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PRACTICE

RATIONAL TESTING

Blood markers for cancer

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What you need to know

- "Triage" blood tests in primary care, such as haemoglobin, platelets, serum calcium level, liver function tests, and inflammatory markers such as C reactive protein and erythrocyte sedimentation rate may provide "clues" to cancer in patients with non-specific symptoms
- Triage tests do not have the performance characteristics of rule-out tests
- Evidence supports the use of only a small number of specific cancer markers, such as CA125 and PSA, in primary care

A 61 year old man with a one month history of back pain visits his general practitioner (GP). He has hypertension, has never smoked, and reports fatigue for several months. The pain is keeping him awake at night. He has not lost weight. Clinical examination is normal. The differential diagnosis for this patient is wide, including potential malignant causes such as pancreatic, myeloma, and prostate cancer or metastatic disease.

Cancer can be difficult to identify, as many of the common symptoms are non-specific and low risk, and even the most well known "alarm" symptoms have relatively low positive predictive values (PPVs) for underlying malignancy.[1] For example, weight loss has a PPV for underlying malignancy of only 0-3.3%,[2] while rectal bleeding has a PPV of 2.2-15.8%.[3] Cancer markers used in hospital settings, when applied to low risk primary care patients, have low positive predictive values and high false positive rates.[4] Identifying patients whose non-specific symptoms may be caused by cancer, rather than benign disease, is therefore a challenge for primary care physicians.

While formal diagnosis usually happens in secondary care, the first suspicion of cancer generally occurs in primary care. Patients whose symptoms represent an approximate risk of cancer of ≥3% are recommended by the National Institute for Health and Care Excellence (NICE) for urgent investigation, often by referral.[5] Those with estimated risk <3% may receive an initial panel of primary care investigations, or triage testing, to stratify risk. Triage tests can provide clues to help identify patients for referral, and crucially can point towards the site of an underlying malignancy. This is particularly useful when the patient's vague symptoms could be caused by several different cancer types, and can guide decision making on any need for further investigation.

This article discusses blood tests to detect or stratify risk for possible cancer in primary care and presents evidence for their use in symptomatic patients. First we consider tests that are not specific for any one type of cancer but which may help primary care providers stratify risk of malignancy. Then we discuss specific markers for certain types of cancer. Blood tests that might be used for screening asymptomatic patients, tests for less common malignancies (eg, gastrin, prolactin) or for monitoring patients with known malignancies, are beyond the scope of this article.

Search strategy

In August 2019 we replicated the search strategy used by NICE in its most recent guidance, NG12, restricted to papers published after 2014 (2011 for ovary) as the NICE searches had been performed before that date. LM, SB, and WH worked in pairs to assess candidate abstracts for blood tests used in primary care, and extracted full texts for relevant hits, supplemented by a large personal library of existing references.

What is the next investigation?

Non-specific blood tests or clues for cancer

Several non-specific tests, commonly used in primary care, can provide "clues" towards possible cancer. Tests with a PPV for cancer of >1%, including haemoglobin, platelet count, serum calcium, liver function tests, and inflammatory markers such as C reactive protein (CRP) and erythrocyte sedimentation rate

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. You can read more about how to prepare and submit an Education article on our Instructions for Authors pageshttps://www.bmj.com/about-bmj/resources-authors/article-types

(ESR), are summarised in fig 1 (infographic). Tests with PPVs <1% for certain underlying malignancies are reported in the same graphic. These blood tests should not be measured routinely but should be considered in patients with low risk, but *not* no risk symptoms, such as unexplained weight loss or persistent tiredness. Rarely, the full blood count may identify a haematological cancer, but most tests act in a bayesian fashion, whereby a "positive test" makes cancer a more likely explanation.

