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Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer ☆

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Abstract ***Background:*** The aim of this study was to compare the performance of the guaiac-based faecal occult blood test (G-FOBT), with that of three immunochemical faecal occult blood tests (I-FOBT) which allow automatic interpretation.
Patients and methods: Under the French organised screening programme, 85,149 average-risk individuals aged 50–74 participating in the third screening round, performed both the G-FOBT (Hemoccult-II test) and one of the I-FOBTs: FOB-Gold, Magstream and OC-Sensor.
Results: Given the chosen threshold, the positivity ratio between the different I-FOBTs and the G-FOBT was 2.4 for FOB-Gold, 2.0 for Magstream and 2.2 for OC-Sensor ($P = 0.17$). The three I-FOBTs were superior to the G-FOBT for colorectal cancer (CRC) detection. The ratios for detection rates were 1.6 (FOB-Gold), 1.7 (Magstream) and 2.1 (OC-Sensor) ($P = 0.74$). For non-invasive CRC they were, respectively, 2.5, 3.0 and 4.0 ($P = 0.83$) and for advanced adenomas 3.6, 3.1 and 4.0 ($P = 0.39$).
Conclusions: This study provides further evidence that I-FOBT is superior to G-FOBT. None of the three I-FOBTs studied appeared to be significantly better than the others.

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1. Introduction

Colorectal cancer (CRC) fulfils the conditions that have been defined for mass screening: it is a major cause of morbidity and mortality in industrialised countries with about 39,500 new cases and 15,000 deaths per year in France.[1] Despite advances in diagnostic techniques and treatment, the 5-year survival rate remains poor.[2,3] However, CRC can be cured if detected at an early stage,[4] and can be prevented by the removal of adenomas.[5] A considerable amount of research has been undertaken over the last 20 years to evaluate the ability of screening tests to decrease CRC mortality or incidence. Currently, the simplest screening method for CRC is periodic stool testing for occult blood. Several faecal occult blood tests have been proposed. Initially, faecal occult blood tests were guaiac-based tests (G-FOBTs) that detected the peroxidase-like activity of haemoglobin. The most extensively evaluated test was the Hemoccult-II (Beckman and Coulter, California). Population-based controlled studies in Europe have shown that G-FOBT followed by colonoscopy in the case of positivity can reduce CRC mortality.[6–8] Thus screening for CRC using G-FOBT has been endorsed by the European Commission[9] and thereafter by the French health authorities. A nationwide organised screening programme has been conducted since 2009.[10] G-FOBTs have been criticised for their fairly low sensitivity and because they react to non-human haem in food. For these reasons, attention has been given to alternative faecal occult blood tests, such as immunochemical faecal occult blood tests (I-FOBTs), which are specific to human haemoglobin.[11] The purpose of this study was to compare, within a population-based organised screening programme, the performance of a G-FOBT (Hemoccult-II) with that of three I-FOBTs.

2. Patients and methods

2.1. Study design

The study population comprised asymptomatic subjects aged 50–74 (born between 1934 and 1958), invited in 2008 to participate in a biennial organised mass-screening programme for CRC in four French administrative areas (Côte-d'Or, Haut-Rhin, Ille-et-Vilaine and Indre-et-Loire). Following French guidelines, subjects with digestive symptoms or a previous history of CRC or adenoma, or with first-degree relatives of an index case who had CRC before 65 or had at least two affected first-degree relatives whatever the age of the index case, or who had a normal total colonoscopy performed during the previous 5 years, or had a severe illness contraindicating screening, were excluded from the study.

During the first 6 months of the screening campaign, general practitioners (GPs) offered the screening test free of charge to the eligible individuals seen at their practices. For patients who did not complete the test during this medical phase, the coordination centre in charge of organising the screening campaign subsequently mailed only the G-FOBT. Individuals participating in the third screening round and during the medical free-offer phase were asked to perform both the G-FOBT (Hemoccult-II) and one of the three selected I-FOBTs. As the I-FOBTs were distributed only during the medical phase, it was not possible to calculate a participation rate. The I-FOBTs were distributed according to geographic area. The screening round began by sending an information letter to each participant along with an information brochure. Prior to this round, GPs were thoroughly informed about the research project. A colonoscopy was performed in case of a positive result for either of the two tests. The study was submitted to, and approved and funded by the National Cancer Institute.

