Predictive value of the official cancer alarm symptoms in general practice – a systematic review

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ABSTRACT

INTRODUCTION: The objective of this study was to investigate the evidence for positive predictive value (PPV) of alarm symptoms and combinations of symptoms for colorectal cancer, breast cancer, prostate cancer and lung cancer in general practice.

METHODS: This study is based on a literature search performed in PubMed, Embase, the Cochrane database and at ClinicalTrials.gov in accordance with the PRISMA guidelines. The main outcome measure used was PPV.

RESULTS: A total of 16 eligible studies were identified. The intervals in the brackets refer to the variation of the results in the studies. Colorectal cancer: The PPV of "rectal bleeding" was high for patients > 60 years (6.6-21.2%), but much lower in younger age groups. For "change in bowel habits" and "significant general symptoms", the PPV was 3.5-8.5%. Breast cancer: "Palpable suspected tumour" was well supported (8.1-24%). No studies on the predictive value of "pitting of the skin", "papil-areola eczema/ulceration" and "suspect axillary lymph nodes" were found. Prostate cancer: One study showed a high PPV for positive rectal examination (12%). The value for "lower urinary tract symptoms" was low (1.0-3.0%). PPV for "perianal pain" and "haemospermia" were not found. Lung cancer: For "haemoptysis" the PPV increased from 8.4 in patients aged 55 years to 20.4 at the age of > 85 years. PPV for "cough", "pain in the thorax", "dyspnoea" and "general symptoms" were low (0.4-1.1%). Using a new algorithm that estimates the PPV of combinations of symptoms and risk factors, a higher PPV may be achieved.

CONCLUSION: A few of the alarm symptoms show a high PPV, whereas the PPV for some symptoms currently remains unknown. To improve the GPs' diagnostic judgment, a new algorithm for calculating the PPV for combinations of symptoms and risk factors seems promising.

Waiting a long time for a diagnosis is associated with a poorer prognosis for cancer patients [1, 2]. In Denmark 2008 saw the introduction of accelerated, well-planned, fast-track diagnostic and treatment pathways, coined cancer packages, for patients suspected of having cancer. For each cancer type, the Danish Health and Medicines Authority developed a manual for general practitioners (GPs) describing the symptoms that should engender a reasonable suspicion of malignancy (alarm symptoms) and trigger the initiation of the diagnostic pathway. Naturally, the relevance of the manual depends on the ability of the alarm symptoms to predict cancer in a general practice population. Low predictive values may imply a waste of resources and unnecessary anxiety for patients. The aim of this review was to examine the evidence for PPV of the alarm symptoms described by the Danish Health and Medicines Authority in relation to the four most commonly occurring cancers in Denmark: colorectal cancer, lung cancer, prostate cancer and breast cancer. Furthermore, tools for calculation of PPV using combinations of symptoms and risk factors were examined.

METHODS

Literature search

The MeSH-terms shown in **Figure 1** were combined. The literature search was performed in PubMed, Embase, the Cochrane database and at ClinicalTrials.gov in accordance with the PRISMA guidelines [3]. The last search was performed on 9 April 2014. The reference lists of the papers we identified were examined for other relevant articles. Each of the identified papers was read independently by the authors and assessed for eligibility. Data from the included studies were extracted and transferred into data sheets (**Table 1**).

Inclusion criteria

Original studies in English or Danish using an unselected population from general practice with a newly recognised alarm symptom were included. The studies had to have positive predictive values (PPV) or likelihood-ratios (LR) for any of the alarm symptoms included in the guidance from the Danish Health and Medicines Authority. The PPV is expressed as the percentage of patients with a given symptom who actually have cancer.

The PPV depends on the prevalence of the disease, which should be kept in mind when interpreting the results. The LR of a symptom is the probability of finding the symptom in patients with cancer divided by the probability of the same finding in patients without cancer. Thus, an LR > 1 indicates an association between the symptom and cancer.

SYSTEMATIC REVIEW

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If a paper described an alarm symptom in terms of more specific symptoms, e.g. fatigue, weight loss and loss of appetite instead of using the term "significant general symptoms", the results for these categories were included.

