PRACTICE

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UNCERTAINTIES

When should unexpected weight loss warrant further investigation to exclude cancer?

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What you need to know

- Unexpected weight loss can be associated with cancer, but also with a range of other conditions
- Weight loss codes in primary care typically represent ≥5% loss within a 6 month period, but there is a lack of evidence on how much weight loss and over what time period increase the likelihood of a cancer diagnosis in primary care
- Urgently refer people over the age of 60 years with unexpected weight loss for investigations to exclude cancer
- The optimal diagnostic strategy to detect cancer in patients with weight loss remains unclear

Unexpected weight loss presents a diagnostic challenge in primary care. It is associated with a wide range of benign and serious conditions (box 1).[1]

Box 1: Differential diagnosis for patients with unexpected weight loss[1]

Cardiovascular—End stage heart failure (cardiac cachexia)

Endocrine—Adrenal insufficiency, diabetes, hyperthyroidism

Gastrointestinal—Diarrhoea, colitis, malabsorption, mesenteric ischaemia

Infection—Chronic infection (such as HIV, tuberculosis)

Malignancy—Solid tumours more likely than haematological malignancies

Medication—Antidepressants, antiepileptics, anxiolytics, diuretics, laxatives, stimulants

Neurological—Dementia, multiple sclerosis, neuromuscular disease, Parkinson's disease, stroke

Psychiatric—Anorexia nervosa, anxiety, bulimia, depression

Renal—End stage renal failure (uraemic cachexia)

Respiratory—Chronic obstructive pulmonary disease (COPD), interstitial lung disease, vasculitis

Rheumatologic—Rheumatoid arthritis

Social—Excess alcohol consumption, neglect, use of opiates, poor oral health, poverty, smoking

Weight loss may be missed or misattributed because of several factors (see box 2). Once it is detected, the uncertainty for clinicians is not about whether unexpected weight loss is a symptom of concern, it is about who should be investigated further and who can be spared unnecessary investigation. Specifically, how much weight loss, over how much time, in combination with what other clinical features makes cancer sufficiently likely to warrant urgent investigation?

Box 2: Challenges in detecting weight loss in primary care

Physiological factors

- Being overweight both increases the risk of cancer and the challenge of detecting weight loss[2]
- Gradual decline in muscle mass is expected from the sixth decade of life[3]
- Diurnal fluctuations in body weight of ±2 kg occur from changes in fluid balance and gut contents[4]

Measurement factors

- Weight measurement is not routine practice in many health systems; it is most commonly measured in people with particular clinical problems[5]
- Clinicians record weight status in kg, pounds, or body mass index (BMI), making detection of weight loss slower[6]
- Patients delay attending their clinician with weight loss for longer than other symptoms of cancer[7]
- Intentional weight loss and exercise complicate the interpretation of weight change[5]

Sources and selection criteria

We searched Embase, Medline, Web of Science, and the Cochrane Library for systematic reviews and primary studies using the following terms and related terms: neoplasia, weight loss, symptoms, diagnosis, general practice, family practice, primary care.

What is the evidence of uncertainty?

How much weight loss over how long?

The degree of weight loss that best indicates underlying cancer in primary care remains poorly defined.[5] Almost all studies in this area are retrospective observational studies that define weight loss by means of a code entered into the electronic health record (table 1).[5] These codes are based on general practitioners' decisions that the degree of weight loss is sufficiently concerning to justify recording it. Studies have not reported associated weight measurement data, quantified how much weight loss has occurred, or established whether patient-reported weight loss is more accurate at identifying disease than clinician-measured weight loss.

