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Role of faecal occult bloods in the diagnosis of iron deficiency anaemia

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Received 17 November 2013

Accepted 8 January 2014

Published Online First

27 January 2014

ABSTRACT

Objective To determine whether faecal occult blood (FOB) testing in patients with iron deficiency anaemia (IDA) can predict the presence of gastrointestinal cancer.

Design Cohort study.

Settings Single secondary care hospital UK.

Patients All individuals aged 20 years and older referred for the investigation for IDA.

Interventions Data was collected from all the patients regarding haemoglobin (Hb), mean corpuscular volume, age, sex, symptomatology and medication. All patients had FOB tests using laboratory guaiac and haemocell methods, and then underwent gastroscopy and colonoscopy.

Main outcome measures Accuracy, sensitivity and specificity of FOBs for identifying cancer in the upper or lower gastrointestinal tract.

Results In total, 292 patients completed the study; 37 patients were diagnosed with carcinoma (colon 34, gastro-oesophageal 3). Using an optimal combination of lab guaiac and haemocell test resulted in just one colorectal cancer being missed, a sensitivity of 97%, specificity of 49% and negative predictive value of 99%. The test was less effective for upper gastrointestinal cancer, with 2/3 tumours missed by the tests.

Conclusions Patients who have negative FOB tests are very unlikely to have a colorectal cancer, and the benefits to further colonic investigation is limited. This should be carefully considered in patients with significant comorbidities, where the risks of investigation may outweigh the benefits.

INTRODUCTION

Iron deficiency anaemia (IDA) is the most common cause of anaemia in the UK.¹ Estimates suggest that 3–5% of men and postmenopausal women have IDA with the level rising to 7% in elderly hospital in-patients.^{2–4} The principal concern in patients presenting with an IDA is that it may be the result of blood loss from an underlying gastrointestinal neoplasm.

Previous studies have shown a prevalence of carcinoma of 10–20%, most commonly of the colon^{5–9} (5–12.5%), but also stomach and oesophagus. Currently, the British Society of Gastroenterology (BSG)¹⁰ and American Gastroenterology association (AGA)¹¹ guidelines recommend that upper and lower gastrointestinal endoscopy be performed in all men and postmenopausal women with IDA. It should be recognised that the risk of cancer is not uniform across all age groups and gender. However, investigation is not risk free, and the complications associated with endoscopy can be more pronounced in frail, elderly patients,¹² or in patients of any age with significant comorbidities, including advanced chronic obstructive airway disease (COPD), severe congestive cardiac failure and advanced multiple sclerosis to name but a few examples. While the decision to investigate healthy high-risk patients is straightforward, there can be a dilemma for clinicians when faced with patients with multiple comorbidities where the morbidity and mortality associated with further investigation is high. There is, therefore, a need for a simple, non-invasive test to use in these groups of patients to stratify risk and predict whether invasive tests are likely to be of benefit.

There have been papers published which have demonstrated that advancing age, IDA and positive faecal occult bloods (FOBs) are positive predictive factors for bleeding gastrointestinal lesions.^{13 14} FOB tests are non-invasive tests on stool samples which are examined for the presence of occult blood. While results have varied between studies, FOB testing is approximately 50% sensitive for cancer in asymptomatic patients, and therefore felt to lack the sensitivity for use as a diagnostic

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To cite: Chowdhury ATMD, Longcroft-Wheaton G, Davis A, et al. *Frontline Gastroenterology* 2014;5:231–236.

test.^{15–21} However, it is unclear how the presence of IDA may affect this. The development of iron deficiency in the context of a colorectal neoplasm is secondary to the tumour bleeding. It would be reasonable to question, therefore, whether this would improve the sensitivity of FOB testing for cancer. Until now no studies have been performed to investigate this.

The aim of this study is to determine whether FOB testing with IDA can predict the presence of gastrointestinal cancer.