Although non-cancer diagnoses can also commonly cause abnormal test results, further investigations or referral to rule out malignancy may be warranted. Conversely, a "negative" test makes cancer less likely, though neither result is definitive; that is, if these test results are normal, cancer may still be present.[6] None of these tests has sufficient sensitivity to act as a "rule out" test, with the possible exception of the combination of a normal plasma viscosity or ESR plus normal full blood count, which may be used as a simple rule out for myeloma.[7] In the context of low risk symptoms, negative tests provide some reassurance. However, if symptoms continue or change, further investigation may still be warranted. Ideally, the rationale for and implications of a negative or positive test result should be discussed before ordering these tests so as to allow for shared decision making with patients.

Specific cancer markers

Despite the proliferation of cancer biomarker research in secondary care, there is a shortage of relevant primary care studies, with no new markers entering primary care usage since Sturgeon et al's review in 2009.[8] The small number of cancer specific tests validated for diagnosis of cancer in primary care settings are summarised in table 1. These tests should be used in symptomatic patients, rather than as a non-specific cancer screen. Even well known cancer markers that are part of routine clinical practice, such as prostate specific antigen (PSA) and cancer antigen 125 (CA125), have a limited primary care evidence base. In the case of PSA, because so many men who develop prostate cancer will be asymptomatic,[11] positive predictive value of a positive test does not necessarily translate into clinical benefit.

Outcome

The general practitioner was concerned by the presence of night pain and fatigue, which, in combination with the patient's age, raised the possibility of underlying malignancy. The patient was therefore referred for initial blood tests, which included a full blood count, liver function tests, serum calcium, and ESR. Results were significant for a slightly raised platelet count (495×10^9/L) and a moderately raised ESR (34 mm/h). Further specific blood tests were therefore performed, including serum electrophoresis and Bence Jones protein. Monoclonal immunoglobulins were detected, suggestive of multiple myeloma. The patient was referred urgently to a suspected cancer clinic, where the diagnosis was confirmed.

Future research

Many cancer biomarkers are being investigated, particularly for cancers considered "hard to diagnose," such as pancreas and ovary,[12] or for early detection of cancer recurrences.[9] However, of the candidate cancer biomarkers, few are expected to be tested for in clinical practice.[13] Future research to evaluate markers for a potential diagnostic role should aim to quantify the false-positive rates, clinician and patient acceptability, and health economic aspects in order to determine how these tests should best be used.

How patients were involved in the creation of this article

A first patient contributor was involved in the early stages of the article but was unavailable during the main creation of the piece. SC joined at that stage, and has helped interpret our findings, especially the patient aspects, and in critical review of the whole manuscript, ensuring it remained patient centred.

Contributors LM performed the searches, LM, SB, and WH reviewed abstracts and extracted full texts. JW, WH, and SB wrote the first draft of the article with input from LM and SC. All authors contributed to the intellectual content, edited the manuscript and approved the final version for submission.

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Table

Table 1| Specific blood tests for diagnosing cancer in symptomatic patients in primary care settings

Target cancer	Test	Available evidence	Positive predictive values (95% confidence interval)	When to consider test
Ovarian cancer	CA125	Cohort study: 4379 women with primary care CA125 results; 152 with newly raised CA125 ≥35u/mL and follow-up data. Sixteen incident ovarian cancers diagnosed[9]	10.5% (5.6 to 15.4)	Women with persistent abdominal distension, feeling full, loss of appetite, pelvic/abdominal pain, urgency or frequency (especially if aged >50) [5]
Myeloma	Serum protein electrophoresis	No primary care evidence found		In patients with symptoms of possible myeloma, plus either a raised inflammatory marker or a raised calcium
Prostate cancer	PSA	Cohort study: 120 697 men aged ≥45 years with PSA results; 7538 incidence prostate cancers diagnosed [10]	PSA <3ng/ml: <1% 3 ≤PSA <4: 1% 4 ≤PSA <6: 6% 6 ≤PSA <10: 18% PSA ≥10: 45%*	Men with lower urinary tract symptoms, erectile dysfunction or haematuria [5]
Liver	AFP	No/minimal primary care evidence could be found		Currently not recommended in primary care by NICE
Colorectal	CEA			
Pancreatic	CA19-9			

