Celiac disease: malignancy and mortality

Several studies have shown an increased risk of malignancy and mortality in patients with celiac disease, but robust data are lacking. Using the UK general practice database—the largest of its kind—West and colleagues have compared rates of malignancy and mortality in 4,732 people with celiac disease and 23,620 matched controls.

The study showed a modest increase in mortality in patients with celiac disease compared with the general population (hazard ratio [HR] 1.31, 95% CI 1.13 to 1.51) and the risk of any malignancy was similarly increased (HR 1.29, 95% CI 1.06 to 1.55). Since the excess risk of malignancy was greatest during the first year after diagnosis of celiac disease, the authors note that ascertainment bias may account for most of the increase. Analysis of subgroups showed that celiac disease patients were at increased risk of gastrointestinal cancer (HR 1.85, 95% CI 1.22 to 2.81) and lymphoproliferative disease (HR 4.80, 95% CI 2.71 to 8.50). Conversely, the risk of lung cancer was lower in people with celiac disease than in the control cohort (HR 0.34, 95% CI 0.13 to 0.95). It could not be ruled out, however, that this decreased risk was related to a lower proportion of smokers in the celiac disease group. The risk of breast cancer was also markedly reduced in the celiac disease group compared with controls (HR 0.35, 95% CI 0.17 to 0.72) and the authors suggest that this warrants further investigation.

Original article West J *et al.* (2004) Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ* **329:** 716–719

Adenoma miss rate in optical colonoscopy

Optical colonoscopy (OC) is well-established as the method of choice for detecting colorectal neoplasms. Estimates of its sensitivity, however, have relied on subsequent polyp detection by the same technique. Pickhardt and colleagues have completed the first study of the OC adenoma miss rate using a separate reference standard.

The study was part of a multicenter trial evaluating the performance of three-dimensional virtual colonoscopy (VC). A total of 1,233 asymptomatic adults who had been referred for colorectal cancer screening were subjected to same-day VC and OC. The prospective OC was carried out without knowledge of the VC interpretation. After unblinding of the VC results, a second-look OC was carried in all cases where polyps had been missed.

Of 511 polyps (≥5 mm) detected by second-look OC, 55 (10.8%) were missed by the prospective OC. Second-look OC revealed that 21 of these were adenomatous polyps (≥6 mm). Fifteen of the missed neoplasms were nonrectal and the majority of these were located on the backside of a fold. The remaining six missed adenomas were in the rectum, and were within 10 cm of the anal verge in five cases. The OC miss rate for large (≥10 mm) adenomas was 12%.

Pickhardt *et al.* conclude that using VC as a reference standard had revealed a higher OC miss rate than had previously been reported. Although OC is a sensitive method for detecting colorectal neoplasia, they note that there are distinct 'blind spots' where important lesions may be missed.

Original article Pickhardt PJ *et al.* (2004) Location of adenomas missed by optical colonoscopy. *Ann Intern Med* **141:** 352–359

Avoiding false positives in *H. pylori* detection

The ^{13}C-urea breath test (UBT) is widely used in the diagnosis of *H. pylori* infection. False-positive results can be generated, however, by other urease-producing bacteria in the mouth and intestine. Several methods have been devised to avoid this problem, including the endoscopic UBT, in which ^{13}C-urea solution is sprayed directly into the stomach. Although this approach is more reliable, it is invasive and relatively inconvenient. Urita and colleagues have recently described a non-invasive modification, based on breath sample collection through the nostril.

The authors analyzed data from 127 patients, of whom 42 had biopsy-confirmed *H. pylori* infection. Within 1 week of endoscopy, the patients were subjected to both the standard and the modified UBT. Breath samples were collected through the mouth

GLOSSARY
PCR
Polymerase chain reaction

or the nostril for the two tests, respectively, at baseline and at 1, 3, 5, 10, 15, 20 and 30 minutes after administration of the ^{13}C-urea solution.

The modified test was able to differentiate between *H. pylori*-positive and *H. pylori*-negative patients at the 1 minute time point, whereas the standard test did not show significant differences until 3 minutes had elapsed. Additionally, the modified test reached 100% sensitivity and specificity at 20 minutes with a 2.5% cut-off, whereas the optimal values at any time point for the standard test were 97.7% and 94.2%, respectively.

In conclusion, the modified test represents an easy, non-invasive means of avoiding false-positive results in *H. pylori* detection.

Original article Urita Y *et al.* (2004) Breath sample collection through the nostril reduces false-positive results of ^{13}C-urea breath test for the diagnosis of *Helicobacter pylori* infection. *Dig Liver Dis* **36:** 661–665

Crohn's disease: new evidence of mycobacterial involvement

Since Crohn's disease is clinically and histopathologically similar to tuberculosis, leprosy and paratuberculosis, it has been suggested that the disease is caused by a mycobacterial infection. Several studies have detected *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in tissue samples and breast milk from patients with Crohn's disease. Results have been inconsistent, however, and the role of this organism in the etiology of the disease remains controversial. A recent study by Naser and colleagues has shown that viable MAP was detected more frequently in peripheral blood from Crohn's disease patients than in controls.

The study included 28 patients with Crohn's disease, 9 with ulcerative colitis and 15 individuals with no inflammatory bowel disease. Whole blood samples (4 ml) were taken from each participant and the buffy coat layer was used either for genomic DNA extraction for PCR analysis, or for culture.

A MAP-specific DNA fragment was amplified by PCR from a higher proportion of the Crohn's disease samples (46%) and ulcerative colitis samples (44%) than in the controls (20%). Positive MAP cultures were obtained from 50% of the patients with Crohn's disease and 22% of those with ulcerative colitis, whereas all control cultures were negative for MAP.

The study provides more evidence that MAP may be involved in the etiology of Crohn's disease, and Naser *et al.* recommend that larger studies be performed to investigate this further.

Original article Naser SA *et al.* (2004) Culture of *Mycobacterium avium* subspecies *paratuberculosis* from the blood of patients with Crohn's disease. *Lancet* **364:** 1039–1044

High-dose imatinib in metastatic GIST

Imatinib, a small-molecule tyrosine-kinase inhibitor, is approved worldwide for the treatment of gastrointestinal stromal tumors (GIST), at a recommended dose of 400 mg daily. A longer time to progression has been shown, however, using daily doses of 600 mg or greater. Verweij and colleagues have carried out an international, randomized trial to compare the recommended dose with the highest feasible dose of 400 mg twice a day.

A total of 946 patients with GIST were randomly allocated in a 1:1 ratio to 400 mg imatinib either once or twice a day. After a median follow-up of 760 days, progression-free survival was significantly higher in the twice-daily imatinib group compared with the once-daily group: 235 (50%) and 263 (56%) patients had progressed in the two groups, respectively ($P = 0.026$). There was no difference in response rates between the two groups. A complete response was recorded in 5% of patients, whereas 47% had a partial response and 32% had stable disease. Side-effects occurred in 99% of patients in both groups and were generally mild, although occasional severe and unpredictable toxicity was recorded.

Verweig *et al.* conclude that the recommended dose of 400 mg daily imatinib is sufficient when response induction is the sole aim of treatment. The twice-daily regimen, however, gave a longer progression-free survival and so might be more appropriate for patients with widespread metastatic disease.

Original article Verweij J *et al.* (2004) Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* **364:** 1127–1134