

A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test

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SUMMARY

Background

The sensitive guaiac faecal occult blood test, Haemoccult SENSa (HOS; Beckman Coulter, Fullerton, CA, USA), is our standard screening test for significant colorectal neoplasia. We evaluated an automatically-developed, quantified human haemoglobin immunochemical faecal test, OC-MICRO (Eiken Chemical Co., Tokyo, Japan), to improve test specificity and so reduce the colonoscopy burden.

Aim

To compare guaiac faecal occult blood test and immunochemical faecal test diagnostic efficacy and costs for identifying significant neoplasia.

Methods

Colonoscopies were performed on patients who prepared three daily guaiac faecal occult blood tests with or without immunochemical faecal tests.

Results

Total colonoscopy was performed on 151 subjects who prepared both guaiac and immunochemical faecal tests (group 1) and the positive predictive values (PPV) were also compared to those of 162 subjects undergoing colonoscopy for positive guaiac faecal occult blood tests (group 2). In group 1, comparative sensitivity, specificity, and PPVs for significant neoplasia with guaiac faecal occult blood test were 75%, 34%, and 12% (PPV, 18% for group 2) and with immunochemical faecal test were 75%, 94% and 60% ($P < 0.01$ for specificity). The number of colonoscopy examinations needed to detect a significant neoplasm because of positive faecal occult blood tests was six to eight with HOS and two with OC-MICRO at 21–31% the cost of evaluating a positive guaiac faecal occult blood test.

Conclusion

An immunochemical faecal test maintains the high sensitivity of guaiac faecal occult blood test, but significantly reduces the colonoscopy burden and screening costs.

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INTRODUCTION

The guaiac faecal occult blood test (G-FOBT) is the standard screening test used in colorectal cancer (CRC) detection programmes for the asymptomatic population.¹⁻³ Several groups, including our own, had performed a comparative evaluation of available commercial G-FOBTs and office-developed immunochemical tests (I-FOBT) of similar sensitivity, but specific for human haemoglobin (Hb).⁴⁻¹³ But, for the office-developed I-FOBT, the manufacturers predetermined the degree of sensitivity for Hb to be at the level of the most sensitive G-FOBT, and we also found that the occasional experience with the more complex office-development was not conducive for large-scale screening and maintaining quality control, and that the G-FOBT was simpler to develop and cheaper.^{2, 11}

However, G-FOBTs have a low specificity for neoplasia because of their non-specificity for human Hb and for being sensitive to dietary peroxidases.^{2, 12, 14, 15} The G-FOBT is also faulted by the possibility of inaccurate development and reading by inadequately trained subjects.^{2, 16, 17} We, and others, did find that adapting the development protocol could minimize the effects of the dietary peroxidases, and centralizing its laboratory development provided better quality control.^{2, 14, 18}

Based on our recommendation, the G-FOBT used in our CRC screening programmes is HaemoccultSENSA™ (HOS) (Beckman Coulter, Fullerton, CA, USA). Our largest national screening programme is performed by a major health medical organization (HMO) and is centrally organized by mail, with voluntary patient participation. Tests are returned to this central service that is responsible for processing the test. Subjects with a positive test are then invited for a colonoscopy examination that is performed in their local gastroenterology clinic or hospital department.¹⁹

In recent years, especially in Japan, more I-FOBTs were developed and the automated-developed and quantitative I-FOBT has become available. It is not only human Hb specific eliminating the need for diet restrictions, but the Hb quantification also allows selection of an appropriate threshold level for follow-up colonoscopy.^{2, 20-26}

The requirement of a CRC-screening test is that it be sensitive and identify subjects with early CRC that is an immediate medical threat to the patient. In addition, if possible, it should also identify advanced adenomatous polyps (AAP) that could be a poten-

tial medical threat to the screening in the near future.^{1-3, 27, 28} These tests are not diagnostic tests, the intention being that screening tests should be repeated periodically, preferably annually, and then provide the opportunity to identify those neoplasia missed in the previous round and/or had become clinically significant, namely CRC or AAP.² But, the screening test should also have both a high specificity and positive-predictive value (PPV) for CRC and AAP that will result in the minimum number of follow-up colonoscopy examinations with their attendant morbidity, costs and demands on the health services.²⁹

