

## COLORECTAL CANCER

# Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population

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**Background:** The guaiac faecal occult blood test (G-FOBT) is recommended as a screening test for colorectal cancer but its low sensitivity has prevented its use throughout the world.

**Methods:** We compared the performances of the reference G-FOBT (non-rehydrated Hemocult II test) and the immunochemical faecal occult blood test (I-FOBT) using different positivity cut-off values in an average risk population sample of 10 673 patients who completed the two tests. Patients with at least one test positive were asked to undergo colonoscopy.

**Results:** Using the usual cut-off point of 20 ng/ml haemoglobin, the gain in sensitivity associated with the use of I-FOBT (50% increase for cancer and 256% increase for high risk adenoma) was balanced by a decrease in specificity. The number of extra false positive results associated with the detection of one extra advanced neoplasia (cancer or high risk adenoma) was 2.17 (95% confidence interval 1.65–2.85). With a threshold of 50 ng/ml, I-FOBT detected more than twice as many advanced neoplasias as the G-FOBT (ratio of sensitivity = 2.33) without any loss in specificity (ratio of false positive rate = 0.99). With a threshold of 75 ng/ml, associated with a similar positivity rate to G-FOBT (2.4%), the use of I-FOBT allowed a gain in sensitivity of 90% and a decrease in the false positive rate of 33% for advanced neoplasia.

**Conclusions:** Evidence in favour of the substitution of G-FOBT by I-FOBT is increasing, the gain being more important for high risk adenomas than for cancers. The automated reading technology allows choice of the positivity rate associated with an ideal balance between sensitivity and specificity.

Colorectal cancer is a major public health issue in all industrialised countries. As a consequence of the characteristics of this cancer (major effect on prognosis depending on stage at diagnosis, long preclinical phase with frequent precancerous lesions), screening is of considerable value. Colonoscopy is the most accurate test for detecting early cancers and for the detection and removal of high risk adenomas. However, because of its potential harm, the availability of qualified endoscopists as well as costs aspects, strategies, including the use of the faecal occult blood test (FOBT), have been proposed for large scale population screening programmes in several areas throughout the world. The efficacy of strategies based on biennial FOBT has been established in three randomised and one non-randomised controlled trial using Hemocult, a guaiac-faecal occult blood test (G-FOBT).<sup>1–4</sup> Such results have been available for many years but several test limitations have, to a great extent, prevented its use throughout the world, the major weakness being its low sensitivity. The higher sensitivity of the immunochemical faecal occult blood test (I-FOBT), using a specific human haemoglobin, has been established in numerous recently reviewed studies.<sup>5–7</sup> However, to represent a valuable alternative screening test in large scale populations, I-FOBT needs to demonstrate other qualities, including reproducibility and high specificity. Several recent studies have emphasised the value of an automated reading process as it ensures reproducibility and provides a quantitative outcome, making it possible to identify the cut-off corresponding to the optimal balance between sensitivity and specificity.<sup>8–10</sup>

The aim of this study was to compare the performances of the reference G-FOBT (non-rehydrated Hemocult II test) and I-FOBT in a general average risk population, with automated reading process (Magstream 1000; Fujirebio, Tokyo, Japan),

enabling a comparison between different positivity cut-off points for I-FOBT.

## MATERIAL AND METHODS

### Study population

Since June 2004, a screening programme has been implemented using a conventional G-FOBT, the Hemocult II, for individuals aged 50–74 years in the geographic area of Calvados (Normandy, France). The beginning of the programme was staggered among six separate zones within the area. Attendees were offered the possibility of joining a study comparing I-FOBT (Immudia/RPHA; Fujirebio, Tokyo, Japan) with the conventional G-FOBT. This preliminary analysis focused on all tests performed from 1 June 2004 to 30 June 2005. During this period, among 11 333 people who were offered the test, 529 declined and participated only in the screening programme with the G-FOBT and 10 804 participated in the study by undertaking the two tests.

