Abdominal symptoms in general practice: Frequency, cancer suspicions raised, and actions taken by GPs in six European countries. Cohort study with prospective registration of cancer

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Abdominal symptoms in general practice: Frequency, cancer suspicions raised, and actions taken by GPs in six European countries. Cohort study with prospective registration of cancer

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Abstract

Background: Abdominal symptoms are diagnostically challenging to general practitioners (GPs): although common, they may indicate cancer. In a prospective

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cohort of patients, we examined abdominal symptom frequency, initial diagnostic suspicion, and actions of GPs in response to abdominal symptoms.

Methods: Over a 10-day period, 493 GPs in Norway, Denmark, Sweden, Belgium, the Netherlands, and Scotland, recorded consecutive consultations: sex, date of birth and any specified abdominal symptoms. For patients with abdominal symptoms, additional data on non-specific symptoms, GPs' diagnostic suspicion, and features of the consultation were noted. Data on all cancer diagnoses among all included patients were requested from the GPs eight months later.

Findings: Consultations with 61802 patients were recorded. Abdominal symptoms were recorded in 6264 (10.1%) patients. A subsequent malignancy was reported in 511 patients (0.8%): 441 (86.3%) had a new cancer, 70 (13.7%) a recurrent cancer. Abdominal symptoms were noted in 129 (25.2%) of cancer patients ($P < 0.001$), rising to 34.5% for the 89 patients with cancer located in the abdominal region. PPV for any cancer given any abdominal symptom was 2.1%.

In symptomatic patients diagnosed with cancer, GPs noted a suspicion of cancer for 85 (65.9%) versus 1895 (30.9%) when there was no subsequent cancer ($P < 0.001$). No suspicion was noted in 32 (24.8%) cancer patients. The GP's intuitive cancer suspicion was independently associated with a subsequent new cancer diagnosis (OR 2.11, 95% CI 1.15–3.89).

Laboratory tests were ordered for 45.4% of symptomatic patients, imaging for 10.4%, referral or hospitalization for 20.0%: all were more frequent in subsequent cancer patients ($P < 0.001$).

Interpretation: Abdominal symptoms pointed to abdominal cancers rather than to other cancers. However, the finding of abdominal symptoms in only one third of patients with an abdominal cancer, and the lack of cancer suspicion in a quarter of symptomatic cancer patients, provide challenges for GPs' diagnostic thinking and referral practices.

Keywords: Medicine, Evidence-based medicine, Public health, Oncology

1. Introduction

The medical concept of alarm symptoms or warning signs of cancer (WSC) goes back to the 1940s [1]. Originally developed to inform the public about what to tell their doctors in order to avoid delayed cancer diagnoses, they did not distinguish between populations at higher or lower risk. In general practice, symptoms are frequent and cancers comparatively rare. General practitioners (GPs) take an active part in the diagnostic process of 80–90% of cancer patients [2, 3, 4]. The GP's challenge is to identify patients who potentially have cancer, in order to make expedient referrals to more specialised investigations and care. In recent years, much primary care research has explored the significance of various symptoms in early cancer diagnosis [5, 6].

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About half of all cancers are in some way related to the abdomen [7]. We undertook an international collaborative prospective cohort study in six northern European countries in 2011–2012, in order to explore the role of specified abdominal symptoms presented to GPs, in relation to suspecting cancer.

In this paper we analyse the frequency of abdominal symptoms in primary care in our cohort, and what patients' GPs thought and did in response to these symptoms, comparing patients who were subsequently diagnosed with cancer with those who were not.

2. Method

2.1. Setting

The study was undertaken in primary care practices in Norway, Denmark, Sweden, Netherlands, Belgium, and Scotland. GPs in these countries have broadly similar medical training and approaches to cancer diagnosis, treatment, and referral, although their gatekeeper role, laboratory facilities in the surgery, and access to GP-requested imaging vary moderately between and within countries [8].

Participating GPs were recruited through academic institutions active in The Cancer and Primary Care Research International Network (Ca-PRI) [9]. In the six countries, 588 GPs were invited to participate: in one country from a sentinel network [10], otherwise more or less randomly. GPs received 100€ for initial participation, and 50€ for completing follow-up registrations.

2.2. Initial registrations (Time 1)

Between 25 February 2011 and 27 July 2011, the GPs registered all consecutive consultations with patients 16 years of age and older, over ten working days. Data were collected through a study questionnaire (Appendix A) which required completion for each patient and which was modified from a previous symptom study [5] and pilot tested before distribution. GPs received a desktop workbook containing daily registration forms: the forms were prepared in different languages, with professional two-way translation from the English original.

The GPs recorded sex and date of birth for all patients, and abdominal symptoms if presented during the consultation. If abdominal symptoms were recorded, the GP completed all remaining fields, including the recording of more general, non-specific symptoms selected from medical literature related to cancer. The GPs noted duration of symptoms, diagnostic action taken by the GP, the degree of cancer suspicion, if any, based on symptoms, clinical findings, and intuition, and whether the patient previously had had a cancer. Free text comments were encouraged when relevant.