2.2. Faecal occult blood tests

The completed tests were sent by mail to the central analysis centre of each area. The maximum time between the date of first faeces deposit and processing of the test had to be less than 14 days. The time between faeces deposit and processing of the stool test was not recorded. Upon receipt, samples were assayed without delay by trained staff. G-FOBT and I-FOBT were processed independently.

The G-FOBT (Hemoccult-II) was performed by taking two samples from separate points of three consecutive stools. The completed test was mailed back in a specially provided envelope to a central laboratory. No diet or drug restriction was required. The idea was to reach a compliance rate that was as high as possible. Furthermore, in studies in the UK and France the positivity rate of the G-FOBT without diet or drug restrictions remained low, under 2.5%.[7,8] This strategy was thus adopted in these two countries within the organised screening programme. We evaluated three I-FOBTs that allow automatic interpretation and determination of the haemoglobin concentration in faeces: FOB-Gold: Beckman Coulter, Brea, California, USA; Magstream: Fujirebio, Tokyo, Japan and OC-Sensor: Eiken, Tokyo, Japan. For the I-FOBTs each participant was provided with two test tubes and instructed to take a faecal sample from the first two consecutive stools. For all three I-FOBTs, the test sampling device is shaped like a small test tube with the faecal probe inserted into it and sealing it. The probe has a serrated tip which is poked into five different areas of the stool and then pushed back into the tube through a septum that removes excess faecal material. The probe tip with the faecal sample is suspended in a standard volume of haemoglobin-stabilising buffer.

The G-FOBT test was processed without rehydration according to a standardised procedure using the

developer provided by the manufacturer. A second reader independently interpreted the result. In cases of discordance in the interpretation of the test, the technicians agreed on the positivity or negativity of the test after discussion. The test was reported as positive if any blue colour was detected within 1 min after the addition of the developer solution in any card window.

Concerning I-FOBTs, an automated analyser provided by each company was used to analyse and quantify faecal haemoglobin. The desktop instrument is self-contained with reagent, buffer, washing and fluid disposal bottles, and is powered by a standard power supply. The instrument automatically mixes the faecal-buffer solution with the antihuman haemoglobin reagent. Manufacturers quote the concentration of haemoglobin not in the faeces, but in the buffer solution used for analysis, and this varies between different devices. Therefore, simple comparisons of cut-offs are not possible. In this study, the OC-Sensor test was considered positive if the concentration of haemoglobin in the specimen was over 150 ng/mL and for the FOB-Gold test if it was over 176 ng/mL (which corresponds to 150 ng/mL for OC-Sensor taking into account differences in dilution of the buffer solution). The Magstream test is a semi-quantitative test with a cut-off at 20 ng/mL of buffer. This cut-off was chosen, taking into account available data in the literature, to get a positivity rate of less than 5%.

Participants receive FOBT results by mail. If the test is positive, the subject is asked to consult his/her GP who has previously been informed by a phone call from the analysis centre. During the consultation, the GP has to complete a medical questionnaire and refer the patient for a colonoscopy.

2.3. Colonoscopy and pathology findings

On the eve of the colonoscopy, patients received a preparation consisting of 3–4 l of a polyethylene glycol-solution or a fleet phospho soda preparation. Qualified gastroenterologists practicing either in public or private hospitals performed the colonoscopies (mainly under general anaesthesia). They were blinded as to which test(s) proved positive. Information on the CRCs and the polyps diagnosed was obtained using standardised forms completed by GPs and gastroenterologists. Pathologists provided a copy of their report. The number of adenomas, their size, location, histology and dysplasia was recorded. If a patient had more than one adenoma, the most advanced lesion was included in the analysis. Advanced adenoma was defined as an adenoma of 10 mm or more in size, or with high-grade dysplasia or a villous component. Cancers were classified according to the TNM classification.[12] According to the TNM classification, intramucosal carcinoma was classified as Tis. They were distinguished in the analysis from invasive carcinoma and advanced adenoma. Non-adenomatous polyps were not included as neoplasia.

