Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study

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ABSTRACT

OBJECTIVE

To quantify the predictive value of unexpected weight loss (WL) for cancer according to patient's age, sex, smoking status, and concurrent clinical features (symptoms, signs, and abnormal blood test results).

DESIGN

Diagnostic accuracy study.

SETTING

Clinical Practice Research Datalink electronic health records data linked to the National Cancer Registration and Analysis Service in primary care, England.

PARTICIPANTS

63 973 adults (≥18 years) with a code for unexpected WL from 1 January 2000 to 31 December 2012.

MAIN OUTCOME MEASURES

Cancer diagnosis in the six months after the earliest weight loss code (index date). Codes for additional clinical features were identified in the three months before to one month after the index date. Diagnostic accuracy measures included positive and negative likelihood ratios, positive predictive values, and diagnostic odds ratios.

RESULTS

Of 63 973 adults with unexpected WL, 37 215 (58.2%) were women, 33 167 (51.8%) were aged 60 years or older, and 16 793 (26.3%) were ever smokers. 908 (1.4%) had a diagnosis of cancer within six months of the index date, of whom 882 (97.1%) were aged 50 years or older. The positive predictive value for cancer was above the 3% threshold recommended by the National Institute for Health and Care Excellence for urgent investigation in male ever smokers aged 50 years or older, but not in women at any age. 10 additional clinical features were associated with cancer in men with unexpected WL, and 11 in women. Positive likelihood ratios in men ranged from 1.86 (95% confidence interval 1.32 to 2.62) for non-cardiac chest pain to 6.10 (3.44 to 10.79) for abdominal mass, and in women from 1.62 (1.15 to 2.29) for back pain to 20.9 (10.7 to 40.9) for jaundice. Abnormal blood test results associated with cancer included low albumin levels (4.67, 4.14 to 5.27) and raised values for platelets (4.57, 3.88 to 5.38), calcium (4.28, 3.05 to 6.02), total white cell count (3.76, 3.30 to 4.28), and C reactive protein (3.59, 3.31 to 3.89). However, no normal blood test result in isolation ruled out cancer. Clinical features co-occurring with unexpected WL were associated with multiple cancer sites.

CONCLUSION

The risk of cancer in adults with unexpected WL presenting to primary care is 2% or less and does not merit investigation under current UK guidelines. However, in male ever smokers aged 50 years or older and in patients with concurrent clinical features, the risk of cancer warrants referral for invasive investigation. Clinical features typically associated with specific cancer sites are markers of several cancer types when they occur with unexpected WL.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The likelihood of an early or late stage cancer diagnosis is increased in the 3-6 months after the first record of unexpected weight loss (WL) in primary care

The malignancies most strongly predicted by unexpected WL are lymphoma, cancer of unknown primary, or pancreatic, gastro-oesophageal, hepatobiliary, lung, bowel, and renal tract cancers

Studies that have investigated the predictive value of clinical features in combination with unexpected WL have not acknowledged that predictive values vary during different periods

WHAT THIS STUDY ADDS

The risk of undiagnosed cancer in adults attending primary care with unexpected WL alone is below the UK's current 3% threshold warranting investigation

In male ever smokers aged 50 years or older and in all patients with other clinical features that could indicate cancer, the risk of undiagnosed cancer across multiple sites rises above the 3% threshold

Clinical features associated with cancer in patients with unexpected WL are abdominal mass, abdominal pain, appetite loss, chest signs, iron deficiency anaemia, jaundice, and lymphadenopathy in both men and women; dysphagia, haemoptysis, and non-cardiac chest pain in men; and back pain, change in bowel habit, dyspepsia, and venous thromboembolism in women

The abnormal individual blood test results associated with cancer in patients with unexpected WL are low albumin levels and raised levels of white cell count, calcium, platelets, and inflammatory markers in men and women

Introduction

Unexpected weight loss (WL) is recorded for about 1.5% of adults attending primary care.[1 2] The likelihood of a cancer diagnosis in such people is increased in the three to six months after the first record of unexpected WL compared with people without unexpected WL: men with unexpected WL are three times as likely as men without unexpected WL to have a diagnosis of cancer within three months and are twice as likely to receive a diagnosis within six months; women with unexpected WL are twice as likely to have a diagnosis of cancer within three months[1] (see table 1). Both early and late stage cancers are associated with unexpected WL.[1 3 4] The greatest risks are from lymphoma, cancer of unknown primary, or cancers of the pancreas, gastro-oesophageal tract, lung, bowel, or renal tract.[1 5] A cancer diagnosis is less likely than in people without recorded unexpected WL after the initial three to six month period.[1]

Table 1 | Number of adults (≥18 years old) with and without unexpected weight loss (WL) and outcome of cancer diagnosis within six months, by sex

Weight loss status	Cancer (n=3019)	No cancer (n=3 27 425)	Sensitivity (%)	Specificity (%)	PPV (%)
All:					
Unexpected WL	908	63 065	30.08	80.74	1.42
No unexpected WL	2111	264 360			0.79
Men:					
Unexpected WL	548	26 210	35.02	81.07	2.05
No unexpected WL	1017	112 227			0.90
Women:					
Unexpected WL	360	36 855	24.76	80.5	0.97
No unexpected WL	1094	152 133			0.71

PPV=positive predictive value.
See Nicholson et al 2020[1] for description of matched cohort of five people with no unexpected WL to one person with unexpected WL.

Unexpected WL can also be caused by a wide range of benign and serious conditions associated with various bodily systems, lifestyle choices, and socioeconomic factors.[3] Differential diagnoses include advanced heart failure, chronic obstructive pulmonary disease, renal disease, pancreatic insufficiency, malabsorption, and endocrine disease, with up to 25% of patients without a diagnosis to explain their weight loss after extended follow-up.[3 6] The non-specific nature of unexpected WL creates the clinical problem of who should be investigated further for cancer—and possibly using invasive methods—and who could be spared investigation. Several clinical reviews have proposed plausible approaches assessing the risk of cancer, but evidence generally has been from studies of older people admitted to hospital for investigation.[3] Such research does not directly help general practitioners to plan investigations in primary care because of spectrum bias.[7] Given the absence of appropriate clinical guidelines, or standardised practice, doctors have been reported to take diverse action, from doing nothing to ordering "extensive blind investigations" because of the fear of underlying cancer.[8 9]

Most research on the predictive value of cancer related unexpected WL in primary care has included patients based on their final cancer diagnosis rather than on the weight loss.[5] The evidence base informed the National Institute for Health and Care Excellence guidance on suspected cancer, which recommended further investigations for patients with a positive predictive value (PPV) for cancer exceeding 3%.[10] Studies have investigated unexpected WL together with other symptoms and signs occurring over a one to two year period preceding the cancer diagnosis without acknowledging that the predictive value of individual symptoms will vary during different periods.[5 11 12] In this context, predictive values could have been reported for pairs of clinical features that occurred months or years apart, potentially with different causes unrelated to the eventual cancer diagnosis.

Although simple blood tests are often used to investigate non-specific symptoms in primary care patients,[13-15] the role of such tests in selecting those with unexpected WL for further cancer investigation is poorly understood. Abnormal test results might facilitate patient triage,[16 17] be poor predictors of cancer,[18 19] or be predictive across several cancer sites.[20] Triage testing in primary care is important to avoid unnecessary urgent referrals of patients for invasive investigation.

We conducted a diagnostic accuracy study using routinely collected electronic health records in primary care to establish the predictive value of unexpected WL for cancer, given the patient's age, sex, smoking status, concurrent symptoms, signs, and blood test results. To identify malignancies that might be prioritised for further investigation after referral, we considered the predictive value for cancer overall and by cancer site.

