3/49 and 3/51 patients respectively).

The effects of statins on the risk of oesophageal adenocarcinoma in Barrett's oesophagus were examined by Alexandre *et al.*^[33], who found two prospective cohort studies. The first was a multicentre study from the Netherlands of 570 patients and demonstrated a hazard ratio of 0.46 (95%CI: 0.21, 0.99) and in patients taking statins and non-steroidal anti-inflammatory drugs the hazards ratio was 0.22 (95%CI: 0.06, 0.85)^[34]. Nguyen *et al.*^[35] examined 812 patients in a case-control cohort in the Veterans Affairs Healthcare System and showed an incidence density ratio of 0.56 (95%CI: 0.36, 0.86) for patients with Barrett's oesophagus taking statins.

Singh *et al.*^[36] also demonstrated a protective effect of statins in their meta-analysis of 5 studies and a greater protective effect of combining statins with non-steroidal anti-inflammatory drugs with respect to oesophageal cancer risk.

Decision to enrol in surveillance

The American College of Gastroenterology and American Gastroenterological Association have defined Barrett's oesophagus as any length of recognisable columnar mucosa which demonstrates intestinal metaplasia at biopsy^[3,4], maintaining the dogma that intestinal metaplasia is necessary for malignant risk on the basis that in many cohort studies intestinal metaplasia has been demonstrated adjacent to adenocarcinoma of the oesophagus. The ACG acknowledge the difficulties associated with sampling error in the detection of intestinal metaplasia and also exclude "ultra-short" segments (< 1 cm) due to poor interobserver reliability of recognition. The BSG broadly agrees with this definition^[2] and whilst there is no requirement for the presence of intestinal metaplasia for diagnosis, on the basis of the higher cancer risk in subjects with intestinal metaplasia in the Northern Ireland pathology database cohort^[37] and low rate of development of high-grade dysplasia and adenocarcinoma in the Danish pathology database cohort which only included subjects with intestinal metaplasia^[38], surveillance is only recommended if intestinal metaplasia is detected during the either the index or the first surveillance endoscopy in patients with short segment (< 3 cm) metaplasia. The rationale for this is that it is felt that the risks of endoscopy probably outweigh the benefits. Both guidelines have excluded very short segments or tongues of metaplasia due to difficulties in clinical assessment rather than on the basis of a proven low risk of complications and there are no good data to support or refute these assertions. The evidence from meta-analyses concerning the role of segment length and intestinal metaplasia is discussed below.

The ACG recommend that the consideration for beginning a surveillance programme should include age, likelihood of survival over the next 5 years, patient's

understanding of the process and its limitations for the detection of cancer and the willingness of the patient to adhere to the recommendations.

The ACG supports surveillance of Barrett's oesophagus as in 7 retrospective series the survival in cancers was improved over those detected outside of surveillance programmes. There has not yet been a trial published demonstrating benefits of surveillance in a prospective fashion, however the BOSS study (endoscopic surveillance *vs* endoscopy at time of need) remains underway at present^[39].

The ACG, AGA and BSG recommend 4-quadrant biopsies taken every 2 cm throughout the metaplastic segment at index endoscopy and surveillance (if no dysplasia has been previously detected or other macroscopic lesions are present). This biopsy protocol has not yet been tested in a meta-analysis. The difficulties involved in adequately sampling the tissue at risk and variability in histopathological interpretation of the tissue examined should be subject to further studies beyond the initial work done by Levine *et al.*^[40].

Risk stratification and frequency of surveillance

The ACG recommend that the first two endoscopies are undertaken within a year and if no dysplasia is detected then the surveillance interval is 3 years. If low-grade dysplasia is detected then surveillance interval should be within 6 mo. This recommendation was based upon a poor level of evidence from cohort studies and expert opinion^[3].

The BSG note that risk factors for cancer development include the presence of intestinal metaplasia (3 × compared to no intestinal metaplasia), low-grade dysplasia (5.67 × non-dysplastic Barrett's oesophagus), male gender (2 × that of females), smoking (2 × non-smokers). They note that longer segment lengths were associated with a trend to increased risk and no relationship was demonstrated with alcohol consumption and obesity^[2].

The ACG and AGA stratify risk based only on the presence of dysplasia after the diagnosis of Barrett's oesophagus and that further work to assess the extent of dysplasia and develop biomarkers is required^[3,4]. The BSG note that in future, surveillance intervals will take into account all of the socio-demographic risk factors and characteristics of the Barrett's segment as well as biomarker panels^[2]. Until such algorithms are developed, surveillance frequency is based on dysplasia and length only. The ACG also note that a randomised controlled trial to assess the impact of surveillance is required. The BSG also incorporate segment length and allow for consideration of other risk factors (see above)^[2]. The BSG have lengthened the recommended surveillance interval for non-dysplastic Barrett's oesophagus (based upon the recent lower cancer incidence estimates) in line with the AGA and allowed some further individualised risk stratification to be incorporated into the frequency of surveillance and in line with the ACG, the interval for low-

grade dysplasia is 6 mo. The AGA recommend surveillance of low-grade dysplasia in 6-12 mo. Inflammatory atypia is difficult to distinguish from true dysplasia^[2,41] and the guidelines recommend repeat biopsy after treatment with acid suppression^[3] and expert pathological review of biopsies which are dysplastic or have changes indefinite for dysplasia^[2-4].