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2.3. Follow up (Time 2)

Participating GPs had consented to providing data on all cancer diagnoses (new or recurring) in their practice. Eight months after the initial registration period, each GP was asked to report all such patients on a standardized proforma. GPs used their electronic records to supply anonymised information about the patients diagnosed with cancer during the follow-up period, regardless of whether they had presented symptoms during the initial survey. We linked sex, date of birth, GP number and date of consultation to the patients registered during the initial 10-days registration. GPs received two reminders.

2.4. Data logistics and management

Completed forms were optically read. Each form was manually checked for clarification of unclear or illogical recordings. Free-text comments were recorded manually.

For patients with more than one consultation within the ten day period, the last consultation was used as date of consultation. Symptoms recorded during different consultations were all included, with the longest duration noted.

We distinguished between abdominal and non-abdominal cancers. Included in the abdominal group were: a. Cancers primarily located in the abdomen, i.e. cancers of digestive organs below the pharynx, female genital organs above the vulva, and urinary organs including testis. b. Carcinoids, lymphomas, soft tissue cancers, endocrine tumours, and generalised cancer if, according to the GP's description, they showed some kind of neoplastic manifestation in the abdomen, and extra-abdominal types of cancer if initial manifestations were abdominal. All remaining cancers were classed as non-abdominal.

Classification as a recurrent cancer required a period of apparent remission before the time of consultation.

2.5. Sample size calculations

A pilot study and incidence data suggested that each GP should encounter zero to two cancer patients during the 10-day registration period. Power calculations in the study protocol, based on estimates of the frequency of abdominal pain in general practice in patients with and without cancer [11], suggested that about 11000 patients were needed in order to have power of 0.9 to detect differences between cancer and non-cancer patients, with a significance level of 0.05. A sensitivity analysis with a 'worst case' scenario with smaller differences, suggested that 70000 patients could be needed.

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2.6. Statistical analyses

We estimated the associations between the GPs' cancer suspicion and clinical action with: subsequent cancer or not, new or recurrent cancer, sex, age and countries. Where appropriate, analyses were restricted to new cases of cancer, or new cases of abdominal cancer diagnosed within six months after consultation (per protocol). Patients who had a stable or progressive cancer at the time of consultation, or who developed pre-cancerous conditions, were excluded from analyses.

Statistical analyses were performed using SPSS, version 22, and STATA, version 14. The chi-square test was used to examine differences between groups. Mantel-Haentzel analysis was used to analyse gradients across groups. Multivariable logistic regression models were applied to estimate associations between cancer suspicion and incidence of cancer. We checked and found no interaction between the independent variables in the models presented. Level of significance was 0.05.

2.7. Ethics

The Regional Committee for Medical and Health Research Ethics of Northern Norway approved the survey protocol (Ref 2010/1056-4). Ethical approval was thereafter given also in the other five participating countries. No patients were contacted. Only the individual GP knew the identity of the patient.

2.8. Role of the funding source

None, beyond financing.

3. Results

3.1. Study population

Completed questionnaires from 67809 consecutive consultations were received from 493 GPs (84% of those invited, 33–191 from each country). After corrections for multiple consultations, 61802 patients were included in the cohort. Follow-up forms on 707 cancer patients were received from 315 GPs, 640 of whom were matched to a prior patient registration. After exclusions, 511 cancer patients (0.8% of all patients in the study) were included (Fig. 1): 441 patients had a new cancer diagnosis, and 70 patients had a recurrent cancer.

Among patients with new cancer, 251 (57%) had abdominal and 190 (43%) non-abdominal cancer. For recurrent cases, these figures were 43 (61%) and 27 (39%), respectively. A previous cancer was noted for 9.7% of symptomatic patients subsequently diagnosed with new cancer, and for 8.3% without cancer.

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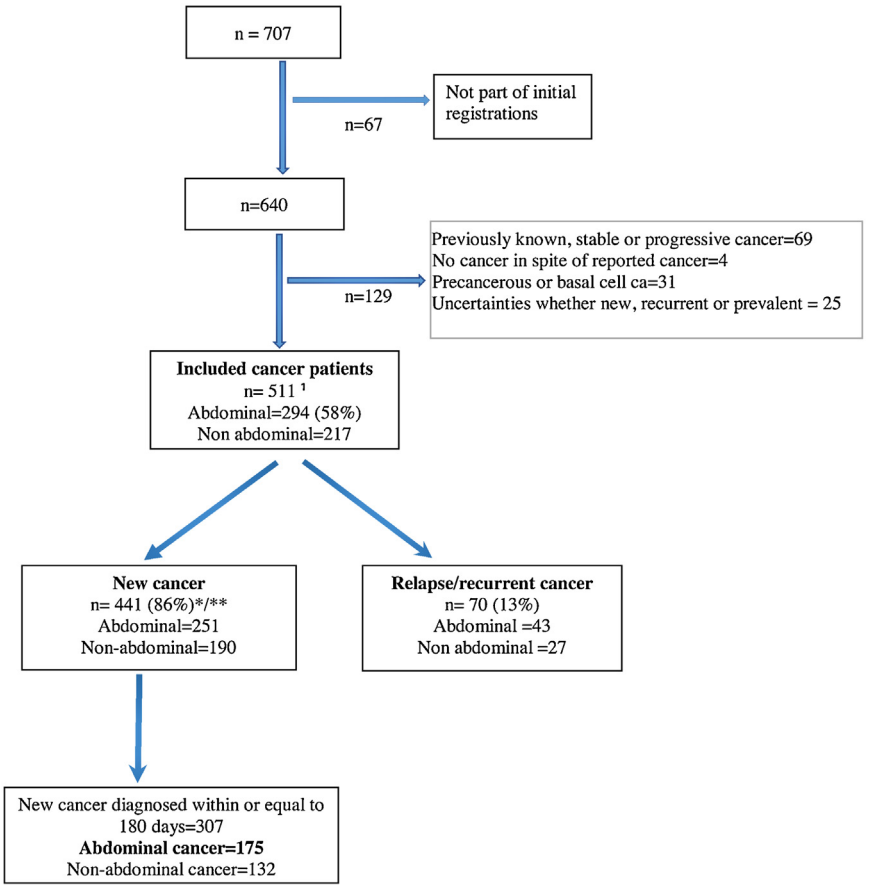