The percentage loss of weight is likely to be most clinically relevant, as change relative to baseline weight is more meaningful than the absolute change.[4] A study of more than 50 000 weight loss codes entered into English electronic health records showed that a code for unexpected weight loss represents a mean weight loss of ≥5% within a six month period in primary care.[33] Across methods of estimation, weight loss ranged from –5.4% to –8.3% in females and –4.8% to –7.4% in males, with greater weight loss being observed in elderly people. This resembles the 5-10% weight loss within 6-12-months that is most commonly cited as significant based on data from high risk populations, such as those referred or admitted to secondary care.[1 4 34-36] One case-control study from a primary care database used weight measurements to define weight loss in relation to the risk of colorectal cancer diagnosis.[6] The odds ratio for a 5-9.9% weight loss was 1.2 (95% confidence interval 0.99 to 1.5), and for ≥10% loss it was 2.5 (2.1 to 3.0). Weight loss was defined by using the highest recorded weight in the preceding two years, meaning it could have been underestimated or overestimated.

We are much less clear how recently weight loss must have occurred to indicate the presence of cancer. Studies have investigated the diagnostic utility of weight loss occurring at any point in the past two years. It seems more plausible that weight loss in the recent past signifies the presence of cancer, though there is no evidence of this.[5]

Which cancers are associated with weight loss in primary care?

A recent systematic review and meta-analysis (25 studies) examined the likelihood of a cancer diagnosis in adults presenting to primary care with weight loss.[5] More than one in 10 people aged over 60 years reporting weight loss were subsequently diagnosed with cancer; a risk of 3-7% in women and 11-14% in men.[5] The National Institute for Health and Care Excellence (NICE) recommends urgent investigation when the risk of cancer exceeds 3% threshold for urgent investigation suggested by.[37] Weight loss predicted the presence of prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkin's lymphoma, ovarian, myeloma, renal tract, and biliary tree cancers.[5] Table 1 describes the findings of studies included in the systematic review. Subsequently two case-control studies using UK and Swedish medical registries suggest that weight loss was associated with a diagnosis of acute and chronic leukaemia and of non-metastatic colorectal cancer.[38 39]

Weight loss in isolation or with other clinical features?

No study in primary care has reported whether weight loss without any other symptoms predicts cancer. However, studies show that weight loss predicts cancer even after adjusting for the presence of other symptoms.[6 8 10 13 14 16-23 25-27 29-31 39 40] For example, in cohort studies, patients with weight loss are 1.6 times to 12.5 times more likely to have cancer than a patient without weight loss (table 1).[13 14 25 27 31] Weight loss is the second most powerful predictor of cancer after: rectal bleeding in colorectal cancer; haemoptysis in lung cancer, rib pain in myeloma; jaundice in pancreatic cancer; and haematuria in renal tract cancer.[41] It is the third most powerful predictor in non-Hodgkin's lymphoma and gastro-oesophageal cancers.[41] Table 2 shows the additive risk of cancer in patients with weight loss in addition to another localising clinical feature as calculated in case-control studies using primary care records data.[6 10 16 17 19 22 29 30 39 40]

Is weight loss associated only with late stage cancer?

Weight loss can occur at any stage of cancer precipitated by biochemical, behavioural, functional, and metabolic factors (box 3).[1] Only a few studies have examined weight loss in relation to cancer stage in primary care. A US case-control study found no relationship between weight loss and stage in pancreatic cancer.[43] A UK case-control study found no association between weight loss and stage IV prostate, colorectal, lung, and breast cancer.[40] Similar positive predictive values for weight loss were reported for colorectal cancer in Swedish and UK case-control studies. The former included cancer stages I-III (PPV 1.0% (95% CI 0.3 to 3.0)) and the latter included stages I-IV (1.2% (0.91 to 1.6)).[38 44]

> **Box 3: Pre-diagnosis causes of weight loss in cancer**
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> - Cytokine, peptide, and hormone induced anorexia and metabolic changes
> - Symptom distress—Depression, pain, nausea, diarrhoea, constipation, fatigue
> - Gastrointestinal dysfunction—Altered taste, obstruction, dysmotility, fistula, malabsorption
> - Cancer cachexia (pre-cachexia, cachexia, refractory cachexia)—Weight loss due to progressive skeletal muscle loss (sarcopenia) with or without fat loss[42]

Is ongoing research likely to provide relevant evidence?