Lately, the large number of follow-up colonoscopies resulting from their G-FOBT screening programmes has perturbed our major HMOs and us. Also, based on our initial and on-going favourable experience with an automated-developed and quantitative I-FOBT (OC-MICRO™, Eiken Chemical Co., Tokyo, Japan), we are considering its use for population screening.²⁵

To address these issues, we: (i) prospectively evaluated the relative sensitivities, specificities and PPV of HOS and OC-MICRO for the detection of significant colorectal neoplasia; (ii) analysed our previous colonoscopy data to obtain the PPV of HOS for detecting significant colorectal neoplasia, and compared them with the above results; (iii) compared the relative efficiency and costs entailed by the two FOBTs in identifying these significant colorectal neoplasia

METHODS

Patients

During the last 2 years, we requested subjects who had performed an HOS test to also prepare the OC-MICRO™ tests before colonoscopy examination (group 1).²⁵ They were ambulatory subjects who were scheduled for colonoscopy follow-up after a positive or even a negative HOS as some were above average-risk for colorectal neoplasia. The two FOBTs were not prepared from the same stool or on the same day. These colonoscopy results were also compared with those obtained in consecutive volunteer subjects, at average-risk, who were referred from the HMO Screening Center for total colonoscopy following a positive HOS screening test (group 2).¹⁹

Exclusions for the G or I-FOBT were visible rectal bleeding, haematuria, menstruation, known diagnosis of inflammatory bowel disease and non-co-operation with preparing a faecal test.

Colonoscopy was to the caecum or to an obstructing carcinoma, if present. Otherwise, an incomplete examination was repeated or excluded from analysis. All lesions were noted, biopsied or removed and numbers of polyps were noted, as were their sites. Polyps were classified as non-adenomas or adenomas. Adenomas were grouped by size: <10 mm, ≥10 mm; by their histology: tubular, tubular-villous, villous; and dysplasia was classified as: low-grade (LGD) or high-grade (HGD). The term 'significant' neoplasia included CRC or AAP; this latter category included adenomas ≥10 mm in diameter, or having ≥20% villous histology or having any amount of HGD independent of size. All AAPs <10 mm were re-examined to confirm their histology diagnosis.

Haemoccult SENSAs (HOS)

Cards are mailed by the HMO Central Screening Service to volunteer asymptomatic HMO members, aged 50–75 years, as a part of the cancer detection programme.¹⁹ Patients are requested to follow the manufacture's instructions on diet and medications before and during preparing the G-FOBT. They apply stool on six windows of three cards and mail them back to the central laboratory for development and reading; the results of the tests are sent to the patient and appear online in the electronic files of the patients. The test is positive if any one HOS window is positive. The family physician then schedules the follow-up colonoscopy.

OC-MICRO

This I-FOBT has been described by us, and by others in Japan.^{25, 26} Briefly, patients scheduled for colonoscopy are invited to prepare the OC-MICROTM tests and all participants received an oral and/or telephone explanation of the tests and written instructions on its preparation. They are given or mailed the test kit for faecal sampling and requested to prepare three consecutive daily samples during the week before colonoscopy examination, without any specific diet or medication limitations. Samples are refrigerated at 4 °C until development within 2 weeks of preparation. The OC-MICROTM FOBT analysing instrument (Eiken, Japan) quantifies the Hb in the I-FOBT and results are given automatically as ngHb/mL. Based on published experience of others and our own initial evaluation by colonoscopy, the 100 ngHb/mL level of I-FOBT was

accepted as being positive for a significant amount of occult blood.^{20, 22, 25, 26, 28}

Analysis and statistical methods

The diagnostic level of the FOBT tests for significant neoplasia was evaluated by three criteria: sensitivity, specificity and PPV. Comparison between the two FOBT tests was carried out by the McNemar test. The statistical significance level was set to 0.05 and results are given as means ± s.d. The SPSS for Windows software, Version 13.0, was used for the analysis.

For clinical correlations with the G-FOBT result and I-FOBT Hb level, the most severe pathology finding recorded was used for each examinee. For these comparisons, only the category 'significant' colorectal neoplasia was considered, namely the analyses included only CRC or CRC and AAP both together. The data presented included that of all subjects having prepared a precolonoscopy G-FOBT or both G-FOBT and I-FOBT. These were used to compare positive predictive rates and calculate the number of colonoscopy examinations, ensuring from positive tests, needed to identify the significant neoplasm.