2.4. Sample size

To calculate the sample size, we made the following assumptions: G-FOBT sensitivity was 45%, the crude difference in sensitivity that we wished to detect with the I-FOBT was 25% and the prevalence of CRC in the studied population was 5‰. With a power of 0.90 to detect the difference between the two tests in the study, a total of 80 CRCs in the screened population was required.

2.5. Statistical analysis

Differences between tests were checked by Chi-square. Statistical tests were two-sided and a P value of less than 0.05 was considered statistically significant. Specificity in the screened population was estimated according to the rare disease assumption as the ratio of the number of all participants with a negative screening test, to the total number of participants reduced by the number of true positives with CRC. The positive predictive value was calculated as the number of true positives (cancer or advanced adenoma) relative to the total number of positives followed-up with colonoscopy. This value was determined with its 95% confidence interval (CI). Since colonoscopy was restricted to subjects classified as positive by at least one of the tests, the sensitivity and specificity of each test could not be estimated directly. We therefore compared the accuracy of the different tests by calculating the ratio of sensitivities (ratio of true positive patients with the I-FOBT and the G-FOBT) and the ratio of false positive (ratio of false positive patients with the I-FOBT and the G-FOBT).[13]

When individuals had both screening tests, and when only one or both tests were positive, a diagnostic work-up was performed to establish the true presence or absence of the disease. In such cases, it was possible to test for a difference in the two sensitivities or specificities using McNemar's test. The number of extra false positives associated with one extra true positive 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. For each diagnosis worth considering, the test results were compared by paired 2×2 analyses. Differences in the detection rates between the two tests and their 95% CI were calculated.

The number of test participants required to detect one cancer (or advanced adenoma), was calculated as was the number of participants relative to the number of subjects with cancer (or advanced adenoma). The number of colonoscopies required to detect one cancer or one advanced adenoma was calculated as was the

number of colonoscopies relative to the number of subjects with cancer or advanced adenoma. We compared the accuracy of G-FOBT with each of the I-FOBT by calculating the ratio of sensitivities and the ratio of false positive rates.[14]

3. Results

3.1. Faecal occult blood test positivity

A total of 85,149 average-risk individuals aged 50–74 simultaneously performed the same G-FOBT and one of the three evaluated I-FOBTs as part of the French organised screening programme for CRC. Among the I-FOBTs 39.6% used the OC-Sensor test, 37.8% the FOB-Gold test, and 22.6% the Magstream test.

Table 1 shows the positivity of the tests in the study by sex and age. The positivity rate of the G-FOBT varied between 1.7% and 2.3% depending on the cohort studied. With the chosen thresholds, the positivity ratio between the different I-FOBTs and the G-FOBT was 2.4 (2.2–2.6) for FOB-Gold, 2.0 (1.8–2.2) for Magstream and 2.2 (2.0–2.4) for OC-Sensor ($P = 0.17$). The G-FOBT and the I-FOBT were more frequently positive in men than in women and positivity increased with age. Among the participants who screened positive, 92% underwent colonoscopy. There was no difference between the different screening arms, the compliance rate varying between 90% and 94% (Fig. 1).

3.2. Relative performance of the I-FOBTs compared with the Hemoccult-II test

The three I-FOBTs were superior to the G-FOBT in detecting both invasive and non-invasive CRC and adenomas (Table 2). Compared with the G-FOBT test, the ratio of the detection rates for CRC was 1.6 for FOB-Gold, 1.7 for Magstream and 2.1 for OC-Sensor ($P = 0.74$). The corresponding ratios for non-invasive CRC were 2.5, 3.0 and 4.0 ($P = 0.83$) and for advanced adenoma 3.6, 3.1 and 4.0 ($P = 0.36$). The detection rate for invasive and non-invasive CRC and advanced adenoma per 1000 participants is given in Table 2. This was significantly higher with I-FOBTs than with the G-FOBT.

For invasive and non-invasive CRC, the positive predictive values of G-FOBT and I-FOBTs were not significantly different (Table 2). For advanced adenomas, these were higher with I-FOBTs than with the G-FOBT. Among I-FOBTs, the PPV was higher for the OC-Sensor test than for the other I-FOBTs.