We searched clinicaltrials.gov, PROSPERO, Cochrane Library, National Cancer Research Institute portfolio, Cancer Research UK, and Macmillan websites and found no ongoing trials examining strategies to investigate patients presenting with unexpected weight loss in primary care. A systematic review aims to identify the value of tools used to assess cachexia, not specifically in cancer.[45]

The UK National Institute of Health Research (NIHR) has funded research into weight loss as a predictor of cancer in primary care using primary care electronic health records data from the UK and US and to establish whether routine weighing is feasible in English primary care.[5] In many healthcare systems, this does not occur, and we need to know how acceptable and useful this would be.

Recent imaging studies have shown evidence of skeletal muscle loss (sarcopenia) suggesting cachexia in patients with non-metastatic cancer with and without weight loss.[46 47] Protein markers of tissue wasting are present in the blood before clinically detectable pancreatic cancer.[43 48 49] These biochemical and radiological signatures of cachexia offer promise in

detecting weight loss related to cancer, but none has been formally investigated in primary care.[50 51]

The UK has introduced multidisciplinary diagnostic centres to assess people with symptoms such as weight loss but no localising symptoms. Each operates differently. Some, modelled on the Danish approach, ask GPs to conduct tests before referral, others offer a clinic appointment before investigation, and some offer imaging as an initial investigation. Emerging evidence from Scandinavia and the UK show that cancer is diagnosed in 11-21% of patients referred to multidisciplinary diagnostic centres and that serious disease is diagnosed in 22-34%.[52]

Recommendations for future research

- To investigate the feasibility and usefulness of patients being weighed routinely on every visit to primary care physicians to help detect unexpected weight loss

- To investigate monitoring of biochemical and radiological signatures of cachexia to detect weight loss related to cancer

- To evaluate the diagnostic yield of multidisciplinary diagnostic centres to see how their different diagnostic approaches compare

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What should we do in the light of the uncertainty?

It is unclear how to investigate people presenting to primary care with weight loss but no other symptoms. Box 4 describes some approaches suggested in clinical reviews, but the data are usually obtained from studies of older people hospitalised for investigation.[1 4 34-36]

Box 4: Summary of approaches to investigating weight loss from clinical reviews

Vanderschueren 2005[4]

Population—Adults

Weight loss—>5% in 6-12 months should prompt clinical evaluation. Seek numerical verification of weight loss and confirm it is involuntary

Investigation:
Medical history and associated complaints including: tobacco/alcohol use; medications (such as diuretics, digoxin, biguanides, leflunomide, SSRIs); psychosocial factors (such as bereaved, institutionalised, mental health); dietary history; travel history; sexual risk behaviour, thorough physical examination

Baseline tests—CBC with differential, renal function, LFTs, albumin, TFTs, blood sugar, markers of inflammation, iron studies, urine analysis, faecal occult blood tests, CXR, USS of abdomen and pelvis

Additional investigations as indicated by clues obtained with the above tests

Rolland 2006[36]

Population—Outpatient older adults

Weight loss—>5% in 6 months

Investigation—Assess for biochemical dehydration and complete SNAQ questionnaire
SNAQ negative (≥14 points)—Suspected sarcopenia: trial of resistance exercise training. Suspected malabsorption: test vitamin A or β carotene

SNAQ positive (<14 points)—Suspected cachexia: test CRP and albumin. Suspected anorexia: use "meals on wheels" mnemonic

McMinn 2011[35]

Population—Older adults

Weight loss—5% over 6-12 months, although smaller losses may be important in frail elderly people

Investigation:
Comprehensive history and physical exam using "meals on wheels" mnemonic and "9 Ds" of weight loss in elderly

Baseline tests—FBC, Renal function, LFTs including GGT, albumin, TFTs, CRP, ESR, glucose, LDH, CXR, urine analysis, FOBT.