Fig. 1. Inclusion and exclusion of patients with cancer.

The median time to diagnosis for the 441 patients with a new cancer was 101 days, mean 118 days.

Sex and age of the patients are shown in Table 1. Patients aged 75 years or over constituted 17% of all patients and 42% of cancer patients.

3.2. Reported symptoms

Abdominal symptoms were recorded in 6264 patients (10.1%) (Fig. 2, Table 2). Of these, 307 (0.5%) were diagnosed with a new cancer within the next six months: with 175 (0.3%) being a new abdominal cancer (Fig. 1). Table 2 shows number of symptoms for all 511 included cancer patients, including those diagnosed more than six months after their consultation. For 10% of patients, this interval was more than 8 months, with a maximum of 11 months. The proportion of symptomatic

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Table 1. Number of patients: all patients, patients with symptoms and patients diagnosed with cancer after consultation, by sex and different age groups. Mean/median age.

Age in years	16–29	%	30–54	%	55–74	%	≥75	%	Total	Mean age	Median age	Range	25–75 percentile
All patients	8457	14	23144	37	19983	32	10218	17	61802	53	54	16–102	38–68
Males	2931	12	8365	35	8689	36	3943	17	23928	55	56	16–102	41–69
Females	5526	15	14779	39	11294	30	6275	16	37874	53	52	16–101	37–68
Patients with symptoms	907	14	2261	36	1992	32	1104	18	6264	54	54	16–100	38–70
Males	236	11	767	35	792	36	401	18	2196	56	57	16–100	42–70
Females	671	16	1494	37	1200	30	703	17	4068	53	52	16–100	36–69
Patients with cancer	2	1	71	14	221	43	217	42	511	69	71	28–96	60–79
Males	0	0	26	11	104	46	101	43	231	70	72	35–94	62–79
Females	2	1	45	16	117	42	116	41	280	69	70	28–96	59–80

patients who were diagnosed with a subsequent cancer did not differ between countries.

Abdominal symptoms were recorded in 100 (34%) of the 294 abdominal cancer patients and in 29 (13%) of the 217 non-abdominal cancer patients ($P < 0.001$). There was no statistical difference between male or female patients with cancer, or between new and recurrent cancer. PPV for any cancer given any abdominal symptom was 2.1%. Combinations of symptoms were more frequent in abdominal

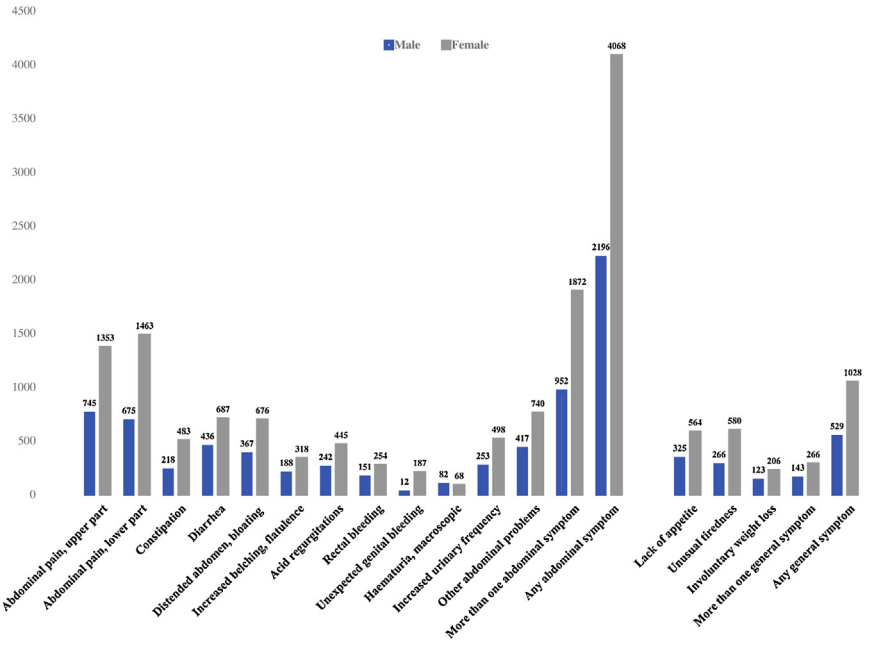

Fig. 2. Distribution of abdominal and general symptoms in 23928 male and 37874 female patients consulting in primary care.