We analysed the accuracy of each I-FOBT compared with the G-FOBT (Table 2). The ratio of sensitivity for CRC was 1.9 (1.5–2.4) for FOB-Gold, 2.0 (1.5–2.7) for Magstream and 2.4 (1.9–3.2) for OC-Sensor. The corresponding values for advanced adenomas were 3.6 (3.0–4.4), 3.1 (2.4–4.0) and 3.9 (3.3–4.7). The estimated specificity of the I-FOBTs was significantly lower than that of the G-FOBT. This was 95.1% (94.9–95.3) for FOB-Gold, 95.7% (95.4–96.0) for Magstream, 96.5% (96.3–96.7) for OC Sensor and 98.1% (98.0–98.2) for Hemoccult-II.

Concordance between the results of the G-FOBT and of the I-FOBTs was poor (Table 3). Among the participants who performed Hemoccult-II and the OC-Sensor test and who were diagnosed with CRC, only 42% tested positive on both tests. The corresponding percentage for Hemoccult-II and Magstream was 38%, and for Hemoccult-II and OC-Sensor tests was 34%. The Kappa test values were, respectively, 0.16, 0.18 and 0.18.

The number of colonoscopies required to detect one invasive or non-invasive CRC was 16.6 (13.9–20.7) with FOB-Gold, 12.7 (10.3–16.6) with Magstream and 12.8 (10.8–15.9) with OC-Sensor. The corresponding numbers for advanced adenoma were 4.8 (4.4–5.4), 3.9 (3.5–4.4) and 2.9 (2.7–3.2). The number of participants that needed to be screened to detect CRC was 354 (286–435) with FOB-Gold, 296 (238–385) with Magstream and 366 (303–455) with OC-Sensor.

Table 4 shows the results of FOBTs according to stage of cancers at diagnosis. The proportion of Tis and stage 1 cancers was higher with I-FOBTs than with the G-FOBT. The differences between I-FOBTs and G-FOBTs, however, were not significant.

4. Discussion

This study was conducted at a population level during the third screening round of the French organised programme. Most previous studies evaluating the performance of I-FOBTs were performed during the first screening round. This study is noteworthy in that it provides data on what can be expected from an ongoing screening programme.

Compliance with screening and performance of the screening test are the two major determinants of the effectiveness of a screening programme. Our study was not intended to compare the participation rate. However, data from other studies indicate that participation is higher with I-FOBT than with G-FOBT.[15,16] The design of the I-FOBT and the smaller number of samples are probably the main reasons for improved participation. The I-FOBTs were significantly better than the G-FOBTs in detecting both cancers and advanced adenomas. The detection of cancers was at least twice as high with the I-FOBT as with the G-FOBT, and the number of advanced adenomas was about three to four times as high. Similar results have been reported in other population-based studies.[15–23] However, these were often obtained on only one bowel movement and associated with a lower threshold. It can be concluded that the high sensitivity of I-FOBT for the detection of

Table 1
Comparison of faecal occult blood test positivity (%) by sex and age.

	Hemoccult-II	FOB-Gold	Hemoccult-II	Magstream	Hemoccult-II	OC-Sensor
	$N = 32,215$		$N = 19,244$		$N = 33,690$	
All cases	2.2 (2.1–2.4)	5.2 (4.9–5.4)	2.3 (2.1–2.5)	4.6 (4.3–4.9)	1.7 (1.5–1.8)	3.7 (3.5–3.9)
Sex						
Men	2.4 (2.2–2.6)	6.6 (6.3–6.9)	2.8 (2.6–3.0)	5.7 (5.4–6.0)	2.0 (1.8–2.1)	5.1 (4.9–5.3)
Women	2.1 (1.9–2.3)	4.0 (3.8–4.2)	1.9 (1.7–2.1)	3.7 (3.4–4.0)	1.4 (1.3–1.5)	2.6 (2.4–2.8)
Age						
50–54	1.9 (1.7–2.1)	3.7 (3.5–3.9)	2.1 (1.9–2.3)	4.4 (4.1–4.7)	1.4 (1.3–1.5)	3.1 (2.9–3.3)
55–59	2.0 (1.8–2.2)	4.7 (4.5–4.9)	2.0 (1.8–2.2)	3.5 (3.2–3.8)	1.6 (1.5–1.7)	3.1 (2.9–3.3)
60–64	2.0 (1.8–2.2)	4.9 (4.7–5.1)	2.2 (2.0–2.4)	4.7 (4.4–5.0)	1.7 (1.6–1.8)	3.7 (3.5–3.9)
65–69	2.7 (2.5–2.9)	5.9 (5.6–6.2)	2.6 (2.4–2.8)	5.2 (4.9–5.5)	1.9 (1.7–2.1)	4.1 (3.9–4.3)
70–74	2.8 (2.6–3.0)	7.2 (6.9–7.5)	2.7 (2.5–2.9)	5.6 (5.3–5.9)	1.8 (1.7–1.9)	5.2 (5.0–5.4)

