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Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care

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Abstract ***Background:*** Early diagnosis is considered a key factor in improving the outcomes in cancer therapy; it remains unclear, however, whether long pre-diagnostic patient pathways influence clinical outcomes negatively. The aim of this study was to assess the association between the length of the diagnostic interval and the five-year mortality for the five most common cancers in Denmark while addressing known biases.

Methods: A total of 1128 patients with colorectal, lung, melanoma skin, breast or prostate cancer were included in a prospective, population-based study in a Danish county. The diagnostic interval was defined as the time from the first presentation of symptoms in primary care till the date of diagnosis. Each type of cancer was analysed separately and combined, and all analyses were stratified according to the general practitioner's (GP's) interpretation of the presenting symptoms. We used conditional logistic regression to estimate five-year mortality odds ratios as a function of the diagnostic interval using restricted cubic splines and adjusting for comorbidity, age, sex and type of cancer.

Results: We found increasing mortality with longer diagnostic intervals among the approximately 40% of the patients who presented in primary care with symptoms suggestive of cancer or any other serious illness. In the same group, very short diagnostic intervals were also associated with increased mortality. Patients presenting with vague symptoms not directly related to cancer or any other serious illness had longer diagnostic intervals and the same survival probability as those who presented with cancer suspicious/serious symptoms. For the former, we found no statistically significant association between the length of the diagnostic interval and mortality.

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Conclusion: In full coherence with clinical logic, the healthcare system instigates prompt investigation of seriously ill patients. This likely explains the counter-intuitive findings of high mortality with short diagnostic intervals; but it does not explain the increasing mortality with longer diagnostic intervals. Thus, the study provides further evidence for the hypothesis that the length of the diagnostic interval affects mortality negatively.

1. Introduction

Over the past few decades, a steady stream of comparative studies of Nordic and European cancer registries has documented survival deficits and an unfavourable stage distribution among Danish cancer patients.[1–4] The Danish government has responded by striving to reduce delays in diagnosis and treatment. Yet, until recently, there was no evidence of any benefit of expediting diagnosis and treatment in symptomatic cancer patients.

Given the complex nature of diagnosing cancer, it is a challenging task to design a study that validly compares cancer patients with short and long delays. Observational studies frequently show the opposite of what we expect: patients with short delays in diagnosis and treatment have higher mortality than the rest.[5–8] Many studies illustrating this paradox take the results to show that there is no association between delay and mortality and find the results reassuring.[9–11] However, by premising their findings on non-random observations, they may have reached wrong conclusions.

We have recently called attention to the fundamental analytical problem of confounding by indication in observational studies caused by differentiated clinical triage.[12,13] This bias arises when general practitioners (GPs) and subsequently diagnostic centres give priority to seriously ill patients who may have higher inherent mortality (the 'sick-quick' group) and are comparatively more reluctant to expedite patients with less obvious symptoms of cancer (the 'low risk–slow diagnosis' group).[14–17] Most studies lack information on what triggered the GP either to refer immediately or to adopt a watchful waiting approach, and they may hence be reporting biased results.

The aim of this study was to assess the association between the length of the diagnostic interval and the five-year mortality for the five most common cancers in Denmark while addressing the above methodological and analytical issues.

2. Materials and methods

We conducted a cohort study with overall five-year mortality as the primary outcome and the length of the diagnostic interval (defined as the time from first presentation of symptoms in primary care to the date of diagnosis) as the exposure variable.

2.1. Setting

The cohort resided in the former Aarhus County, Denmark, which had 640,000 inhabitants and approximately 3000 new cancer cases per year in the study period.[18] Denmark's publicly funded healthcare system provides free access to general practice and hospital care. More than 98% of Danish citizens are registered with a GP. The GP acts as a gatekeeper to the rest of the healthcare system by carrying out initial diagnostic investigations and referring patients to hospitals or outpatient clinics when necessary. Danish GPs are legally bound to keep detailed medical records of their patients including mandatory discharge letters provided by hospitals at the end of treatment.[19]

2.2. Study population

Our study included all patients with newly diagnosed colorectal, lung, melanoma skin, breast or prostate cancer above the age of 17 in the former Danish County of Aarhus during 1 year (inclusion period from 1 September 2004 to 31 August 2005), which was equivalent to 56% of all new cancers in Denmark during that year.[18] The study population was subsequently restricted to patients whose GPs were involved in diagnosing the cancer (87% of all cancer patients with participating GPs, see Fig. 1).

During the inclusion period, cancer patients were identified consecutively from the County Hospital Discharge Registry, a population-based medical database which records dates of all inpatient and outpatient visits and discharge diagnoses classified according to the International Classification of Diseases (ICD-10). By means of the civil registry number (a unique personal identifier assigned to all Danish citizens at birth), we linked these data to a historical database hosted at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark. This enabled prospective inclusion of new cancer cases, while excluding patients with a cancer recurrence. Each patient's GP was subsequently identified by linking the patient's data to the Health Service Registry (comprising demographic data on GPs and specialist doctors). Later in 2009, we used data from the Danish Cancer Registry to decisively verify incident cancer cases and to obtain information on tumour stage classification. This registry retrospectively records all incident cancer cases in Denmark and is known for its

