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Cancer Survival and the Duration of Symptoms. An Analysis of Possible Forms of the Risk Function

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The time interval between onset of symptoms and the diagnosis of cancer [symptom to diagnosis interval (SDI), or duration of symptoms] is a highly complex variable reflecting patient behaviour, the clinical course, the functioning of the health system and tumour biology. In order to assess possible forms of the risk function of SDI upon cancer survival whilst taking into account the effects of age, sex, tumour site and stage at diagnosis, 1887 symptomatic cases of lung, breast, stomach, colon, rectal, bladder cancer and lymphomas registered in the Tumour Registry of the Hospital del Mar (Barcelona) were analysed by means of survival curves and Cox proportional hazards regression. Subjects (mean age 64 years) were followed for a median length of 15 months after diagnosis (follow-up rate 93.5%). SDI showed a weak relationship with tumour stage at diagnosis and with survival: out of the seven sites studied, only in breast cancer was tumour extension at diagnosis significantly influenced by duration of symptoms, and only lung and rectal cancers showed a detectable form of the risk function of SDI upon survival; neither was linear, and for rectal cancer the relationship was complexly related with tumour stage. Hence, results show that forms of the risk function of duration of symptoms on cancer survival are specific to tumour sites, and that the interval should not be represented as a linear, continuous term. Studies analysing more complex sets of factors, processes and forms of the SDI function are needed.

Key words: cancer, lymphomas, survival, duration of symptoms, diagnostic delay, epidemiological methods
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INTRODUCTION

SOLID SCIENTIFIC evidence exists that prognosis of some cancers is improved by high quality screening programmes, i.e. population-based programmes targeting asymptomatic disease [1–6]. In addition, the idea that many cancers are curable if discovered early in the clinical course is appealing, and is gaining public acceptance in numerous areas. However, the effect upon survival of early clinical detection (advancing the diagnosis in symptomatic individuals) has been shown to be weak by many studies, particularly when stage at diagnosis was accounted for [6–22]. Although such studies belong to the minority that assessed survival instead of other indirect measures of prognosis such as stage at diagnosis and surgical outcomes, their analytic approach was often overtly simple, they often dichotomised "diagnostic delay" (e.g. presence/absence, above/below 6 months) and, to our knowledge, none explicitly attempted to assess possible forms of the risk function.

Decades of research on delays in seeking care for cancer indicate that the time interval between onset of symptoms and the diagnosis of cancer [symptom to diagnosis interval (SDI), or duration of symptoms] is a highly complex variable reflecting patient behaviour, the clinical course, the functioning of the health system, and tumour biology [7–13, 16–23]. In a previous study [23] of five different cancers (n = 1247), we found that SDI very weakly influenced tumour's spread at the time of diagnosis (with the exception of breast cancer), and did not significantly affect survival beyond the effect of stage at diagnosis. Among the variables analysed, only age, tumour site and extension were related to survival time. Possible reasons for such findings were discussed, notably the complex interaction of biological, clinical and psychosocial processes influencing SDI [23]. Importantly, in that study, SDI was represented as a continuous, monotonic variable in a standard Cox proportional survival analysis. Yet, the possibility exists for the risk function of SDI upon survival to actually have different, non-linear forms; if at all true, that fact would have been overlooked in ours and in previous studies that assumed the function to be linear,

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i.e. prognosis to gradually change with increasing duration of symptoms [7, 9, 17, 22, 24, 25].

Using a larger data base with a recently updated follow-up, the present report aims to evalute the risk function of the duration of symptoms upon survival after diagnosis, whilst taking into account the effects of such factors as age, sex, tumour site and tumour stage at diagnosis. In consideration of the complexities that the interval may comprise of, and the lack of previous findings, SDI will be investigated whilst making no assumption of the underlying risk function form.

MATERIALS AND METHODS

Data were obtained from the Tumour Registry of the Hospital del Mar (TRHM), a 450-bed teaching hospital primarily serving a low-income area in Barcelona. A detailed description of the registry and other analyses based on it have been described previously [23, 26, 27]. In summary, the registry was initiated in 1978 and currently includes over 6000 neoplasms. It follows standard data collection and quality assurance procedures [28], which are implemented under the supervision of a group of oncologists and epidemiologists. Information is obtained from clinical and pathology records. Over 95% of tumours were microscopically confirmed, 7% are of unknown origin and 5% are double neoplasms. Practically all cases are residents in the city of Barcelona.