Methods

Study design and population

We used electronic health records from the Clinical Practice Research Datalink (CPRD), a representative database of anonymised primary care records covering 6.9% of the UK population,[21] linked to the National Cancer Registrations and Analysis Service (NCRAS) cancer register. The "Performance of diagnostic strategies" section of the published protocol pertains to this analysis.[9] We followed the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) reporting guidelines.[22] Study entry was from 1 January 2000 to 31 December 2012 to allow two years or more to accommodate the time it takes for NCRAS to release validated data.

Patients were included if they were aged 18 years or older, registered with a CPRD general practice, eligible for linkage to NCRAS and Office for National Statistics data and the index of multiple deprivation, and had at least one code for unexpected WL and at least 12 months of data before the first recorded unexpected WL code (the index date). These unexpected WL codes equated to a mean weight loss of 5% or more within a six month period in our previous internal validation study of weight related coding in CPRD.[2] Unexpected WL could be coded according to a range of clinical scenarios, including unexpected WL reported as the patient's presenting condition, after targeted history taking, and after weight measurement as part of the clinical examination or as part of a routine health check or chronic disease review.

We excluded patients if they had a prescription of weight reducing treatment (orlistat) or a code for bariatric surgery in the previous six months, or if they had a cancer diagnosis before the index date.

Cancer (reference standard)

To identify cancers, we updated an existing library of codes to include all high level ICD-O (international classification of diseases for oncology) categories.[1] Cancers classified as non-melanoma skin, in situ, benign, ill defined, or uncertain were excluded. Furthermore, we grouped cancer sites that would usually be investigated using the same test or by the same specialty—for example, renal, ureteric, and bladder as renal tract cancers, and liver, gallbladder, and biliary tree as hepatobiliary cancers. All cancers diagnosed in the six months after the index date were identified in the CPRD and linked NCRAS data. We used the first site specific cancer code after the index date to define cancer site. Cancer of unknown primary was defined if a code identifying a secondary cancer (such as lymph node metastasis or cerebral metastasis) was found but there was no code for a primary cancer.

Sociodemographic and clinical features

Sociodemographic details coded on or before the index date were extracted from the CPRD records. We identified codes related to signs and symptoms and blood test results in the three months before to one month after the index date. A long list of symptoms and signs shown to have an independent association with undiagnosed cancer were selected either through their inclusion in the NICE NG12 guidance for suspected cancer or based on studies published after the NICE guidance (ie, central nervous system malignancies and head and neck cancers) (supplementary appendix 1). For blood tests, we identified those most commonly requested within the four month period, dropped outliers and erroneous results, and dichotomised continuous test results as abnormal or normal using standard laboratory ranges (supplementary appendix 2).

Box 1: Classification of true and false positive and negative test results

True positive result
- Presence of a clinical feature recorded in Clinical Practice Research Datalink (CPRD) in the three months before to one month after the index date of unexpected weight loss (WL) in patients with a cancer diagnosis (recorded in CPRD or National Cancer Registrations and Analysis Service (NCRAS) cancer registry) in the six months after the index date

False positive result
- Presence of a clinical feature recorded in CPRD in the three months before to one month after the index date of unexpected WL in patients with no cancer diagnosis (recorded in CPRD or NCRAS cancer registry) in the six months after the index date

False negative result
- Absence of a clinical feature recorded in CPRD in the three months before to one month after the index date of unexpected WL in patients with a cancer diagnosis (recorded in CPRD or NCRAS cancer registry) in the six months after the index date

True negative result
- Absence of a clinical feature recorded in CPRD in the three months before to one month after the index date of unexpected WL in patients with no cancer diagnosis (recorded in CPRD or NCRAS cancer registry) in the six months after the index date

Statistical analysis

Box 1 shows the definitions of true positive, false positive, false negative, and true negative test results for clinical features. For combinations of unexpected WL and age group, sex, smoking status, clinical features, and abnormal blood test results, we estimated diagnostic accuracy statistics for the cancer outcome using 2×2 tables with the DIAGT Stata module: positive likelihood ratios, negative likelihood ratios, positive predictive values, and diagnostic odds ratios along with 95% confidence intervals. A rule of thumb is that a test with a positive likelihood ratio of 5 or more is good for ruling in disease and a test with a negative likelihood ratio of 0.2 or less is good for ruling out disease.[23 24] The analysis was conducted for cancer overall and by cancer site. To select symptoms and signs, we used multivariable backwards stepwise logistic regression starting with all symptoms, signs, and sociodemographic factors as independent covariates, using a P value of 0.05 or less for retention (supplementary appendix 1). We elected to use an indicator variable over multiple imputation to replace missing data on lifestyle factors, as the main purpose of including the covariates was to reduce confounding in variable selection rather than to identify the association between the lifestyle covariate with missing data and cancer.

In discrete analyses we also calculated diagnostic accuracy statistics for each of the 10 most commonly recorded blood tests, and included only patients with each blood test result. When tests were components of another test, we chose the quantum—for example, using total white cell count rather than white cell subtypes.

Sensitivity analysis

We repeated the selection process for clinical features using an interval of three months before the index date to the first date of either three months after or the cancer diagnosis to explore whether broadening the window for inclusion of clinical features changed our findings.

Patient and public involvement

Patients and the public were involved in an advisory capacity in the application for funding to support this research. An advisory panel of patient and public members provided comments on a related article that informed the current analysis. Patients were not directly involved in the conduct or analysis of the study. The results of this study will be disseminated through the media channels of the host institution of the lead author and the funder for scientific and lay audiences.

Results

Figure 1 shows the flow of participants through the trial. Of 63 973 patients with a code for unexpected WL, 37 215 (58.2%) were women and 26 758 (41.8%) were men; 33 156 (51.8%) were aged 60 years or older, 33 846 (52.9%) had a normal body mass index, and 16 793 (26.3%) were ever smokers (table 2). The most

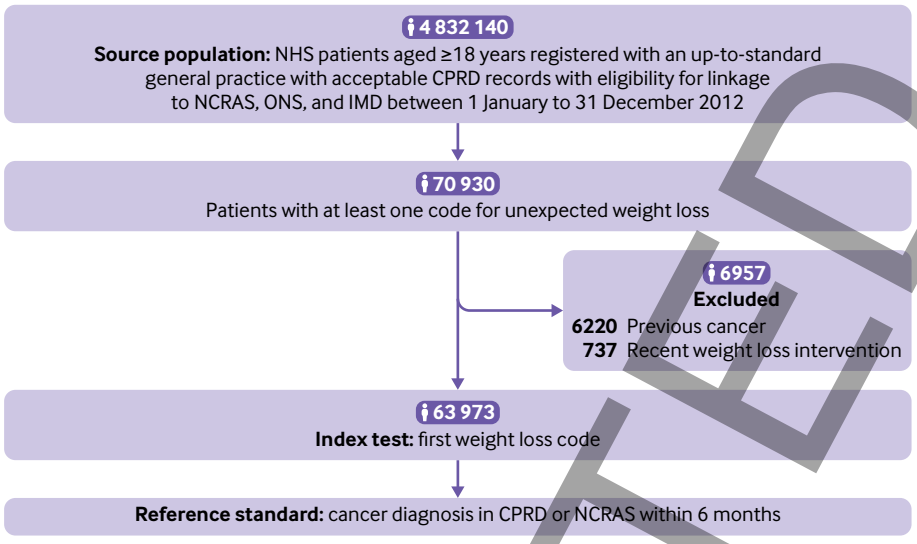

Fig 1 | Flow chart of participants through trial. NHS=National Health Service; CPRD=Clinical Practice Research Datalink; NCRAS=National Cancer Registrations and Analysis Service; ONS=Office for National Statistics; IMD=index of multiple deprivation

common features to be recorded alongside unexpected WL were cough (7.6%), abdominal pain (5.9%), back pain (5.1%), chest infection (4.7%), and fatigue (4.5%) (supplementary appendix 3). The most commonly recorded tests were full blood count (predominantly for haemoglobin (72.1%), platelets (70.7%), total white cell count (69.9%)), and creatinine (69.8%)), and liver function tests—namely, bilirubin (65.5%), albumin (65.1%), and alkaline phosphatase (64.5%) (supplementary appendix 2).