Exclusion criteria

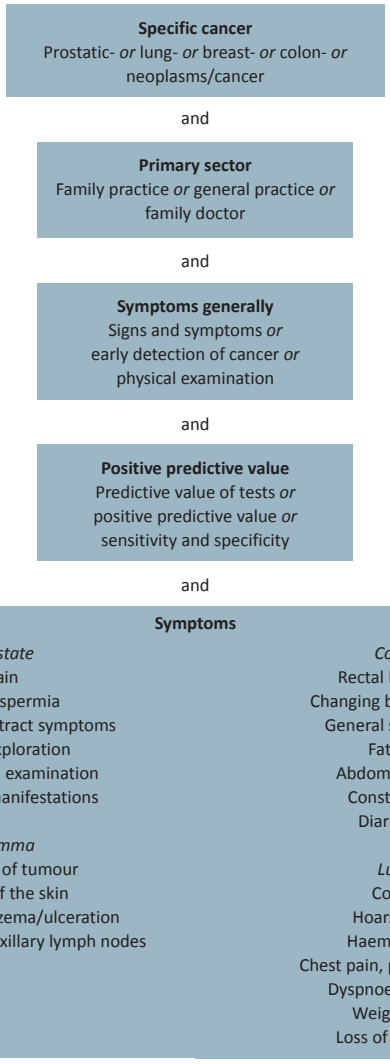
Studies originating from secondary health-care services or screening programmes were excluded.

Quality assessment of the studies

The studies identified were assessed using the Newcastle-Ottawa Quality Assessment Scales (NOQAS) [4] for cohort and case-control studies. An article was rated according to three elements: the selection of study groups, the comparability of these groups, and the evaluation of exposure and outcome, graded from 1 to 9 stars.

FIGURE 1

Literature search.



RESULTS

The search yielded 46 studies, and 16 studies met the inclusion criteria and were included in the final analysis (**Figure 2**). The results from studies of individual symptoms will be presented first, followed by combinations of symptoms.

Colorectal cancer

In the guidance from the Danish Health and Medicines Authority aiming to assist access to the pathways for fast track cancer diagnosis, the following alarm symptoms are described: rectal bleeding, changes in bowel habits and significant general symptoms in patients more than 40 years old [5, 6].

Rectal bleeding

Several studies showed a significant association between rectal bleeding and colorectal cancer [7-19] (Table 1). A total of seven prospective cohort studies, four retrospective cohort studies and one case-control study were identified. The range in PPV was considerable; from 0.22 to 21.1. The highest PPV was demonstrated in a Belgian retrospective study of people aged 70-79 years [8]. The same study found that younger people aged < 50 and 50-59 years only showed a PPV of 0.7 and 1.7, respectively. Wauters and Jones [8, 9] described a decreasing PPV at the age of > 75 and 80 years. Conversely, Lawrenson [11] found an increasing PPV in the group aged > 80. Jones describes a difference in gender with men having a higher PPV, particularly in the age group 75-84 years. In the study, only small differences in PPV were found in relation to colorectal cancer diagnosed after six months and diagnosed after three years from the first presentation of rectal bleeding with the GP. One study detected an elevated PPV on the first occasion of bleeding compared to later events (14.8 compared to 4.4). Two studies on rectal bleeding and development of colorectal cancer achieved the highest rating of 9, and seven studies were rated from 3 to 7 (Table 1).

Changes in bowel habits

Two studies, a case control study and a retrospective cohort study, presented PPV for later diagnosis of colorectal cancer [7, 11, 18]. The studies showed a PPV from 3.5 to 8.5 in the age groups 60-69, 70-79 and 80-89 years. Both studies showed a trend towards a higher PPV in the 70-79 years age range than in the other age groups. Six studies described a change in bowel habits with an LR ranging from 1 to 2.9 [13, 15-17]. Hamilton [19] found low PPVs for constipation and diarrhoea, amounting to respectively 0.42 and 0.94, without taking age into ac-

count. Most studies were of good quality (Table 1).