If results are normal, 3 months of "watchful waiting" is preferable to further blind investigations

Gaddey 2014[34]

Population—Older adults

Weight loss—≥5% within 6-12 months, unintentional. If no baseline weight available, evidence of change in clothing size, confirmation of weight loss by a relative or friend, and a numerical estimate of weight loss can be used

History and physical examination, in particular ask about fever, fatigue, dysphagia, oral/gum problems, dyspnoea, exertional fatigue, indigestion, abdominal pain, change in stool pattern, early satiety. Check medications and social and psychological history Assess nutritional status, such as with the Nutritional Health Checklist

Baseline tests—CBC, basic metabolic panel, LFTs, TFTs, CRP, ESR, glucose, LDH, CXR, FOBT, and possibly USS of abdomen

If baseline tests are normal, close observation for 3-6 months is justified

Wong 2014[1]

Population—Adults

Weight loss—≥5% within 6-12 months, unintentional. Use clinical judgement to guide investigation in patients with weight loss <5% or longer duration
History and physical exam covering differential diagnoses (see box 1)

Baseline tests—CBC, LFTs, albumin, renal function, glucose, calcium, TSH, HIV, ESR, CRP, LDH, PSA, CXR

Consider abdominal USS or CT and age-appropriate screening for breast, colorectal, and cervical cancer

SSRIs = selective serotonin reuptake inhibitors. CBC = complete blood count. LFTs = liver function tests. TFTs = thyroid function tests. CXR = chest x ray. USS = ultrasound scan. CRP = C reactive protein. FBC = full blood count. GGT = gamma-glutamyl transferase. ESR = erythrocyte sedimentation rate. LDH = lactate dehydrogenase. FOBT = faecal occult blood test. PSA = prostate-specific antigen. CT = computed tomography.
SNAQ questionnaire = Q1. My appetite is: A. V. poor, B. Poor, C. Average, D. Good, E. V. good. Q2. I feel full after eating: A. a few mouthfuls, B. 1/3 of a meal, C. >1/2 a meal, D. most of the meal, E. hardly ever. Q3. Food tastes: A. V. bad, B. Bad, C. Average, D. Good, E. V. good. Q4. Meals I normally eat each day: A. <1, B. 1, C. 2, D. 3, E. >3. (Score: A=1, B=2, C=3, D=4, E=5.)
MEALS ON WHEELS = Medication effects, Emotional problems (especially depression), Anorexia nervosa, alcoholism, Late life paranoia, Swallowing disorders, Oral factors (poorly fitting dentures, caries), No money, Wandering and other dementia related behaviours, Hyper/hypothyroidism, hyperparathyroidism, hypoadrenalism, Enteric problems, Eating problems (such as inability to feed self), Low salt, low cholesterol diet, Stones, social problems (such as isolation, poverty, mobility)
9 Ds of weight loss in elderly = Dementia, Depression, Disease (acute and chronic), Dysphagia, Dysgeusia, Diarrhoea, Drugs, Dentition, Dysfunction (functional disability), Don't know

In the UK, NICE reviewed the evidence in 2015 from studies in primary care and recommends investigating patients with weight loss and localising symptoms for cancer (table 3).[37] These guidelines focus on ruling out individual cancer types rather than establishing the cause of the symptom. This could lead to multiple referrals for exclusion of specific cancers and a delay in diagnosis. Since then, evidence from the 2018 systematic review indicates that weight loss predicts cancer in patients 60 years and older sufficiently commonly to warrant investigation across cancer sites.[5] This supports early referral for testing focused on weight loss rather than pathways focused on individual cancer types.

What patients need to know

- Losing weight without trying to do so is abnormal and should prompt a visit to your doctor
- Most people with unexpected weight loss do not have cancer, but cancer is possible, particularly in adults over 60 years old. Further tests in a hospital might be needed to rule out cancer
- It is unclear how much weight loss, or over what time period, increases the likelihood of cancer
- Report any accompanying symptoms to your doctor as these may help in reaching a diagnosis and guide appropriate investigations

Education into practice

- Which clinical scenarios prompt you to measure your patient's weight?
- What is your current approach to the investigation of unexpected weight loss? How would you alter this based on reading this article?