Table 2 | Baseline characteristics of study population

Characteristics	No (%) (n=63 973)
Men	26 758 (41.8)
Women	37 215 (58.2)
Age (years):	
18-39	14 290 (22.3)
40-49	8016 (12.5)
50-59	8511 (13.3)
60-69	9017 (14.1)
70-79	11 565 (18.1)
≥80	12 574 (19.7)
Smoking status:	
Current smoker	9629 (15.1)
Former smoker	7164 (11.1)
Non-smoker	14 457 (22.6)
Missing	32 723 (51.2)
Alcohol intake status:	
Current drinker	18 435 (28.8)
Non-drinker	8095 (12.7)
Former drinker	1087 (1.7)
Missing	36 356 (56.8)
Body mass index:	
Underweight	6691 (10.9)
Normal	33 846 (52.9)
Overweight	10 790 (16.9)
Obese	5141 (8.0)
Missing	7235 (11.3)
Cancer diagnosis:	
Yes	908 (1.4)
No	63 065 (98.6)

Age, sex, and smoking status

The positive predictive value for a cancer diagnosis was higher in people who were older and those who smoked (fig 2)—it was more than 2% in patients aged 50 years or older. Analysis by sex, however, showed that the positive predictive value was more than 3% for male ever smokers aged 50 years or older, whereas the positive predictive value remained less than 2% for women, except in smokers aged 70 years or older.

Signs and symptoms

In multivariable analysis, features selected to be positively associated with cancer in people with unexpected WL were abdominal pain, appetite loss, abdominal mass, iron deficiency anaemia, jaundice, chest signs, and lymphadenopathy (table 3). Dysphagia, haemoptysis, and non-cardiac chest pain were associated with cancer only in men with unexpected WL, and back pain, change in bowel habit, dyspepsia, and venous thromboembolism only in women with unexpected WL. Positive likelihood ratios in men ranged from 1.86 (95% confidence interval 1.32 to 2.62) for non-cardiac chest pain to 6.10 (3.44 to 10.79) for abdominal mass, and in women from 1.62 (1.15 to 2.29) for back pain to 20.9 (10.7 to 40.9) for jaundice. Although four symptoms and signs had positive likelihood ratios greater than 5, they were relatively uncommon, each occurring in six to 10 people with a diagnosis of cancer, depending on sex. No negative likelihood ratio was below 0.2, with values ranging from 0.94 to 1.00 (table 3).

For men and women aged 60 years or older, unexpected WL and the co-occurrence of the selected symptoms and signs were associated with an increase in the positive predictive value by 3% or higher and above the underlying positive predictive value for all people with unexpected WL in each age group (first row of fig 3 for women and fig 4 for men). For men aged

40 to 59 years with unexpected WL, the co-occurrence of jaundice and lymphadenopathy was also associated with an increase in the positive predictive value of 3% or higher, whereas only abdominal mass reached this level for women in this age group (fig 3 for women and fig 4 for men).

Blood tests

Several abnormal blood test results in combination with unexpected WL showed the highest positive likelihood ratio values, some with upper 95% confidence intervals greater than 5: low albumin (4.67 (95% confidence interval 4.14 to 5.27), raised platelet levels (4.57 (3.88 to 5.38)), raised calcium levels (4.28 (3.05 to 6.02)), raised total white cell counts (3.76 (3.30 to 4.28)), and raised C reactive protein levels (3.59 (3.31 to 3.89)) (table 3). Normal inflammatory markers had the lowest negative likelihood ratios: C reactive protein (0.35 (95% confidence interval 0.29 to 0.43)) and erythrocyte sedimentation rate (0.42 (0.36 to 0.49)). Individual blood tests therefore did not reach the ideal threshold of 5 to rule in a cancer diagnosis or the threshold of 0.2 to rule out a diagnosis.

In men and women aged 60 years or older, however, all individual abnormal blood test results showed a positive predictive value of 3% or higher, above the underlying positive predictive value for all people with unexpected WL (fig 3 for women and fig 4 for men), except for raised creatinine levels. For patients aged 40-59 years, positive predictive values of 3% or higher were observed in men for thrombocytosis, low albumin levels, raised alkaline phosphatase levels, and raised calcium levels, and in women for thrombocytosis. Some combinations of abnormal test results in younger age groups had positive predictive values of 3% or higher, but confidence in these estimates was less because not all patients had all tests (fig 5).

Cancer diagnoses

Cancer was diagnosed in 908 (1.4%) patients within six months of the index date, of whom 882 (97.1%) were aged 50 years or older and 902 (99.3%) were aged 40 years or older. The most commonly diagnosed malignancies were cancers of the lung (n=220, 24.2%), bowel (114, 12.6%), gastro-oesophagus (103, 11.3%), and pancreas (80, 8.81%), and lymphoma (68, 7.49%).

Individually, some clinical features are generally considered to be associated with a single cancer site; however, when they co-occurred with unexpected WL, they were associated with several cancer types. For example, women with dyspepsia and unexpected WL were diagnosed as having cancers of the following types or site (in rank order): stomach or oesophagus,

Age group (years)	PPV for cancer in next 6 months			
	UWL	UWL in smokers*	UWL in non-smokers	UWL alone†
Overall	n=63 973	n=16 793	n=14 457	n=54 080
≥40	1.82 (1.70 to 1.94)	1.98 (1.75 to 2.23)	1.01 (0.85 to 1.19)	1.44 (1.32 to 1.55)
≥50	2.12 (1.98 to 2.26)	2.35 (2.07 to 2.65)	1.26 (1.06 to 1.48)	1.69 (1.56 to 1.83)
≥60	2.52 (2.35 to 2.69)	2.83 (2.48 to 3.21)	1.46 (1.23 to 1.72)	2.02 (1.86 to 2.20)
≥70	2.83 (2.62 to 3.04)	3.23 (2.79 to 3.73)	1.64 (1.38 to 1.94)	2.32 (2.11 to 2.54)
≥80	2.78 (2.50 to 3.09)	3.31 (2.66 to 4.06)	1.77 (1.46 to 2.13)	2.36 (2.08 to 2.67)
Men	n=26 758	n=7974	n=4819	n=23 365
≥40	2.54 (2.34 to 2.76)	2.64 (2.26 to 3.06)	1.58 (1.24 to 1.97)	2.05 (1.85 to 2.26)
≥50	2.98 (2.74 to 3.24)	3.06 (2.62 to 3.55)	1.97 (1.56 to 2.46)	2.43 (2.19 to 2.68)
≥60	3.65 (3.34 to 3.98)	3.70 (3.15 to 4.31)	2.38 (1.88 to 2.96)	3.00 (2.70 to 3.33)
≥70	4.35 (3.94 to 4.78)	4.34 (3.62 to 5.16)	2.78 (2.17 to 3.50)	3.63 (3.23 to 4.07)
≥80	4.58 (3.98 to 5.25)	4.60 (3.51 to 5.91)	3.38 (2.59 to 4.34)	3.98 (3.37 to 4.66)
Women	n=37 215	n=8819	n=9638	n=30 715
≥40	1.26 (1.14 to 1.40)	1.31 (1.04 to 1.61)	0.73 (0.57 to 0.92)	0.94 (0.82 to 1.07)
≥50	1.47 (1.32 to 1.63)	1.59 (1.27 to 1.97)	0.90 (0.70 to 1.14)	1.10 (0.96 to 1.26)
≥60	1.71 (1.53 to 1.90)	1.90 (1.50 to 2.37)	1.02 (0.79 to 1.29)	1.29 (1.12 to 1.48)
≥70	1.86 (1.65 to 2.09)	2.10 (1.59 to 2.70)	1.15 (0.89 to 1.46)	1.45 (1.24 to 1.68)
≥80	1.83 (1.56 to 2.15)	2.12 (1.42 to 3.03)	1.16 (0.87 to 1.51)	1.48 (1.21 to 1.80)