Significant general symptoms

Four studies described LR for abdominal pain [13, 15, 17]. A variation from 0.7 to 2.2 was found. Fitjen et al [16] detected decreased appetite and nausea with an LR of 0.7 and 0.4, respectively. Nørrelund & Nørrelund [17] found discomfort with a PPV of 1.3 and 0.9. Weight loss was described in nine studies [7, 8, 13, 15-19] and LR varied from 1.3 to 5.1. The studies were of variable quality (Table 1).

Breast cancer

In relation to breast cancer, the following alarm symptoms were described: Suspected tumour at palpation, new papil retraction, new indentation of the skin, eczema or ulceration of the papil/areola and clinically suspect axillary lymph nodes [20, 21].

Suspected tumour at palpation

Three retrospective cohort studies described PPV of suspected tumour at palpation [22-24]. The variation of PPV was substantial, from 8.1- 24. The quality of the studies was quite good (Table 1).

Papil retraction

No studies were found. A single study of moderate quality quantified LR for nipple complaint [22] and found an LR of 3.1.

Other symptoms

The PPV of newly onset papil retraction, indentation of the skin, eczema or ulceration of the papil/areola and clinically suspect axillary lymph nodes was not examined in the literature; therefore no conclusion could be drawn.

Prostate cancer

The following alarm symptoms were described: symptoms from the lower urinary tract, positive rectal exploration, perianal pain and haemospermia [25, 26] (Table 1).

Symptoms from the lower urinary tract

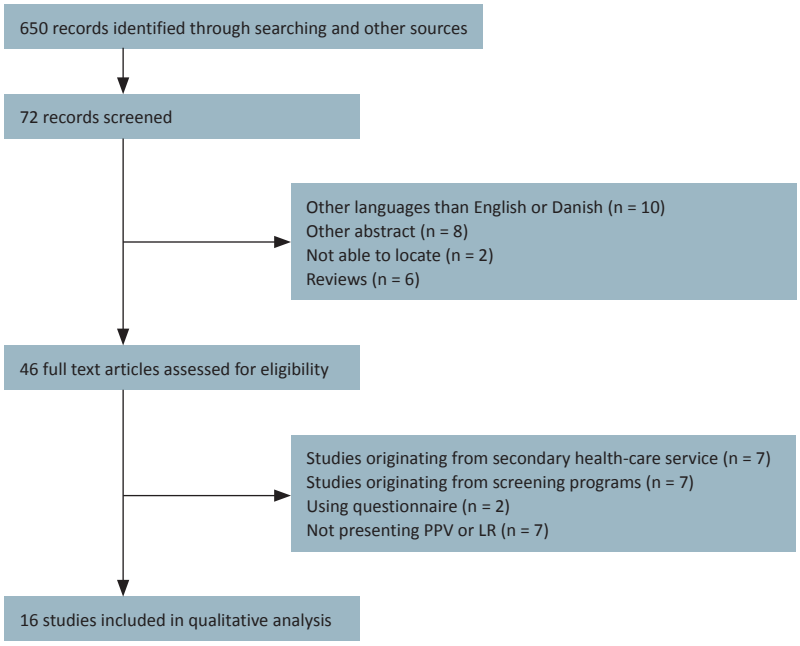
Hamilton et al [27] described PPV for more symptoms originating from the lower urinary tract. The symptom hesitancy has a PPV of 3.0, nocturia 2.2 and haematuria 1.0. LR of urinary retention reached 9. The quality of the studies was very good.

Rectal exploration

Hamilton et al [27] have described PPVs for this symptom in patients over 40 years of age. Hamilton found a PPV of 12 for a positive exploration and 2.8 for a negative one in a high-quality study (Table 1).

FIGURE 2

Flow chart of retrieved, excluded and analyzed trials.



LR = likelihood-ratio; PV = positive predictive value.

Perianal pain and haemospermia

No studies were identified and PPV is unknown.

Lung cancer

The following alarm symptoms were described: cough, haemoptysis (> 50 years), thoracal pain (> 50 years), unexplained dyspnoea and general symptoms > 40 years [28, 29] (Table 1).

KEY POINTS

Alarm symptoms are used as the entry point into the Danish diagnostic fast track for cancer.