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Table 2. Number of abdominal and general symptoms in different patient groups, and positive predictive value (PPV) as an estimate of cancer risk in case of at least one abdominal symptom.

Symptoms	All patients (N = 61802)			Sum	Males (N = 23928)			Sum	Females (N = 37874)			Sum	New cancer (N = 441)		Recurrent cancer (N = 70)	
	Cancer N = 511 (0.8[b])	PPV[c]	No cancer N = 61291		Cancer N = 231 (1.0[b])	PPV[c]	No cancer N = 23697		Cancer N = 280 (0.7[b])	PPV[c]	No cancer N = 37594		Abdominal N = 251	Non-abdominal N = 190	Adominal N = 43	Non-abdominal N = 27
Abdominal symptoms																
Abdominal pain, upper part	45	2.1	2053	2098	23	3.1	722	745	22	1.6	1331	1353	34	8	2	1
Abdominal pain, lower part	37	1.7	2101	2138	17	2.5	658	675	20	1.4	1443	1463	25	8	3	1
Constipation	22	3.1	679	701	10	4.6	208	218	12	2.5	471	483	19	2	1	0
Diarrhea	16	1.4	1107	1123	7	1.6	429	436	9	1.3	678	687	9	4	3	0
Distended abdomen, bloating	27	2.6	1016	1043	14	3.8	353	367	13	1.9	663	676	21	4	2	0
Increased belching, flatulence	17	3.4	489	506	12	6.4	176	188	5	1.6	313	318	11	4	2	0
Acid regurgitation	14	2.0	673	687	7	2.9	235	242	7	1.6	438	445	12	1	1	0
Rectal bleeding	18	4.4	387	405	4	2.6	147	151	14	5.5	240	254	16	0	1	1
Unexpected genital bleeding[a]	4	2.0	195	199	0		12	12	4	2.1	183	187	3	0	1	0
Haematuria, macroscopic	7	4.7	143	150	5	6.1	77	82	2	2.9	66	68	7	0	0	0
Increased urinary frequency	14	1.9	737	751	9	3.6	244	253	5	1.0	493	498	12	2	0	0
Other abdominal problems	34	2.9	1123	1157	20	4.8	397	417	14	1.9	726	740	20	7	3	4
One symptom only	66	1.9	3374	3440	29	2.3	1215	1244	37	1.7	2159	2196	44	13	6	3

(*Continued*)

Table 2. (*Continued*)

Symptoms	All patients (N = 61802)			Sum	Males (N = 23928)			Sum	Females (N = 37874)			Sum	New cancer (N = 441)		Recurrent cancer (N = 70)	
	Cancer N = 511 (0.8[b])	PPV[c]	No cancer N = 61291		Cancer N = 231 (1.0[b])	PPV[c]	No cancer N = 23697		Cancer N = 280 (0.7[b])	PPV[c]	No cancer N = 37594		Abdominal N = 251	Non-abdominal N = 190	Adominal N = 43	Non-abdominal N = 27
More than one abdominal symptom	63	2.2	2761	2824	34	3.6	918	952	29	1.5	1843	1872	45	11	5	2
Any abdominal symptom[d]	129 (25.2%)	2.1	6135	6264 (10.1%)	63 (27.3%)	2.9	2133	2196 (9.2%)	66 (23.6%)	1.6	4002	4068 (10.7%)	89 (35.5%)	24 (12.6%)	11 (25.6%)	5 (18.5%)
No symptom	382		55156	55538	168		21564	21732	214		33592	33806	161	167	32	22
General symptoms (given at least one abdominal symptom)																
Lack of appetite	26	2.9	863	889	10	3.1	315	325	16	2.8	548	564	19	2	4	1
Unusual tiredness	25	3.0	821	846	10	3.8	256	266	15	2.6	565	580	18	3	4	0
Involuntary weight loss	18	5.5	311	329	8	6.5	115	123	10	4.9	196	206	12	4	2	0
More than one general symptom	19	4.6	390	409	7	4.9	136	143	12	4.5	254	266	14	1	4	0
Any general symptom[d]	43 (8.4%)	2.8	1514	1557 (2.5%)	17	3.2	512	529 (2.2%)	26 (9.3%)	2.5	1002	1028 (2.7%)	30 (12.0%)	7 (3.7%)	5 (11.6%)	1 (3.7%)

N = Number of patients.

[a]84 of the 187 females, including the four cancer patients, were postmenopausal.

[b]Percentage of all patients in the study, or of all males or all females.

[c]Percentages for symptoms are in relation to all patients, or all males or all females, who presented at least one abdominal symptom, and hence corresponds to the positive predictive value (PPV) for any cancer.

[d]Percentages are in relation to the total number of patients in each column.

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than in non-abdominal cancer ($P < 0.001$). The frequency of abdominal symptoms did not differ significantly between patients with non-abdominal cancer and patients without cancer.

Among patients with abdominal symptoms, 1557 (25%) also had general symptoms. Among patients with a subsequent cancer diagnosis this figure was 33%: 35% in patients with abdominal cancer, and 28% for non-abdominal cancer ($P = 0.67$).