For the calculations of costs, we used the maximum costs authorized by our Health Authorities. These were \$340 for colonoscopy and \$13 for the three HOS tests including administration costs for the screening programme. For pricing OC-MICRO, we used the local agent's pricing and added the administration costs for the screening programme, namely \$20 for three tests.

The institution's Ethics Committee authorized the study in 2004. All subjects gave a signed, informed consent for the I-FOBT and colonoscopy examination.

RESULTS

Patients, colonoscopy and FOBT results

Group 1 included 151 patients, who had prepared a G-FOBT and were also requested to prepare the I-FOBT before their colonoscopy examination, and group 2 included 162 consecutive patients who had undergone colonoscopy because of a positive G-FOBT. Their mean ages ranged from 62 to 65 years and 51–56% of the groups were males (NS).

The colonoscopy findings and FOBT used, and the results are shown in Table 1 and Figure 1. Significant colorectal neoplasia was found by colonoscopy in 11% of group 1 and 18% of group 2. In group 1, both tests

Table 1. The groups studied, faecal occult blood test (FOBT) used, FOBT positivity and neoplasia identified by colonoscopy

Group	Patients (n)	FOBT	n	AAP* (n)	CRC† (n)	AAP + CRC (n)
1	151	G-FOBT				
		Positive	50	8	4	12
		Negative	101	4	0	4
	151	I-FOBT				
		Positive	20	9	3	12
		Negative	131	3	1	4
2	162	G-FOBT				
		Positive	162	18	11	29

* Advanced adenomatous polyp.

† Colorectal cancer.

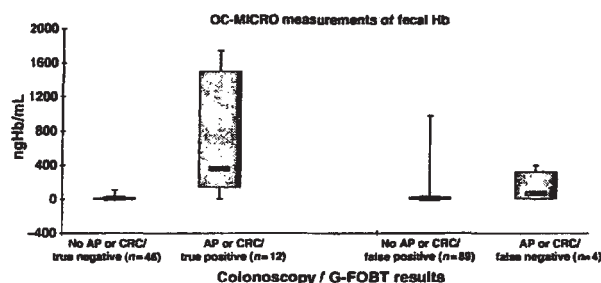


Figure 1. OC-MICRO immunochemical faecal Hb measurements according to colonoscopy findings and HOS (G-FOBT) results in comparison group 1 ($n = 151$). Box plots of faecal Hb values for each diagnostic category. Dark line indicates median Hb value, shaded block covers the upper and adjacent two lower quartiles, and bars are the maximum and minimum levels measured; 100 ngHb/mL being the cut-off for a positive test. The left column is the low level of faecal Hb in subjects not having CRC or AAP on colonoscopy, and having a true negative G-FOBT. The second column is the elevated level of faecal Hb in subjects with CRC or AAP on colonoscopy, and having a true positive G-FOBT. The third column is the low level of faecal Hb in subjects not having CRC or AAP on colonoscopy, but having a false positive G-FOBT. The right column is the elevated level of faecal Hb in subjects having CRC or AAP on colonoscopy, and having a false negative G-FOBT.

were positive in the same 11 of 12 patients having positive FOBTs, out of the 16 having significant neoplasia identified by colonoscopy (Table 1).

The respective specificity and PPVs for significant neoplasia of the faecal occult blood tests are presented in Table 2. In the comparison group 1, having both FOBTs before colonoscopy, the sensitivities of both FOBTs were identical (75%) for significant neoplasia, but their specificities were significantly different ($P < 0.01$). This was reflected in their PPVs and the number of colonoscopies that would have been generated by positive tests in order to identify a significant neoplasm. These results are also seen in Figure 1, which shows that the large number of false-positive G-FOBTs for significant neoplasia did not have elevated levels of faecal occult blood. The predictive value for the G-FOBT in group 2, although better than that of the G-FOBT in group 1, was also significantly worse than that of the I-FOBT in group 1 (Table 2).