The SDI was operationally defined as the time between the dates of the first symptom attributable to cancer and its pathological (or, in a few instances, clinical) diagnosis. The registry obtains such dates from clinical notes. Stage of tumour dissemination at diagnosis is classified as local, regional or disseminated; tumours with regional dissemination are those with regional nodal involvement (N+) or invasion of structures surrounding the primitive tumour. In order to achieve at least 1 year of individual follow up, only cases registered between 1978 and 1989 were selected for the present study. Analysis was retricted to the seven most common malignant primary neoplasms in the TRHM, namely lung, breast, colon, rectal, stomach, lymphoma and urinary bladder cancer. As extremely long SDI values were thought to be unreliable and probably corresponding to symptoms not related to the cancer, an upper limit on SDI, above which cases were excluded, was agreed upon beforehand; specifically, limits were up to 120 months for breast cancer, up to 60 months for bladder cancer and up to 36 months for lung, stomach, colon and rectum cancers. No limit was set for lymphomas. The registry provided 1920 symptomatic cases of the abovementioned seven cancer sites. Of these, we excluded 9 cases of breast cancer, 8 cases of urinary bladder cancer and 16 cases of lung, stomach, colon or rectal cancers as SDI exceeded the specified limits. The remaining 1887 cases were used in the analyses.

The variables of sex, age and tumour stage at diagnosis were also obtained from the cancer registry, as were the diagnosis and follow-up dates and whether the patient had died or was living by the last follow-up record. Survival was defined as the time elapsed between the diagnosis and the last registered entry of the patient. On 30 November 1992 the data base was updated and a 93.5% patient follow-up was achieved.

To compare a categorical variable with more than two levels and a continuous variable with a non-normal distribution, the Kruskal–Wallis test was used [29]. Survival curves were estimated by the Kaplan–Meier method [30], and homogeneity of curves was assessed using the log-rank [30] and the Lee–Desu test statistics [31]. Survival analysis was carried out using Cox proportional hazards methods. The assumption of proportional hazards was checked for each variable [32]. Results are expressed in terms of hazard ratios, which have the same interpretation as relative risks between two groups.

In order to assess the risk function that SDI might possess, quintile groupings based on SDI were derived and introduced into the model as dummy variables. The estimated hazard ratio of each quintile of categorical SDI was plotted against its mid-class value to allow visual evaluation of the risk function of SDI. Similarly, age was initially introduced as a factor derived from the quintile groupings, and the shape of the effect assessed to determine whether this discrete variable was more representative of the age effect than the linear variable. Histology was included as an explanatory variable for lung cancer only, as this was the only site to have different histology types sufficiently numerous to permit analysis.

To assess the importance that a variable may have in the models fitted, the statistical significance was estimated from the Z-test and the likelihood ratio test [33], the latter specifically measuring improvement of model fit on introducing the variable.

RESULTS

The distribution of age, sex, SDI and tumour stage among the 1887 cases is provided in Table 1. Overall, mean age at diagnosis was 64 years, with significant differences among primary tumour sites ($P < 0.001$). Age was also related to tumour stage at diagnosis ($P < 0.001$), the lowest median age (64 years) belonging to patients diagnosed with regional tumour spread. Age was not associated with SDI (rank correlation coefficient = -0.029). A clear relationship was evident between SDI and primary tumour site ($P < 0.001$), with median SDI ranging from 5 months in urinary bladder cancer to 2 months in lung cancer. Only breast cancer showed increasing tumour spread with increasing SDI ($P < 0.001$) (Table 1).

Median survival, stage at diagnosis and SDI

The observed survival patterns by primary tumour site are presented by stage and SDI quintile groups in Table 2. As expected, median survival time was affected by primary tumour site (log-rank test: $P < 0.001$); half the population of lung cancer patients would have died within 6 months of diagnosis, whereas the same proportion of breast cancer patients would be expected to die within 6 years. A decrease in median survival time is seen with increasing stage of tumour spread at diagnosis in all sites ($P < 0.001$) except for lymphoma, where disseminated tumours have a longer median survival than tumours of regional spread.

Table 2 also presents the median survival by SDI quintile group [SDI increasing from the first quintile (Q1) to Q5, the quintile comprising the 20% of cases with longest duration of symptoms]. Survival varied significantly only in lung cancer ($P = 0.001$), with the most favourable survival being that of patients in Q1 (SDI < 1 month). The relationship of survival and SDI was seen to be marginally significant in breast cancer ($P = 0.109$), with the third quintile (2–5 months) having a median survival about twice that of the other quintile groups. Because several factors may cause the interval to be inaccurately recorded, the two upper SDI quintiles ("short delay") and the two lowest SDI quintiles ("long delay") were next grouped [18], and the corresponding median survival of the two groups (Q1 + Q2 versus Q4 + Q5) was compared through a simple ratio (Table 2). Values above unity (such as seen in breast cancer) indicate an inverse relationship between SDI and survival,

Table 1. Characteristics of cases and distribution of the duration of symptom to diagnosis interval (SDI) by primary tumour site