3.3. Cancer suspicion in symptomatic patients, and relationship with cancer

The GP's cancer suspicion was raised for 1980 (31.6%) of patients with abdominal symptoms (Table 3), 782 male and 1198 female: in 29.1% of patients this was based on symptoms, in 16.5% based on clinical findings, and in 17.5% based on the GP's intuition; there was considerable overlap. In most cases, suspicion was slight. "Strong" cancer suspicion was relatively less frequent for symptom-based suspicion than for suspicion based on intuition ($P < 0.001$), or on clinical findings ($P = 0.007$).

Cancer suspicion was higher for patients who had a subsequent cancer diagnosis ($P < 0.001$). For symptom based suspicion, a suspicion was noted for 76 (58.9%) of cancer patients versus 1742 (28.4%) of patients with no subsequent cancer. Any suspicion was present for 65.9% vs. 30.9%, respectively. In 24.8% of subsequent cancer cases, the GP noted no suspicion at the time of consultation.

Differences between countries were modest. GPs in Sweden (40.1%) and Norway (35.3%) tended to have cancer suspicion in a higher proportion of their patients than GPs in the other countries.

A logistic regression analysis based on patients with symptoms, with cancer or no cancer as the dependent variable (Table 4), showed significant associations with suspicion based on intuition and for increasing patient age, for all subgroups analysed. For all new cancers, male sex was also associated with cancer. A sensitivity analysis with all missing cases set to 'no suspicion' did not change conclusions. There was an interaction between symptom-based and intuition-based suspicion in the crude analyses, but the effect disappeared when adjusted for age. In these analyses of these two kinds of cancer suspicion, OR for intuition in relation to cancer was highest when there was no symptom-based suspicion (OR 3.94, 95% CI 1.45–10.71) (Table 4), and OR for symptom based suspicion was highest when there was no intuition based suspicion (OR 1.82, 0.97–3.40, not shown in table).

In order to assess the effect of possible variation in GP symptom recording, conditional logistic regression was performed with statistical stratification for the

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Table 3. General practitioners' cancer suspicion[a] during consultation, based on symptoms, clinical findings and intuition.

Cancer suspicion		N	Slight	%[b]	Medium	%[b]	Strong	%[b]	Positive suspicion	%[c]	Not at all	%[c]	Missing	%[c]
Symptoms suggest cancer														
Subsequent cancer or not	Cancer	129	29	38.2	28	36.8	19	25	76	58.9	39	30.2	14	10.9
	Not cancer	6135	1303	74.8	281	16.1	158	9.1	1742	28.4	3756	61.2	637	10.4
Clinical findings suggest cancer														
Subsequent cancer or not	Cancer	129	20	37.7	17	32.1	16	30.2	53	41.1	59	45.7	17	13.2
	Not cancer	6135	710	72.3	153	15.6	119	12.1	982	16.0	4446	72.5	707	11.5
My intuitition suggests cancer														
Subsequent cancer or not	Cancer	129	23	35.9	19	29.7	22	34.4	64	49.6	49	38.0	16	12.4
	Not cancer	6135	733	71	150	14.5	150	14.5	1033	16.9	4398	71.7	704	11.5
Any suspicion														
Subsequent cancer or not	Cancer	129	28	32.9	29	34.1	28	32.9	85	65.9	32	24.8	12	9.3
	Not cancer	6135	1378	72.7	327	17.3	190	10	1,895	30.9	3,636	59.3	604	9.9
Country	Norway	2501	669	75.7	130	14.7	85	9.6	884	35.3	1418	56.7	199	8.0
	Denmark	1535	282	65.1	97	22.4	54	12.5	433	28.2	873	56.9	229	14.9
	Sweden	583	153	65.4	49	20.9	32	13.7	234	40.1	332	57.0	17	2.9
	Belgium	598	125	74.4	31	18.5	12	7.1	168	28.1	406	67.9	24	4.0
	Netherlands	556	92	69.7	22	16.7	18	13.6	132	23.7	350	62.9	74	13.3
	Scotland	491	85	65.9	27	20.9	17	13.2	129	26.3	289	58.9	73	14.9
	Sum	6264	1406	71	356	18	218	11	1980	31.6	3668	58.6	616	9.8

Number of patients, by subsequent cancer or not, and by country. 6264 patients with at least one abdominal symptom. N = Number of patients.

[a]Cancer suspicion was reported only for patients who presented symptoms.

[b]Per cent of Positive suspicion (Slight + Medium + Strong = 100%).

[c]Per cent of all patients in that row.

Table 4. GPs' cancer suspicion in a mutually adjusted logistic regression model for cancer or not following a consultation with recording of at least one abdominal symptom, analysed for all new cancer (N = 441), all new abdominal cancer, diagnosed within 6 months (N = 175), and for recurrent cancer (N = 70).