Fig 2 | Positive predictive values (PPVs) for cancer by sex, age group, and smoking status. *Current and former smokers; †=unexpected weight loss (UWL) without symptoms and signs (see table 3). Red shading represents a PPV of 3% or higher, the threshold above which the National Institute for Health and Care Excellence recommends investigation for cancer. Yellow shading represents a PPV of 2-3%

Table 3 | Predictive values for cancer over six months by clinical features and blood tests in adults aged 18 years or older attending primary care with unexpected weight loss

Clinical features	True positive	False positive	False negative	True negative	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
Men							
Symptoms:							
Abdominal pain	61	1336	487	24 874	2.18 (1.71 to 2.78)	0.94 (0.91 to 0.96)	2.33 (1.78 to 3.06)
Appetite loss	38	615	510	25 595	2.96 (2.15 to 4.06)	0.95 (0.93 to 0.98)	3.10 (2.21 to 4.35)
Dysphagia	21	290	527	25 920	3.46 (2.24 to 5.35)	0.97 (0.96 to 0.99)	3.56 (2.28 to 5.57)
Haemoptysis	9	101	539	26 109	4.26 (2.17 to 8.38)	0.99 (0.98 to 1.00)	4.32 (2.20 to 8.47)
Non-cardiac chest pain	32	823	516	25 387	1.86 (1.32 to 2.62)	0.97 (0.95 to 0.99)	1.91 (1.33 to 2.75)
Signs:							
Abdominal mass	13	102	535	26 108	6.10 (3.44 to 10.79)	0.98 (0.97 to 0.99)	6.22 (3.50 to 11.1)
Chest signs	6	53	542	26 157	5.41 (2.34 to 12.5)	0.99 (0.98 to 1.00)	5.46 (2.39 to 12.5)
Iron deficiency anaemia	22	212	526	25 998	4.96 (3.23 to 7.64)	0.97 (0.95 to 0.98)	5.13 (3.29 to 8.00)
Jaundice	7	59	541	26 151	5.67 (2.60 to 12.4)	0.99 (0.98 to 1.00)	5.74 (2.66 to 12.4)
Lymphadenopathy	4	73	544	26 137	2.62 (0.96 to 7.14)	1.00 (0.99 to 1.00)	2.63 (1.00 to 6.96)
Women							
Symptoms:							
Abdominal pain	52	2313	308	34 542	2.30 (1.78 to 2.97)	0.91 (0.87 to 0.95)	2.52 (1.88 to 3.39)
Appetite loss	23	916	337	35 939	2.57 (1.72 to 3.84)	0.96 (0.93 to 0.99)	2.68 (1.75 to 4.09)
Back pain	30	1895	330	34 960	1.62 (1.15 to 2.29)	0.97 (0.94 to 1.00)	1.68 (1.15 to 2.44)
Change in bowel habit	12	347	348	36 508	3.54 (2.01 to 6.24)	0.98 (0.96 to 0.99)	3.63 (2.04 to 6.46)
Dyspepsia	25	1004	335	35 851	2.55 (1.74 to 3.74)	0.96 (0.93 to 0.98)	2.66 (1.77 to 4.01)
Signs:							
Abdominal mass	6	112	354	36 743	5.48 (2.43 to 12.4)	0.99 (0.97 to 1.00)	5.56 (2.48 to 12.5)
Chest signs	3	26	357	36 829	11.8 (3.59 to 38.9)	0.99 (0.98 to 1.00)	11.9 (3.82 to 37.2)
Iron deficiency anaemia	19	526	341	36 329	3.70 (2.37 to 5.78)	0.96 (0.94 to 0.98)	3.85 (2.42 to 6.13)
Jaundice	10	49	350	36 806	20.9 (10.7 to 40.9)	0.97 (0.96 to 0.99)	21.5 (10.9 to 42.2)
Lymphadenopathy	3	129	357	36 726	2.38 (0.76 to 7.44)	1.00 (0.99 to 1.00)	2.39 (0.80 to 7.15)
Venous thromboembolism	7	112	353	36 743	6.40 (3.00 to 13.6)	0.98 (0.97 to 1.00)	6.51 (3.06 to 13.8)
Men and women							
Liver function tests:							
Low albumin	202	2665	463	38 292	4.67 (4.14 to 5.27)	0.74 (0.71 to 0.78)	6.27 (5.29 to 7.43)
Raised alkaline phosphatase	271	6753	372	33 882	2.54 (2.31 to 2.78)	0.69 (0.65 to 0.74)	3.66 (3.12 to 4.28)
Raised bilirubin	47	2028	598	39 222	1.48 (1.12 to 1.96)	0.98 (0.95 to 1.00)	1.52 (1.13 to 2.05)
Full blood count:							
Low haemoglobin	341	7099	374	38 315	3.05 (2.82 to 3.30)	0.62 (0.58 to 0.67)	4.92 (4.24 to 5.71)
Raised total white cell count	179	3066	505	40 964	3.76 (3.30 to 4.28)	0.79 (0.76 to 0.83)	4.74 (3.98 to 5.64)
Raised platelets	127	1776	570	42 766	4.57 (3.88 to 5.38)	0.85 (0.82 to 0.88)	5.37 (4.40 to 6.54)
Inflammatory markers:							
Raised C reactive protein	194	2891	76	11 542	3.59 (3.31 to 3.89)	0.35 (0.29 to 0.43)	10.2 (7.80 to 13.3)
Raised erythrocyte sedimentation rate	274	6511	116	16 030	2.43 (2.27 to 2.60)	0.42 (0.36 to 0.49)	5.80 (4.67 to 7.24)
Biochemistry:							
Raised calcium	31	398	351	19 432	4.28 (3.05 to 6.02)	0.93 (0.90 to 0.96)	4.59 (3.18 to 6.64)
Raised creatinine	254	12 971	445	31 001	1.23 (1.12 to 1.36)	0.90 (0.85 to 0.96)	1.36 (1.17 to 1.59)

PLR=positive likelihood ratio; NLR=negative likelihood ratio; DOR=diagnostic odds ratio.

bowel, pancreas, lung, bone connective or soft tissues, lymphoma, unknown primary, other, breast, central nervous system, and leukaemia (fig 3).

Similarly, abnormal test results in patients with unexpected WL were also associated with multiple cancer sites. For example, women aged 60-79 years with low albumin levels were diagnosed as having cancers of the following types or site (in rank order): lung, lymphoma, bowel, unknown primary, renal tract, stomach or oesophagus, ovary, hepatobiliary, uterus, other, pancreas, central nervous system, breast, myeloma, and leukaemia (fig 3).

Isolated unexpected WL

Positive predictive values for patients without any of the selected clinical features were lower across every age range compared with the full cohort (fig 2). In addition, 13 941 (21.8%) patients had no record of a blood test, 142 (1.0%) of whom had a diagnosis of cancer. Overall, 89 patients with unexpected WL and cancer had neither a clinical feature nor blood test on record: 52 out of 57 men and 27 of 32 women were aged 60 years or older.