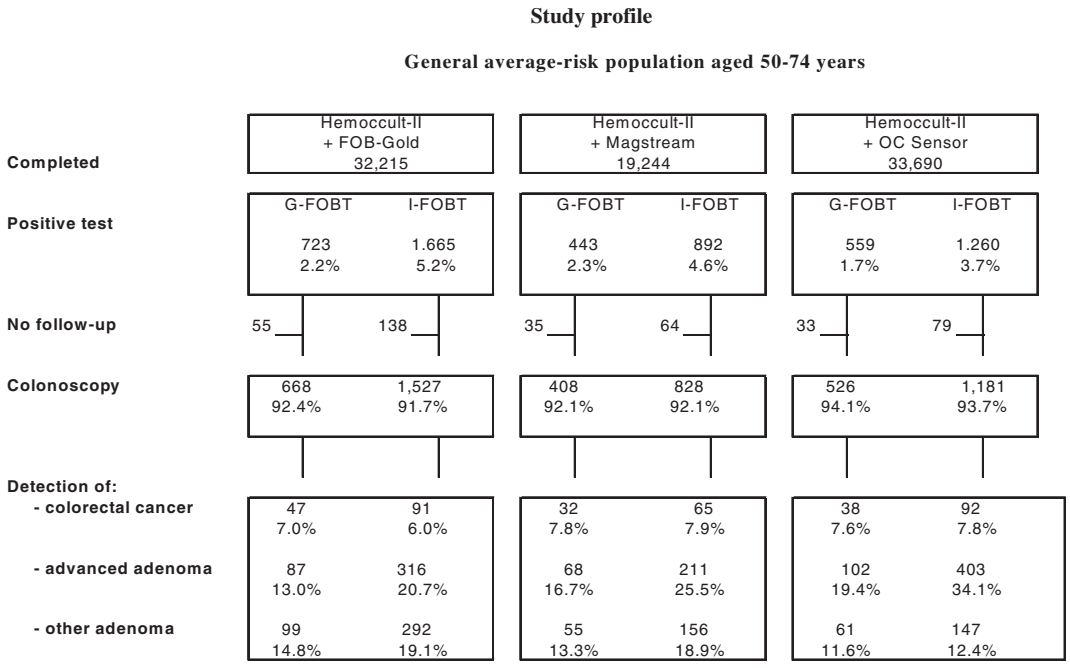

Fig. 1. Study profile.

CRC and advanced adenomas is now well established. As the I-FOBT performs better than the G-FOBT, it is reasonable to assume that an organised programme using an I-FOBT would lead to a greater reduction in mortality.

The development of automated systems for the interpretation of the test has increased the advantage of I-FOBTs. Accurate interpretation of G-FOBTs is not easy and requires well-run laboratories. An automated I-FOBT is easier to interpret, and minimises human error in test processing, thus making it a more objective laboratory test with excellent quality control. Furthermore, it measures the concentration of haemoglobin in the buffer, thus making it possible to choose the cut-off value. It is also possible to reinterpret the test in case of a technical problem. One limit of the I-FOBT is that globin (the measured component of haemoglobin) in these tests is not stable in faeces. Some studies suggest that high storage and transport temperatures accelerate the deterioration of haemoglobin.[24–26] The implications of these results for the organisation of I-FOBT based screening are not completely clear.