### Study design

The targeted population was contacted by post to explain the aim of the study, and invited to contact their practitioner to undergo both tests. Practitioners were supplied with study kits and invited to administer tests to patients aged 50–74 years at the end of their regular consultation. Study kits contained a short description of the study, instructions for the collection of faeces and mailing of samples to the laboratory, a consent form, two sample tubes for collection of faeces (Immudia/RPHA), a

**Abbreviations:** G-FOBT, guaiac faecal occult blood test; I-FOBT, immunochemical faecal occult blood test; RFP, ratio of false positive rate; RSN, ratio of sensitivity

test kit card (Hemoccult II) and a prestamped envelope for mailing of samples.

The screening procedure was considered positive when at least one of the tests was positive. The patient and practitioner were informed of the overall screening procedure result, blinded to each individual test result. In the case of a positive result, the patient was invited to consult his/her practitioner. The primary care provider was responsible for referring patients with positive test results for further evaluation.

The study was approved by the local ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) and all participants gave written informed consent.

**Faecal occult blood test**

Patients were asked to obtain two faecal samples at home on two different days for the I-FOBT and two faecal samples each from three consecutive stools for the conventional G-FOBT. The same stools could be used for both tests. No specific dietary restriction was stipulated. Samples for the Hemoccult II test were spread directly onto filter paper containing guaiac gum through oval spaces on the test kit card. Samples for the Immudia/RPHA test were obtained using a brush contained within the collection tube. Samples of both tests were sent to the central analysis centre (Institut inter-Régional pour la Santé, Tours, France).

All immunochemical tests were processed at the central laboratory using the Magstream 1000 automated device (Fujirebio). Faecal occult blood was detected using immunological indirect agglutination. Magnetic gelatin particles attached to antihuman haemoglobin placed in a magnetic field were used to quantify the level of haemoglobin using an optical reader. When a plate with 80 samples was tilted 60° from the horizontal position, free magnetic particles could slide down the slope of the well, thus forming a measurable line. The higher the presence of human haemoglobin, the more the

particles are prevented from sliding down the well, and therefore the shorter the line is. Thus haemoglobin level was expressed as a quantitative outcome. According to the manufacturer’s instructions, the test was considered positive when at least one of the two samples contained at least 20 µg/ml haemoglobin (0.1–0.2 mg haemoglobin/g stool).

All guaiac tests were processed at the central laboratory. Reading was not automated but was performed by trained staff and under strict quality control (double reading, control of frequency of positive tests, reproducibility). Readers of the guaiac test were blinded to the patient’s history and to the result of the immunochemical test. Hemoccult II tests with at least one positive oval were considered positive.

According to the recommendations of the manufacturers of Hemoccult, the delay from first faeces deposit to processing must not exceed 14 days. Where there was a delay of more than 14 days (0.11%), the test was returned to the patient with a new test requested.

**Colonoscopy**

Colonoscopies were performed in 20 centres (public hospitals or private clinics). Data on colonoscopies were recorded on a specific form with information on the quality of the investigation (quality of preparation, completeness of colonoscopy) and results (number, size and localisation of adenomas and colorectal cancers, and whether a biopsy was performed). Histological results were also requested. Patients were excluded from the analysis if the endoscopic examination was incomplete (caecum not visualised) and no double-contrast barium enema confirmed the absence of polypoid lesions. However, if a colonoscopic examination was incomplete because of obstructing tumours, the results were included in the analysis. If a patient had more than one polyp, the most advanced pathological lesion or the largest lesion was included in the analysis.

