

Positive occult blood and negative colonoscopy – should we perform gastroscopy?

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Colorectal cancer (CRC) is the fourth most commonly diagnosed type of cancer and the second leading cause of cancer death in Canada. It has been estimated that there will be 20,800 new cases of CRC in Canada in 2007 and 8700 deaths (1). Overall, Canadian men have a one in 14 lifetime risk and women have a one in 12 lifetime risk of developing CRC; these risks are among the highest worldwide. The five-year survival rate for early cancer is more than 90%, but this number falls to below 10% for those diagnosed with widespread disease (2). Early cancers and precancerous polyps are often asymptomatic, and because early diagnosis and treatment may significantly affect prognosis, there is strong support for population screening for CRC. CRC screening has also been shown to be cost effective, with a cost of less than US\$20,000 per life saved compared with no screening (3). Screening with fecal occult blood testing (FOBT) followed by colonoscopy for positive FOBT, reduces CRC mortality by 15% to 33% (4-6). There is no formal screening program for CRC in Canada, but the National Committee on Colorectal Cancer Screening, supported by Health Canada, recommends biennial FOBT for individuals aged 50 to 74 years (7). If the test is positive, then a follow-up test (usually colonoscopy, but possibly flexible sigmoidoscopy and/or barium enema depending on local resources) should be performed. In a screening population, approximately 40% of positive FOBT will lead to a positive diagnosis (CRC or adenoma) at the time of colonoscopy (8,9). It is reasonable to assume that some cases of positive FOBT with negative colonoscopy may be due to an upper gastrointestinal (GI) malignancy. Therefore, should we be performing a gastroscopy on all patients who have a negative colonoscopy following positive FOBT? No method of screening for gastric cancer has been shown to be cost-effective or reliable in Western countries in detecting potentially curable disease. To date, there are no formal guidelines on whether routine esophagogastroduodenoscopy (EGD) should be performed for FOBT-positive, colonoscopy-negative patients.

FOBT may be performed with a guaiac-based test, an immunochemical test or a heme-porphyrin test. The most commonly used method is the guaiac-based test, eg, Hemoccult II Fecal Occult Blood Test (Beckman Coulter Inc, USA). The mixture turns blue with the pseudoperoxidase activity of hemoglobin and, in general, is best at detecting large, distal lesions. However, small amounts of blood from the upper GI

tract have been shown to be detected by guaiac-based FOBT (10). Red meat and peroxidase-containing foods (eg, turnips, horseradish) (5,6) can lead to falsely positive results. Nonsteroidal anti-inflammatory drugs or acetylsalicylic acid use may also produce a positive FOBT (11). Fecal rehydration increases sensitivity but reduces specificity (12). For asymptomatic colonic neoplasms, the sensitivity of the test has been found to range from 22% to 92% (11,13-15). This wide variation is the result of differences between study designs and sample hydration.

The heme-porphyrin test detects heme and the portion of heme that is converted to iron and porphyrins within the GI tract; these are not detected by guaiac-based tests (16). The heme-porphyrin test allows an exact measurement of total stool hemoglobin but does not differentiate between upper and lower GI tract bleeding, and it has a high false-positive rate. It also requires laboratory processing, and this further limits its use. Immunochemical tests use antibodies to detect human globin epitopes. Globin from the upper GI tract is digested by intestinal enzymes, so it is not detected by immunochemical tests. Therefore, these tests are most likely to localize bleeding to the colon. Again, however, they require laboratory processing, and falsely negative results may arise due to loss of globin antigenicity.

Several studies (17-20) have investigated the diagnostic yield of EGD for positive FOBT results (Table 1). When a FOBT result is positive, most clinicians elect to examine the lower GI tract initially, usually by colonoscopy. However, some studies (17-19) in which patients had bidirectional endoscopy to investigate positive FOBT found a higher yield of abnormal lesions for EGD than for colonoscopy (24% to 36% versus 13% to 26%, respectively, with findings in both examinations in 2% to 9% of patients). CRC was detected in 1% to 6% of patients and colonic adenomas were detected in 8% to 14% of patients, compared with gastric cancer, which was detected in 1% to 1.6% of patients. Although the overall sensitivity of symptoms for the detection of GI lesions was low in a study by Rockey et al (17), there was a 2.6-fold increased risk of an upper GI source of blood loss in the presence of upper GI symptoms (OR 2.6, 95% CI 1.4 to 4.7; P=0.003). The presence of lower GI symptoms were also predictive of a colonic lesion (OR 3.3, 95% CI 1.2 to 9.3; P=0.02). The authors of the above studies argued for EGD and colonoscopy screening for all FOBT-positive patients.