How patients were involved in the creation of this article

Four patient representatives who were advisory panel members for the study related to this article reviewed earlier versions of this article. They provided comments leading to revisions to improve clarity. A patient reviewer kindly reviewed this article for *The BMJ*. He suggested emphasising the importance of weight measurement in primary care, but also cautioned about "false positives" (when a patient with weight loss is sent for specialist investigations but turns out not to have cancer) which could cause unnecessary alarm to the patient and family and is wasteful of resources. We have presented guidance for clinicians on identifying patients at higher risk of cancer and when to refer for investigations. We are grateful for the input from patients.

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Tables

Table 1| Studies included in systematic review by Nicholson 2018[5] of association between weight loss and cancer in primary care

Study and design	How weight loss defined	Data source	Sample size	Age (years)	Male (%)	Positive likelihood ratio (95% CI)*	QUADAS quality score
Biliary tree cancer							
Keane 2014[8]; Ret C-C	Code	UK EHR	18 021	Mean 72 (SD 12)	47.1	3.2 (2.4 to 4.2)	6/7
Colorectal cancer							
Curless 1994[9]; Ret C-C	Pt report	UK questionnaire	546	25-93	56	5.9 (5 to 6.9)	4/7
Hamilton 2005[10]; Ret C-C	Any entry	UK paper and EHR	2 093	>40	50.7	5.1 (4.2 to 6.3)	6/7
Hamilton 2009[11]; Ret C-C	Measured	UK EHR	43 791	>30	NR	2.6 (2.4 to 2.8)	6/7
Collins 2012[12]; Ret Chrt	Code	UK EHR	2 135 540	30-84	49.6	4.4 (3.8 to 5)	7/7
Hippisley-Cox 2012[13]; Ret Chrt	Code	UK EHR	1 235 547	30-84	50.2	3.6 (3 to 4.4)	6/7
Gastro-oesophageal cancer							
Hippisley-Cox 2011[14]; Ret Chrt	Code	UK EHR	963 040	30-84	50.2	8.5 (7 to 10.2)	6/7
Collins 2013[15]; Ret Chrt	Code	UK EHR	2 140 194	30–84	49.6	9.4 (8.2 to 10.7)	7/7
Stapley 2013[16]; Ret C-C	Code	UK EHR	40 348	≥40	64.2	9.8 (9.1 to 10.6)	6/7
Lung cancer							
Hamilton 2005[17]; Ret C-C	Any entry	UK paper and EHR	1 482	>40	68.8	6.2 (4.9 to 7.9)	6/7
Iyen-Omofoman 2013[18]; Ret C-C	Code	UK EHR	132 805	>40	49.1	4.5 (4.1 to 5.1)	6/7
Myeloma							
Shephard 2015[19]; Ret C-C	Code	UK EHR	14 860	≥40	52.5	5.6 (4.6 to 6.8)	6/7
Multiple cancers							
Hippisley-Cox 2013[20]; Ret Chrt	Code	UK EHR	667 603	25-89	0	3.5 (3.2 to 3.8)	7/7
Hippisley-Cox 2013[21]; Ret Chrt	Code	UK EHR	679 174	25-89	100	6.8 (6.3 to 7.4)	7/7
Non-Hodgkin's lymphoma							
Shephard 2015[22]; Ret C-C	Code	UK EHR	23 830	≥40	51.3	6.4 (5.5 to 7.4)	6/7
Ovarian cancer							
Lim 2012[23]; Ret C-C	Code	UK GP records	398	50-78	0	3.3 (1.4 to 7.9)	3/7
Collins 2013[24]; Ret Chrt	Code	UK EHR	1 054 818	30–84	0	3.3 (2.4 to 4.7)	7/7
Hippisley-Cox 2012[25]; Ret Chrt	Code	UK EHR	472 114	30-84	0	3.7 (2.5 to 5.7)	6/7
Pancreatic cancer							
Holly 2004[26]; Ret C-C	Pt report.	US questionnaire	300	21-85	54	8.4 (6.2 to 11.3)	3/7
Hippisley-Cox 2012[27]; Ret C-C	Code	UK EHR	971 706	30–84	50.2	8.1 (6.3 to 10.4)	6/7
Collins 2013[28]; Ret Chrt	Code	UK EHR	2 135 962	30-84	49.6	9.7 (7.8 to 12.1)	7/7
Keane 2014[8]; Ret C-C	Code	UK EHR	19 982	Mean 71 (SD 11)	47.1	6 (5.4 to 6.7)	6/7
Stapley 2012[29]; Ret C-C	Code	UK EHR	20 094	≥40	48.0	15.2 (13.7 to 16.9)	6/7
Prostate cancer							
Hamilton 2005[30]; Ret C-C	Any entry	UK paper and EHR	1 297	>40	100	11.4 (8.6 to 15.1)	6/7
Renal tract cancer							
Hippisley-Cox 2012[31]; Ret Chrt	Code	UK EHR	967 681	30–84	50	2.4 (1.8 to 3.4)	6/7
Collins 2013[32]; Ret Chrt	Code	UK EHR	1 081 778	30-84	49.6	2.4 (1.5 to 3.6)	7/7