Costs

Using the FOBT-positive predictive data for each type of FOBT used in group 1, the number of colonoscopy examinations needed was calculated to detect a subject with a significant neoplasm (Table 2). The number of colonoscopies needed with the G-FOBT or I-FOBT in group 1 was eight and two, respectively. Thus, for positive G-FOBTs, four times more colonoscopy examinations were needed to identify a significant neoplasm when compared with using the I-FOBT, and the costs would be more than four times greater (Table 2). Conversely, the cost with OC-MICRO™, for identifying a significant neoplasm, was 23% of the cost entailed from evaluating the positive HOS tests and identifying this neoplasm.

Comparing the OC-MICRO results in group 1 with those of HOS in group 2, the cost would still be only 31% of those ensuring from positive HOS tests.

DISCUSSION

This colonoscopy-controlled comparative evaluation of HOS and OC-MICRO FOBTs demonstrated a similar sensitivity of both tests for significant colorectal neoplasia, but having significantly different specificities and resulting PPVs. From evaluation of the data of both groups studied, the costs resulting from positive HOS tests were three to four times more than those resulting from positive OC-MICRO tests.

The limitations of this comparison study were that the population was a mixture of subjects at average and above average-risk for CRC who had colonoscopy

Table 2. Neoplasia found at colonoscopy, analysis of each FOBT specificity and PPV for neoplasia, number of colonoscopy examinations needed to identify a significant neoplasm because of positive tests, and the resulting costs

Group	Patients (n)	FOBT	CRC or AAP	Specificity (%)	PPV (%)	Number of colonoscopies needed/CRC or AAP detected	Cost/significant neoplasia
1	151	G-FOBT	16 (11%)	34*	12	8	\$2965
		I-FOBT	16 (11%)	94†	60	2	\$612
2	162	G-FOBT	29 (18%)	NA	18	6	\$1977

NA, not applicable; PPV, positive-predictive value; AAP, advanced adenomatous polyp; CRC, colorectal cancer.

* < † $P < 0.01$.

after a positive or negative FOBT, and volunteered for the study. Nor were the two FOBTs prepared from the same stool. So, we cannot truly compare sensitivities or extrapolate the diagnostic yield to the average-risk population. Even so, being colonoscopy-controlled provided an opportunity to compare the efficiency of the two tests in identifying clinically significant neoplasia and their relative costs.

Our average-risk group 2 enabled us to evaluate by colonoscopy the true predictive value of those referred after a positive HOS had been identified in the HMO Central Screening Center. This is a unit independent from the endoscopy units. The specificity of HOS, in this colonoscopy-controlled study, was lower than anticipated from our own and published experience.^{6, 9, 12, 15, 19} There are several reasons that might contribute to this; the HOS preparation, development and reading were not controlled or carried out by us; the published data often included specificity deduced by clinical follow-up, only a few studies were partially or fully colonoscopically controlled.^{9, 15} This discrepancy between published results and what we found illustrates the problems of quality control related to preparation, development and reading of a guaiac FOBT.

In this initial evaluation, both HOS and OC-MICRO had similar sensitivities for significant neoplasia. However, we have demonstrated that the I-FOBT is far more specific, has a better PPV and so would generate fewer follow-up colonoscopy examinations. This has also been the international clinical experience with I-FOBTs.^{7, 10, 15, 23, 30} The automated and quantitative test for human faecal Hb minimizes human errors because of uncontrolled diet and in test development, and makes it a more objective laboratory test with its attendant quality control.

The I-FOBT also has its limitations. In our on-going colonoscopy-controlled evaluation, we found that three faecal samples provided the optimal OC-MICRO sensitivity for significant neoplasia. This is in contrast to others' experience with I-FOBTs where only one or two annual or even one sample biennially is requested.^{20, 21, 23} In our evaluation, we also found that the faecal samples were temperature sensitive and Hb degradation occurred if the samples were not stored at 4 °C.^{25, 26} Both of these issues may explain the poorer I-FOBT result recently published, where only one sample was tested.²⁴

Based on our positive on-going experience with the I-FOBT, we will now initiate an average-risk population comparison study with HOS. The aims will be to compare compliance for preparing the two tests and to evaluate the resulting neoplasia yield and cost.

In conclusion, the I-FOBT (OC-MICROTM) maintains the high sensitivity of the G-FOBT (Haemoccult SENSTM), but can significantly reduce the colonoscopy burden and expenses resulting from a guaiac FOBT-based screening programme.

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