METHODS

The study has ethical approval from the Portsmouth and South East Hampshire ethics committee (LREC Reference No. 01/02/1298). Data was collected on adult patients referred for the investigation for IDA. Patients with a history of colonic polyps, inflammatory bowel disease or angiodysplasia, lynch syndrome, familial adenomatous polyposis syndrome, oesophageal, gastric or colon cancer, or a family history of bowel cancer, were excluded from the study. Information was collected from the patients regarding haemoglobin (Hb), mean corpuscular volume (MCV), age, sex, symptomatology and medication. All patients had MCV and ferritin measured. An MCV of less than 82 with a serum ferritin <12 was required for inclusion, which accounted for 90% of the recruited patients. However, it was recognised that ferritin is an indirect measure of iron stores. It is an acute-phase protein and will be elevated in the presence of inflammation. Therefore, in cases where ferritin was normal, then serum iron, total iron binding capacity (TIBC) and transferrin were measured. If serum iron was less than 65 µg/dL, with an elevated TIBC greater than 66 µmol/L and transferrin saturation of less than 15%, patients were included regardless of MCV or ferritin.

All data was prospectively collected on an electronic computer database. All patients were requested to undertake FOB testing using the laboratory guaiac and haemocell kits, used independently on six stool samples collected on six separate days. Patients were trained how to use the haemocell kit by a nurse experienced in the test, with the laboratory guaiac test requiring the patient to return to the laboratory for analysis three stool samples taken on three separate days. All patients then underwent gastroscopy and colonoscopy as per standard protocol. The endoscopist was blinded to the result of the FOB test. Diagnosis at endoscopy was then compared with the FOB test results. From this sensitivity, specificity and positive and negative predictive values (NPV) of the FOB tests were calculated.

The guaiac FOB test method is based upon the peroxide-like activity of the haem moiety of whole or digested blood. Hydrogen peroxide in the presence of blood will liberate oxygen, which reduces

phenolphthalein (colourless) to a coloured pink product. A normal person is thought to pass up to 4.5 mL blood a day via the faeces. Sensitivities of the kit for detecting haemoglobin varies from 0.01 mg to 6 mg Hb/g faeces. 6 mg Hb/g faeces equates to about 4 mL blood/100 g faeces. A positive control was used. This was made by diluting 0.025 mL of EDTA blood (with a normal Hb) in 100 mL H₂O. This gives a result of '2+', which corresponds to 4 mg Hb/g faeces (2.7 mL blood/100 g faeces).

0+ represents no/trace of Hb/g faeces (<1.4 mL blood/100 g faeces).

1+ represents 2 mg Hb/g faeces (1.4 mL blood/100 g faeces).

2+ represents 4 mg Hb/g faeces (1.4 mL blood/100 g faeces).

3+ represents 6 mg Hb/g faeces (4.1 mL blood/100 g faeces)

4+ represents 8 mg Hb/G faeces (5.4 mL blood/100 g faeces) or more.

The haemocell test is based on similar principles, but is a card-based test. Faeces are applied to one side of a thick piece of paper attached to a thin film coated with guaiac using an applicator. This is done by the patient at home. In the laboratory, hydrogen peroxide is applied to the inner guaiac paper. This oxidises the α-guaiaconic acid to a blue coloured quinone. In the presence of haemoglobin, this reaction is catalysed and occurs very rapidly. The test kit is reported as either 0 (negative) or 1 (positive). Three samples are returned, taken on three separate days. If any of these tests turns positive the test is defined as positive. SPSS V.18 (IBM) was used for the statistical calculations. A Fisher's exact test was used for significance testing.

RESULTS

In total, 317 patients were enrolled, with 292 patients completing the study. In total, 25 patients failed to complete the study, either for not returning all of their FOB kits or by declining definitive investigation. The median age was 70 (range 21–90) years. One hundred and fifty-six were men. The median haemoglobin was 10 g/dL (range 7–14). The median MCV was 75 fL (range 57.3–97.2). The median ferritin was 17 ng/mL (range 2–660). The true pathology found at definitive investigation is shown in table 1.

Receiver operating characteristic curve for laboratory guaiac test

To determine the optimum cut-off point, receiver operating characteristic (ROC) curves were produced. There were 37 cancer cases in the series, 3 upper gastrointestinal and 34 colon cancers. The fitted ROC area was 0.781. Using the optimum cut-off point of 2+ for positive, six true positive cases (two upper gastrointestinal and 4 lower gastrointestinal) were missed. There were 122 false positive cases. This resulted in a sensitivity of 83.8% (95% CI 68% to

Table 1 Breakdown of the true diagnosis found at gastroscopy and colonoscopy

Gastroscopy	
Normal	137
Barrett's	10
Oesophagitis	43
Hiatus hernia	73
Gastritis/gastric erosions	39
Gastric ulcer	4
Duodenal ulcer	4
Other (polyp, GAVE)	36
Coeliac	2
Oesophageal cancer	1
Gastric cancer	2
Colonoscopy	
Normal	133
IBD	3
Angiodysplasia	5
Diverticulosis	75
Adenomatous Polyps (VA+TVA with LGD)	35
Hyperplastic	22
Cancer	34
Benign stricture	4

GAVE, gastric antral vascular ectasia; IBD, inflammatory bowel disease; LGD, low grade dysplasia; TVA, tubulovillous adenoma; VA, villous adenoma.