Sensitivity analyses

Appendix 3 shows the results of the sensitivity analysis. Widening the time window made almost no difference to the clinical features selected for inclusion in the final analysis.

Clinical guideline

Appendix 4 summarises the current NICE guideline recommendations for suspected cancer in patients with unexpected WL. Table 4 outlines an updated clinical guideline based on the results of this analysis.

UWL plus	PPV (95% CI) by age group (years)				Cancer sites from highest to lowest risk
	≥18	40-60	60-80	≥80	
All women with UWL	0.97 (0.87 to 1.07)	0.29 (0.19 to 0.43)	1.61 (1.38 to 1.86)	1.83 (1.56 to 2.15)	
Symptoms					
Abdominal pain	2.20 (1.65 to 2.87)	1.22 (0.49 to 2.50)	3.99 (2.69 to 5.68)	3.55 (2.00 to 5.79)	Pancreas, bowel, hepatobiliary, cancer of unknown primary, gastro-oesophageal, lymphoma, lung, ovary central nervous system, renal tract, myeloma, uterine, leukaemia, other
Appetite loss	2.45 (1.56 to 3.65)	0.00 (0.00 to 2.09)	3.43 (1.72 to 6.05)	3.69 (1.86 to 6.51)	Bowel, lung, pancreas, gastro-oesophageal, head and neck, hepatobiliary, cancer of unknown primary, lymphoma, other
Back pain	1.56 (1.05 to 2.22)	0.88 (0.24 to 2.23)	2.54 (1.51 to 3.98)	1.64 (0.66 to 3.35)	Lung, pancreas, cancer of unknown primary, renal tract, bowel, gastro-oesophageal, breast, myeloma, other, hepatobiliary, bowel connective and soft tissue, ovary, lymphoma
Change in bowel habit	3.34 (1.74 to 5.77)	1.10 (0.03 to 5.97)	2.86 (0.78 to 7.15)	7.37 (3.01 to 14.59)	Bowel, lymphoma, pancreas, hepatobiliary, gastro-oesophageal, renal tract, ovary, uterine
Dyspepsia	2.43 (1.58 to 3.57)	1.06 (0.22 to 3.07)	3.21 (1.67 to 5.54)	4.05 (1.87 to 7.56)	Gastro-oesophageal, bowel, pancreas, lung, bowel connective and soft tissue, lymphoma, cancer of unknown primary, other, breast, central nervous system, leukaemia
Signs					
Abdominal mass	5.08 (1.89 to 10.74)	3.03 (0.08 to 15.76)	8.89 (2.48 to 21.22)	2.86 (0.07 to 14.92)	Bowel, gastro-oesophageal, lung, head and neck, renal tract
Chest signs	10.34 (2.19 to 27.35)	0.00 (0.00 to 52.18)	10.00 (0.25 to 44.50)	14.29 (1.78 to 42.81)	Lung, bowel, cancer of unknown primary
Iron deficiency anaemia	3.49 (2.11 to 5.39)	1.83 (0.22 to 6.47)	5.70 (2.64 to 10.54)	4.02 (1.63 to 8.11)	Bowel, gastro-oesophageal, lung, renal tract, bowel connective and soft tissue, uterine, ovary, cancer of unknown primary, other
Jaundice	16.95 (8.44 to 28.97)	0.00 (0.00 to 21.8)	33.30 (14.59 to 56.97)	15.00 (3.21 to 37.89)	Hepatobiliary, pancreas, bowel, gastro-oesophageal
Lymphadenopathy	2.27 (0.47 to 6.50)	0.00 (0.00 to 10.28)	0.00 (0.00 to 14.82)	27.27 (6.02 to 60.97)	Lymphoma
Venous thromboembolism	5.88 (2.40 to 11.74)	0.00 (0.00 to 18.53)	8.00 (2.22 to 19.23)	6.98 (1.46 to 19.06)	Lung, cancer of unknown primary, pancreas, lymphoma, ovary
Liver function tests					
Albumin (low)	4.79 (3.76 to 6.01)	1.83 (0.38 to 5.25)	8.91 (6.55 to 11.77)	3.17 (2.04 to 4.68)	Lung, lymphoma, bowel, cancer of unknown primary, renal tract, gastro-oesophageal, ovary, hepatobiliary, uterine, other, pancreas, central nervous system, breast, myeloma, leukaemia
Alkaline phosphatase (raised)	2.65 (2.21 to 3.15)	1.07 (0.49 to 2.03)	3.35 (2.60 to 4.25)	3.12 (2.31 to 4.10)	Lung, bowel, lymphoma, gastro-oesophageal, pancreas, hepatobiliary, cancer of unknown primary, renal tract, central nervous system, ovary, uterine, other, breast, melanoma, bowel connective and soft tissue, head and neck, myeloma
Bilirubin (raised)	1.85 (1.01 to 3.08)	0.00 (0.00 to 2.07)	4.64 (2.34 to 8.15)	1.83 (0.38 to 5.25)	Hepatobiliary, pancreas, lung, gastro-oesophageal, bowel, breast
Full blood count					
Haemoglobin (low)	1.69 (1.47 to 1.95)	1.52 (0.56 to 3.27)	4.16 (3.03 to 5.57)	3.17 (2.32 to 4.21)	Lung, bowel, lymphoma, gastro-oesophageal, cancer of unknown primary, renal tract, hepatobiliary, pancreas, ovary, uterine, breast, bowel connective and soft tissue, central nervous system, myeloma, leukaemia, other, head and neck
Total white cell count (raised)	4.45 (3.54 to 5.52)	2.29 (1.05 to 4.30)	5.86 (4.18 to 7.96)	6.92 (4.75 to 9.68)	Lung, bowel, cancer of unknown primary, gastro-oesophageal, pancreas, lymphoma, hepatobiliary, renal tract, uterine, ovary, breast, other, bowel connective and soft tissue, head and neck
Platelets (raised)	4.66 (3.54 to 6.00)	3.08 (1.14 to 6.58)	6.41 (4.53 to 8.76)	3.72 (2.00 to 6.29)	Bowel, lung, renal tract, cancer of unknown primary, hepatobiliary, gastro-oesophageal, ovary, lymphoma, other, pancreas, bowel connective and soft tissue, breast, uterine
Inflammatory markers					
C reactive protein (raised)	4.83 (3.81 to 6.02)	2.00 (0.55 to 5.04)	5.58 (3.98 to 7.58)	5.78 (3.96 to 8.11)	Lung, cancer of unknown primary, lymphoma, bowel, gastro-oesophageal, renal tract, pancreas, ovary, uterine, breast, hepatobiliary, bowel connective and soft tissue, central nervous system, melanoma, head and neck, leukaemia
Erythrocyte sedimentation rate (raised)	2.94 (2.40 to 3.55)	1.24 (0.50 to 2.53)	4.10 (3.10 to 5.30)	2.91 (1.97 to 4.13)	Lung, lymphoma, bowel, gastro-oesophageal, cancer of unknown primary, pancreas, renal tract, hepatobiliary, ovary uterine, other, central nervous system, breast, head and neck, central nervous system, melanoma, leukaemia
Biochemistry					
Calcium (raised)	4.50 (2.93 to 6.57)	2.50 (0.06 to 13.16)	8.63 (4.54 to 14.59)	4.90 (1.61 to 11.07)	Lung, renal tract, lymphoma, cancer of unknown primary, bowel, bowel connective and soft tissue, myeloma
Creatinine (raised)	1.33 (1.11 to 1.58)	0.15 (0.02 to 0.53)	1.74 (1.32 to 2.25)	1.79 (1.38 to 2.28)	Lung, bowel, renal tract, lymphoma, cancer of unknown primary, pancreas, gastro -oesophageal, hepatobiliary, ovary, other, uterine, breast, bowel connective and soft tissue, central nervous system, melanoma, myeloma, head and neck