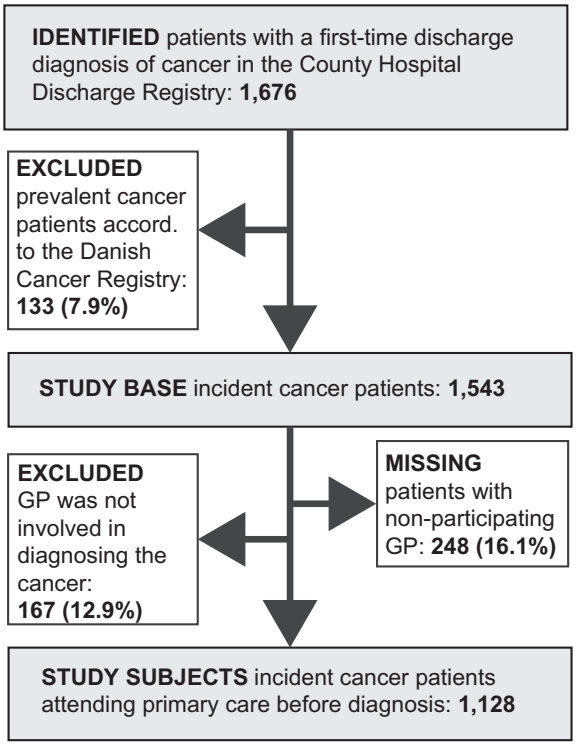

Fig. 1. Flowchart showing identification of incident colorectal, lung, melanoma skin, breast and prostate cancer patients in Aarhus County, Denmark 2004–2005 for whom general practice was involved in diagnosing the cancer. The last criterion could not be determined for patients with non-participating GPs.

high validity.[20] Patients were singled out using the following ICD-10 codes: C18 and C19 (colon cancer), C20 (rectal cancer), C33 and C34 (lung cancer), C43 (melanoma skin cancer), C50 (breast cancer) and C61 (prostate cancer). Patients were allowed to have had other kinds of cancer before the inclusion period, except malignant neoplasm of ill-defined, secondary and unspecified sites (C76-80) because such lesions could be related to the index cancer.

2.3. Data collection

A questionnaire was sent to each patient's GP 2–4 weeks after the patient had been identified. In practices with more than one GP, we asked the GP most familiar with the patient to complete the questionnaire. The GPs received compensation for their participation (DKK 240 ~ EUR 32). Non-responders received a reminder after 3 weeks. The GPs were asked to confirm the diagnosis and to provide a detailed description of the patient's diagnostic pathway on the basis of the electronic medical record and discharge letters from hospitals and specialists (e.g. dates of reported symptoms, encounters, tests, referrals and involvement of other providers). The date of presentation and the date of diagnosis were defined in line with the Aarhus Statement by asking the GP "*when did the patient first present to your practice with symptoms which you thought were related to the current cancer diagnosis? (date)*" and "*when was the final cancer diagnosis established? (check discharge summary if necessary) (date)*".[21] The questionnaire also requested information about the symptoms presented by the patients at the first consultation and about the GP's interpretation of those symptoms, i.e. as either alarm symptoms suggestive of cancer, symptoms suggestive of any serious illness, or vague symptoms not directly suggestive of cancer or other serious illness. This allowed us to distinguish between patients presenting with either 'alarm or any serious symptoms' or 'vague symptoms'. The GP's symptom interpretation was subjective, i.e. it was not based on a pre-specified list of alarm symptoms. The data collection has been described in further detail elsewhere.[22,23]

2.4. Data on covariates

We obtained information on age and sex from the civil registry number. The patient's complete hospital discharge history 10 years before the date of first presentation of symptoms to the GP was used to compute a Charlson Comorbidity Index score.[24] We grouped levels of comorbidity into 'no comorbidity' (patients with no recorded disease), 'patients with moderate comorbidity' (index score of 1 and 2) and 'patients with high comorbidity' (index score of 3 or more). To describe data in further detail, we obtained information from The Danish National Registry of Patients on emergency admission (yes = sub-acute and acute; no = elective and missing) and from the Danish Cancer Registry on previous cancers in other sites (yes/no) and tumour staging classified according to the TNM Staging System. We re-grouped the staging information using the following principle: stage I (T1-2/N0/M0), II (T3-4/N0/M0), III (T1-4/N1-2/M0), IV (T1-4/N0-2/M1) and unknown.

2.5. Defining time and mortality

We retrieved information on migration and death from the Danish Civil Registration System. The study outcome was death. All patients were followed up until death or 5 years after diagnosis – as defined by the GPs. The date of the first-time discharge diagnosis of cancer in the County Hospital Discharge Registry was defined as the date of diagnosis in the comparison of mortality in patients with participating and non-participating GPs.

2.6. Statistical analyses

We stratified analyses according to the GP's interpretation of symptoms (alarm or any serious symptoms versus vague symptoms) as we expected the diagnostic pathways to be very different for these two groups of patients. We analysed each cancer separately and com-

bined. As the distribution of the diagnostic intervals differed between cancers, we combined data by allocating patients according to their cancer and symptom-specific diagnostic interval quartiles or percentiles, i.e. by re-scaling the diagnostic interval using the corresponding cancer- and symptom-specific cumulative frequencies (see Fig. 2).

Patients who died on the date of diagnosis were included in the analyses. We plotted the survival function up till 5 years after diagnosis using the Kaplan–Meier method. Data were modelled in two ways. First, we compared patients experiencing long (4th quartile) and short (1st quartile) with medium (2nd + 3rd quartile) diagnostic intervals. Second, to avoid assuming a linear or piecewise constant association, we treated the re-scaled diagnostic interval as a continuous variable using restricted cubic splines with four knots and the cancer and symptom-specific 50th percentile as reference point.[25] In both models, we estimated five-year mortality odds ratios (ORs) as a function of the length of the diagnostic interval, and using logistic regression we adjusted for Charlson Comorbidity Index at presentation (0/1–2/⩾3), age at diagnosis and sex. Using overly broad categories of age may cause residual confounding. To mitigate this problem, we adjusted for age as a linear and quadratic term. In the analysis of the combined data, we adjusted for differences in cancer-specific five-year mortality by using conditional logistic regression and thus allowed for between-cancer variability.