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TABLE 1
Yield of gastroscopy in patients with a positive fecal occult blood test (FOBT)

Author	Year	Patients, n	Type of study	Population investigated	Yield of EGD, n (%)	Patients with malignancy, n (%)	Type of malignancy (n)
Hsia and al-Kawas (24)	1992	70	Prospective	Asymptomatic patients with a positive FOBT and a negative colonoscopy; anemic patients were included	19 (27)	0 (0)	NA
Zuckerman and Benitez (19)	1992	100	Prospective	Patients with occult gastrointestinal bleeding (FOBT-positive, IDA-positive or both); symptomatic patients were included	36 (36)	1 (1)	Gastric
Chen et al (22)	1993	211	Retrospective	Patients with positive FOBT and a negative colonoscopy; symptomatic and anemic patients were included	88 (42)	0 (0)	NA
Geller et al (25)	1993	67	Retrospective	Patients with positive FOBT and colonic polyps; symptomatic patients were included	53 (79)	0 (0)	NA
Rockey et al (17)	1998	248	Prospective	Patients with positive FOBT (22% of the patients had a positive colonoscopy); symptomatic patients were included	71 (28.6)	4 (1.6)	Carcinoma (4)*
Bini et al (23)	1999	498	Retrospective	Asymptomatic patients with positive FOBT and a negative colonoscopy	67 (13)	5 (1.2)	Gastric (4) Esophageal (1)
Velez et al (18)	2002	100	Retrospective	Patients with positive FOBT (13% of the patients had a positive colonoscopy); symptomatic and anemic patients were included	24 (24)	1 (1)	Gastric
Ali et al (20)	2003	260	Retrospective	Patients with positive FOBT (52% of the patients had a positive colonoscopy); symptomatic and anemic patients were included	42 (16)	NR	NA
Hisamuddin et al (21)	2006	99	Retrospective	Patients with positive FOBT (29% of the patients had a positive colonoscopy); symptomatic and anemic patients were included	35 (35)	1 (1)	Duodenal lymphoma†

*Site not specified; †This patient had already been diagnosed with a gastrointestinal lymphoma and cecal carcinoma colonoscopy. EGD Esophagogastroduodenoscopy; IDA Iron deficiency anemia; NA Not applicable; NR Not reported

However, in a retrospective study of 260 patients with positive FOBT followed by upper and lower endoscopy, Ali et al (20) found a greater yield for colonoscopy. In total, 135 patients (52%) had positive colonoscopy findings with 83 polyps and/or masses identified, and 42 patients (16.1%) had positive EGD findings with eight polyps and/or masses identified, although the exact number of neoplasms was not specified. Sixteen patients (6.1%) had a positive EGD and negative colonoscopy, and 109 patients (42%) had a positive colonoscopy and negative EGD.

In those studies, all patients had an EGD and colonoscopy on the basis of positive FOBT results, symptoms and/or anemia. The variation in results may be attributed to differences between the patient populations, as well as to variations in what was deemed to be a clinically significant lesion at the time of endoscopy. Rockey et al (17), for example, designated the following lesions in the colon as potential causes of occult bleeding: carcinomas, adenomas larger than 1 cm in diameter, multiple vascular ectasias, active colitis, and one or more ulcers larger than 1 cm in diameter. In the upper GI tract, the lesions included carcinomas, severe esophagitis, gastritis or duodenitis, a single duodenal or gastric ulcer larger than 1 cm in diameter or two ulcers larger than 0.5 cm in diameter, adenomas larger than 1 cm in diameter, or multiple vascular ectasias). The results cannot be extrapolated to a screening population who, for the most part, is asymptomatic. In trials (21-24) that investigated the yield of gastroscopy only after a negative colonoscopy, the detection of an upper GI source of occult bleeding was 6.1% to 42%, with cancer in 0% to 1.6%. Hisamuddin et al (21) carried out a retrospective audit of 99 FOBT-positive patients who underwent same-day

colonoscopy and gastroscopy. One colonoscopy-negative patient had a duodenal adenoma, and another patient who had a cecal adenocarcinoma and colonic lymphoma was found to have a duodenal lymphoma. No other upper GI tumours were identified in either group, and there was no difference in the detection of benign upper GI lesions between patients with a negative and positive colonoscopy (36% versus 34%). Chen et al (22) found upper GI pathology in 88 of 211 FOBT-positive, colonoscopy-negative patients (42%); 53 patients had erosive gastritis. However, only 25 of those patients (12% of the total patients) had a lesion amenable to treatment. No upper GI cancers were detected. Patients that were older than 60 years of age were significantly more likely to have positive findings at EGD than those younger than 60 years of age (51% versus 22%; $P=0.00003$).

Two studies (23,24) that investigated the need for EGD when FOBT was positive and colonoscopy was negative excluded symptomatic patients. Bini et al (23) found an upper GI source of occult bleeding in 67 of 498 asymptomatic patients (13%), with one esophageal cancer (0.2%), four gastric cancers (1%) and seven gastric polyps larger than 1 cm in diameter (1%) detected. A further 74 patients (15%) had lesions that were not thought to be a cause of occult bleeding (eg, small ulcers or polyps, Barrett's esophagus, nonbleeding varices, nonerosive gastritis, esophagitis or duodenitis). Hsia and al-Kawas (24) found pathology in 19 of 70 asymptomatic patients (27%). The diagnostic yield was 38% in the 13 patients with iron deficiency anemia and 25% in nonanemic patients. There was no significant difference between the two groups, although this was probably due to the small number of anemic patients that were included.