Fig 3 | Positive predictive values (PPVs) of symptoms, signs, and blood tests for a cancer diagnosis within six months in women with unexpected weight loss (UWL) by age group. Red shading represents a PPV of 3% or higher, the threshold above which the National Institute for Health and Care recommends investigation for cancer. Yellow shading represents a PPV of 2-3%

UWL plus	Age group (years)				Cancer sites from highest to lowest risk
	≥18	40-60	60-80	≥80	
All men with UWL	2.05 (1.88 to 2.22)	0.56 (0.40 to 0.75)	3.22 (2.88 to 3.60)	4.58 (3.98 to 5.25)	
Symptoms					
Abdominal pain	4.37 (3.36 to 5.57)	2.02 (0.87 to 3.93)	7.03 (5.00 to 9.57)	7.58 (4.40 to 12.02)	Bowel, pancreas, lung, cancer of unknown primary, lymphoma, gastro-oesophageal, renal tract, hepatobiliary, prostate, bowel connective and soft tissue
Appetite loss	5.82 (4.15 to 7.90)	2.14 (0.44 to 6.13)	8.40 (5.27 to 12.55)	8.19 (4.55 to 13.36)	Lung, gastro-oesophageal, bowel, pancreas, renal tract, cancer of unknown primary, lymphoma, leukaemia, bowel connective and soft tissue, myeloma, prostate
Dysphagia	6.75 (4.23 to 10.14)	1.59 (0.04 to 8.53)	10.42 (5.95 to 16.6)	6.17 (2.03 to 13.82)	Gastro-oesophageal, lung, head and neck, bowel, myeloma
Haemoptysis	8.18 (3.81 to 14.96)	3.57 (0.09 to 18.35)	13.33 (5.05 to 26.79)	9.52 (1.17 to 30.38)	Lung, lymphoma, cancer of unknown primary
Non-cardiac chest pain	3.74 (2.57 to 5.24)	0.79 (0.10 to 2.82)	6.19 (3.82 to 9.40)	7.30 (3.56 to 13.01)	Lung, gastro-oesophageal, lymphoma, bowel, cancer of unknown primary, prostate, hepatobiliary, pancreas myeloma, leukaemia
Signs					
Abdominal mass	11.30 (6.16 to 18.55)	7.69 (0.95 to 25.13)	9.62 (3.20 to 21.03)	20.00 (7.71 to 38.57)	Bowel, gastro-oesophageal, lung, lymphoma, cancer of unknown primary
Chest signs	10.17 (3.82 to 20.83)	0.00 (0.00 to 45.93)	12.50 (3.51 to 28.99)	9.52 (1.17 to 30.38)	Bowel connective and soft tissue, lung, bowel, gastro-oesophageal, other
Iron deficiency anaemia	9.40 (5.99 to 13.89)	0.00 (0.00 to 12.77)	12.80 (7.50 to 19.95)	8.57 (3.21 to 17.73)	Bowel, gastro-oesophageal, lung, renal tract, pancreas, hepatobiliary, lymphoma, bowel connective and soft tissue
Jaundice	10.61 (4.37 to 20.64)	11.76 (1.46 to 36.44)	7.41 (0.91 to 24.29)	30.00 (6.67 to 65.25)	Pancreas, hepatobiliary, lung, bowel connective and soft tissue
Lymphadenopathy	5.19 (1.43 to 12.77)	8.33 (1.03 to 27.00)	7.14 (0.18 to 33.87)	16.67 (0.42 to 64.12)	Lymphoma, renal tract, cancer of unknown primary
Liver function tests					
Albumin (low)	9.45 (7.96 to 11.12)	3.81 (1.66 to 7.37)	11.95 (9.53 to 14.73)	9.20 (6.84 to 12.04)	Lung, bowel, gastro-oesophageal, renal tract, lymphoma, hepatobiliary, cancer of unknown primary, pancreas, prostate, leukaemia, bowel connective and soft tissue, head and neck, central nervous system, myeloma
Alkaline phosphatase (raised)	6.31 (5.35 to 7.38)	3.01 (1.73 to 4.85)	8.25 (6.61 to 10.14)	8.30 (6.17 to 10.89)	Lung, pancreas, cancer of unknown primary, hepatobiliary, bowel, lymphoma, prostate, renal tract, gastro-oesophageal, bowel connective and soft tissue, other, melanoma, myeloma, leukaemia
Bilirubin (raised)	2.50 (1.73 to 3.50)	0.54 (0.07 to 1.95)	3.71 (2.21 to 5.80)	6.13 (3.31 to 10.26)	Hepatobiliary, pancreas, lung, bowel, lymphoma, cancer of unknown primary, gastro-oesophageal, renal tract, prostate, leukaemia
Full blood count					
Haemoglobin (low)	4.03 (3.61 to 4.49)	2.09 (1.05 to 3.70)	6.76 (5.68 to 7.97)	6.34 (5.21 to 7.63)	Lung, lymphoma, bowel, gastro-oesophageal, renal tract, prostate, cancer of unknown primary, pancreas, hepatobiliary, bowel connective and soft tissue, myeloma, leukaemia, head and neck, other
Total white cell count (raised)	6.80 (5.57 to 8.21)	2.49 (1.25 to 4.41)	9.85 (7.56 to 12.54)	11.65 (8.06 to 16.13)	Lung, bowel, gastro-oesophageal, prostate, renal tract, lymphoma, pancreas, cancer of unknown primary, hepatobiliary, bowel connective and soft tissue, head and neck, leukaemia
Platelets (raised)	10.14 (8.01 to 12.62)	4.71 (2.05 to 9.06)	12.57 (9.22 to 16.62)	15.33 (9.75 to 22.47)	Lung, bowel, renal tract, lymphoma, gastro-oesophageal, cancer of unknown primary, prostate, pancreas, bowel connective and soft tissue, hepatobiliary, head and neck
Inflammatory markers					
C reactive protein (raised)	7.73 (6.45 to 9.17)	3.58 (1.80 to 6.32)	10.11 (8.00 to 12.57)	8.82 (6.26 to 12.01)	Lung, lymphoma, renal tract, bowel, pancreas, cancer of unknown primary, gastro -oesophageal, hepatobiliary, prostate, bowel connective and soft tissue, head and neck
Erythrocyte sedimentation rate (raised)	5.82 (5.00 to 6.72)	0.83 (0.33 to 1.70)	7.01 (5.81 to 8.36)	6.94 (5.33 to 8.84)	Lung, gastro-oesophageal, bowel, lymphoma, renal tract, prostate, cancer of unknown primary, pancreas, hepatobiliary, myeloma, bowel connective and soft tissue, head and neck, leukaemia
Biochemistry					
Calcium (raised)	7.55 (4.74 to 11.32)	8.00 (0.98 to 26.03)	17.86 (8.91 to 30.40)	10.71 (2.27 to 28.23)	Lung, lymphoma, renal tract, cancer of unknown primary, gastro-oesophageal, hepatobiliary, other
Creatinine (raised)	3.34 (2.80 to 3.96)	0.67 (0.14 to 1.94)	3.44 (2.64 to 4.41)	4.41 (3.43 to 5.56)	Lung, prostate, gastro-oesophageal, renal tract, lymphoma, bowel, cancer of unknown primary, pancreas, hepatobiliary, leukaemia, bowel connective and soft tissue, myeloma, other

Fig 4 | Positive predictive values (PPVs) of symptoms, signs, and blood tests for a cancer diagnosis within six months in men with unexpected weight loss (UWL) by age group. Red shading represents a PPV of 3% or higher, the threshold above which the National Institute of Health and Care Excellence recommends investigation for cancer. Yellow shading represents a PPV of 2-3%

Discussion

The risk of undiagnosed cancer in adults with recorded unexpected WL alone is below the UK's current 3% threshold that warrants investigation. However, in male ever smokers aged 50 years or older and in all patients with concurrent clinical features (certain symptoms and signs or abnormal results for simple blood tests) the probability of undiagnosed cancer rises above 3%. These features are abdominal mass, abdominal pain, appetite loss, chest signs, iron deficiency anaemia, jaundice, and lymphadenopathy in both men and women; dysphagia, haemoptysis, and non-cardiac chest pain in men; and back pain, change in bowel habit, dyspepsia, and venous thromboembolism in women. The abnormal blood test results in men and women are low albumin levels and raised levels of white cell counts, calcium, platelets, and inflammatory markers. The absence of individual clinical features in the three months before and up to one month after the index date, or the presence of individual normal blood tests in this time window, does not confidently rule-out cancer in patients with unexpected WL.