The main drawback of I-FOBT is its higher positivity rate compared with the G-FOBT. This is related to the lower detection level of occult blood, making I-FOBT less specific and more sensitive than G-FOBT. I-FOBTs are more expensive than G-FOBTs and generated twice as many colonoscopies with the cut-off values chosen in this study. The increased number of colonoscopies could lead to problems of colonoscopy capacity. The screen positive rate that staff and financial resources can accommodate is not clear. Taking into account the large size of the target population (16 million in the 50–74 year age group in France) and the experience gathered

Table 2
Most advanced lesions identified by screening.

	Hemoccult-II	Fob-Gold	Hemoccult-II	Magstream	Hemoccult-II	OC-Sensor
Completed screening test	$N = 32,215$		$N = 19,244$		$N = 33,690$	
Colonoscopy performed	668	1527	408	828	526	1181
Complete colonoscopy	96.5%		97.2%		96.7%	
Detection rate (‰)						
Invasive colorectal cancer	1.1 (0.7–1.5)	1.8 (1.3–2.3)	1.4 (0.9–1.9)	2.4 (1.7–3.1)	0.9 (0.8–1.0)	1.9 (1.4–2.4)
Non-invasive colorectal cancer	0.4 (0.2–0.6)	1.0 (0.6–1.4)	0.3 (0.1–0.5)	0.9 (0.5–1.3)	0.2 (0.1–0.3)	0.8 (0.5–1.1)
Advanced adenoma	2.7 (2.1–3.3)	9.8 (8.7–10.9)	3.5 (2.7–4.3)	10.9 (9.4–12.4)	3.0 (2.4–3.6)	12.0 (10.8–13.2)
Other adenoma	3.1 (2.5 –3.7)	9.1 (8.1–10.1)	2.8 (2.0–3.5)	8.1 (6.8–9.4)	1.8 (1.3–2.3)	4.4 (3.7–5.1)
Positive predictive value (%)						
Invasive colorectal cancer	5.2 (3.5–6.9)	3.9 (2.9–4.9)	6.4 (4.0–8.8)	5.7 (3.9–7.1)	5.9 (3.9–7.9)	5.6 (4.3–6.9)
Non-invasive colorectal cancer	1.8 (0.8–2.8)	2.1 (1.4–2.8)	1.5 (0.3–2.7)	2.2 (1.2–3.2)	1.3 (0.3–2.3)	2.2 (1.4–3.0)
Advanced adenoma	13.0 (10.4–15.5)	20.7 (18.7–22.7)	16.7 (13.1–20.3)	25.5 (22.6–28.6)	19.4 (16.0–22.8)	34.1 (31.4–36.8)
Other adenoma	14.8 (12.1–17.5)	19.1 (17.1–21.1)	13.3 (11.0–15.6)	18.9 (16.2–21.6)	11.6 (8.9–14.3)	12.4 (10.5–14.3)
Sensitivity ratio						
Invasive colorectal cancer	1.7 (1.3–2.1)		1.8 (1.3–2.3)		2.1 (1.6–2.8)	
Non-invasive colorectal cancer	2.7 (1.6–4.4)		3.0 (1.4–6.4)		3.7 (1.8–7.5)	
Advanced adenoma	3.6 (3.0–4.6)		3.1 (2.4–3.9)		4.0 (3.3–4.7)	
Ratio of false positive rates						
Invasive colorectal cancer	2.3 (2.1–2.5)		2.0 (1.8–2.3)		2.2 (2.0–2.5)	
Non-invasive colorectal cancer	2.3 (2.1–2.5)		2.0 (1.8–2.3)		2.2 (2.0–2.4)	
Advanced adenoma	2.1 (1.9–2.3)		1.8 (1.6–2.1)		1.8 (1.6–2.0)	

Table 3
Comparison of paired guaiac and immunochemical faecal occult blood tests.

	FOB-Gold		Magstream		OC-Sensor	
	+	–	+	–	+	–
Cancer						
Hemoccult-II +	41	6	27	5	33	5
Hemoccult-II –	50		38		59	
Advanced adenoma						
Hemoccult-II +	65	22	33	35	73	29
Hemoccult-II –	251		178		330	

from pilot studies, a manageable overall screen positive rate in France could be in the range of 3–5%, given the number of available endoscopists, which is the highest in Europe. The cut-offs chosen in this study are compatible with an acceptable positivity rate.