93%), specificity of 52.2% (95% CI 50% to 54%) and overall accuracy of 56.2% (95% CI 52% to 59%). This equates to a NPV of 96% (95% CI 92% to 98%) and a PPV of 20% (95% CI 17% to 23%). See table 2 and figure 1.

The analysis was repeated with upper gastrointestinal cancers excluded. The fitted ROC area was 0.792. In total, four cancers were missed. Using the optimum cut-off point of 3+, a sensitivity of 88.2% (95% CI 73% to 96%), specificity of 52.3% (95% CI 50% to 53%) and overall accuracy of 56.5% (95% CI 53% to 58%) is achieved. This corresponds to a NPV of 97% (95% CI 93% to 99%) and a positive predictive value of 20% (95% CI 16% to 21%). See tables 3 and 4 and figure 2.

The haemocell test

There were three cases where haemocell samples were not processed. These were excluded from analysis. For haemocell testing alone a sensitivity was 26/37=70.3% and specificity of 223/252=88.5% was achieved. When upper gastrointestinal cancers were excluded the

Figure 1 Receiver operating characteristic curve for detection of upper and lower gastrointestinal neoplasia using the faecal guaiac test (blue curve) with 95% CIs (green and red curves).

sensitivity increased to 25/34=73.5%. The specificity was unchanged. When combined with the guaiac test (3+ positive) a sensitivity of 34/37=92% and specificity of 123/252=49% was achieved. When upper gastrointestinal cancers were excluded this increased the sensitivity to 33/34=97%. Specificity was unchanged. This is summarised in table 5.

Cases diagnosed with cancer

Of the 37 patients diagnosed with carcinoma, one was oesophageal, two gastric and 34 were colonic cancers. All the upper gastrointestinal tumours were symptomatic and would have required gastroscopy on the basis of symptoms alone. Of the four colon cancers missed by laboratory guaiac testing alone, two were symptomatic. The other two were both right-sided lesions. These would not have been diagnosed by a flexible sigmoidoscopy. Both were over 80 years of age. One had no comorbidities, the other having a history of previous jaundice (resolved) and hypertension.

DISCUSSION

FOBs have not traditionally been felt to be useful as a diagnostic test for gastrointestinal malignancy. However, this data suggests that in a population with IDA, a combination of the haemocell and guaiac tests can achieve a NPV of 99% for colorectal cancer. This is perhaps not surprising. For a tumour to cause an IDA, requires it to bleed. Therefore, it is biologically plausible that in this population the sensitivity for cancer would be much better than in a surveillance population where non-bleeding tumours would be missed. This has implications for frail patients where

Table 2 Frequency of findings of guaiac test by pathology for all gastrointestinal cancers

Guaiac result	0	1+	2+	3+	4+
Cancer	3	3	3	11	17
No cancer	81	52	46	50	26

Table 3 Frequency of findings of guaiac test by pathology for colorectal cancer

Guaiac result	0	1+	2+	3+	4+
Cancer	3	1	3	11	16
No cancer	81	52	46	50	26

Table 4 Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of guaiac test for the identification of colorectal cancer

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
4+ FOB	47% (32 to 62)	91% (89 to 93)	86% (82 to 93)	41% (28 to 54)	93% (91 to 95)
3+ FOB+ve	79% (63 to 91)	71% (69 to 73)	72% (68 to 75)	27% (21 to 30)	96% (93 to 98)
2+FOB +ve	88% (73 to 96)	52% (50 to 53)	57% (53 to 58)	20% (16 to 21)	97% (93 to 99)
1+ FOB+ve	91% (76 to 98)	31% (29 to 32)	38% (35 to 40)	15% (12 to 16)	96% (90 to 99)

FOB, faecal occult blood.

investigation with either colonoscopy or CT scanning carries increased risks.