* confidence intervals not reported. CA125=cancer antigen 125. PSA=prostate specific antigen

Figure

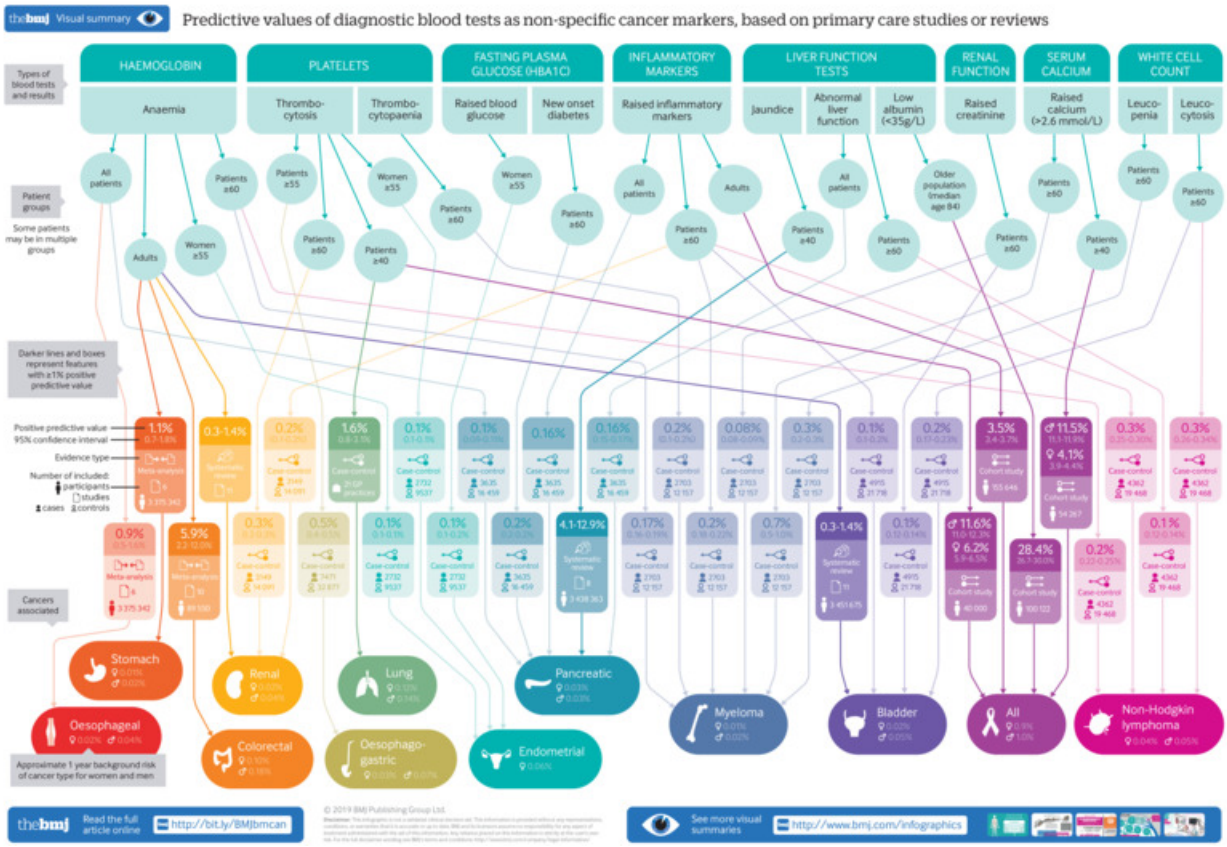

Fig 1 Primary care studies or review investigating the diagnostic role of blood tests as non-specific cancer markers: with positive predictive values (PPVs) ≥1% and <1%