Another group of investigators (25) argued for upper endoscopy even in FOBT-positive patients who were found to have colonic polyps after finding lesions at gastroscopy in 53 of 67 patients (79%). Ulcers were the most common lesion in symptomatic and asymptomatic patients, but again, no cancers were found.

Long-term follow-up studies (6,8,9,26) of FOBT-positive, colonoscopy-negative patients in a CRC screening program have shown a very low risk of developing gastric carcinoma. In each case, the authors reviewed cancer registries and hospital records to assess the number of patients who had been screened for CRC and were subsequently diagnosed with an upper GI tract cancer. Thomas and Hardcastle (9) carried out large bowel investigations in 447 FOBT-positive patients of the 16,985 patients who were screened (2.6%). Neoplasia was detected in 164 of those patients (37%) and 14 patients (5%) also underwent EGD because of upper GI symptoms. One of those patients had a gastric tumour. The remaining 269 patients were followed up for a median of five years. One patient, who had a previous partial gastrectomy and persistent upper GI symptoms, subsequently died from gastric cancer. No other patients had been diagnosed with an upper GI malignancy. In another trial (8), 30,967 patients were screened over a 15-year period. 1767 tests were positive (5.7%), and 1536 complete colonic investigations were performed. 182 patients (10.3%) had a colonic malignancy, and a further 440 patients (24.9%) had an adenoma that was larger than 10 mm in diameter. Of the 209 patients diagnosed with an upper GI malignancy within two years of FOBT, only 10 patients had positive FOBT. Two of those patients were diagnosed because of upper GI symptoms at the time of screening.

In an Italian study (26), 83,489 individuals who were 40 to 74 years of age were screened with FOBT between 1985 and 2001. 5580 individuals (6.7%) were FOBT-positive and proceeded to colonoscopy or barium enema. 3555 patients had a negative assessment, and 2025 patients were deemed to have a positive diagnosis in the lower GI tract: CRC in 354 patients (6.3%), adenomas in 1276 patients (22.9%), hyperplastic polyp in 357 patients (6.4%) and inflammatory bowel disease in 38 patients (0.7%). Gastric cancer incidence was compared between these groups and the expected standardized incidence in the area using a cancer registry. No increased gastric cancer risk was observed between FOBT-negative patients and patients with positive FOBT and lower GI pathology. There was a fourfold increased incidence in the first year of follow-up examinations for patients with positive FOBT and negative colonic assessment, but the total number of excess cases was very small (10 observed cases versus 2.5 expected cases), and this increase did not persist beyond 12 months. The positive predictive value for detecting gastric cancer in this group of patients was determined to be 0.4%, ie, 254 endoscopies would need to be performed to detect one cancer. The positive predictive value increased slightly for patients over 60 years of age to 0.7%. Of note, the type of FOBT changed from guaiac to immunochemical in 1995, but no differences in the association of gastric cancer risk to FOBT positivity were seen between the two types of tests. It is unclear whether patients diagnosed with gastric cancer had other risk factors, because data relating to subjective symptoms, anemia or other risk factors for gastric cancer were not recorded in the cancer registry and hence were not available to the authors. In the Minnesota trial by Mandel

et al (6), in which 46,551 subjects were screened for CRC with FOBT, the diagnostic protocol for a positive test included routine upper endoscopy. However, this practice was abandoned five years into the study because no asymptomatic gastric cancers had been detected. The authors of each trial concluded that routine gastroscopy was not justified for patients in a screening program with positive FOBT and negative colonoscopy, and should be reserved for symptomatic patients or those with other risk factors.

The issue of whether an EGD is required for FOBT-positive, colonoscopy-negative patients remains controversial. An attempt to reduce the frequency of false-positives by performing an immunochemical FOBT prior to colonoscopy in patients with a positive guaiac-based test improved specificity for the detection of colorectal neoplasms (27). However, this was shown to be at the expense of sensitivity (28), which inevitably reduces the usefulness of FOBT as a screening test.

There appears to be little doubt that an upper GI cause for occult bleeding may be found in a significant number of patients with positive FOBT and negative colonoscopy, with one study (22) quoting a yield for gastroscopy of 42%. The actual incidence of cancer in these patients is very low (1.6%), and long-term follow-up has shown that only 0.5% of those patients develop gastric cancer (8). Although several studies (19,22,25) have shown a similar prevalence of upper GI pathology in symptomatic and asymptomatic patients, Rockey et al (17) showed a positive correlation between symptoms and abnormal endoscopy, although with a low sensitivity. In any case, it is likely that many of the lesions in nonanemic, asymptomatic patients are not of clinical significance.

Because we are hopefully beginning an era of population-based CRC screening with FOBT in Canada, it is unlikely to be feasible or cost-effective to perform EGD in all FOBT-positive, colonoscopy-negative patients. In the absence of formal guidelines, we feel that routine EGD is not indicated. On an individual patient basis, the presence of symptoms, anemia or risk factors for gastric cancer will influence this decision. A large, prospective trial evaluating the outcomes of EGD in this patient population would provide valuable evidence to guide future decision-making.

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