	Patients with cancer					
	Positive suspicion	**Not at all suspicion**	**Crude OR**	**Adjusted OR**	**P value**	**95% CI**
All New cancer (N in adjusted analysis = 5471)						
Symptoms suggest cancer	69	34	4.40	1.49	0.193	0.82–2.71
Clinical findings suggest cancer	45	53	3.89	1.19	0.548	0.68–2.09
My intitution suggests cancer	55	45	5.26	2.11	0.016	1.15–3.89
sex (female = 0, male = 1)				1.71	0.010	1.14–2.56
age at consultation, in years				1.03	0.000	1.02–1.05
All New Abdominal cancer, diagnosed within 6 months (N in adjusted analysis = 5437)						
Symptoms suggest cancer	53	15	7.66	1.81	0.158	0.79–4.09
Clinical findings suggest cancer	36	28	5.89	1.21	0.574	0.63–2.33
My intitution suggests cancer	45	20	9.69	3.62	0.001	1.65–7.93
sex (female = 0, male = 1)				1.39	0.200	0.84–2.29
age at consultation, in years				1.03	0.000	1.02–1.05
Recurrent cancer (N in adjusted analysis = 5385)						
Symptoms suggest cancer	7	5	3.03	0.36	0.243	0.61–2.03
Clinical findings suggest cancer	8	6	6.11	1.36	0.704	0.28–6.72
My intitution suggests cancer	9	4	9.69	8.89	0.017	1.49–53.02
sex (female = 0, male = 1)				1.05	0.929	0.33–3.36
age at consultation, in years				1.01	0.026	1.00–1.00
Subgroup analysis, All New cancer[a] (N in adjusted analysis = 1764)						
A. When 'Symptoms suggest cancer' = Yes						
My intitution suggests cancer	50	16	2.59	2.12	0.012	1.18–3.79
sex (female = 0, male = 1)				1.52	0.099	0.92–2.49
age at consultation, in years				1.02	0.009	1.01–1.04
B. When 'Symptoms suggest cancer' = Not at all (N in adjusted analysis = 3723)						
My intitution suggests cancer	5	29	7.68	3.94	0.007	1.45–10.71
sex (female = 0, male = 1)				2.15	0.029	1.08–4.26
age at consultation, in years				1.06	<0.001	1.03–1.08

OR = odds ratio, N = Number of patients. Model adjusted by sex, age at consultation and cancer suspicion. Excluded from these analyses: The 129 patients excluded as cancer patients because not new or recurrent cancer, cfr Fig. 1.

A corresponding subgroup analysis for 'All new abdominal cancer, diagnosed within 6 months', gave similar results, with sex not significant in Model B. ORs were a little higher.

[a]'Clinical findings suggest cancer' has been omitted from this analysis. If included, OR changes only slightly.

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different countries, and a separate stratification for individual GPs. Both gave only minimal changes in ORs.

3.4. Diagnostic actions performed by GPs, symptomatic patients

Laboratory tests were performed for 45.4% of patients with abdominal symptoms. Imaging was ordered for 10.4%, and referral or hospitalisation was undertaken for 20.0%. For 26.4% of patients a follow-up appointment in general practice was arranged. None of these four options were used for 24.3% of patients (Table 5). Combinations of actions are shown in Table 6.

Subsequent cancer patients had more of all three categories of investigation ($P < 0.001$) (Table 5). Follow-up appointment with the GP did not differ for cancer and non-cancer patients. The frequency of each category of investigation, and follow-up appointment with the GP, increased with increasing age group, but for laboratory tests this gradient was not significant ($P = 0.08$). X-ray/imaging and referral/hospitalization were used relatively more for patients 55–74 years and relatively less for patients 16–29 years ($P < 0.001$). There were no differences between men and women in relation to actions performed (data not shown).

There were clear differences between countries in actions taken for patients with abdominal symptoms (Table 5). In Sweden, 11.8% of patients had no such further diagnostic action, compared to 45.3% of patients in Belgium and 33.2% in Scotland. Swedish GPs arranged more follow-up appointments in their own practice but referred less frequently. Danish GPs referred most frequently. Scandinavian GPs ordered more laboratory tests than GPs in the other countries ($P < 0.001$ for all these differences).

4. Discussion

4.1. The basis for cancer suspicion, and the importance of abdominal symptoms

Abdominal symptoms were common (10.1% of patients) and elicited cancer suspicion in more patients than did clinical findings and intuition. However, intuition based cancer suspicion was most strongly associated with subsequent cancer. We think these results suggest that, while symptoms give the GP a basis to consider a possible cancer, the complete clinical picture and the GP's experience and clinical competence [12] are necessary to guide further action. In clinical work, GPs should pay attention to the important role of clinically justified intuition and be careful to consider both symptom-based and intuition-based suspicion separately.

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Table 5. Further diagnostic action by GPs, by cancer and non cancer group and by countries. 6264 patients with at least one abdominal symptoms.

