

Chemical and immunological testing for faecal occult blood in screening subjects at risk of familial colorectal cancer

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Abstract

Background—People with a family history of colorectal cancer have an increased risk of the disease themselves. Many centres are advocating family history screening by endoscopy.

Aims—The performance of chemical and immunological faecal occult blood tests (Haemoccult and Hemeselect) in 212 subjects with a family history of colorectal cancer was assessed.

Results—Both Hemeselect and Haemoccult were positive in the only patient with colorectal cancer. Hemeselect was more sensitive than Haemoccult for adenomas (40% compared with 20%) (adenomas larger than 1 cm 75% compared with 50%). No additional abnormality was detected by the addition of Haemoccult or Hemeselect to 60 cm flexible sigmoidoscopy in screening people at lower levels of familial risk. A false positive rate of 16% for Hemeselect resulted in a high proportion of additional colonoscopies in this group.

Conclusions—At present faecal occult blood tests are not sufficiently sensitive or specific to replace endoscopy in screening people at risk of familial colorectal cancer.

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The guaiac based Haemoccult (HO) (Rohm Pharma) has been widely investigated in mass population screening studies. It is cheap, simple, and quick to use. It has a sensitivity of 50-65% for asymptomatic colorectal cancer^{1 2} and 33% for large adenomas.³ Its sensitivity is lowest in the rectum and caecum.^{1 2} Sensitivity can be increased by rehydration, but this also increases the false positive rate from 1-2% to 6-10%.^{4 5}

Immunological faecal occult blood tests (FOBT) are highly specific for human haemoglobin, offering the prospect of greater sensitivity without loss of specificity. In symptomatic patients, HemeSelect (HS) (Smith-Kline Diagnostics) has a sensitivity for cancer of 94%, and adenomas larger than 1 cm of 67%. However, increased sensitivity is accompanied by some loss of specificity when compared with HO (84% compared with 96%).³ High risk groups, such as those with a family history of colorectal cancer, are currently screened by colonoscopy when the risk is very high; for example, hereditary non-polyposis colorectal

cancer (HNPCC) but by flexible sigmoidoscopy or FOBT for lesser degrees of risk. We wished to investigate the sensitivity and specificity of HemeSelect in a group at high risk undergoing colonoscopy and the effect of adding HS to flexible sigmoidoscopy in people at lesser risk.

Methods

PATIENTS

HO and HS were examined in two groups of subjects, detailed below. Subjects were asked to complete HO and HS tests on each of three daily bowel motions before endoscopy. Rehydration of HO test cards was not performed. A blue discolouration at 30 seconds was taken as a positive reaction after the application of two drops of 1% w/w hydrogen peroxide.³ Erythrocyte agglutination at a 1:8 dilution was taken as a positive reaction for HS.³ No dietary restriction was enforced. Participants were recruited, to the study, from an open access clinic for relatives of colorectal cancer patients and a number of case finding initiatives ongoing in our unit. Overall compliance, with endoscopy was 73% at the time of study, but many people were self referring volunteers. The male:female ratio was 1:1.58. Subjects who presented with symptoms were excluded from analysis.

Group 1

A total of 125 people at high risk of familial colorectal cancer (two or more first degree relatives or first degree relative affected under the age of 50 years) had a colonoscopy, (plus completion barium enema in 19 patients) and completed HO and HS tests before examination. The mean age of those completing FOBT was 46 years (range 20-73; median 46). Of the 125 subjects completing all tests, 10 were found to have neoplasia. No cancers were found. Four subjects had adenomas larger than 1 cm (ages 18, 30, 44 and 46 years).

Group 2

A total of 87 people at lower levels of familial risk (single first degree, or first and second degree relative over the age of 50 years), scheduled for 60 cm flexible sigmoidoscopy completed both HO and HS tests. The mean age of those completing FOBT was 49 years (range 40-75; median 50). Neoplasia was

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detected in six (7%) of these subjects. One person had cancer (age 67 years) and five had adenomas, two of whom had adenomas larger than 1 cm (ages 55 and 73 years).

Results

GROUP 1

Haemoccult

Four subjects (3%) had a positive HO test. Two were true positive tests, colonoscopy revealing adenomas (both larger than 1 cm) and two were false positive tests, colonoscopy revealing no abnormality. One hundred and twenty one subjects had negative HO tests, 113 (91%) being true negative results and eight false results, adenomas being detected at colonoscopy. Two people with a false negative HO test had adenomas larger than 1 cm.