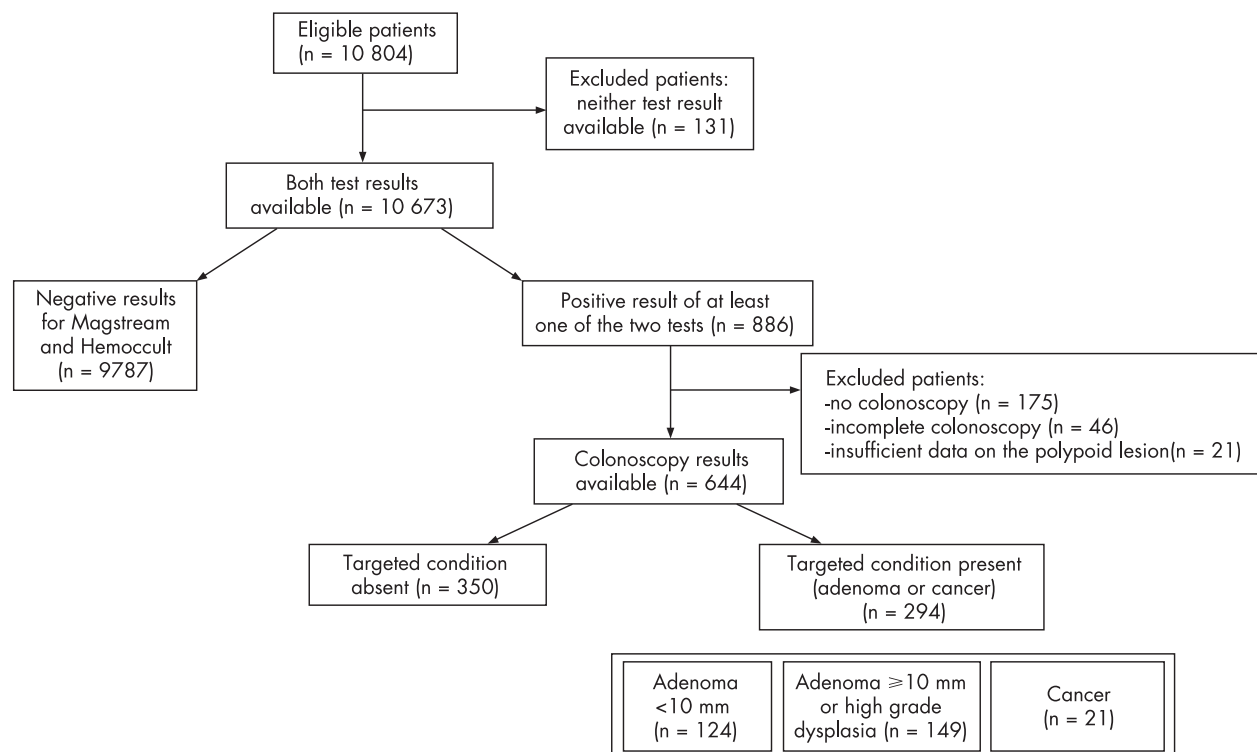


Figure 1 Study design.

**Table 1** Characteristics of the study population

	Number of patients (%)	
	Patients with two analysable tests (n = 10 673)	Analysed patients (negative tests or analysable colonoscopy) (n = 10 431)
Sex (n (%))		
Male	4553 (42.7)	4427 (42.4)
Female	6120 (57.3)	6004 (57.6)
Age		
Mean (SD) (y)	62.1 (6.9)	62.1 (6.9)
50–54 (n (%))	2020 (18.9)	1991 (19.1)
55–59 (n (%))	2584 (24.2)	2532 (24.3)
60–64 (n (%))	2052 (19.2)	2001 (19.2)
65–69 (n (%))	2190 (20.5)	2134 (20.5)
70–74 (n (%))	1827 (17.1)	1773 (17.0)
FOBT (n (%))		
G-FOBT and/or I-FOBT positive	886 (8.3)	644 (6.2)
G-FOBT positive	260 (2.4)	191 (1.8)
I-FOBT positive	733 (6.9)	530 (5.1)
I-FOBT and G-FOBT negative	9787 (91.7)	9787 (93.8)

G-FOBT, guaiac faecal occult blood test.

The immunochemical faecal occult blood test (I-FOBT) was used at the usual cut-off value.

### Pathological findings (histology)

Histological characteristics of the polyps included normal mucosa, hyperplastic polyps and adenoma (tubular, tubulovillous, or villous). Hyperplastic polyps were not included as neoplasias. Advanced colonic neoplasia was defined as adenomas measuring 10 mm or more, adenomas with high grade dysplasia or invasive cancer. Intramucosal carcinoma and carcinoma in situ were classified as adenoma with high grade dysplasia. The criterion for diagnosing cancer was an invasion of malignant cells beyond the muscularis mucosa.