Strengths and limitations of this study

We took the following steps to maximise the likelihood that the unexpected WL cohort was accurately defined. First we confirmed that insufficient weight measurements were recorded in UK primary care to define unexpected WL, with clustering of weight recording noted in women with higher body mass index and in those with comorbidity.[2] We then conducted an internal validation study to identify which codes most consistently defined unexpected WL and investigated whether weight measurements could be used in preference to codes.[2] We included each patient once in the analysis by choosing the first unexpected WL code and excluded patients with a history of cancer to ensure we were investigating unexpected WL associated with a first diagnosis of cancer.[7] We excluded patients with objective evidence of deliberate weight loss (ie, prescription records and coding for bariatric surgery). The presence of advanced comorbid conditions might be more likely to be associated with unexpected WL and could modify the association of unexpected WL and cancer. As it is problematic to identify disease

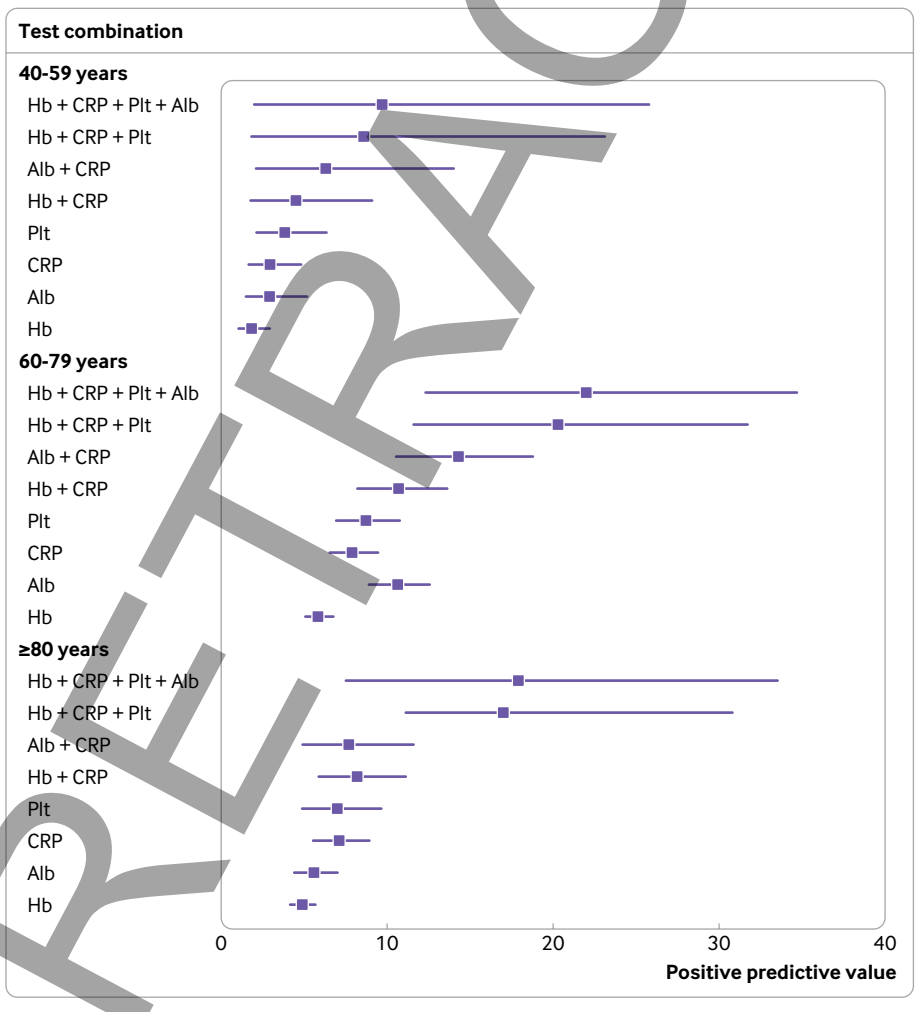

Fig 5 | Positive predictive values for combinations of abnormal laboratory tests by age group. Whiskers represent 95% confidence intervals. Hb=haemoglobin; CRP=C reactive protein; Plt=platelets; Alb=albumin

Table 4 | Revised clinical recommendations for specialised investigation for cancer in patients with unexpected weight loss

Age (years)	Men and women	Men	Women
≥40	Abdominal mass, thrombocytosis	Jaundice, lymphadenopathy, hypoalbuminaemia, hypercalcaemia, raised alkaline phosphatase level, raised C reactive protein level	
≥50		Ever smokers	
≥60	Abdominal pain., anaemia, appetite loss, chest signs, hyperbilirubinaemia, leucocytosis	Dysphagia, haemoptysis, non-cardiac chest pain, raised erythrocyte sedimentation rate	Dyspepsia, jaundice, venous thromboembolism, hypoalbuminaemia, hypercalcaemia, raised alkaline phosphatase level, raised C reactive protein level, raised erythrocyte sedimentation rate
≥80			Change in bowel habit, lymphadenopathy

severity using CPRD data, however, we did not exclude patients with these conditions.

We analysed clinical features as occurring with unexpected WL if they were coded in the three months before and the one month after the index date. This was a clinical decision, as the epidemiology on this topic is limited, based on consideration that a general practitioner is likely to look back at recent notes and investigate unexpected WL within a month of presentation. Symptoms occurring more than three months before the index date might well be unlinked to the unexpected WL. Some studies have reported the frequency of individual clinical features for cancer cases and controls before a cancer diagnosis, with few symptoms more common in cases than controls earlier than six months before the cancer diagnosis.[17 25 26] None of these studies, however, reported the timing of multiple symptoms leading up to a cancer diagnosis. We have shown previously that cancers are likely to be diagnosed in patients within three to six months of presentation with unexpected WL, and our findings did not change significantly in sensitivity analysis extending the period to capture co-occurring symptoms and signs up to the day of cancer diagnosis.[1] The high number of false negatives observed for individual symptoms and signs accompanying unexpected WL indicates the varied clinical presentation of cancer associated with unexpected WL. Accompanying symptoms and signs are only recorded if patients experience them, remember to report them, or they are uncovered by the doctor during a clinical examination.