		Actions recorded, singly or in different combinations									The most frequent combinations of actions			
		Laboratory tests		X-ray/Imaging		Referral/hospitalisation		Follow-up with GP		None of these four		Lab test + Follow up with GP (N = 685)		Lab test + Referral/Hospitalisation(N = 339)	
Cancer or not	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cancer	129	67	51.9	26	20.2	52	40.3	41	31.8	16	12.4	14	10.9	12	9.3
Not cancer	6135	2778	45.3	627	10.2	1200	19.6	1613	26.3	1505	24.6	671	10.9	327	5.3
Country															
Norway	2501	1401	56.0	287	11.5	470	18.8	605	24.2	484	19.3	261	10.4	188	7.5
Denmark	1535	613	39.9	103	6.7	398	25.9	405	26.4	378	25.0	201	13.1	78	5.1
Sweden	583	394	67.6	90	15.4	92	15.8	231	39.6	69	11.8	123	21.1	34	5.8
Belgium	598	148	24.7	55	9.2	104	17.4	120	20.1	271	45.3	26	4.3	17	2.8
Netherland	556	139	25.0	78	14.0	111	20.0	152	27.3	156	28.1	28	5	8	1.4
Scotland	491	150	30.5	40	8.1	77	15.7	141	28.7	163	33.2	46	9.4	14	2.9
Total	6264	2845	45.4	653	10.4	1252	20.0	1654	26.4	1521	24.3	685	10.9	339	5.4

N = Number of patients, %: Per cent of total number of patients in each group.

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Table 6. Further diagnostic action by GPs. 6264 patients with at least one abdominal symptom.

		N	%
Single actions	Lab tests only	1350	
	X-ray/imaging	174	
	Referral/hospitalisation	698	
	Follow-up appointment with GP	643	
Sum		2865	45.7
Combination of 2 actions	Lab tests + X-ray/imaging	193	
	Lab tests + Referral/hospitalisation	339	
	Lab tests +Follow up appointment with GP	685	
	X-ray/imaging + Referral/hospitalisation	23	
	X-ray/imaging + Follow up appointment with GP	43	
	Referral/hospitalisation+ Follow up appointment with GP	44	
Sum		1327	21.2
Combination of 3 actions	Lab tests + X-ray/imaging + Referral/Hospitalisation	46	
	Lab tests + X-ray/imaging + Follow up appointment with GP	137	
	Lab tests + Referral/hospitalisation + Follow up appointment with GP	65	
	X-ray/imaging + Referral/hospitalisation + Follow up appointment with GP	7	
Sum		255	4.1
All 4 actions	Lab tests + X-ray/imaging + Referral/hospitalisation + Follow up appointment with GP	30	0.5
Sum, number of patients with actions recorded		4477	71.5
Patients with recordings that they had none of these actions		1521	24.3
Patients with missing data		266	4.2
Total, patients with any abdominal symptom		6264	100

4.2. How the GP acted

Active investigative and/or referral strategies were more frequent for the subsequent cancer patients than for the other patients: for example referrals and imaging were performed twice as often for patients who turned out to have cancer. No further investigation or follow-up for one fourth of the patients with abdominal symptoms may seem like a relatively high proportion. A correlation has been shown between GPs' readiness to investigate symptoms indicative of cancer and cancer survival [13].

Follow-up with the GP may represent a form of watchful waiting and safety netting. The increasing use of such follow-up with older patient age could be justified by the increasing multimorbidity and the increased cancer prevalence seen in ageing patients. However, given the value of the watchful waiting strategy, it was unexpected and may seem worrisome that follow-up with the GP was not greater for cancer than for non-cancer patients. Nonetheless, given that there was no cancer suspicion for one quarter of the subsequent cancer patients, it is perhaps only moderately surprising.

Even in the countries with the lowest rates of supplementary investigations, the number of actions performed may seem high in relation to finding 511 cancer patients. However, testing has more aims than diagnosing cancer, and it may be seen as encouraging that modern GPs have at their disposal many practical tests with discriminatory power in relation to cancer and other important diseases. The differences between countries may be related to the level of cancer suspicion, to practice traditions and within-country norms, and the availability of testing and referral. Possibly, blood testing and other laboratory analyses are more readily available in Nordic surgeries as point-of-care-tests. GPs' readiness to make subsequent appointments may vary with GP availability and workload. All GPs know the difficult balance between acting appropriately when needed, and avoiding unnecessary actions and cost. Possible actions in unclear clinical situations range from fast track referral to watchful waiting, and GPs try hard to find the best solution for individual patients.

4.3. Discussion within the context of the literature

Failure to appropriately suspect cancer may result from an insufficient medical history, lack of a focused clinical examination, inappropriate supplementary testing or follow-up of positive tests [1], but also from lack of consideration of contextual data related to the patient and the patient environment [12]. A well-recognised doctor's cognitive fallacy is to stop gathering new data after reaching a diagnosis and thus neglecting other possibilities, or to make symptoms fit a prototypical context or frame, missing atypical variants [14]. The GPs' reporting of intuition as an important basis for suspecting cancer, may be rooted in an

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interaction between analytic and non-analytic processes during diagnostic work [15]. Such dual reasoning strategies have been shown to help diagnosticians overcoming misleading information [16]. Patient discourse may be vague and does not always help the GP identify a chief complaint [17], although in our study symptoms had been recorded when there was cancer suspicion. GPs interviewed about how the thought of cancer arises in a consultation, discussed 'intuitive knowing' as a tacit feeling of alarm which could be difficult to verbalise, but nevertheless was helpful. Such intuition is built on basic knowledge, experience, and personal awareness [18]. We think such observations de-mystify intuition and give it a natural place in the diagnostic reasoning of GPs. Previous cases, the GP's relationship with this particular patient, and cultural factors are some of the elements throwing light on how the patient presents an illness and how the GP interprets. Clinical observations rather than vague impressions may be the basis for "gut feeling" [19, 20], this was neither apparent nor contradicted in our study.