As yet, there are no clear guidelines on the optimum number of faecal specimens to collect in mass screening programmes for CRC in an average-risk population. Our choice of 2-day sampling was based on the fact that CRC bleeding is often intermittent, and because a Japanese study suggested that a 2-day faecal collection method with a cut-off $\geqslant$150 ng/mL (OC-Sensor test) may be a cost-effective, accurate option.[27] One study, performed mostly on high-risk subjects, provided data on positivity rates, sensitivity and specificity of OC-Sensor for 1- to 3-day sampling and for cut-off values from 50 to 200 ng/mL.[28] In this study, the sensitivity of 2-day sampling with a cut-off value of 150 ng/mL was similar to that of 1-day sampling with a cut-off value of 50 ng/mL, but with a lower positivity rate, respectively, 7.1% and 9.7%. Theoretically, multiple sampling is more unpleasant for the participant. However, it has

Table 4
Stage of colorectal cancer for the Hemoccult-II test and for the immunochemical faecal occult blood tests.[a]

	Hemoccult-II	FOB-Gold	Hemoccult-II	Magstream	Hemoccult-II	OC-Sensor
	$N = 47$	$N = 91$	$N = 32$	$N = 65$	$N = 38$	$N = 92$
Non-invasive carcinoma	12 (26%)	32 (35%)	6 (19%)	19 (29%)	7 (18%)	26 (28%)
Invasive carcinoma						
Stage 1	9 (19%)	20 (22%)	12 (37%)	27 (42%)	9 (24%)	33 (36%)
Stage 2	11 (23%)	17 (19%)	5 (16%)	9 (14%)	5 (13%)	6 (7%)
Stage 3	13 (28%)	15 (16%)	4 (12%)	4 (6%)	13 (34%)	22 (24%)
Stage 4	2 (4%)	6 (7%)	5 (16%)	6 (9%)	4 (11%)	5 (5%)
Unknown		1 (1%)				

[a] According to the TNM classification.

been shown that compliance using 1-day sampling was similar to that for 2-day sampling.[29] Two-day testing does not appear to be a barrier to compliance with regard to test returns. Before taking a definitive decision, cost-effectiveness analyses will have to be undertaken.

The FOB-GOLD and the OC-Sensor measure the concentration of human haemoglobin in faecal samples by quantitative latex antigen–antibody assay that uses polyclonal anti-human haemoglobin antibodies. The cut-off limit for the two tests can thus be easily compared by taking into account differences in dilution in the buffer solution. The measurement system for the Magstream, however, is based on magnetic particles coated with rabbit' anti-human haemoglobin antibodies. Because of this, the cut-off limit cannot be directly compared with that of the two other tests. However, the results from our study suggest that the performance of the Magstream test is comparable to those of the FOB-GOLD with a cut-off of 176 ng/mL and the OC-Sensor with a cut-off of 150 ng/mL.

The definitions of advanced adenoma and cancer can differ from one study to another. The most recent TNM classification[12] included carcinoma in situ (i.e. mucosal carcinomas and intraepithelial carcinomas) as cancers, while in the Vienna classification they are classified as severe dysplasia.[30] Because of the discrepancies between classifications, we decided to present data on invasive carcinoma, carcinoma in situ and advanced adenoma separately. Furthermore, it has been shown that the distinction between carcinoma in situ and invasive carcinoma is not always accurate. In a population-based study, a misclassification between Tis and T1 carcinomas was reported in 20% of cases.[31] Due to this problem, malignant non-invasive carcinomas must be distinguished from adenomas with severe dysplasia.

When each I-FOBT was compared with the G-FOBT, the positivity ratio and the ratio of detected cancers or advanced adenomas were quite similar, with no statistically significant differences between the I-FOBTs. Similarly, the detection rate and the positive predictive value for both cancers and advanced adenomas were not significantly different. The number of test participants and the number of colonoscopies required for the detection of one cancer or one advanced adenoma were similar. Hence, none of the three studied I-FOBTs clearly appeared to be better than the others.