A few of the individual symptoms show high positive predictive values (PPV), and for some symptoms PPV is unknown.

Rectal bleeding (colorectal cancer) yields PPV 0.4-21.4, haemoptysis (lung cancer) PPV 2.4-20.4, suspected breast tumour PPV 8.1-24.6 and pathological rectal explorations (prostate cancer) PPV 12.

Algorithms calculating the PPV of combinations of symptoms and risk factors yield more precise and higher PPV.

Knowledge of PPV for alarm symptoms will support good clinical practice.

TABLE 1

Positive predictive values (PPV), likelihood-ratios (LR) and Newcastle-Ottawa Quality Assessment Scale (NOQAS) scores of alarm symptoms.

Symptom	Reference, subgroup	Age, yrs	PPV (95% CI), %	LR (95% CI)	NOQAS score
Colorectal cancer					
Rectal bleeding					
	Wauters et al, 2000 [8]				6
		60-69	11.2 (5.0-21.0)		
		70-79	21.1 (12.0-33.0)		
	Jones et al, 2007 [9]				9
	Males	75-84	7.7 (5.8-10.1)		
		> 85	5.1 (2.2-9.8)		
	Females	75-84	7.2 (5.1-9.1)		
	Parker et al, 2007 [10]	75-84	5.5 (4.7-6.3)		7
	Lawrenson et al, 2006 [11]				9
	Males	60-69	6.6		
		70-79	7.7		
		80-89	9.1		
		> 80	5.8 (1.2-16.2)		
	du Toit et al, 2006 [12]				6
		45-54			0.7
		55-64		0.2	
		65-74	9.5 (4.4-19.3)	1.8	
		> 75	7.9 (3.7-16.2)	1.4	
	Heintze et al, 2005 [13]	> 50	5.6 (3.4-9.0)	1.9	7
	Ellis & Thompson, 2005 [14]	> 60	5.2 (2.6-9.9)	2.9	6
	Metcalf et al, 1996 [15]	> 40	8.1 (4.2-15.1)	1.2	5
	Fitjen et al, 1995 [16]				6
	Males	18-75	5.9 (2.9-11.7)		
	Males + females		20.0 (10.5-34.8)	8	
	Nørrelund & Nørrelund, 1996 [17]	> 40			3
	First episode		14.8 (11.6-18.9)		
	Not first episode		4.4 (1.2-14.8)		
	Hamilton, 2009 [18]	> 40	2.4 (1.9-3.2)	10	9
	Hamilton et al, 2005 [19]				8
	Males	< 60	0.5 (0.3-0.7)		
		60-69	2.4 (1.8-3.2)		
		70-79	3.5 (2.7-4.6)		
		> 80	4.5 (5.9-3.3)		
	Females	< 60	0.4 (0.3-0.5)		
		60-69	2.2 (2.5-3.1)		
		70-79	2.3 (2.9-1.7)		
		> 80	2.7 (3.7-2.1)		
Significant general symptoms					
	Fitjen et al, 1995 [16]				6
	Decreased appetite	18-75		0.7	
	Nausea	18-75		0.4	
	Weight loss			3	
	Heintze et al, 2005 [13]				7
	Abdominal pain			0.7	
	Weight loss	40-95		1.3	
	Metcalf et al, 1996 [15]	40-86			5
	Abdominal pain			0.9	
	Weight loss			1.8	
	Nørrelund & Nørrelund, 1996 (1) [17]	18-75			3
	Abdominal pain			1.5	
	Weight loss			1.6	
	Discomfort			1.3	