### Statistical analysis

The population of eligible patients comprised all patients who had given written consent, from 1 June 2004 to 30 June 2005 (n = 10 804). Patients in whom one or both tests was not performed or who had inconclusive results (n = 131) were excluded from the study, as were those with a positive screening test but no satisfactory colonoscopy result (n = 242). Figure 1 shows a summary of the study.

As the confirmatory procedure (colonoscopy) was restricted to subjects classified as positive on at least one of the tests, the sensitivity and specificity of each test could not be directly estimated. We therefore compared the accuracy of both tests by calculating the ratio of sensitivities (RSN) and the ratio of false positive rates (RFP), as originally suggested by Schatzkin *et al.*<sup>11</sup> Briefly, if the number of true positive patients for the I-FOBT is denoted by  $m'_1$ , and the number of true positive patients for the G-FOBT by  $n'_1$ , RSN is calculated as

$$RSN_{I-FOBT/G-FOBT} = m'_1/n'_1.$$

If the number of false positive patients for the I-FOBT is denoted by  $m''_1$  and the number of false positive patients for the G-FOBT by  $n''_1$ , RFP is calculated as

$$RFP_{I-FOBT/G-FOBT} = m''_1/n''_1.$$

Confidence intervals (95%) were calculated according to the formulas proposed by Cheng and Macaluso.<sup>12</sup> The number of extra false positives associated with the detection of one extra true positive, if the I-FOBT was used instead of the G-FOBT, denoted FP:TP, was calculated as the ratio between the difference in the number of false positive patients with I-FOBT versus G-FOBT and the difference in the number of true positive patients with I-FOBT versus G-FOBT.<sup>13</sup>

Comparison of the two tests (G-FOBT and I-FOBT) was conducted using different cut-off points for I-FOBT: the usual cut-off point (20 ng/ml) and two alternative cut-off points (50 and 75 ng/ml).

Statistical analysis was performed using SAS software version 9.1.

## RESULTS

### Patients

Table 1 shows the characteristics of the study population. Of the 10 673 patients who completed the G-FOBT and I-FOBT, 886 had at least one positive test. Using the usual cut-off point, the positivity rate of the I-FOBT was markedly higher than that of the Hemoccult test (6.9% v 2.4%). A total of 711 (80.2%) patients with at least one positive FOBT test underwent colonoscopy. Among them, 46 had an incomplete colonoscopy and 21 lacked sufficient information on the polypoid lesion

**Table 2** Colonoscopy findings according to the test results

	Positive G-FOBT	Hb level (I-FOBT) (ng/ml)			Positive G-FOBT or I-FOBT
		20–50	50–75	>75	
No neoplasia	108	167	28	72	350
Adenoma <10 mm	30	67	15	21	124
Advanced neoplasia	53	50	20	90	170
Adenoma ≥10 mm or high grade dysplasia <10 mm	39	48	17	74	149
Invasive cancer	14	2	3	16	21

Hb, haemoglobin; G-FOBT, guaiac faecal occult blood test; I-FOBT, immunochemical faecal occult blood test.

**Table 3** Comparison of the relative performance of I-FOBT versus G-FOBT, according to the positivity level of I-FOBT

	Positivity threshold (I-FOBT ng/ml)	Positivity rate (%) <sup>*</sup>	Adenoma $\geq 10$ mm or high grade dysplasia (RSN $\dagger$ )	Colorectal cancer				Advanced neoplasia (colorectal cancer or adenoma $\geq 10$ mm or high grade dysplasia)			
				PPV	RSN $\dagger$	RFP $\ddagger$	FP:TP $\S$	PPV	RSN $\dagger$	RFP $\ddagger$	FP:TP $\S$
I-FOBT	20 ng/ml	6.9	3.56 [2.66–4.77]	4.0	1.50 [1.11–2.03]	2.88 [2.46–3.36]	47.43 [22.32–100.80]	30.2	3.02 [2.38–3.84]	2.68 [2.24–3.22]	2.17 [1.65–2.85]
	50 ng/ml	3.3	2.08 [1.63–2.64]	7.7	1.36 [0.99–1.87]	1.28 [1.08–1.53]	10.00 [2.86–34.97]	44.7	2.33 [1.73–3.14]	0.99 [0.79–1.23]	–
	75 ng/ml	2.4	1.70 [1.33–2.16]	8.7	1.14 [0.83–1.58]	0.94 [0.78–1.14]	–	49.2	1.90 [1.41–2.56]	0.67 [0.53–0.86]	–
G-FOBT		2.4		7.3				27.7			

G-FOBT, guaiac faecal occult blood test; I-FOBT, immunochemical faecal occult blood test; PPV, predictive positive value; RFP, ratio of false positive rate; RSN, ratio of sensitivity. Values for RSN, RFP and FP:TP are mean [95% confidence interval].