Studies have been conducted to determine the value of immunological FOB testing in high-risk populations. One small study of 50 patients looked at FOBs in patients with anaemia, achieving an overall sensitivity for adenomas and cancer of 53% and specificity of 86%.²² However, this was attempting to find benign adenomas as well as cancer, most of which do not bleed unless large. Another study has suggested that patients with IDA who test positive with a faecal-immunochemical test (FIT) are more likely to have a lesion detected at endoscopy (79% vs 27% $p<0.001$).¹⁴ In this study, testing was performed on a single day, and this may have limited its effectiveness. We believe that testing on multiple days improves accuracy of FOBs and, therefore, our data is not contradictory to this. While we have not used the FIT test, the principle behind the test is essentially the same. There has been data published which suggests that FIT is a more effective test than the guaiac test.^{23–25} We believe that better results would be achieved if FIT testing were used in place of the guaiac test. These were unavailable when we started this study, but are now widely available, and we feel that it would be valuable to repeat this study using FIT testing to investigate this concept further.

The key strengths of our study are that it is large and based in a real-world unselected population of patients with IDA. We would stress that we do not see this as a replacement for the endoscopic investigation

of patients with IDA; this remains the gold standard investigation, and for the majority of patients, this is the best form of investigation. However, there is a significant group of patients with asymptomatic IDA who are frail with multiple comorbidities where colonoscopy is a high-risk procedure. It is not always ideal to perform CT imaging in this group when renal impairment is a factor, as intravenous contrast is nephrotoxic. Furthermore, if a pneumocolon is performed, bowel preparation is still required which, in a patient with limited mobility, can be very challenging. With an ageing population, this is an increasingly common presentation, and one which poses a difficult dilemma for investigation. We feel that if a non-invasive test, such as the faecal guaiac and haemocell tests could be used with a 99%NPV, it would potentially be a good option, and much safer than invasive investigations which may cause more harm than they solve.

It could be argued that in patients where investigation is a high risk, the likelihood of successful treatment, were a cancer to be found, is very low, and the question could be asked whether any investigation in this group of patients is justified. However, diagnosis is not just about treatment. Patients need to be able to plan their lives. It is a reality of modern medical practice that we are often referred patients to investigate for potential cancer who would not be fit for curative treatment. While it may be true that a diagnosis will not alter management, and observation may be a reasonable option, this often leads to unsatisfactory discussions with prolonged anxiety for patients, the vast majority of who will not have cancer. It is in these situations that FOB testing may have a role.

There may also be implications for this data in younger, low-risk patients. In young, premenopausal women with IDA and no other risk factors, the risk of colon cancer is very low. FOB tests may be a reasonable measure in this cohort, providing an additional degree of reassurance without the risks associated with an invasive colonoscopy.

The combination of tests appears to provide the optimum detection of cancer. There are a number of potential reasons for this. The haemocell test and laboratory guaiac test work along essentially the same principles. The haemocell test in isolation missed nine colorectal cancers. The guaiac test detected 8/9 of

Figure 2 Receiver operating characteristic curve for diagnosis of colorectal cancer using the faecal guaiac test (blue curve) with 95% CIs (green and red curves).

Table 5 Accuracy, sensitivity and specificity of the haemocell test +/- guaiac test for the diagnosis of colorectal cancer

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
Haemocell alone	74% (57 to 86)	89% (86 to 90)	87% (83 to 90)	46% (36 to 54)	96% (94 to 98)
Haemocell with 3+ guaiac	97% (84 to 100)	49% (47 to 49)	55% (51 to 55)	20% (18 to 21)	99% (96 to 100)

NPV, negative predictive value; PPV, positive predictive value.

these missed lesions. By contrast, the guaiac test missed four cancers. The haemocell test detected three of these. In 23 cases, there was agreement between the two tests. Therefore, whilst both tests were effective in isolation, there was additional gain when used together. We suspect that the reason for the improvement in cancer yield is simply an increase in the number of samples examined. Taking the additional samples for the haemocell test also effectively increases the period of time over which collection takes place. This may also result in an increased likelihood of detecting cancers which are intermittently bleeding. This is speculative, and warrants examination in further studies.