TABLE 1 CONTINUED

Symptom	Reference, subgroup	Age, yrs	PPV (95% CI), %	LR (95% CI)	NOQAS score
	Nørrelund & Nørrelund, 1996 (2) [17]	18-75			3
	Abdominal pain			2.2	
	Weight loss			1.8	
	Discomfort			0.9	
	Wauters et al, 2000 [8]				6
	Weight loss	50-80		2.5	
	Hamilton, 2009 [18]				9
	Weight loss	> 40	1.2 (0.9-1.6)	5.1	
	Hamilton et al, 2005 [19]				8
	Weight loss > 10%				
	Males	< 60	0.2 (0.1-0.3)		
		60-69	0.7 (0.5-0.9)		
		70-79	1.5 (1.2-1.9)		
		> 80	0.8 (0.5-1.3)		
	Females	< 60	0.1 (0.1-0.1)		
		60-69	0.5 (0.3-0.7)		
		70-79	0.8 (1.1-0.6)		
Changes in bowel habits					
	Lawrenson et al, 2006 [11]				9
	Males	60-69	6.9		
		70-79	8.5		
		80-89	7.7		
	Hamilton et al, 2005 [19]				8
	Males	< 60	1.1 (0.6-2.4)		
	Heintze et al, 2005 [13]			1.2	7
	Metcalf et al, 1996 [15]	40-86		1.3	5
	Nørrelund & Nørrelund, 1996 (1) [17]	18-75	29	2.6	3
	Nørrelund & Nørrelund, 1996 (2) [17]	18-75	31	1.6	3
	Hamilton, 2009 [18]	> 40			9
	Constipation		0.42 (0.3-0.5)	1.8	
	Diarrhoea		0.94 (0.7-1.1)	3.9	
Breast cancer					
Suspect tumour at palpation					
	Eberl et al, 2008 [22]		8.1 (6.3-10.3)	15.04 (11.74-19.28)	5
	Barton et al, 1999 [23]	40-69	10.7 (4.6-16.9)		8
	Bywaters, 1977 [24]		24.6 (15.2-37.1)		6
Eczema or ulceration of the papil/areola					
	Eberl et al, 2008 [22]			3.13 (1.17-8.39)	5
New indentation of the skin	No articles found				
New papil retraction	No articles found				
Clinically suspect axillary lymph nodes	No articles found				
Prostate cancer					
Perianal pain	No articles found				
Haemospermia	No articles found				
Symptoms from the lower urinary tract					
	Hamilton et al, 2006 [27]	> 40			7
	Urinary retention			9	
	Hesitancy		3.0 (1.5-5.5)	9	

TABLE 1 CONTINUED

Symptom	Reference, subgroup	Age, yrs	PPV (95% CI), %	LR (95% CI)	NOQAS score
	Impotence			9	
	Frequency		2.2 (1.1-3.5)	7	
	Nocturia		2.2 (1.2-3.6)	6	
	Haematuria		1.0 (0.6-1.8)	3	
Rectal exploration					
	Hamilton et al, 2006 [27]	> 40			7
	Deemed malignant		12 (5.0-37)		
	Deemed benign		2.8 (1.6-4.6)		
Lung cancer					
Cough					
	Hamilton et al, 2005 [19]	> 40	0.4 (0.3-0.5)	2	9
Haemoptysis (first event)					
	Jones et al, 2007 [9]				9
	Males	55-64	8.4 (6.1-11.1)		
		65-74	14.9 (12.0-18.1)		
		75-84	17.1 (13.5-21.1)		
		> 85	20.4 (12.8-30.1)		
	Females	65-74	8.4 (5.7-11.8)		
		75-84	10.5 (7.0-14.9)		
	Hamilton et al, 2005 [19]		2.4 (1.4-4.1)	13	9
Thoracal pain					
	Hamilton et al, 2005 [19]	> 40	0.82 (0.6-1.1)	3	9
Unexplained dyspnoe and general symptoms					
	Hamilton et al, 2005 [19]	> 40			9
	Dyspnoe		0.66 (0.5-0.8)	4	
	Weight loss		1.1 (0.8-1.6)	6	
	Loss of appetite		0.87 (0.6-1.3)	5	

Cough

Only one study was found in the literature search. The PPV of cough for lung cancer was 0.4 in this study of good quality [30].

Haemoptysis

In a study by Jones et al [9] the PPV of haemoptysis was very low for younger people (< 45 years: males 0.21 and females 0.36), increasing with age to high levels (males > 85 years: 20.4, females 75-84 years: 10.5, > 85 years: 2.6) Hence, a significant gender difference was shown. This may be explained by higher prevalence of lung cancer in men than in women. In the study, a higher PPV was also described for development of lung cancer after 3 years than after 6 months from the first presentation of haemoptysis to the GP. In another study, Hamilton et al found a PPV of 2.4 for development of lung cancer [30].