	Breast	Lung	Bladder	Colon	Rectum	Stomach	Lymphomas	All
No. of cases	377	566	136	261	180	217	150	1887
Non-censored (%)	50.9	91.9	50.0	66.3	75.6	84.3	70.7	73.0
Follow-up*								
Median	53	5	36	22	16	9	25	15
(%)	87.7	95.9	94.1	95.6	93.9	93.9	89.3	93.5
Age†								
Mean	59.5	64.6	65.9	66.9	69.1	68.6	53.9	64.0
S.D.	14.4	10.2	11.6	12.4	11.6	12.1	20.0	13.6
Sex (% female)	100	7.95	20.6	47.9	45.0	36.9	55.3	43.4
Stage (%)								
Local	37.9	19.3	69.1	38.3	38.3	22.6	14.7	31.1
Regional	43.5	31.4	11.0	39.8	34.3	36.9	53.3	36.2
Disseminated	13.5	41.7	7.4	18.0	21.1	30.0	26.7	25.8
Unspecified	5.0	7.6	12.5	3.8	6.1	10.6	5.3	6.9
SDI*								
Mean	9.93	3.13	9.06	4.49	4.50	4.66	5.46	5.60
S.D.	17.2	3.79	11.0	5.53	5.03	5.91	10.7	9.91
Median	3	2	5	3	3	3	3	3
SDI* by stage (median)								
Local	3	2	5	3	3	2	3.5	3
Regional	3	2	3	2	3	3	3	3
Disseminated	6	2	10	2	2	3	3	2
Kruskall–Wallis test (*P*-value)	<0.001	0.677	0.324	0.992	0.345	0.182	0.427	0.302

* In months; † in years.

whereas values below 1 (as observed for rectal cancer) indicate that a shorter SDI may be associated with lower survival.

Additionally, the ratio of the median SDI to the median survival was computed for each site (SDI to survival ratio, SSR; Table 2).SSR can be thought of as an estimate of the relative opportunity for clinical lead-time bias [6, 7, 23, 34]. The figure was highest for lung and stomach cancers, the two sites with worst prognosis, and lowest for breast and urinary bladder cancer, the two sites with more favourable survival. This indicates that an SDI of a given magnitude (say, 2 months) represents a lower fraction of the time from first symptom to death or to censoring in breast and bladder cancers than in lung and stomach cancers. Thus, the opportunity for a decrease in SDI to appear spuriously associated to increased survival would be lower in the former two sites than in the latter two.

It is worth noting that the values of median survival may become unstable if a great deal of censoring occurred before median survival was reached, or if the number of cases is small, as was the case in the subgroups of urinary bladder cancer. The Kaplan–Meier survival curves by tumour site reflected the median survival results given in Table 2, with lung cancer showing the highest death rate, followed by cancer of the stomach; breast cancer cases had the lowest death rate.

Table 2. Median survival times (in months) by site for stage at diagnosis and symptom to diagnosis interval (SDI) quintile groups

	Breast	Lung	Bladder	Colon	Rectum	Stomach	Lymphomas	All
Total	74.89	5.49	63.31	26.63	17.62	9.88	26.26	16.94
Stage								
Local	>140	12.48	129.4	64.85	34.44	30.94	85.47	61.29
Regional	62.72	6.81	21.50	18.43	18.95	11.39	15.71	16.87
Disseminated	20.64	2.98	11.00	7.01	7.3	3.15	41.95	5.14
Unspecified	88.24	4.53	49.38	14.00	3.50	9.19	13.50	11.33
P value*	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.003	<0.001
P value†	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.006	<0.001
SDI quintiles								
Q1	59.19	9.02	35.83	23.75	27.51	11.88	37.42	16.81
Q2	79.86	5.96	137.50	36.60	11.67	10.40	27.95	9.22
Q3	133.70	4.49	47.04	20.96	16.59	9.13	23.75	17.31
Q4	61.28	4.82	59.88	32.83	24.17	8.12	21.67	16.94
Q5	55.40	6.73	>130.00	31.39	18.05	10.22	33.75	33.13
P value*	0.109	0.001	0.627	0.248	0.732	0.568	0.923	<0.001
P value†	0.065	0.004	0.322	0.178	0.972	0.655	0.781	<0.001
(Q1 + Q2)/(Q4 + Q5)‡	1.25	1.18	1.05	0.89	0.62	1.21	1.00	0.59
SSR§	0.04	0.36	0.08	0.11	0.17	0.30	0.11	0.18

*Lee–Desu test of differing survival by strata; †logrank test; ‡ratio of the median survival of cases in the two upper SDI quintiles ("short delay") to the median survival of cases in the two lowest SDI quintiles ("long delay"); §SDI to survival ratio: SSR = median SDI/median survival.