We calculated 95% confidence intervals (95%CI) for all estimates and tested each model against a model with no diagnostic interval term using the Wald test. A two-sided p-value of 0.05 or less was defined as statistically significant.

3. Results

We identified 1543 incident colorectal, lung, melanoma skin, breast and prostate cancer patients above the age of 17. In 248 (16%) of the cases, the GPs did not participate or complete the questionnaire (Fig. 1). We compared patients with participating GPs to patients with non-participating GPs and found no differences with respect to age, gender, comorbidity,

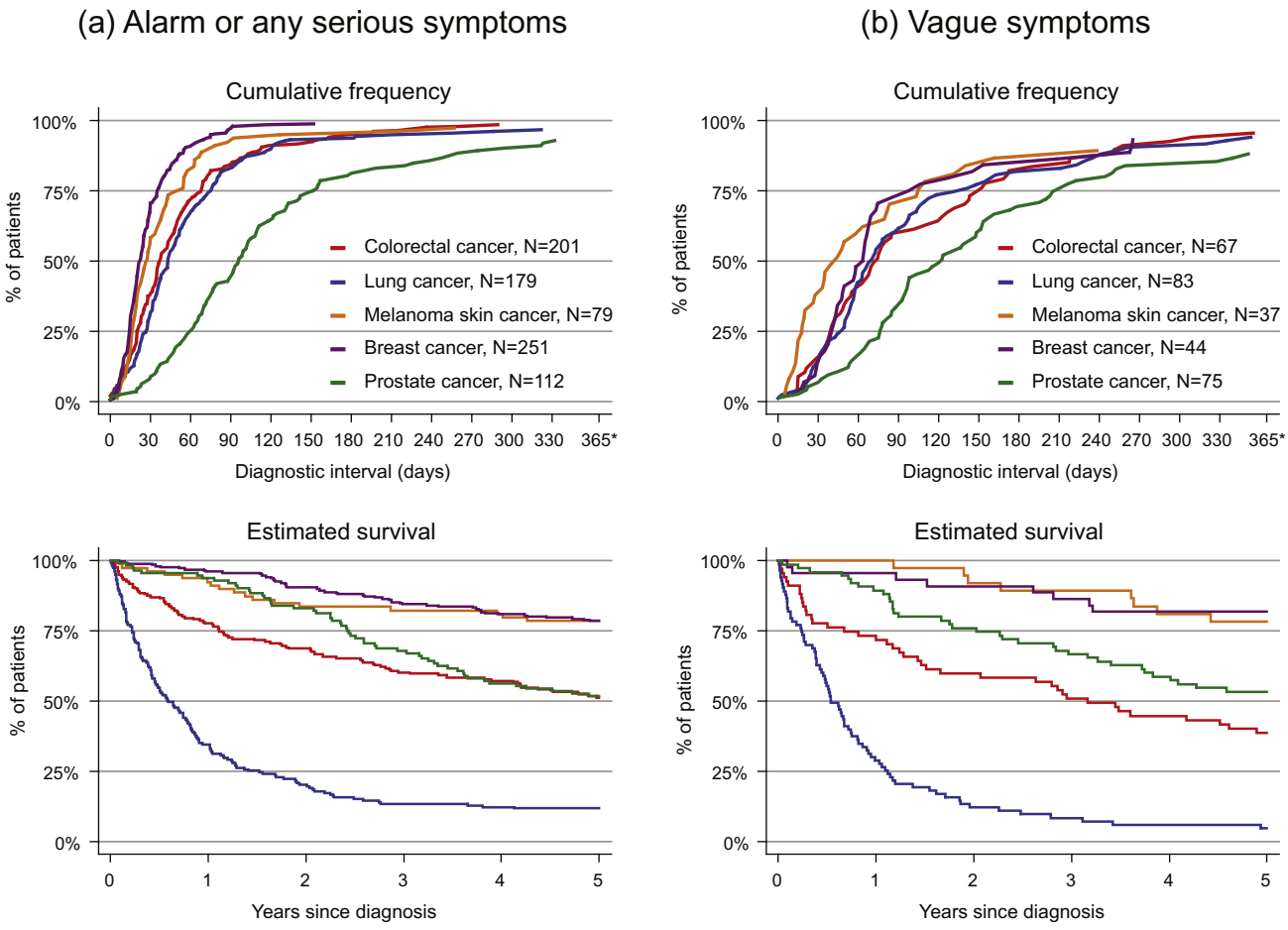

Fig. 2. Distribution of the diagnostic intervals (time from first presentation of symptoms in primary care to diagnosis) and estimated survival in each type of cancer for patients presenting with (a) alarm symptoms of cancer or symptoms related to any serious illness; and (b) vague or ill-defined symptoms not directly related to cancer or any other serious illness. *Patients with diagnostic intervals longer than 365 days not shown (colorectal cancer $n = 6$; lung cancer $n = 11$; melanoma skin cancer $n = 6$; breast cancer $n = 6$; prostate cancer $n = 17$).

emergency admission, previous cancer, tumour stage or five-year mortality after discharge. However, compared with patients with participating GPs, lung cancer patients with non-participating GPs were more likely to be admitted to hospital as an emergency, to have other types of cancer and more advanced or unknown stage tumours; and melanoma skin cancer patients with non-participating GPs were more likely to be older and males. Finally, colorectal and lung cancer patients listed with non-participating GPs had a statistically significantly higher one-year mortality after discharge and – in the case of lung cancer – also a higher five-year mortality after discharge (data not shown) than patients listed with participating GPs.