Conflict of interest statement

None declared.

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References

1. Belot A, Grosclaude P, Bossard N, et al. Cancer incidence and mortality in France over the period 1980–2005. *Rev Epidemiol Sante Publique* 2008;**56**:159–75.
2. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007;**8**:773–83.
3. Bossard N, Velten M, Remontet L, et al. Survival of cancer patients in France: a population-based study from the Association of the French Cancer Registries (FRANCIM). *Eur J Cancer* 2007;**43**:149–60.
4. Monnet E, Faivre J, Raymond L, Garau I. Comparability of colorectal cancer survival data in three European population-based registries. *Eur J Cancer Prev* 1998;**7**:127–34.
5. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am* 2002;**12**:1–9.
6. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomized study as screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;**348**:1467–71.
7. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomized controlled trial of fecal-occult-blood screening for colorectal cancer. *Lancet* 1996;**348**:1472–7.
8. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a controlled study in France. *Gastroenterology* 2004;**126**:1674–80.
9. Council of the European Union. Council recommendation of 2 December 2003 on cancer screening. Official Journal of the European Union. 2003/878/EC, L327/34-38.
10. Goulard H, Boussac-Zarebska M, Ancelle-Park R, Bloch J. French colorectal cancer screening pilot programme: results of the first round. *J Med Screen* 2008;**15**:143–8.
11. Holden DJ, Jonas DE, Porterfield DS, Reuland D, Harrio R. Systematic review: enhancing the use and quality of colorectal cancer screening. *Ann Intern Med* 2010;**152**:668–76.
12. Sobin LH, Wittekind Ch. *TNM classification of malignant tumours*. 7th ed. New York: Wiley; 2009.
13. Schatzkin A, Connor RJ, Taylor PR, Bunnag B. 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.
14. Cheng H, Macaluso M. Comparison of the accuracy of two tests with a confirmatory procedure limited to positive results. *Epidemiology* 1997;**8**:104–6.
15. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;**135**:82–90.
16. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomized trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoïdoscopy. *Gut* 2010;**59**:62–8.
17. Castiglione G, Grazzini G, Miccinesi G, et al. Basic variables at different positivity threshold of a quantitative immunochemical test for faecal occult blood. *J Med Screen* 2002;**9**:99–103.
18. Guittet L, Bouvier V, Mariotte N, et al. Performance of immunochemical faecal occult blood test in colorectal cancer screening in average-risk population according to positivity threshold and number of samples. *Int J Cancer* 2009;**125**:1127–33.
19. Grazzini G, Visioli CB, Zorri M, et al. Immunochemical faecal occult blood test: number of samples and positivity cut-off. What

is the best strategy for colorectal cancer screening? *Br J Cancer* 2009;**100**:259–65.
20. Guittet L, Bouvier V, Mariotte N, et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* 2007;**56**:210–4.
21. Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *Eur J Cancer* 2008;**44**:2254–8.
22. Segnan N, Senore C, Andreoni B, et al. SCORE3 Working Group-Italy. Comparing attendance and detection rate of colonoscopy with sigmoïdoscopy and FIT for colorectal cancer screening. *Gastroenterology* 2007;**132**:2304–12.
23. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol* 2010;**105**:2017–25.
24. Van Rossum LG, Van Rijn AF, Van Oijen MGH, et al. False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening test. *Int J Cancer* 2009;**125**:746–50.
25. 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.
26. Grazzini G, Ventura L, Zappa M, et al. Influence of seasonal variations in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from the Florence district. *Gut* 2010;**59**:1511–5.
27. Nakama H, Zhang B, Zhang X. The evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. *Eur J Cancer* 2001;**37**:398–401.
28. Rozen P, Comaneshter D, Levi Z, et al. Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer* 2010;**116**:2115–25.
29. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology* 1987;**93**:1009–13.
30. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastro intestinal epithelial neoplasia. *Gut* 2000;**47**:251–5.
31. Denis B, Peters C, Chapelain C, et al. Diagnostic accuracy of community pathologists in the interpretation of colorectal polyps. *Eur J Gastroenterol Hepatol* 2009;**21**:1153–60.