No cancer suspicion for approximately one quarter of the subsequent cancer patients is similar to findings in a study of more general warning signs of cancer [21]. All the symptoms investigated are common, and they may have been vague or atypical in relation to cancer. The finding demonstrates that a GP must be willing to revise diagnostic thinking regarding a symptomatic patient on subsequent consultations.

We cannot assume that all cross-sectionally recorded symptoms were related to a subsequent cancer. In an earlier study based on medical records, a probable relationship between a 'warning signal' symptom and subsequent cancer was found in 17 of 20 patients with such symptoms [22]. Abdominal symptoms may or may not trigger cancer suspicion, and the GP's intuition may agree with or overrule what the symptom seems to suggest. Also, during an illness episode, symptoms as well as clinical signs and intuition may change with time.

We have not found other articles documenting examination and referral strategies when symptoms are presented to GPs. Patients typically express a preference for diagnostic testing even at relatively low risk levels [23].

Abdominal symptoms presented in general practice require the same degree of attention as classical alarm symptoms [24, 25]. Because all such symptoms are unspecific and many are vague, the GP must gather further information for a rational follow-up and safety-netting in cancer detection [26, 27]. In our abdominal cancer patients, symptoms were recorded in only one third of the individuals. Cancer can initially present in many ways, and no single symptom has close to a 100% sensitivity to any form of cancer. In our case, symptom registration was limited to one discrete time during the progression of the not yet diagnosed disease. Fortunately, many components of the diagnostic process contribute constructively

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to cancer suspicion [25]: clinical findings, supplementary testing, and as shown here, GP intuition.

GPs contribute to modern cancer detection guidelines [28] and are able to provide important triage and follow-up of patients, of large value to patients and society [29].

4.4. Strength and limitations of the study

The prospective nature of the study ensured that neither the patient nor the GP knew about the cancer diagnosis at the time of symptom registration. This eliminates some of the bias inherent in observational retrospective and case-control studies. However, data from one consultation that may become part of an illness episode with a continuous pathway, will only be a point estimate of the GP's suspicion of cancer and inevitably underestimate the amount of symptom information and actions gathering with time until diagnosis. Continuity over time is an important aspect of general practice and implies repeated gathering and patient-doctor discussion of new information. The information presented in this article is limited to the two cross-sectional registrations, at Time 1 and Time 2.

Consecutive patients with face-to-face consultations were registered, with no selection bias. The detailed instructions supported consistent data recording across study sites, optimizing data quality. However, the GPs knew they were participating in a study about cancer diagnosis, and this may have made them more likely to suspect cancer and perform supplementary tests.

An important aspect of data validity is to what extent the GPs recorded all patients where the reason for consultation was related to abdominal symptoms, or only where the GP found an abdominal problem relevant. The GPs were instructed to record all instances where symptoms were presented by the patient, either on the patient's own initiative or if it arose during the consultation. The minimal changes in ORs for cancer suspicion when a conditional logistic regression analysis was performed with stratification on countries and on GPs, suggest that accounting for differences in the GPs' symptom registration did not affect conclusions.

Cancer patients are haphazardly distributed among GPs, but some cancer patients may have been missed when the GPs searched their records. Therefore, cancer patients in the cohort are similar to but hardly representative of all cancer in these countries

Combining data from six countries with different health systems has its limitations and advantages. Our study benefits from a large sample size, and data reliability increases if country differences seem reasonable in relation to differences in the organisation of primary care. We find many similarities in the nature of general practice consultations across the six included countries, even if the respective

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health systems may introduce some country-specific limitations in follow-up and referral procedures [3, 8]. Documented variation may inspire re-thinking of one's own routines.

4.5. Implications for policy, practice and research

GPs initially may consider cancer located in the abdomen when abdominal symptoms spur a cancer suspicion. Abdominal symptoms do not seem to increase the possibility of non-abdominal cancer. However, this remains a challenge in general practice: to have in mind the unusual, especially when it is of high clinical importance. Therefore, in unclear cases, non-abdominal cancer sites should remain a relevant consideration during diagnostic work-up. In general, our study adds weight to the concept that GPs should have confidence in their traditional way of working with patients, combining evidence from clinical epidemiology and qualitative studies with tacit, experience based knowledge as a basis for listening and communicating in order to understand patient ailments.

Studies of symptoms must primarily come from primary care settings. Review articles about colorectal cancer from other settings hardly mention symptoms [30, 31]. Research data from the clinical setting in general practice provide important complementary insights to hospital data, especially when it comes to understanding the diagnostic pathway from first symptom to treatment of cancer. Our study adds to this understanding. The study further demonstrates the feasibility of setting up large studies in primary care in several countries, with benefits for study size and for understanding of differences between countries.

Declarations

Author contribution statement

Knut Holtedahl: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Peter Vedsted, Gé A. Donker, Frank Buntinx, Christine Campbell: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lars Borgquist, David Weller, Peter Hjertholm : Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Tonje Braaten, Ranjan Parajuli: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jörgen Månsson, Eva Lena Strandberg, Lisbeth Ellegaard: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

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Additional information

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