The evidence from the meta-analyses in supporting intestinal metaplasia and low-grade dysplasia as markers of increased risk of malignancy is poor with no significant difference demonstrated in patients with low-grade dysplasia at index endoscopy^[26] and no papers on the necessity for the detection of intestinal metaplasia to confer a malignant risk.

Evidence for difference in risk dependent on segment length is also poor with only trends demonstrated^[26,27] and it is only on weak evidence that decisions on consideration of surveillance as well as surveillance interval are made on these features.

There is greater evidence for a lower risk of oesophageal cancer development in patients who have *H. pylori* infection^[30] and for a higher risk in males over females^[27].

What steps to minimise risk of developing Barrett's

The ACG notes that older Caucasian males with chronic reflux symptoms are the group with the highest prevalence of Barrett's oesophagus and there were no direct recommendations from the ACG to reduce the risk of development of Barrett's oesophagus^[3]. The BSG state that the known risk factors are male gender, older age and history of reflux symptoms as well as an association with white race, higher waist: hip ratio and abdominal circumference. There is a less clear relationship with obesity as measured by body mass index and cigarette smoking. The BSG also note the small degree of familial clustering^[2]. The AGA go one step further in recommending consideration of screening for Barrett's oesophagus in patients with multiple risk factors for oesophageal adenocarcinoma (age 50 years or older, male sex, white race, chronic gastro-oesophageal reflux disease, hiatal hernia, elevated body mass index and intra-abdominal distribution of body fat).

The published meta-analyses have demonstrated that the significant risk factors associated with Barrett's oesophagus are male gender^[6], smoking^[7], obesity^[8-10], prolonged symptoms of gastro-oesophageal reflux^[11], absence of *H. pylori* infection^[12,13] and the presence of hiatus hernia^[14]. Age has not been demonstrated to influence cancer risk in the meta-analyses^[26].

Minimisation of risk of cancer development in Barrett's

The ACG, AGA and BSG did not recommend fundoplication over medical therapy to reduce cancer development^[2-4] and this review supports this strategy^[16,17], however there were encouraging data concerning reduction in risk of development of dysplasia with surgical therapy over acid suppression therapy^[18].

The question of ablation of the metaplastic mucosa

is a complex one requiring further examination, however there are promising results^[25] and the SURF trial comparing radiofrequency ablation to surveillance in low-grade dysplasia remains underway^[42].

The ACG note that a meta-analysis did demonstrate a lower risk of cancer development in patients taking non-steroidal anti-inflammatory drugs^[43] and that the ASPECT study (a randomised study of aspirin and low and high-dose esomeprazole) remains underway^[44]. The ACG, AGA and BSG did not recommend chemoprevention with aspirin or non-steroidal anti-inflammatory drugs. The ACG cites two cohort studies demonstrating a lower risk of dysplasia development in patients taking PPI therapy, but no evidence to support a reduction in cancer development^[3]. The BSG recommendations are similar to those of the ACG and also do not advocate acid suppression drugs as chemopreventive agents^[2], but they are effective in symptom control.

The AGA note that the patients may derive benefit from aspirin if they have cardiovascular risk factors for which aspirin therapy is indicated, but that neither the use of aspirin or non-steroidal anti-inflammatory drugs are recommended solely to prevent oesophageal adenocarcinoma and that the evidence to support the use of PPI therapy to reduce the risk of cancer and dysplasia is indirect and not been proven in a long-term controlled trial^[4]. The results from the meta-analyses of Alexandre *et al.*^[33] and Singh *et al.*^[36] showing the protective effect of aspirin and in particular the effect in conjunction with statins is exciting and may form the basis for effective chemoprevention in the future.

CONCLUSION

The evidence to support the current decisions to enrol patients with Barrett's oesophagus in surveillance programmes and surveillance interval are based on weak evidence on the clinical outcome of features of the metaplastic segment. Further consideration should be given to the role of gender and helicobacter status in examining cancer risk as well as the role of aspirin and statins in chemopreventive strategies and ablation of the metaplastic segment. Public health programmes should also examine measures to reduce the associations of Barrett's oesophagus, notably, smoking and obesity. The relevance of male gender and absence of helicobacter infection should also be considered.

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