* Positive likelihood ratio is how many times more likely is a patient with weight loss to be diagnosed with cancer compared with somebody without weight loss. Ret = retrospective, C-C = case-control, Chrt = cohort, EHR = electronic health records.

Table 2| Clinical features associated with ≥3% risk of cancer when patients also complain of weight loss

Clinical feature	Patients' age (years)	Positive predictive value (%)	
		Of clinical feature alone	Of feature + weight loss
Pancreatic cancer			
Jaundice	>60	22.0	31.6
Prostate cancer			
Nocturia	>40	2.2	12
Benign rectal exam	>40	2.4	9.4
Non-Hodgkin's lymphoma			
Lymphadenopathy	>60	13	>10
Raised gamma globulin	>60	0.2	3.5
Lung cancer			
Haemoptysis	>40	4.8	9.2
Thrombocytosis	>40	1.6	6.1
Gastro-oesophageal cancer			
Dysphagia	>55	4.8	9.2
Epigastric pain	>55	0.9	4.2
Gastro-oesophageal reflux	>55	0.6	3.1
Colorectal cancer			
Abnormal rectal exam	>40	1.5	7.4
Abdominal tenderness	>40	1.1	6.4
Haemoglobin <10	>40	2.3	4.7
Rectal bleeding	>40	2.4	4.7
Abdominal pain	>40	1.1	3.4
Diarrhoea	>40	0.9	3.1
Constipation	>40	0.4	3.0

Table 3| **NICE recommendations for the investigation of unexplained weight loss**[37]

Unexplained weight loss *plus*	Action	Possible cancer
Any age		
Lymphadenopathy or splenomegaly	Urgent specialist referral*	Lymphoma
Female	CA125 test in primary care	Ovarian
Patients ≥40 years old		
Abdominal pain	Urgent specialist referral*	Colorectal
Ever smoked or asbestos exposure	Urgent chest x ray	Lung
Never smoked *plus* cough, fatigue, shortness of breath, chest pain, or appetite loss		
Patients <50 or ≥50 years old		
Rectal bleeding <50	Consider urgent specialist referral	Colorectal
Rectal bleeding ≥50	Faecal occult blood test	
Patients ≥55 years old		
Upper abdominal pain, reflux, or dyspepsia	Urgent gastroscopy	Gastro-oesophageal
Thrombocytosis, nausea and vomiting	Non-urgent gastroscopy	
Patients ≥60 years old		
Diarrhoea, back pain, abdominal pain, nausea, vomiting, constipation, or new onset diabetes	Consider urgent CT of abdomen	Pancreas

CA125 = cancer antigen 125. CT = computed tomography.

* To be assessed within 2 weeks.