It should be noted that guaiac testing alone produced very good results, with a NPV of 97%. This raises a very critical question; what is an 'acceptable' cancer miss rate for a diagnostic test? There are many factors which influence this decision, and it is not an easy question to answer. It is a controversial issue which this paper cannot answer. We feel that before it can be addressed with confidence, the results from this paper need to be replicated in further studies to confirm the NPV for guaiac testing alone and in combination with the haemocell test.

There are known clinical variables which are strongly predictive for the risk of gastrointestinal cancer in IDA. This includes age, sex and haemoglobin. We did not find any significant difference in the age or gender of patients with cancer compared with patients without cancer in this cohort, but this does not constitute an analysis of these variables, and the study was not designed or powered for this purpose. We suspect that FOBs would provide further gain in addition to these established risk factors, and would be an important area for future study.

There are some limitations to our study. It is a single-centre study in the UK and the population may differ elsewhere in the world. Patients were recruited across the entire adult age range, and by definition, did not contain any patients unfit for either colonoscopy or CT pneumocolon. In practice, it is very difficult to study a population unfit for colonoscopy, as it is not possible to establish the true diagnosis without definitive investigation. It is not simply a basis of age as many older patients are very suitable for colonoscopy and simply restricting the population to fit elderly patients would not alter this situation. We feel that the extrapolation is reasonable and probably unavoidable. It should also be noted that the number

of upper gastrointestinal cancers in this series was small, and it is not possible to draw any meaningful conclusions from just three cases. However, given that 2/3 of the upper gastrointestinal cancers were missed, it seems probable that the guaiac FOB test is not effective for the identification of oesophageal or gastric malignancies. This should be confirmed by larger studies, but at present, could not be recommended for this purpose. Practically, gastroscopy carries a much lower risk than colonoscopy, and even very frail patients can usually tolerate a gastroscopy with very limited risk, so from a clinical position, this is less of an issue.

We did not perform an analysis for the sensitivity of FOBs for the detection of adenomas. There is a good volume of published literature which has demonstrated that the sensitivity of FOBs for adenoma detection is poor and we are not challenging this position. We would stress that we are not proposing FOBs as a replacement for colonoscopy. In patients where the identification of adenomas is important, colonoscopy or CT pneumocolon is required. There are, however, patients where we simply wish to exclude cancer (ie, patients with extensive comorbidities and a limited life expectancy) where adenoma detection is not important. It is in these circumstances where we see FOBs as having a role.

The positive predictive value of this test is poor. There are a number of possible explanations for this. Any cause for blood in the stools can cause the FOB test to be positive, including haemorrhoids and fissures. This is not unexpected and represents a limitation of FOBs as a technique for investigating anaemia using a non-invasive test such as FOBs. We do not propose that FOBs can be seen as a definitive diagnostic test. We feel, however, that they potentially have a value as a screening test with a potential value in excluding patients who test negative from further investigation.

CONCLUSIONS

FOB testing using a combination of the guaiac and haemocell tests is a sensitive test for cancer in patients with IDA. We feel negative FOB testing in patients with IDA is an effective way of screening out low-risk patients where further invasive investigations pose a significant risk. This data needs repeating in a similar study to establish whether this concept can become a routine aspect of clinical care.

What is already known on this topic

Guaiac based faecal occult blood testing can be used for the identification of patients at risk of cancer. However, as a diagnostic test in an asymptomatic population it has a low sensitivity and specificity and is currently considered inadequate for the diagnosis of cancer.

What this study adds

In a patient population with iron deficiency anaemia the sensitivity of faecal occult bloods is excellent, with a 99% negative predictive value for colorectal cancer.

How it might impact on clinical practice in the foreseeable future

In patients with iron deficiency anaemia a negative faecal occult blood test appears to be very effective at excluding cancer. If these results can be replicated in further studies this may prove to be an effective method of screening out patients with multiple co-morbidities from further invasive investigations where such tests pose a significant risk.

Contributors ATMD: 1st author, data collection, project management. GL-W: Data analysis, writing of the paper. AD: Initial protocol and ethics application. DM: Advice on pathological aspects and review of manuscript. PG: Senior author and guarantor of the paper.

Funding NHS sponsored study

Competing interests None.

Ethics approval South East Hampshire ethics committee LREC No. 01/02/1298.

Provenance and peer review Not commissioned; externally peer reviewed.

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