<sup>\*</sup>Patients with both analysable tests, independent of whether or not a colonoscopy was performed or not (n=887).

$\dagger$ RSN $>1$ , sensitivity of I-FOBT is greater than that of G-FOBT.

$\ddagger$ RFP $>1$ , false positive rate of I-FOBT is greater than that of G-FOBT, the specificity of I-FOBT is therefore inferior to G-FOBT.

$\S$ FP:TP, number of extra false positives associated with the detection of one extra true disease case using I-FOBT instead of G-FOBT.

detected. Colonoscopy was performed within two months after the test reading for half of the patients and within 8 months for 98% of patients. The frequency of patients undergoing endoscopic examination did not differ regardless of whether one or both screening tests were positive (G-FOBT and I-FOBT positives, 80.4%; G-FOBT positive only, 81.7%; I-FOBT positive only, 79.9%,  $p = 0.88$ ).

### Colonoscopic findings

A total of 21 (3.3%) colorectal cancers and 149 (23.1%) patients with high risk adenomas (size  $\geq 10$  mm or high grade dysplasia) were detected in 644 colonoscopies. Table 2 shows the results of colonoscopy according to the FOBT results and amount of haemoglobin detected by the I-FOBT. One perforation was recorded after colonoscopy (0.2%).

### Performance comparison between G-FOBT and I-FOBT at the usual positive threshold of 20 ng/ml (table 3)

Using the usual cut-off point, the sensitivity of I-FOBT was higher than that of G-FOBT for cancer (RSN = 1.50) and for high risk adenoma (RSN = 3.56). The predictive positive value of I-FOBT was lower than that of G-FOBT for cancer (4.0%  $v$  7.3%) and similar for high risk adenomas (22%  $v$  27%). As the positivity rate was more than twofold higher for I-FOBT than for G-FOBT, the RFP was unfavourable to I-FOBT. Using this usual cut-off point, the gain in sensitivity associated with the use of I-FOBT (50% increase for cancer and 256% increase for high risk adenoma) was balanced by a decrease in specificity. The number of extra false positives associated with the detection of one extra invasive colorectal cancer was 47.43 (95% confidence interval 22.32–100.80). For the detection of one extra advanced neoplasia (cancer or high risk adenoma) the corresponding value was 2.17 (1.65–2.85).

### Analysis of the relative performance of I-FOBT compared with G-FOBT at two alternative thresholds (table 3)

The use of two alternative thresholds (50 and 75 ng/ml) for the I-FOBT test provided a lower gain in sensitivity but allowed a decrease in the positivity rate as well as an increase in the predictive positive value for both cancer and high risk adenomas. FP:TP for advanced neoplasia was not calculated for these two alternative cut-off points as both RSN and RFP were in favour of I-FOBT. With a threshold of 50 ng/ml, I-FOBT detected more than twice as many advanced neoplasias as G-FOBT (RSN = 2.33), without any loss in specificity (RFP = 0.99). With a threshold of 75 ng/ml, sensitivity and specificity were higher with the I-FOBT than with the G-FOBT for both invasive colorectal cancer and advanced neoplasia.

Using this cut-off point associated with a similar positivity rate to G-FOBT (2.4%), the use of I-FOBT allowed a gain in sensitivity of 90% and a decrease in false positive rate of 33% for advanced neoplasia.

