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Commentary

Use of upper endoscopy to evaluate patients with a positive faecal occult blood test and negative colonoscopy: Is it appropriate?

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Screening for colorectal cancer (CRC) with annual faecal occult blood testing (FOBT) is effective and cost-effective, and the cost is less than $20,000 per year of life saved compared with no screening [1]. Based on strong evidence that population-based screening can reduce the incidence of CRC [2] and CRC-related mortality [3–5], the U.S. Preventive Services Task Force [6], the American Cancer Society [7], the U.S. Multisociety Task Force on Colorectal Cancer [8] and others [9,10] have recommended annual FOBT alone or in combination with flexible sigmoidoscopy as acceptable screening options for persons at average risk for CRC.

Guaiac-based FOBTs make use of the pseudoperoxidase activity of haeme or haemoglobin. These tests turn blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as the hydrogen peroxide that is present in the developing solution [11]. Although guaiac-based tests detect the pseudoperoxidase activity of haemoglobin, they are not specific for human haemoglobin. There are currently several guaiac-based tests that are available for the detection of faecal occult blood, and the characteristics of these tests vary considerably.

Haemoccult II is the FOBT most widely used to screen for CRC [12–14]. The sensitivity of Haemoccult II test kits is approximately 30–50% for the detection of CRC and even lower for the diagnosis of polyps, with the wide range of estimates reflecting different study designs and whether or not the test was rehydrated [8,12,15]. In contrast, the specificity of the Haemoccult II test is substantially higher, ranging from 97% to 99% [8,12,15].

Despite a high specificity, the positive predictive value of FOBT for the detection of CRC (2–18%) and polyps $\geq$1 cm in diameter (17–27%) is low [6,11,12]. There are several reasons that may explain the low positive predictive value of FOBT for CRC and large polyps, including use of the test in a low-risk screening population, bleeding from trivial colonic lesions other than CRC or large polyps, blood loss from the upper gastrointestinal tract, non-compliance with dietary restrictions, use of rehydration and other factors [11].

Current guidelines recommend colonoscopy as the procedure of choice to evaluate patients with a positive FOBT because it was the diagnostic procedure used in most of the FOBT screening trials and because it is substantially more accurate than double-contrast barium enema or other tests for the detection of advanced adenomas and cancers [8,9,11]. However, when colonoscopy fails to identify a source of occult bleeding, there are no formal recommendations regarding further endoscopic evaluation of these patients.

In this issue of *Digestive and Liver Disease*, Hisamuddin et al. [16] present the results of a retrospective study of 99 patients with a positive FOBT who underwent same-day oesophagogastroduodenoscopy (EGD) and colonoscopy. The primary aim of their study was to address the question of whether EGD should be performed in patients with a positive FOBT who have a negative colonoscopy.

Among the 99 patients, 70 had a normal colonoscopic examination and 29 had a potential source of occult bleeding identified by colonoscopy. Overall, the authors found that 35 of the 99 patients (35%) had an abnormal EGD. Interestingly, the proportion of patients who had an abnormal EGD did not differ between subjects with a normal colonoscopy

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and those with an abnormal colonoscopic examination (36% versus 34%). Based on their findings, the authors concluded that routine use of EGD in FOBT-positive individuals is not indicated and should be undertaken only for appropriate symptoms.

Although the findings of this study are interesting and provocative, there are several issues that should be considered when interpreting their findings. First, only 10 of the 99 individuals were truly asymptomatic and had colonoscopy for CRC screening; the remaining 89 subjects had colonoscopy performed for other indications (rectal bleeding, anaemia, diarrhoea, abdominal pain or weight loss) or were referred for CRC screening but were not truly asymptomatic. Therefore, it is difficult to generalise these findings to asymptomatic average risk patients undergoing CRC screening. Second, the reasons why these patients had EGD performed are unclear, and were at the discretion of the endoscopist. This has the potential to bias the findings of their study. Finally, the study was retrospective and 193 of the 292 patients who had bidirectional endoscopy were excluded for various reasons, including such reasons as the FOBT was not performed or was negative.

Despite these limitations, the results of this study are interesting and highlight an important and controversial issue—should EGD be performed in asymptomatic patients with a positive FOBT who have a negative colonoscopy? To date, there are no formal recommendations regarding further evaluation of the gastrointestinal tract in this population.

Several previous studies have addressed this controversial issue and a summary of these studies is shown in Table 1. The reported frequency of lesions identified by EGD in patients with a positive guaiac-based FOBT ranges from 13% to 79%, with cancers of the upper gastrointestinal tract being identified in 0–2% of subjects [17–25]. The wide variability in the frequency of upper gastrointestinal lesions is likely due to marked differences in the patient populations studied and differences in the definition of what constitutes a clinically important lesion.

The optimal approach to colonoscopy-negative patients with a positive FOBT is unknown, and the pros and cons of performing EGD in these individuals should be carefully considered. The obvious benefit of performing EGD is to diagnose curable malignant lesions and other clinically important lesions of the upper gastrointestinal tract that would result in a change in management.

Although none of the 99 patients in the study by Hisamuddin et al. [16] had a cancer of the upper gastrointestinal tract diagnosed, several patients had lesions identified that could potentially result in a change in clinical management, including erosive gastritis in eight, duodenal ulcer in six, gastric ulcer in three, gastric polyps in three, oesophageal strictures in two, Savary–Miller grade II or III oesophagitis in two patients, as well as Barrett's oesophagus, duodenal adenoma and duodenal lymphoma in one patient each. In an ongoing prospective study of over 1000 asymptomatic patients at average risk

Table 1
Published studies of EGD for the evaluation of patients with a positive guaiac-based FOBT

Author [reference number]	Year published	Number of patients	Study design	Patient population	Proportion with a clinically important lesion (%)	Proportion with cancer (%)
Zuckerman and Benitez [17]	1992	100	Prospective	53 were FOBT+, 31 were FOBT+ and had IDA, 16 were FOBT− and had IDA; 31 had GI symptoms; not all patients had a negative colonoscopy	36	1
Hsia and Al Kawas [18]	1992	70	Prospective	Asymptomatic FOBT+ patients with a negative colonoscopy; 13 had IDA	27	0
Geller et al. [19]	1993	67	Retrospective	FOBT+ patients with colon polyps; 27 had GI symptoms	79	0
Chen et al. [20]	1993	211	Retrospective	FOBT+ with a negative colonoscopy; 33 had anaemia; 37 had GI symptoms	42	0
Rockey et al. [21]	1998	248	Prospective	FOBT+; 91 had GI symptoms; not all patients had a negative colonoscopy	29	2
Bini et al. [22]	1999	498	Retrospective	Asymptomatic FOBT+ patients at average risk for CRC; all patients had a negative colonoscopy; 133 had anaemia	13	1
Velez et al. [23]	2002	100	Retrospective	FOBT+ patients; not all patients had a negative colonoscopy; 19 had anaemia	24	1
Ali et al. [24]	2003	260	Retrospective	FOBT+ patients; not all patients had a negative colonoscopy; some were anaemic	16	NS
Bini et al. [25]	2005	420	Prospective	FOBT+ patients; not all patients had a negative colonoscopy; 184 had anaemia; 132 had GI symptoms; 210 were taking warfarin	37	1

Note: FOBT, faecal occult blood test; IDA, iron deficiency anaemia; GI, gastrointestinal; CRC, colorectal cancer; and NS, not stated.