Epidemiology of microscopic colitis

We read the interesting paper by Pardi *et al* on the epidemiology of microscopic colitis in Olmsted County, Minnesota, USA (*Gut* 2007; **56**: 504–8). They concluded that the incidence of microscopic colitis increased significantly over time, and by the end of the study, the incidence and prevalence were significantly higher than reported previously. In fact, compared with other epidemiological studies, in the last years of the study period they describe the highest incidence figures of microscopic colitis ever reported.

However, is difficult to compare the crude incidence rates of several studies if we do not know the age structure of the population pyramid of each geographical area. As microscopic colitis is associated with older age, a higher incidence will be expected among aging populations. A solution for this is to report the standardised incidence rates; however, they are not reported in most of the published epidemiological studies. Another possibility is to describe the population pyramid of each geographical area. We think that the paper of Pardi *et al* would have been more understandable if they had described the population pyramid of Olmsted County. In our epidemiological study on the incidence of microscopic colitis in Terrassa, Spain,¹ we reported the population pyramid. Thus, Pardi *et al* should assess if there are any differences in the age structure and sex structure of the population pyramids between Olmsted County and Terrassa. In this sense, if population pyramids were similar, they could conclude that there is a true difference in the incidence of microscopic colitis.

Fernando Fernández-Bañares, Maria Esteve, Josep Maria Viver

Department of Gastroenterology, Hospital Universitari Mutua Terrassa, Terrassa (Barcelona), Spain

Correspondence to: Dr F Fernández-Bañares, Department of Gastroenterology, Hospital Universitari Mutua Terrassa, Plaça Dr Robert 5, 08221 Terrassa (Barcelona), Spain; digestiu@mutuaterrassa.es

Competing interests: None.

References

- 1 Fernández-Bañares F, Salas A, Forné M, *et al*. Incidence of collagenous and lymphocytic colitis: a five-year population based study. *Am J Gastroenterol* 1999;**94**:418–23.

Authors' response

As Fernández-Bañares *et al* point out, it is difficult to compare crude incidence or prevalence rates across populations with different demographic structures. They suggest that we report our population pyramid to aid in interpreting the difference in microscopic colitis incidence observed in Minnesota compared with Spain. However, this would not be appropriate as there is no simple way to integrate the population structure with the various age- and sex-specific incidence rates and arrive at any kind of coherent conclusion. Instead, as they suggest, one should standardise the local incidence rates to an external reference population, which we, in fact, did in our paper.¹ As we standardised our rates to the 2000 US white population, it would be the demographic "pyramid" to consider. Standardising their age- and sex-specific incidence rates to this same reference population

to enable a direct comparison would be even better. Unfortunately, the age- and sex-specific incidence rates with which to accomplish this comparison are not reported in their paper.

The remaining alternative is to carry out an indirect standardisation, whereby we apply our own age- and sex-specific incidence rates to their population structure. Thus, if the age- and sex-specific incidence rates for microscopic colitis in Olmsted County, Minnesota, USA, in 1985–2001¹ are applied to the comparable age- and sex-specific denominator populations in the Hospital Mútua de Terrassa health district of Terrassa, Spain in 1993–7, then one would expect to see 73 cases of microscopic colitis instead of the 60 cases that were actually observed. Thus, the Olmsted County rates are still higher even after accounting for any demographic differences between the two populations.

Therefore, explanations other than differences in the underlying age structure in our respective populations must be considered. One possible explanation, as discussed in our paper, is different exposure rates in the two populations to certain environmental factors, such as medications, associated with microscopic colitis.² Higher incidence rates could also be expected if a higher percentage of our population underwent sigmoidoscopy or colonoscopy with mucosal biopsies for the evaluation of diarrhoea—that is, differential application of the diagnostic test.

Darrell S Pardi, Edward V Loftus Jr, L Joseph Melton III, Alan R Zinsmeister

Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Correspondence to: Dr D S Pardi, 200 First Street SW, Rochester, MN 55905, USA; pardi.darrell@mayo.edu

Competing interests: None.

References

- 1 Pardi DS, Loftus EV, Smyrk TC, *et al*. The epidemiology of microscopic colitis: a population-based study in Olmsted County, Minnesota. *Gut* 2007;**56**:504–8.
- 2 Beaugerie L, Pardi DS. Drug-induced microscopic colitis: a proposal for a scoring system and review of the literature. *Aliment Pharmacol Ther* 2005;**22**:277–84.

Non-endoscopic immunocytological screening test for Barrett's oesophagus

Surveillance strategies or chemoprevention of clinically diagnosed Barrett's oesophagus are unlikely to alter population mortality from oesophageal adenocarcinoma since it is estimated that only 5% patients with Barrett's oesophagus are diagnosed, despite the increasing use of endoscopy.¹ Endoscopic screening for Barrett's oesophagus in white men aged over 50 years with chronic heartburn has therefore been advocated in the US.² However, the prohibitive cost of endoscopy and the pathological expertise required make this screening programme problematic.