GPs were involved in diagnosing 1128 (87%) of the 1295 patients with participating GPs (Fig. 1). In comparison with colorectal and lung cancer patients, melanoma skin and breast cancer patients were more likely to present with alarm symptoms of cancer and to be diagnosed at earlier stages (Table 1).

The distributions of the diagnostic intervals were comparable across cancer diagnoses when stratified according to the GP's symptom interpretation, except for prostate cancer patients who generally experienced much longer diagnostic intervals (Table 2 and Fig. 2a).

The odds of experiencing long versus short diagnostic intervals (adjusted for comorbidity, age and sex) were 3.1-fold (95%CI: 2.3, 4.3) higher for the 306 patients presenting with vague symptoms than for the 822 patients presenting with alarm symptoms or any serious symptoms. Patients presenting with vague symptoms had lower comorbidity, were more likely to be admitted to hospital as an emergency and had more advanced stage tumours (especially stage IV, i.e. with distant spreading) than patients with clear symptoms.

3.1. Diagnostic interval and mortality

Mortality varied across cancer diagnoses. Thus, the overall five-year cumulative mortality ranged from

Table 1
Characteristics of the 1128 incident cancer patients according to diagnosis.

	Colorectal cancer		Lung cancer		Melanoma skin cancer		Breast cancer		Prostate cancer		Total	
Number of subjects (%)	268	(24)	262	(23)	116	(10)	295	(26)	187	(17)	1128	(100)
Days of diagnostic interval												
Median [inter quartile interval, IQI]	44	[23–77]	52	[30–86]	30	[17–60]	25	[15–44]	101	[66–177]	44	[22–87]
The GP's interpretation of symptoms at first presentation of symptoms in primary care												
Alarm symptoms	125	(47)	85	(32)	69	(59)	243	(82)	73	(39)	595	(53)
Any serious symptoms	76	(28)	94	(36)	10	(9)	8	(3)	39	(21)	227	(20)
Vague symptoms	67	(25)	83	(32)	37	(32)	44	(15)	75	(40)	306	(27)
Age at first presentation of symptoms in primary care												
18–59 years	56	(21)	66	(25)	64	(55)	149	(51)	17	(9)	352	(31)
60–74 years	105	(39)	133	(51)	35	(30)	96	(33)	99	(53)	468	(41)
⩾75 years	107	(40)	63	(24)	17	(15)	50	(17)	71	(38)	308	(27)
Median years of age [IQI]	71	[63–80]	68	[60–75]	58	[42–67]	60	[49–70]	72	[65–78]	67	[58–76]
Sex												
Female	132	(49)	130	(50)	68	(59)	294	(100)	0	(0)	624	(55)
Male	136	(51)	132	(50)	48	(41)	1	(0)	187	(100)	504	(45)
Comorbidity at first presentation of symptoms in primary care												
Low (0)	167	(62)	143	(55)	87	(75)	234	(79)	111	(59)	742	(66)
Moderate (1–2)	79	(29)	90	(34)	23	(20)	50	(17)	64	(34)	306	(27)
High (⩾3)	22	(8)	29	(11)	6	(5)	11	(4)	12	(6)	80	(7)
Previous cancer												
Yes	40	(15)	48	(18)	17	(15)	32	(11)	26	(14)	163	(14)
No	228	(85)	214	(82)	99	(85)	263	(89)	161	(86)	965	(86)
Tumour stage												
I	25	(9)	40	(15)	72	(62)	126	(43)	68	(36)	331	(29)
II	94	(35)	18	(7)	10	(9)	9	(3)	47	(25)	178	(16)
III	71	(26)	69	(26)	11	(9)	127	(43)	11	(6)	289	(26)
IV	56	(21)	123	(47)	9	(8)	13	(4)	54	(29)	255	(23)
Unknown	22	(8)	12	(5)	14	(12)	20	(7)	7	(4)	75	(7)
Emergency admission												
Yes	65	(24)	58	(22)	1	(1)	10	(3)	8	(4)	142	(13)
No	203	(76)	204	(78)	115	(99)	285	(97)	179	(96)	986	(87)

Table 2
Characteristics of cancer patients presenting with: (a) alarm symptoms of cancer or symptoms related to any serious illness or with (b) vague or ill-defined symptoms not directly related to cancer or any other serious illness.