Thoracal pain

Only one study was found. A low PPV of 0.82 for thoracal pain was demonstrated [30].

Unexplained dyspnoea and general symptoms

Low PPV was found in a single high-quality study by Hamilton [30]. For dyspnoea, the value was 0.66, weight loss 1.1 and reduced appetite 0.87 [18, 30].

Hoarseness

No studies were identified therefore no conclusion can be drawn.

Combination of more symptoms

Three systematic reviews concerning PPV for a combination of symptoms relating to colorectal cancer have recently been published. Rectal bleeding, weight loss, abdominal pain, change in bowel habits and perianal symptoms were combined. These studies showed a lack of evidence from the primary care sector, and unconvincing diagnostic values were presented [31-33].

One recent very comprehensive review concerning symptoms, signs and diagnostic tests for colorectal cancer, urological cancer, lung cancer, oesophageal cancer, breast cancer and gynaecological cancer was found. In this review, it was not possible to make any significant

conclusion for patients presenting with combinations of symptoms. This was due to the small size of the study populations and the unpersuasive quality of the studies included in this comprehensive review [34]. Hamilton et al conducted studies that are examples of this. In these studies, he described PPV for combinations of two symptoms, but did not calculate confidence intervals due to a small sample size [18].

Hippisley-Cox et al have recently developed a new algorithm to estimate the PPV for cancer of combinations of symptoms. It is based on data capture in 452 general practices in England and Wales including 3.8 million patients [35, 36]. The estimation incorporates both symptoms (e.g. lump in the breast, haemoptysis and weight loss) and risk factors (e.g. age, gender, smoking, family history and social determinants) in a multivariate analysis. The algorithm has been used to estimate the absolute risk of having a lung cancer and colorectal cancer. Meanwhile, an extensive presentation of calculations of PPV has not been published, but some examples have [37, 38]. For haemoptysis as the only symptom without any other symptoms and risk factors included in the calculation, the PPV is 6%. A 78-year old female ex-smoker with haemoptysis, anaemia, cough and chronic obstructive pulmonary disease (COLD) has an estimated risk of 37% of having lung cancer. If the patient also has loss of appetite and weight loss, the estimated risk increases to 76% [37]. For a patient with rectal bleeding alone, the PPV for colorectal cancer is 3%. A 60-year-old male with rectal bleeding, recent change in bowel habits, anaemia, loss of appetite and a positive family history of gastrointestinal cancer has a 49% risk of colorectal cancer [38]. At a website connected to the project [39] , a so-called risk calculator is publicly available for calculation of PPVs given different symptoms and risk factors, e.g. for a 69-year-old female with a breast lump and nipple discharge, who is a light drinker and an ex-smoker, the cancer risk is 74% of which 73% is due to breast cancer. If the patient only has a lump, the PPV for breast cancer is 21%.

DISCUSSION

The PPV of alarm symptoms formulated by the Danish Health and Medicines Authority shows large variation among the published studies. Often the results have no segmentation for gender or age. Some alarm symptoms have no published evidence to support them as no studies were found and no conclusions could be drawn about the value of these symptoms in daily clinical practice. However, significant and good quality evidence was found describing rectal bleeding and colorectal, suspect tumour at palpation and cancer mamma, positive findings from rectal exploration and cancer of the prostate as well as haemoptysis and lung cancer. A few studies have interesting results concerning age and gender. Rectal bleeding, changing of bowel habits and haemoptysis are more predictive for cancer in men than in women. Rectal bleeding is more predictive for colorectal cancer in age groups over 70 years, and haemoptysis is more predictive for lung cancer in age groups over 55 years. However, many of these methodological problems have been addressed in the method developed by Julia Hippisley-Cox et al allowing inclusion of many variables in the estimation of PPV of symptoms [35, 36]. As mentioned above, the results are based on data from a very large sample of patients and GPs which contributes to a high statistical power in the calculations.