The aim of this study was to develop a screening test that did not rely on endoscopy and would be applicable to primary care. A non-endoscopic cytological test, which has been successfully used for the diagnosis of oesophageal squamous carcinomas in high-risk areas, was adapted by combining it with immunocytology. The device (bought from

Nanru Technologies, Bellville, South Africa) consists of a sponge contained within a gelatine capsule that dissolves in the stomach within 5 min (fig 1A,B).³ Liquid-based cytology was used to create a cell monolayer and the slides created were stained for minichromosome maintenance protein 2 (Mcm2). Mcm2 is a proliferation marker that is abnormally expressed at the luminal surface in Barrett's oesophagus, with expression indices that correlate with the degree of dysplasia.⁴

Following approval from the Cambridge Local Research Committee, 43 patients with known Barrett's oesophagus (defined by endoscopy and a diagnosis of intestinal metaplasia) and 54 healthy volunteers were recruited (table 1). Diagnostic endoscopy was voluntary for healthy subjects, and, unfortunately, almost all (95%) refused. The participants rated the acceptability of the capsule sponge as 4.0 (2.0–9.0) using a linear scale of 0 (worst imaginable experience) to 10 (very enjoyable experience), where 5 was neither pleasant nor unpleasant. Of the patients with Barrett's oesophagus, 80% stated that they would choose the capsule sponge in preference to endoscopic surveillance. There were no complications, and 91 of 96 (94.8%) samples were adequate for analysis. The squamous (red arrow) and columnar cells (black arrow) were easily distinguishable (fig 1C,D) and good-quality immunostaining for Mcm2 was obtained (fig 1D).

A total of 27 of 40 (67.5%) specimens of Barrett's oesophagus were positive compared with 17 of 52 (32.6%) specimens from healthy volunteers, giving a sensitivity and specificity of 67.5% and 67.3%, respectively. However, patients with Barrett's oesophagus with a positive test had a statistically longer segment than those with a negative test ($p = 0.01$); therefore, if only patients with Barrett's oesophagus with a segment longer than 3 cm are considered as true Barrett's oesophagus, the sensitivity and specificity become 76.0% and 62.7%, respectively. Since most volunteers did not undergo endoscopy, it was impossible to ascertain if they had Barrett's oesophagus. Heartburn is the primary risk factor for the presence of Barrett's oesophagus, and since nine (53%) Mcm2 positive controls were patients with a history of heartburn vs three (8%) for the Mcm2 negative patients, there is a possibility that patients with heartburn might have Barrett's oesophagus. To correct for this possible bias, a post hoc analysis excluding all patients with heartburn was performed and the percentage of controls with a positive test result decreased from 37.5% to 20%. In this subgroup analysis, the sensitivity and specificity were 67.5% and 80% for all patients, and 54.3% and 86.7%, respectively, for patients with Barrett's oesophagus with a segment longer than 3 cm.

In summary, the capsule sponge is acceptable to patients and applicable to primary care, thus bypassing the need for screening endoscopy. The immunostained monolayer specimen is amenable to automated microscopy processing. However, further refinements in technique to increase the sensitivity and specificity of this test are necessary before population-based studies can be performed, especially since the quoted specificity applies to a population with a 44% incidence of Barrett's oesophagus, and will be much lower if used in the general population. Overall, this proof-of-principle study suggests that a non-endoscopic

Figure 1 Capsule sponge and cytological specimen. The capsule within its sheath (A) and in its expanded state (B). Papanicolaou-stained slide (C; magnification $\times 200$) and minichromosome maintenance protein 2-stained cellular clumps (D; magnification $\times 400$) in which columnar cells (red arrow) and squamous cells can be clearly seen (black arrow).

Table 1 Patients' demographics

	Patients with Barrett's oesophagus	Controls	p Values
Total number	43	54	
Male:female ratio	13:1	1.2:1	<0.001
Mean (SD) age (years)	62.5 (1.5)	34.0 (1.9)	<0.001
Mean (SD) length of Barrett's oesophagus (cm)	4.7 (0.5)	NA	
Median (range) acceptability rating	5.0 (2.0 to 8.0)	4.0 (2.0 to 9.0)	NS
Mean (SD) number of slides	12.1 (1.1)	11.0 (1.0)	<0.001
Unsuitable specimens	3	2	

NA, not applicable; NS, not significant.

screening test for Barrett's oesophagus is attainable and warrants further investigation.