	(a) Alarm or any serious symptoms				(b) Vague symptoms			Total	
Number of subjects (%)		822	(73)		306	(27)		1128	(100)
Days of diagnostic interval	*p25*	*p50*	*p75*	*p25*	*p50*	*p75*	*p25*	*p50*	*p75*
Colorectal cancer*	21	37	68	40	74	152	23	44	77
Lung cancer*	27	43	76	47	70	141	30	52	86
Melanoma skin cancer*	16	27	54	18	44	105	17	30	60
Breast cancer*	14	22	36	41	64	102	15	25	44
Prostate cancer*	61	96	153	76	122	216	66	101	177
Overall*	19	35	68	42	76	153	22	44	87
Age at first presentation of symptoms in primary care	*p25*	*p50*	*p75*	*p25*	*p50*	*p75*	*p25*	*p50*	*p75*
	57	67	76	58	67	75	58	67	76
Age groups		*n*	(%)		*n*	(%)		*n*	(%)
18–59 years		258	(31)		94	(31)		352	(31)
60–74 years		330	(40)		138	(45)		468	(41)
⩾75 years		234	(28)		74	(24)		308	(27)
Sex									
Female		486	(59)		138	(45)		624	(55)
Male		336	(41)		168	(55)		504	(45)
*Comorbidity at first presentation of symptoms in primary care***									
Low (0)		521	(63)		221	(72)		742	(66)
Moderate (1–2)		237	(29)		69	(23)		306	(27)
High (⩾3)		64	(8)		16	(5)		80	(7)
Previous cancer									
Yes		116	(14)		47	(15)		163	(14)
No		706	(86)		259	(85)		965	(86)
*Tumour stage***									
I		251	(31)		80	(26)		331	(29)
II		129	(16)		49	(16)		178	(16)
III		226	(27)		63	(21)		289	(26)
IV		159	(19)		96	(31)		255	(23)
Unknown		57	(7)		18	(6)		75	(7)
*Emergency admission***									
Yes		92	(11)		50	(16)		142	(13)
No		730	(89)		256	(84)		986	(87)

* $p \leqslant 0.05$ using independent sample *t*-test for difference in median diagnostic intervals (log-transformed distributions) comparing alarm or any serious with vague symptoms.
** $p \leqslant 0.05$ using χ^2-test for difference between groups (alarm or any serious versus vague symptoms).

21% in breast cancer to 91% in lung cancer (Table 3). Within each type of cancer, the prognoses were comparable for patients presenting with alarm or any serious symptoms and with vague symptoms (Fig. 2).

Alarm or any serious symptoms. Among the 822 patients presenting with alarm or any serious symptoms, 381 (46%) died within 5 years of diagnosis. Within each type of cancer, survival was lowest for the 1st diagnostic interval quartile (Fig. 3a). The categorical analysis revealed that the adjusted five-year mortality OR for all cancers combined was 2.0 (95%CI: 1.3, 2.9) for the 1st and 1.5 (95%CI: 1.0, 2.2) for the 4th quartile compared with the 2nd + 3rd diagnostic interval quartiles (Table 3a). This association was confirmed by the spline regression analyses, which revealed convex (U-shaped) associations for all cancers except breast cancer: The risk of dying within 5 years decreased with longer diagnostic intervals up to approximately the 60th percentile and then increased. The associations were statistically significant for colorectal cancer and for all cancers combined ($p < 0.01$ in both cases, see Fig. 4a).

3.2. Vague symptoms

A total of 171 (56%) of the 306 patients presenting with vague symptoms died within 5 years of diagnosis. Comparison within these strata could not be performed as almost all lung cancer patients and only few melanoma skin and breast cancer patients died within 5 years of diagnosis. Furthermore, pooling was not applicable in the case of prostate cancer as the stratum-specific effect went counter to the effect in the other groups. The adjusted five-year mortality OR for the 231 combined colorectal, lung, melanoma skin and breast cancer

Table 3
Cumulative five-year mortality rates (MRs) and crude and adjusted mortality odds ratios (ORs) for the 1st and 4th compared with the 2nd + 3rd diagnostic interval quartiles for cancer patients presenting with: (a) alarm symptoms of cancer or symptoms related to any serious illness and with (b) vague or ill-defined symptoms not directly related to cancer or any other serious illness.

Diagnostic interval quartiles	(a) Alarm or any serious symptoms						(b) Vague symptoms					
	n	MR (%)	Crude		Adjusted[a]		*n*	MR (%)	Crude		Adjusted[a]	
			OR	(95%CI)	OR	(95%CI)			OR	(95%CI)	OR	(95%CI)
Colorectal cancer												
	201	48.8					67	61.2				
1st	54	66.7	3.44	(1.71–6.93)	4.74	(2.20–10.19)	18	50.0	0.50	(0.15–1.62)	0.74	(0.19–2.80)
2nd + 3rd	98	36.7	1	(reference)	1	(reference)	33	66.7	1	(reference)	1	(reference)
4th	49	53.1	1.95	(0.97–3.90)	2.01	(0.93–4.36)	16	62.5	0.83	(0.24–2.89)	1.08	(0.28–4.12)
Lung cancer												
	179	88.3					83	95.2				
1st	46	95.7	3.67	(0.79–17.00)	5.16	(1.03–25.94)	21	100.0				
2nd + 3rd	91	85.7	1	(reference)	1	(reference)	42	92.9		Comparison unjustified		
4th	42	85.7	1.00	(0.35–2.84)	1.13	(0.37–3.46)	20	95.0		(too many events)		
Melanoma skin cancer												
	79	21.5					37	21.6				
1st	20	20.0	1.00	(0.26–3.83)	1.83	(0.37–8.96)	10	10.0				
2nd + 3rd	40	20.0	1	(reference)	1	(reference)	18	27.8		Comparison unjustified		
4th	19	26.3	1.43	(0.40–5.15)	1.88	(0.44–8.00)	9	22.2		(too few events)		
Breast cancer												
	251	21.5					44	18.2				
1st	63	20.6	1.02	(0.48–2.15)	1.05	(0.47–2.35)	12	8.3				
2nd + 3rd	128	20.3	1	(reference)	1	(reference)	21	28.6		Comparison unjustified		
4th	60	25.0	1.31	(0.63–2.70)	1.18	(0.52–2.66)	11	9.1		(too few events)		
Prostate cancer												
	112	48.2					75	46.7				
1st	29	62.1	2.45	(0.97–6.18)	2.35	(0.89–6.22)	19	63.2	2.22	(0.72–6.85)	2.93	(0.79–10.88)
2nd + 3rd	55	40.0	1	(reference)	1	(reference)	39	43.6	1	(reference)	1	(reference)
4th	28	50.0	2.46	(0.94–6.44)	1.42	(0.54–3.74)	17	35.3	0.71	(0.22–2.29)	0.63	(0.14–2.77)
All cancers combined[b]												
	822	46.4					231	58.9				
1st	212	54.2	1.98	(1.34–2.91)	1.98	(1.34–2.91)	61	52.5	0.53	(0.23–1.22)	0.51	(0.21–1.24)
2nd + 3rd	412	41.3	1	(reference)	1	(reference)	114	63.2	1	(reference)	1	(reference)
4th	198	48.5	1.49	(1.01–2.22)	1.49	(1.01–2.22)	56	57.1	0.70	(0.30–1.65)	0.67	(0.26–1.71)

