Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis

BMJ 2010;340:c1269 doi:10.1136/bmj.c1269
Mr DC

62 year old man
Borderline anaemia 3 years
Initially slightly low B12 - treated
Raised Alk Phos 5 years (on statin)
Normal haematinics
Borderline iron studies
Assymptomatic
Would you refer?
Mr DC

Letter to haematologist

No investigation

7 months later c/o 2 stone weight loss

Jaundiced

Grossly enlarged hard craggy liver edge

Acute admission

Metastatic rectal carcinoma
Colorectal cancer

2nd most common cancer in Europe

5 year survival early stage 90%

5 year survival metastatic <10%
Two week rule

Criteria (when at least one criterion is positive the patient should be referred):

Rectal bleeding with a change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks. Age threshold: all ages.

Change in bowel habit as above without rectal bleeding and persistent for 6 weeks. Age threshold: over 60 years.

Rectal bleeding persistently without anal symptoms*. Age threshold: over 60 years.

A definite palpable right-sided abdominal mass. Age threshold: all ages.

A definite palpable rectal mass (not pelvic). Age threshold: all ages.

Unexplained iron deficiency anaemia. In men: below 11 g/dl, all ages. In women: below 10 g/dl, post menopausal.

* Anal symptoms include soreness, discomfort, itching, lumps and prolapse as well as pain.
Changes in practice

Haematinics falsely reassuring

Ferritin acute phase protein - may be increased in inflammation, malignancy or liver disease

Iron studies most reliable method to r/o iron deficiency

How else could I have picked up his cancer?
Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis

To summarise available evidence on diagnostic tests that might help primary care physicians to identify patients with an increased risk for colorectal cancer among those consulting for non-acute lower abdominal symptoms
Sensitivity & Specificity

Sensitivity - true positive rate
How good is this test at picking up people with the disease?
High sensitivity = low false positives

Specificity - True negative rate.
How good is this test at correctly excluding people without disease?
SR & Meta-analysis

Age
Family history
Weight loss
Individual signs and symptoms
Combinations of symptoms
Referral guidelines
Blood tests
Faecal occult blood tests
Citations identified by PubMed/Embase search strategy (n=3237):
- PubMed (n=1934)
- Embase (n=1303)
- In both databases (n=378)

Citations (title, abstract) screened by first reviewer (n=2859)

Citations (title, abstract) screened by second reviewer (n=578)
- All references assessed by first reviewer as relevant or maybe relevant

References assessed by second reviewer as relevant or maybe relevant (n=421)
- Papers excluded after assessment (n=383):
  - No relevant study population (n=219)
  - No relevant study design or publication type (n=72)
  - No relevant index test (n=41)
  - No relevant reference test (n=9)
  - No relevant target disease (n=19)
  - Publication could not be retrieved (n=3); excluded languages (n=20)

Relevant papers identified in PubMed/Embase (n=38):
- Studies in both PubMed and Embase (n=18)
- Studies in PubMed only (n=15)
- Studies in Embase only (n=5)

Relevant papers identified by reference checking (n=11)

Primary diagnostic studies included in the review (n=47)
- 2 of 43 papers identified in PubMed/Embase reported on same study
- 1 paper identified by checking references in study already identified on PubMed/Embase
Checklist for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)

1. Valid selection and representativeness of study participants. Score ‘+’ if consecutive patients or a random sample has been selected and when the inclusion or exclusion criteria do not jeopardize the representativeness of the study population.

2. The index test results were interpreted without knowledge of the results of the reference standard. Score ‘+’ if the index test results are interpreted blind to the results of the reference standard.

3. The index test did not form part of the reference standard. Score ‘+’ if the index is no explicit part of the reference standard.

4. When the index test results were interpreted the same clinical data were available as would be available in clinical practice. Score ‘+’ if no additional clinical data are available, and if no usually available clinical data are missing.

5. The reference standard is likely to classify the target condition correctly. Score ‘+’ if the reference test is colonoscopy plus histopathology, or clinical follow-up of at least one year.

6. The whole sample or a random selection of the sample received a reference standard. Score ‘+’ if it is clear that all patients who received the index test went on to receive a reference standard, even if the content of the reference standard was not the same for all patients.

7. The patients received the same reference standard. Score ‘+’ it is clear that all patients receiving the index test were subjected to the same reference standard.

8. The reference standard results were interpreted without knowledge of the results of the index test. Score ‘+’ if the reference standard results were interpreted blind to the results of the index test.

9. The time period between the index test and reference standard is short enough to be reasonably sure that the target condition did not change between the two tests. Score ‘+’ if the time period is one month or less.

10. No (bias by) withdrawals. Score ‘+’ if all patients who enrolled the study received both the index test and the reference standard. In case of withdrawals: score the potential bias by these withdrawals.

11. No (bias by) missing values or uninterpretable test results. Score ‘+’ if all test results are reported for all patients who received the index test and reference standard (including uninterpretable results). In case of missings: score the potential bias by these missing values.
### 2 x 2 table

<table>
<thead>
<tr>
<th>Result of screening test</th>
<th>Disease</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>True + (a)</td>
<td>False + (b)</td>
</tr>
<tr>
<td>Test -</td>
<td>False - (c)</td>
<td>True - (d)</td>
</tr>
</tbody>
</table>
Comparing studies

Sensitivity
Specificity
Positive Predictive Value
Negative Predictive Value

PPV and 1-NPV used to calculate probability of cancer in those with + & - results
Analysis

Individual factors

Combinations of factors

Subgroup analyses - why?
Key findings

Performance of tests vary widely

Sensitivity high for >50s and TWR but specificity low - what does this mean?

FOB reasonable sensitivity and specificity
Useful symptoms

Weight loss most useful with fairly high specificity

Diarrhoea, constipation, change in bowel habit, abdominal pain poor diagnostic performance

High degree of heterogeneity between studies
Family history

High specificity
Low sensitivity
Why might this be?
Combinations of symptoms

Improve sensitivity at cost of specificity

Casting the net wider

What are the sensitivity and specificity of TWR criteria?
FOB

May be the most useful first line test, but evidence lacking about performance in primary care populations.
Should Mr DC have been to colorectal?

How useful is iron deficiency anaemia at predicting cancer?

Are these results applicable to this patient?