Pierre Lao-Sirieix

MRC-Cancer Cell Unit, Hutchison MRC Research Centre, Cambridge, UK

Brian Rous, Maria O'Donovan

Department of Histocytology, Addenbrooke's Hospital, Cambridge, UK

Richard H Hardwick

Cambridge Oesophago-Gastric Centre, Addenbrooke's Hospital, Cambridge, UK

Irene DeBiram, Rebecca C Fitzgerald

MRC-Cancer Cell Unit, Hutchison MRC Research Centre, Cambridge, UK

Correspondence to: Dr R Fitzgerald, MRC-Cancer Cell Unit, Hutchison MRC Research Centre, Hills Road, Cambridge CB2 2XZ, UK; rcf@hutchison-mrc.cam.ac.uk

doi: 10.1136/gut.2007.123257

Competing interests: None.

References

- 1 Cameron AJ, Zinsmeister AR, Ballard DJ, *et al.* Prevalence of columnar-lined (Barrett's) oesophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* 1990;99:918-22.

- 2 Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's oesophagus. *Am J Gastroenterol* 2002;97:1888-95.
- 3 Nabeya K, Onozawa K, Ri S. Brushing cytology with capsule for the esophageal cancer. *Chir Gastroint* 1979;13:101-7.
- 4 Sirieix P, O'Donovan M, Brown J, *et al.* Surface expression of mini-chromosome maintenance proteins provides a novel method for detecting patients at risk for developing adenocarcinoma in Barrett's oesophagus. *Clin Cancer Res* 2003;9:2560-6.

Chronic subclinical bowel inflammation may explain increased risk of colorectal cancer in obese people

We read with interest the recent articles on obesity, inflammation and colorectal cancer (CRC).¹⁻³ Although insulin resistance is the most widely accepted underlying mechanism explaining the association between obesity and CRC, recent evidence suggests that the effects of obesity on the immune system in general and on the gut in particular may play a role. We propose that obesity predisposes to CRC through its effects on innate immune activation (IIA) and consequent subclinical bowel inflammation. We further propose that the role of insulin resistance is either complementary or might merely represent an epiphenomenon.

The justification of our argument is explained below.

Recently, we studied the determinants of whole gut inflammation in a normal middle-aged population by determining levels of calprotectin in faeces. Calprotectin is a calcium-binding protein found only in neutrophils and monocytes. Levels in faeces correlate well with faecal levels of indium-labelled white cells and inflammatory bowel disease activity. It is well established that many risk factors for CRC influence levels of IIA in a healthy individual. Lack of physical exercise, for instance, is associated with increased serum levels of C reactive protein, as are body mass index, smoking and increasing age.⁴ We confirmed that faecal levels of calprotectin also correlated directly with increasing age, obesity, and lack of physical activity and fibre intake, demonstrating that these same environmental risk factors are also associated with bowel inflammation⁵ (fig 1).

The link between chronic inflammation and CRC is well documented in patients with ulcerative colitis. In our late middle-aged population, 25% of subjects had increased faecal levels of calprotectin similar to those found in patients with inflammatory bowel disease. Although these cancers follow a different histological course as compared with sporadic CRC, similar genetic mutations tend to occur with similar frequencies in both the groups, suggesting that sporadic CRC could arise or be promoted on a background of chronic subclinical inflammation.⁶ Many other common cancers are associated with chronic inflammation, including oesophageal, gastric, pancreatic and lung cancers. Furthermore, epidemiological studies have shown the chemoprophylactic benefits of non-steroidal anti-inflammatory agents in colorectal and oesophageal cancers, supporting the role of chronic inflammation in their pathogenesis.

The association between obesity, chronic subclinical bowel inflammation and ultimately CRC could result from the effects of obesity to promote generalised innate immune activation or through paracrine effects of mesenteric or serosal adipose tissue. The enlarged adipocytes of obese individuals synthesise increased amounts of various proinflammatory adipokines such as tumour necrosis factor α (TNF α) and interleukin (IL)6, as well as other adipokines known to modulate immune function such as leptin (proinflammatory) and adiponectin (anti-inflammatory).⁷ Adipokines exert autocrine, paracrine or endocrine effects, influencing various metabolic and immune processes. Many of these cytokines and adipokines contribute strongly to insulin resistance, which may merely be an epiphenomenon of this activation rather than playing a direct role in the pathogenesis of CRC. Increased levels of proinflammatory cytokines and reduced levels of adiponectin have been noted in the serum of asymptomatic obese individuals, levels corresponding to the degree of obesity.⁷ Circulating mononuclear cells from the obese individuals have been shown to exhibit increased nuclear factor (NF) κ B nuclear binding with decreased levels of NF κ B inhibitor, together with increased mRNA expression of IL6, TNF α and migration inhibition factor. Furthermore, there is a good correlation between the markers of macrophage activation and plasma levels of free fatty acids, which represents an additional mechanism whereby adipose tissue could influence systemic inflammatory activity.⁸ Central or abdominal obesity correlates more