[a] Adjusted for Charlson Comorbidity Index, age and sex (combined analysis further adjusted for differences in cancer-specific five-year mortality).
[b] In combined analyses, patients were allocated according to cancer and symptom-specific diagnostic interval quartiles. Prostate cancer was omitted from the analysis of the combined data of patients with vague symptoms because the strata-specific effect went counter to the rest.

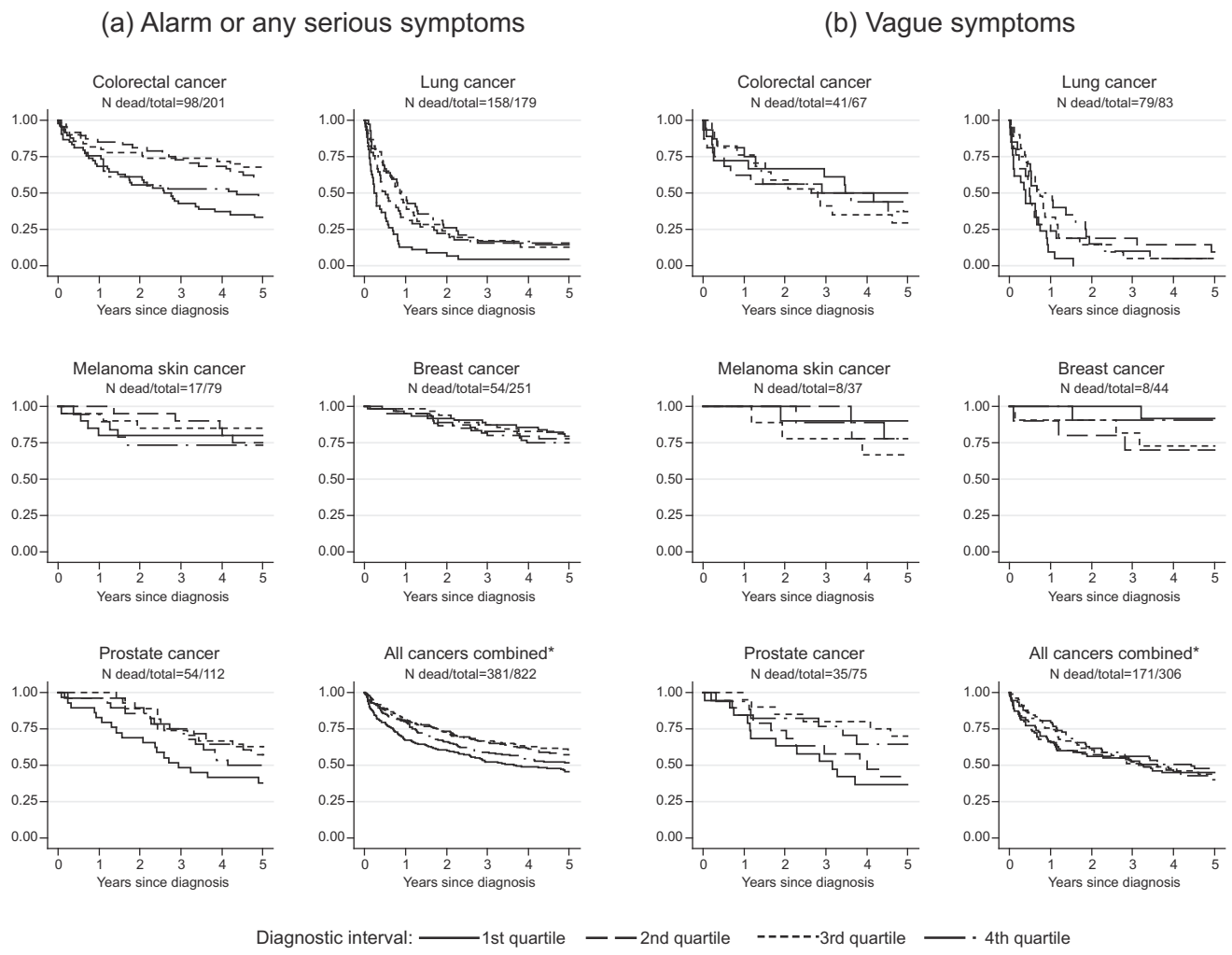

Fig. 3. Estimated survival for the diagnostic interval quartiles for each type of cancer and all combined in patients presenting with: (a) alarm symptoms of cancer or symptoms related to any serious illness and with (b) vague or ill-defined symptoms not directly related to cancer or any other serious illness. *Patients allocated according to cancer and symptom-specific diagnostic interval quartile in combined analysis.

patients was 0.51 (95%CI: 0.21, 1.2) for the 1st and 0.67 (95%CI: 0.26, 1.7) for the 4th quartile compared with the 2nd + 3rd diagnostic interval quartiles (Table 3b). The corresponding spline regression analyses revealed a concave (∩-shaped) association ($p = 0.191$), whereas the strata-specific trend for prostate cancer was convex ($p = 0.06$) (see Fig. 4b).