General shortcomings

Most of the studies identified were of good quality, but some weaknesses were apparent. The pattern for seeking a GP's help may vary between countries. A low iatropic threshold of patients could imply a lower PPV. The missing information about gender and age could lead to results that are difficult to use in practice. For elderly people with the largest risk of cancer, the estimated PPV will be too low if younger people are included in the studies without controlling for it. In this context, it must be remembered that the PPV is dependent on the prevalence of the disease. The follow-up period was often missing in the studies. This could lead to underestimation of the PPV. Publication bias is probably a smaller problem in this research subject. However, selective publishing of results with high PPVs will lead to an overestimation of the real PPV. Some studies may have been overlooked, as only papers in Danish and English were included.

The quality of patients' records in general practice

In England, uncertainty and lack of agreement when using data collected in general practice has been reported [38]. The quality of the data has been questioned. GPs may report patients with more serious symptoms, or the clinical examination may include other symptoms. This selection bias implies an overestimation of PPV for a single symptom. Some researchers have used prospective computerised coding of symptoms. Others have made a retrospective reading of the patient record looking for alarm symptoms. The completeness of the latter method is probably lower than that of the former. It may imply overestimation of PPV if the GP does not register the symptoms in the patient record at the time of the clinical examination.

Alarm symptoms in general practice

Knowing alarm symptoms is necessary for the GP in daily clinical decision-making. However, it is very important to know the PPV in order to ensure that these clinical deci-

sions are evidence-based. Selecting a patient for diagnostic fast track has a great impact on the resources used in health care. Admitting patients to fast track services with a low PPV for their symptoms could lead to unnecessary anxiety and medicalisation. Many diagnostic methods have side effects and a mortality rate, e.g. colonoscopy [41]. In the clinical situation, the physician typically does not make a judgement based on one symptom, but on a combination of factors, e.g. all symptoms together, the way the symptom is presented, how long it has been present, etc. Until recently, it has been disappointing that the published literature makes it difficult to determine the importance of a combination of symptoms. The methods developed by Julia Hippisley-Cox et al [35, 36] for risk estimation seem very promising. The public risk calculator established in relation to the method may be useful in daily practice.

It is clear that research estimating PPV or LR is needed for symptoms traditionally interpreted as serious as well as for other symptoms. The diagnosis of advanced cancer is relatively easy; the challenge is to detect cancers early. The generalist knowledge of GPs, combined with the high-level communication skills needed to get the necessary information from patients, is vital.

In this review, one large review conducted by Shapley [34] has investigated the prognostic factors of symptoms. However, he only included symptoms with a PPV > 5.

Our aim was to investigate the evidence supporting the symptoms described in the manual developed by The Danish Health and Medicines Authority for the four largest cancers. This gave us 17 different symptoms that needed to be investigated. The selection of these symptoms as entry points to the packages has not been addressed. Other symptoms could be relevant. Use of methods for combinations of symptoms and risk factors would be relevant.

Based on evidence, we were looking for the level of PPV that should trigger a diagnostic fast track. This is also studied by Shapley, who argues that a PPV of 5 should be considered as highly predictive [34]. But 19 out of 20 patients admitted to a cancer package following examination by their GP would not have a cancer in this instance. Meanwhile, compared to the values found in screening programmes, a PPV of 5 is much higher [42]. In this context, a fact-based ethical discussion is needed concerning the number of patients that should be referred to diagnostic fast track to find an early cancer.

Future research

As this paper shows, there is a lack of knowledge about the significance of symptoms in relation to cancer. In particular, more research is needed in the general practitioner's judgment of the entire clinical picture. Also, the level at which PPVs determine further diagnostic investigation calls for research into the costs and ethics of fast tracks. It may be worthwhile to determine if some clinicians are particularly good at diagnosing cancer and, if so, what information they use. Electronic data capture in general practice with classification of the patient's reason for the contact and the diagnosis managed in the domains of the GP, with transmission to central databases offers good opportunities for research into the significance of symptoms [43] as shown in English large scale studies [35, 36] .

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