The positive predictive value of HO in this group was 50% for adenomas greater than 1 cm. The sensitivity was 20% for all adenomas and 50% for adenomas larger than 1 cm. The specificity of HO was 98%.

HemeSelect

Twenty one subjects (17%) had a positive HS test and had a colonoscopy. Four were true positive tests, showing adenomas (three larger than 1 cm) and 17 were false positive tests, with no abnormality. Some 104 subjects had negative HS tests, 98 (94%) being true negative results and six false negative results, adenomas being detected at colonoscopy. Only one person with a false negative HS test had an adenoma larger than 1 cm found at colonoscopy.

The positive predictive value of HS in this group was 20% for adenomas greater than 1 cm. The sensitivity was 40% for all adenomas and 75% for adenomas larger than 1 cm. The specificity of HS was 86%. Three subjects (2.4%) had positive HO and HS tests and all had adenomas (two larger than 1 cm).

Group 2

Two subjects had positive HO test with a negative HS test, both were false positives. Twelve had a positive HS test with a negative HO, only one being a true patient (patient with 1 cm rectal adenoma). Two subjects had positive HO and HS tests. One of these had a Dukes's stage B cancer of the sigmoid colon. In the other no colonic abnormality was found but the patient reported profuse epistaxis on several days immediately before and during completion of the tests. Four subjects with negative HS and HO tests had adenomas detected on flexible sigmoidoscopy. HO, HS, and flexible sigmoidoscopy were all negative in 67 (77%) of subjects.

In this group, the positive predictive value of HO was 25% and HS 14%. The sensitivity and specificity of the tests cannot be calculated in this cohort as most people did not undergo colonoscopy. Sixteen underwent colonoscopy

because of a positive FOBT, 14 of whom had no abnormality detected. Two had neoplasia detected, both within reach of the 60 cm flexible sigmoidoscope, (one rectal and one sigmoid colon). Therefore, in this cohort no additional abnormality was detected by FOBT. The high false positive rate of HS (16%) resulted in a large proportion of 'unnecessary' colonoscopies.

Discussion

First degree relatives of patients with colorectal cancer have a threefold to fourfold increased risk of developing the disease themselves.⁶⁻⁸ Screening studies have consistently shown relatives of colorectal cancer patients have more neoplasia than control populations⁹⁻¹² and screening of familial colorectal cancer is widely recommended.^{1 14}

There is debate over the screening modality of choice.¹⁴ The risk of colorectal cancer to which a person is subject is dependent upon the number and ages of affected relatives.^{8 15} Most authorities feel that high risk subjects (two or more affected relatives or a first degree relative affected before the age of 45 years) should be screened by colonoscopy.¹⁶ Making screening recommendations for those at lower levels of risk (single older first degree relative with colorectal cancer) is difficult as much published screening data fails to give details of family risk and the age of those screened. Recommendations vary from full colonoscopy¹⁴ to FOBT with Haemoccult.¹³

Among people at high levels of familial risk, although the incidence of adenomas is not especially high, their rate of conversion to cancers may be significantly increased.¹⁷ A screening test for these people will therefore need to be sensitive for adenomas. Our study has confirmed other reports^{10 13} that found Haemoccult is not sufficiently sensitive for familial colorectal cancer screening. We found HemeSelect to be more sensitive for adenomas in this group but associated with a higher false positive rate. Its performance in this group was similar to that in symptomatic patients.³

In people with lower levels of familial risk it has been suggested that FOBT may be a useful adjunct to left sided endoscopy in screening subjects at lower levels of familial risk.¹² This has not been shown by our study, with no additional neoplasia being detected by the addition of HO and HS to 60 cm flexible sigmoidoscopy. Furthermore the high false positive rate of HS, and therefore high level of colonoscopy will add considerably to the cost of a screening programme using this test.

Detection of tumour associated antigens such as carcinoembryonic antigen¹⁸ or the protein products of tumour mutations potentially provide more specific markers, although mutant p53 has proved initially disappointing.¹⁹ Therefore at least for the present time there is no FOBT that appears sufficiently sensitive to replace endoscopy in screening people at risk of familial colorectal cancer.

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