4. Discussion

In patients with alarm or any serious symptoms, mortality grew the longer the diagnostic intervals in those 40% from this group who experienced the longest delays. In patients with alarm or any serious symptoms, having very short diagnostic intervals was also associated with a high mortality. Inversely, in patients presenting with vague symptoms, we saw much longer diagnostic intervals, the same survival probability and an opposite, concave trend between the length of the diagnostic interval and mortality. However, the latter association was not statistically significant and the association did not apply to prostate cancer.

4.1. Strengths of the study

A main strength of the present population-based cohort study of 1128 patients with incident colorectal, lung, melanoma skin, breast and prostate cancer is that follow-up was complete and selection and information bias reduced owing to the uniform organisation of the Danish healthcare system and the availability of highly reliable registries with histological data on diagnoses. A high response rate among GPs (84%) also reduced the potential for selection bias. By excluding those patients whose GPs had not been involved in their diagnosis, we ensured a highly homogeneous group with respect to confounders and thus obtained better internal validity. Furthermore, a main analytical strength of the study is that it addresses the premise of confounding by indication by acknowledging a flexible relationship

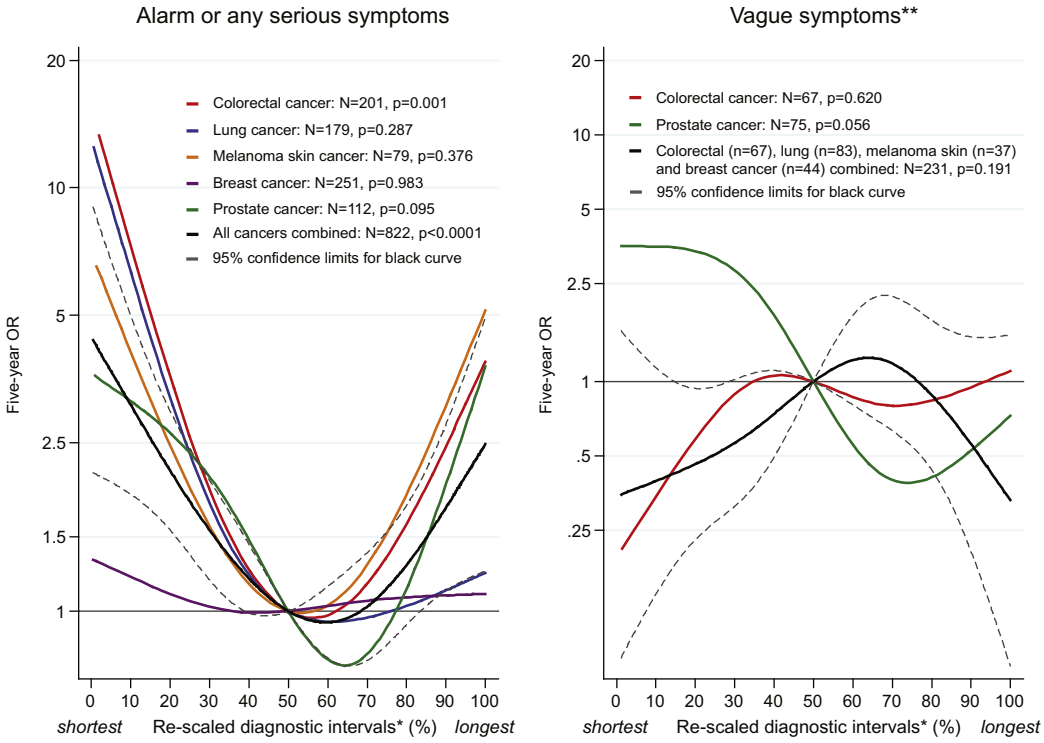

Fig. 4. Estimated five-year mortality odds ratios (OR) as a function of the diagnostic interval analysed for each type of cancer and cancers combined in patients presenting with (a) alarm symptoms of cancer or symptoms related to any serious illness and (b) vague or ill-defined symptoms not directly related to cancer or any other serious illness. Adjusted for Charlson Comorbidity Index, age and sex (combined analysis further adjusted for differences in cancer-specific five-year mortality). *The chosen reference point '50' represents the cancer and symptom-specific median, whereas '0' and '100' represent patients with shortest and longest diagnostic intervals, respectively. **Comparisons within lung, melanoma skin and breast cancer patients presenting with vague symptoms were not justified because of too many or few events. Prostate cancer was omitted from the combined analysis as the strata-specific effect went counter to the rest.

between exposure and outcome and by stratifying data according to the GP's interpretation of symptoms.

4.2. Limitations of the study

A limitation of the present study design is that it invites a risk of selection and information bias and residual confounding.

Firstly, 16% of the study base could not be included in the final analyses due to GP non-participation. This creates a problem perhaps most apparent for lung cancer, where patients whose GPs did not participate in the diagnostic process were found to have more advanced tumours and a higher mortality. Some GPs may have chosen not to participate because they retrospectively believed that they had caused undue diagnostic delays. Alternatively, GPs may not have replied because they were uninvolved in the process (if patients e.g. were diagnosed through other routes like on-call services, were nursing home residents or attended private clinics).