We also conducted individual analyses for each blood test, including only patients with a result for that blood test. Previous studies have replaced missing blood tests with negative results to allow full case multivariable analysis. We decided against this for two reasons. Firstly, patients who have been tested represent a higher risk population than those who have not been tested,[19 27] and therefore people with a normal test result might not have the same likelihood of undiagnosed cancer as people who have not been tested. It is unclear how this testing bias relates to the study participants with unexpected WL, for whom the blood test was taken close enough to the index date for us to be confident that the test and the result pertained to it. Secondly, classifying absent tests as negative results inflates the number of "true" negatives and misestimates diagnostic accuracy, making it difficult to interpret negative likelihood ratios and negative predictive values. However, as not all patients had been tested with all blood tests, we could not calculate precise estimates for combinations of multiple blood test results. We also dichotomised continuous test results at thresholds used in clinical practice to signify an abnormal result. By dichotomising we lose information by classifying markedly abnormal test results together with mildly abnormal results. The positive predictive values presented can therefore be considered conservative estimates of the associated cancer risk. The high number of false positive blood test results represent that doctors decided to use blood tests to investigate unexpected WL in most cases, that cancer was associated with unexpected WL in fewer than 2% of cases, and that abnormal results in the blood tests studied are not only found in cases of cancer. Finally, we classified people as having cancer if a code was entered within six months of presenting with unexpected WL. Previous research has shown that if cancer is not diagnosed within six months, the risk of cancer being the cause of the unexpected WL is low.[1 28]

Comparison with other studies

A 2018 systematic review reported higher positive predictive values of unexpected WL than we found here.[5] This could be accounted for by the considerable heterogeneity between studies included in that review. For example, sensitivity was higher in studies at risk of recall bias. Positive predictive values also varied by the method of data collection and were higher in case-control studies than in cohort studies reporting on the same tumour site. A recent clinical review reported 17 symptoms, signs, and test results, which in combination with unexpected WL had a positive predictive value for cancer of more than 3%.[3] These estimates were taken from case-control studies using primary care records that included clinical features occurring in the 1-2 years before the diagnosis of a specific cancer. We studied a much shorter interval around the presentation with unexpected WL, included all cancer sites, and had a study size sufficient to allow separate estimates to be produced for each age group and by smoking status and sex. We found evidence for clinical features and abnormal blood test results that were predictive of cancer in combination with unexpected WL not previously reported: abdominal pain, appetite loss, non-cardiac chest pain, chest signs, dyspepsia, raised alkaline phosphatase levels,

low albumin levels, and a raised white cell count. In addition, our study confirms the importance of jaundice, lymphadenopathy, haemoptysis, dysphagia, thrombocytosis, and anaemia, but the implication of these features co-occurring with unexpected WL differ from when they occur alone.

Conclusions and policy implications

The risk of cancer in patients presenting with unexpected WL alone and who have not smoked, with the exception of men older than 80 years, is below the threshold for referral for intensive cancer investigation set by NICE. However, in combination with the clinical features shown in table 4, the risk of cancer increases such that referral for invasive investigation becomes justified. In the absence of these features, these results might suggest that doctors arrange simple routine blood tests, in particular for a full blood count, liver function, erythrocyte sedimentation rate, C reactive protein, and calcium (figs 3 and 4). Almost any abnormal test result increases the risk of cancer sufficiently to trigger invasive testing. A higher or lower threshold of cancer risk could be chosen to trigger cancer investigation by primary care clinicians practising outside the United Kingdom. The positive predictive values presented will allow clinicians worldwide to use whichever threshold applies locally. However, as negative likelihood ratios were never lower than 0.2, and while normal blood test results might reassure patients, clinicians should be aware that in isolation a normal blood test result does not reduce the probability of cancer downward enough to rule-out the disease in patients with unexpected WL.[24]

A pro-inflammatory state underpins cancer cachexia,[29 30] and prognostic scores composed of markers of the systemic inflammatory response are used in patients with cachexia to predict survival and response to treatment in secondary care.[31-33] A potential avenue for future research is to investigate the utility of inflammatory marker scores and combinations of negative test results in selecting who should (and who should not) undergo invasive testing for cancer.

These findings might also have implications for cancer referral pathways. For example, NICE guidelines suggest that patients with unexpected WL and abdominal pain should be investigated for colorectal cancer (supplementary appendix 4).[3] In this study, more than 10 additional cancers presented in this way that would be missed by colonoscopy (fig 3). Likewise, some non-alarm symptoms, such as loss of appetite and non-cardiac chest pain, indicated a probability of cancer that was above the threshold for invasive investigation in the presence of unexpected WL. Throughout Denmark and in some experimental centres in the UK, multidisciplinary diagnostic centres (MDCs) operate that rapidly investigate non-specific symptoms across a broad range of cancer sites.[34-37] Rapid diagnostic centres are being commissioned throughout the English National Health Service based on the MDC model.

Lastly, women presenting with unexpected WL were at markedly lower risk of having cancer than men with unexpected WL. Different, but interrelated, mechanisms might underpin this finding. Firstly, women might be more likely to visit their doctor to discuss their weight: they are also more likely to have a weight measurement recorded in UK primary care.[2] Secondly, women may be more likely to report earlier symptoms of cancer to prompt investigation before weight loss occurs. Thirdly, men may delay presentation until weight loss is noticeable.[38] This study could not examine these possibilities. Nevertheless, routine weight measurement in primary care could lead to the earlier detection of weight change.

Conclusion

Unexpected WL alone in people who do not smoke is unlikely to be due to cancer and immediate referral for invasive testing might not be justified. In male ever smokers aged 50 years or older, onward referral might be justified without additional clinical features recorded in the three months before and up to one month after the index date. Some additional clinical features recorded in this time window increase the risk of cancer substantially over the 3% threshold, justifying further investigation. Clinical features thought to be specific to an individual cancer site are markers of several different types of cancer when they co-occur with unexpected WL, which support new, broader investigative approaches for patients with unexpected WL.

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Contributors: BDN (principal investigator) conceived and oversaw the study, wrote the protocol, developed the code lists for use in the study, conducted the data management, conducted the statistical analysis with guidance from CK, and interpreted the statistical analysis. SJP collated the CPRD code lists for the features of cancer. BDN wrote the first draft of the manuscript. All members of the team were involved in the drafting and commenting on further revisions of the manuscript. All authors read and approved the final manuscript. BDN is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) (ISAC protocol No 16_164A2A). Ethical approval for observational research using the CPRD with

approval from ISAC was granted by a National Research Ethics Service committee (Trent Multiresearch Ethics Committee, REC reference No 05/MRE04/87).

Data sharing: This study is based on CPRD data and is subject to a full licence agreement, which does not permit data sharing outside of the research team. Code lists are available from the corresponding author.

The lead author (BDN) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Preprint: This manuscript was not registered as a preprint.

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Supplementary information: appendices 1-4

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EXPRESSION OF CONCERN: Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study

BMJ alerts readers to a problem with the content of this paper by Nicholson and colleagues (*BMJ* 2020;370:m2651, doi:, published 13 August 2020). The authors of the paper recently identified an error in their approach to the research. Some patients were excluded from the study because their healthcare records contained a code that was not associated with weight loss. Sometime later, however, some of these patients are likely to have had a code included in their healthcare record that was associated with unintended weight loss and cancer. This created an unintended selection bias in the work; some patients were excluded from the study who should have been included in the study. Rectifying this error would result in substantially more patients being included in the study. Reanalysis changes the study's key results and messages. It corrects an underestimate of the likelihood of cancer for some men, and a larger group of women. BMJ is working with the authors to review a new version of the paper and to determine what post-publication action is suitable in this case. An update will be provided when our evaluation has concluded.

Update 16 October 2024: The paper by Nicholson and colleagues[1] described in this expression of concern was retracted. The details are described in a retraction notice.[2] An updated version of the paper has been published by *The BMJ*, which corrects the error.[3]

1 Nicholson BD, Virdee P, Aveyard P, etal. RETRACTED: Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study. *BMJ* 2020;370:.
2 The BMJ. RETRACTION: Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study. *BMJ* 2024;387:.
3 Nicholson BD, Virdee P, Aveyard P, etal. Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study (update). *BMJ* 2024;387:e080199.