### DISCUSSION

In patients who performed the two tests, the I-FOBT had a higher sensitivity for both cancer and high risk adenomas irrespective of the cut-off value used for I-FOBT. With the usual cut-off point (20 ng haemoglobin/ml), this gain in sensitivity was associated with a decrease in specificity, 2.17 extra false positives being associated with the detection of one extra advanced neoplasia (cancer or high risk adenoma). Using a higher cut-off point, our results suggest that the I-FOBT rather than the G-FOBT offers a gain in both sensitivity and specificity. When I-FOBT was used at a cut-off value associated with a positivity rate similar to G-FOBT, it offered a gain in sensitivity of 90% and a decrease in false positive rate of 33% for advanced neoplasia.

The study had several drawbacks. To estimate screening test performances for cancers and high risk adenomas, the ideal is to obtain the disease status for all individuals, independent of the screening test results. With the exception of the recent study by Morikawa *et al*,<sup>9</sup> large scale asymptomatic populations have not undergone screening, and available direct estimation of I-FOBT performance originates mainly from high risk individuals referred for colonoscopy.<sup>10–14</sup> Hence the results may not be directly applicable to the general average risk population. Studies conducted in large samples of the general population, with follow-up for individuals with negative tests, provided complete and reliable information on cancer but not on high risk adenomas.<sup>15–17</sup> Our study was conducted in an average risk population but our analysis was conducted before the collection of cancers by local registries, and does not therefore provide an estimation of the sensitivity and specificity of each test. However, it does enable direct comparison of the sensitivity and specificity of the two tests by calculating proper ratios (RSN and RFP), as suggested by Schatzkin *et al* and Cheng *et al*,<sup>11–18</sup> and thus quantification of the potential gain obtained by the substitution of G-FOBT by I-FOBT. This method allowed the calculation of the 95% confidence interval for each ratio; the 95% confidence interval for RSN for detection of invasive colorectal cancer was probably underestimated in our study because of the small number of cases.

A significant proportion (20%) of individuals with a positive screening test did not undergo colonoscopy. This proportion was no higher than those usually observed in mass screening campaigns in France. However, it produced potential bias as the

risk of cancer has been suggested in a previous French study<sup>17</sup> to be higher for people refusing a colonoscopy after a positive test. In our case, as the proportion of people not having colonoscopy after a positive test did not differ with regard to whether one or both screening tests were positive, it did not produce bias in the comparison between the tests.

Despite extensive studies, including several randomised studies, there is still no consensus on the best strategy for colorectal cancer screening for average risk populations, and guidelines vary from one country to another and from one society to another. Nevertheless, FOBT is included in all recent guidelines and reviews.<sup>19–20</sup> Limitations of the guaiac tests, in particular their low sensitivity, encourage researchers to search extensively for alternative FOBT techniques. An increasing number of recent papers highlighted their interest in the use of immunochemical tests. Our study is in agreement with these studies, conducted in general or high risk populations, emphasising the high sensitivity of I-FOBT for cancer and adenomas,<sup>9–10–21–22</sup> and its superiority over G-FOBT.<sup>14–16–23</sup> The development of automated systems has increased the reliability and decreased the cost of test processing and reading. The technology evaluated in our study, Magstream 1000/Hem SP (Fujirebio), has previously been studied in individuals referred for colonoscopy,<sup>10</sup> and in two population based studies.<sup>9–24</sup> The recent study by Morikawa *et al* comparing this I-FOBT technology with colonoscopy in 21 805 Japanese asymptomatic individuals provided reliable and promising results.<sup>9</sup> However, using the usual threshold of 20 ng haemoglobin/ml, and although the study population was younger than those usually screened (mean age 48.2 years), the proportion of patients with a positive test was relatively high (5.6%). Such a high positivity rate, which would be even higher in older populations, could be inappropriate in biennial strategies. As suggested in previous studies,<sup>17–25</sup> by increasing the positivity threshold of quantitative I-FOBT, an appropriate positivity rate can be obtained while maintaining a substantial gain in sensitivity. The ideal balance between sensitivity and specificity/positivity rate depends on health care organisation and cost, and is likely to vary between countries. Our study, conducted in a 50–74 year average risk population, showed that with a positivity rate of 2.4%, identical to the Hemoccult test, I-FOBT increased the number of true positives (cancers and high risk adenomas) by nearly 2 (1.9) and decreased the number of false positive results by 1.5.