Secondly, the length of the diagnostic interval may be subject to differential misclassification. Non-random measurement bias could apply to the recalling of dates and the GP's symptom interpretation, particularly where symptomatology is fuzzy like in colorectal, lung and prostate cancer. Given the observed convex and concave trends, it is difficult to predict the direction of both selection and information bias; but we know from a recent study that a U-shaped association cannot likely be explained by such bias.[13]

Lead time bias may be at play because early detection advances what would have been the original date of diagnosis to an earlier point in time, while not necessarily delaying the patient's time of death.[7] This could explain the finding of increasing mortality with longer diagnostic intervals, especially in patients with prostate cancer where diagnosis and treatment often imply active surveillance. Calculating mortality from the onset of symptoms has been suggested as a way of mitigating this problem.[5,26] However, this approach may create an immortal time bias, because given the exposure definition, death cannot occur until after diagnosis. Instead, we adjusted for age at diagnosis to make sure that the increase in five-year mortality was not a natural function of becoming older.

Residual confounding may have resulted from imperfect adjustment and misclassification of one or more confounding variables, such as comorbidity. Despite its high specificity, the Charlson comorbidity index is

inferior to clinical data that measure comorbidity.[27] Against the presence of residual confounding speaks the argument that we observed no major change in the estimates when controlling for measured comorbidity.

Finally, although the stratification procedure was used to limit the risk of confounding and selection bias, the procedure also reduced the statistical precision of the study. A larger study is needed to assess the cancer-specific effects, especially in patients presenting with vague symptoms.

4.3. Comparison with findings from other studies

Many studies have reported high mortality for patients with short diagnostic delays in various types of cancer.[5–8,28] In many cases, authors seem unprepared for meeting contradictory results. Instead of questioning the design, many ignore statistically significant reverse effects and claim that the time duration of the diagnostic and treatment processes is too short to have any clinical relevance.[9–11,29–31] Polissar and colleagues even maintained that the effect of time to diagnosis up to approximately 1 year seemed unimportant.[32] Others are more moderate and state that waiting time reductions may produce only comparatively small gains in survival rates.[33,34] As pointed out by Maguire et al., many studies do not apply models that allow for a continuous, non-monotonic effect, and they may therefore draw wrong conclusions.[35] Future studies clearly need to address this important analytical issue. Yet, what remains to be explained is why we observe reverse associations that contradict our basic understanding of the exponential growth of tumours.

4.4. Underlying mechanisms and clinical implications

It is a widely held assumption that the waiting time paradox can be explained by the effect of high-risk precursors such as phenotype, biological virulence or tumour aggressiveness, which are thought to act as unmeasured confounders that mask the effect of the exposure.[7,36–39] According to this theory, rapidly growing or proliferating tumours are believed to present with more alarming symptoms (e.g. sudden big lumps or heavy bleeding), which both patients and doctors may take to suggest cancer. By contrast, slowly growing, less well-differentiated tumours may present initially with occasional, vague symptoms that are more difficult to detect.[9,10,40–42]

However, for this theory to hold true, we would expect patients presenting with vague symptoms to have an overall better survival than patients presenting with alarm or any serious symptoms. This was apparently not the case: the results of the present study showed that patients presenting with alarm and vague symptoms had equal survival probabilities within the cancer-specific strata, and we observed opposite trends in the two groups.

As stated in the introduction, we believe the paradoxical findings of observational studies generally reflect confounding by indication. GPs expedite patients presenting with high-risk symptoms – especially if patients look ill. At the same time, they are bound to be more reluctant to refer healthy looking people with low-risk symptoms.[16,43] But, as many patients in primary care do not fall squarely into set categories, delays should be less contingent upon prognosis and thus more randomly assigned for a significant part of grey-zone patients.[44,45] Along these lines, we propose that the observation of increasing mortality with longer diagnostic intervals reflects the actual effect of diagnostic delays.

We found similar trends in different types of cancers. In a previous study, we found the same trend for colorectal cancer when using different sources of information, for different time periods and in two different health care systems (Denmark and the UK).[13] This strengthens the belief that the results may be generalised to other groups of cancer patients. The study displays the immense complexity and difficulty of diagnosing cancer. Yet, we can infer from the increasing trends in mortality that a few weeks can make a difference – that time matters.

5. Conclusion

This study challenges the conclusions of many previous studies and provides evidence for the hypothesis that the length of the diagnostic interval affects mortality negatively. The study thereby supports efforts to shorten the clinical pathway such as standardised cancer packages that guarantee a fast track from referral to diagnosis and treatment in patients with suspected cancer.

Contributors

MLT was responsible for data acquisition from public and medical databases, performed the statistical analyses and wrote the paper. She is the guarantor. MF supervised the statistical analyses and designed programmes in Stata (version 11) for generating cubic splines with specific reference values (centercsplines.ado) and estimates with standard errors for linear combinations (calcest.ado) – both applied in Fig. 2. RPH designed the GP and patient questionnaires and was responsible for this part of the data acquisition. PV and FO initiated the study. MF, FO and PV provided critical revision of the intellectual contents of the manuscript. All authors contributed to the writing of and approved the final manuscript.

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Conflict of interest statement

None of the authors have received any support from or have any relationship with companies that might have an interest in the submitted work, but FO is chairman of the Danish Cancer Society, which is a charity-based and independent national patient organisation.

Ethical approval

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health. According to the Committees on Biomedical Research Ethics in the Central Denmark Region, the Act on the Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects does not apply to this project. All authors had full access to data and take full responsibility for the accuracy of the data analysis.

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