Evidence in favour of the use of the I-FOBT over the G-FOBT is increasing. I-FOBT tests have no dietary or medication restrictions. These tests have superior sensitivity and specificity, the gain being more important for high risk adenomas than for cancers. They also have a higher compliance rate<sup>23–26–27</sup> and the automated reading technology allows the choice of the ideal positivity rate. As suggested in recent reviews,<sup>5–7</sup> it is time to give colorectal cancer screening a new future by using I-FOBT instead of G-FOBT.

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## REFERENCES

- Mandel JS, Bond JH, Church TR, *et al*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993;**328**:1365–71.
- Kronborg O, Fenger C, Olsen J, *et al*. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;**348**:1467–71.
- Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;**348**:1472–7.
- Faivre J, Dancourt V, Lejeune C, *et al*. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004;**126**:1674–80.
- Allison JE. Colon Cancer Screening Guidelines 2005: the fecal occult blood test option has become a better FIT. *Gastroenterology* 2005;**129**:745–8.
- Greenwald B. From guaiac to immune fecal occult blood tests: the emergence of technology in colorectal cancer screening. *Gastroenterol Nurs* 2005;**28**:90–6.
- Bond JH. The place of fecal occult blood test in colorectal cancer screening in 2006: the U.S. perspective. *Am J Gastroenterol* 2006;**101**:219–21.
- Vilkin A, Rozen P, Levi Z, *et al*. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol* 2005;**100**:2519–25.
- Morikawa T, Kato J, Yamaji Y, *et al*. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005;**129**:422–8.
- Wong WM, Lam SK, Cheung KL, *et al*. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer* 2003;**97**:2420–4.
- Schatzkin A, Connor RJ, Taylor PR, *et al*. Comparing new and old screening tests when a reference procedure cannot be performed on all screenees. Example of automated cytometry for early detection of cervical cancer. *Am J Epidemiol* 1987;**125**:672–8.
- Cheng H, Macaluso M. Comparison of the accuracy of two tests with a confirmatory procedure limited to positive results. *Epidemiology* 1997;**8**:104–6.
- Chock C, Irwig L, Berry G, *et al*. Comparing dichotomous screening tests when individuals negative on both tests are not verified. *J Clin Epidemiol* 1997;**50**:1211–17.
- Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. *Cancer* 2000;**89**:46–52.
- Allison JE, Tekawa IS, Ransom LJ, *et al*. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;**334**:155–9.
- Zappa M, Castiglione G, Paci E, *et al*. Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. *Int J Cancer* 2001;**92**:151–4.
- Launoy GD, Bertrand HJ, Berchi C, *et al*. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. *Int J Cancer* 2005;**115**:493–6.
- Cheng H, Macaluso M, Hardin JM. Validity and coverage of estimates of relative accuracy. *Ann Epidemiol* 2000;**10**:251–60.
- Winawer S, Fletcher R, Rex D, *et al*. Colorectal cancer screening and surveillance: clinical guidelines and rationale—Update based on new evidence. *Gastroenterology* 2003;**124**:544–60.
- Achkar E, Moayyedi P. Colorectal cancer screening with fecal occult blood testing (FOBT): an international perspective. *Am J Gastroenterol* 2006;**101**:212.
- Young GP, St John DJ, Winawer SJ, *et al*. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. *Am J Gastroenterol* 2002;**97**:2499–507.
- Nakama H, Zhang B, Kamijo N. Sensitivity of immunochemical fecal occult blood test for colorectal flat adenomas. *Hepatogastroenterology* 2004;**51**:1333–6.
- Hughes K, Leggett B, Del Mar C, *et al*. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. *Aust N Z J Public Health* 2005;**29**:358–64.
- Berchi C, Bouvier V, Reaud JM, *et al*. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. *Health Econ* 2004;**13**:227–38.
- Castiglione G, Grazzini G, Miccinesi G, *et al*. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. *J Med Screen* 2002;**9**:99–103.
- Cole SR, Young GP, Esterman A, *et al*. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen* 2003;**10**:117–22.
- Federici A, Giorgi Rossi P, Borgia P, *et al*. The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial. *J Med Screen* 2005;**12**:83–8.