Table 3. Results of the proportional hazards modelling in the three cancer sites that evidenced a possible risk function for symptom to diagnosis interval (SDI) or duration of symptoms

Tumour	Model	SDI group limits*	HR	HR 95% CI†	Coefficient (*P* value)‡	Improvement in fit (*P* value)§
Breast						
1.1	SDI		1.012	1.005–1.019	0.001	0.004
1.2	SDI(1)	SDI<1	1.0‖			
	SDI(2)	1≤SDI≤2	0.724	0.456–1.148	0.169	
	SDI(3)	2<SDI<5	0.598	0.355–1.006	0.053	
	SDI(4)	5≤SDI≤12	0.898	0.562–1.433	0.651	
	SDI(5)	13≤SDI	1.116	0.695–1.792	0.650	0.065
1.3¶	SDI		1.003	0.995–1.010	0.477	0.486
1.4¶	SDI(1)		1.0‖			
	SDI(2)		0.989	0.618–1.584	0.964	
	SDI(3)		0.827	0.483–1.417	0.489	
	SDI(4)		1.057	0.652–1.713	0.822	
	SDI(5)		1.062	0.656–1.719	0.806	0.861
Lung						
2.1	SDI	0.992	0.971–1.013	0.458	0.450	
2.2	SDI(1)	SDI<1	1.0‖			
	SDI(2)	1≤SDI<2	1.292	0.968–1.725	0.082	
	SDI(3)	SDI=2	1.753	1.310–2.344	<0.001	
	SDI(4)	2<SDI≤4	1.377	1.016–1.866	0.039	
	SDI(5)	5≤SDI	1.271	0.936–1.725	0.125	0.004
2.3¶	SDI		0.993	0.971–1.015	0.512	0.506
2.4¶	SDI(1)		1.0‖			
	SDI(2)		1.223	0.915–1.636	0.174	
	SDI(3)		1.634	1.220–2.189	<0.001	
	SDI(4)		1.293	0.953–1.753	0.099	
	SDI(5)		1.183	0.871–1.608	0.282	0.015
Rectum						
3.1	SDI	1.006	0.973–1.040	0.724	0.727	
3.2	SDI(1)	SDI<1	1.0‖			
	SDI(2)	1≤SDI<2	1.059	0.628–1.788	0.829	
	SDI(3)	2≤SDI≤3	0.985	0.513–1.889	0.963	
	SDI(4)	3<SDI≤6	0.896	0.512–1.566	0.699	
	SDI(5)	7≤SDI	1.010	0.568–1.797	0.973	0.972
3.3¶	SDI		0.990	0.958–1.023	0.535	0.528
3.4¶	SDI(1)		1.0‖			
	SDI(2)		1.980	1.126–3.482	0.018	
	SDI(3)		1.398	0.712–2.743	0.331	
	SDI(4)		1.265	0.709–2.256	0.427	
	SDI(5)		1.180	0.660–2.112	0.576	0.134
3.5	SDI(1) × stage**		—	—	—	0.037

*In months. †95% confidence interval of the hazard ratio. ‡Z-test for each variable coefficient. §Likelihood ratio test for improvement of model fit by the introduction of the denoted variable. ‖Reference category. ¶Adjusted by age and stage. **Test for interaction between SDI (categorical) and stage.

Proportional hazards modelling of the risk function for SDI

The factor of tumour site violated the assumption of proportionality, i.e. the risks (hazards) converged over time. This, together with the opinion that different neoplasms should be treated as separate disease entities, led to the separate analysis of each tumour site. The hazards were deemed to be proportional for the other covariates and for SDI. For the interpretation of the categorical SDI variable, the reference category is always taken to be the first SDI quintile (shortest duration of symptoms). Out of the seven cancer sites studied, only three gave any evidence of a possible risk function for SDI, namely breast, lung and rectal cancers (Table 3). The other sites produced near unity, non-significant estimates of the hazard ratio (HR) for both the linear SDI and the categorical SDI functions, equally in the covariate adjusted model as in the non-adjusted model. For breast cancer, increasingly poor prognosis was linearly associated ($P = 0.001$) with increasing SDI (Table 3, model 1.1). In turn, analysis of categorical SDI showed that patients diagnosed from 2 to 5 months after initial symptom had a somewhat better survival ($P = 0.053$); specifically, the HR of 0.598 indicates that the risk of death of this group was about 40% lower than the risk of the group with SDI less than 1 month (Table 3, model 1.2). The effects of both variables (linear and categorical) disappeared when adjusted by age and tumour stage at diagnosis (models 1.3, 1.4, and Figure 1a). Prognosis continued to worsen with increasing stage at diagnosis in the age- and SDI-adjusted model.

For lung cancer there was no detectable effect of the linear function of SDI in either the non-adjusted or adjusted models (Table 3, models 2.1 and 2.3). Age was adequately modelled as a linear variable and prognosis worsened with stage. Sex was not included as no effect was detected ($P = 0.758$). The categorical

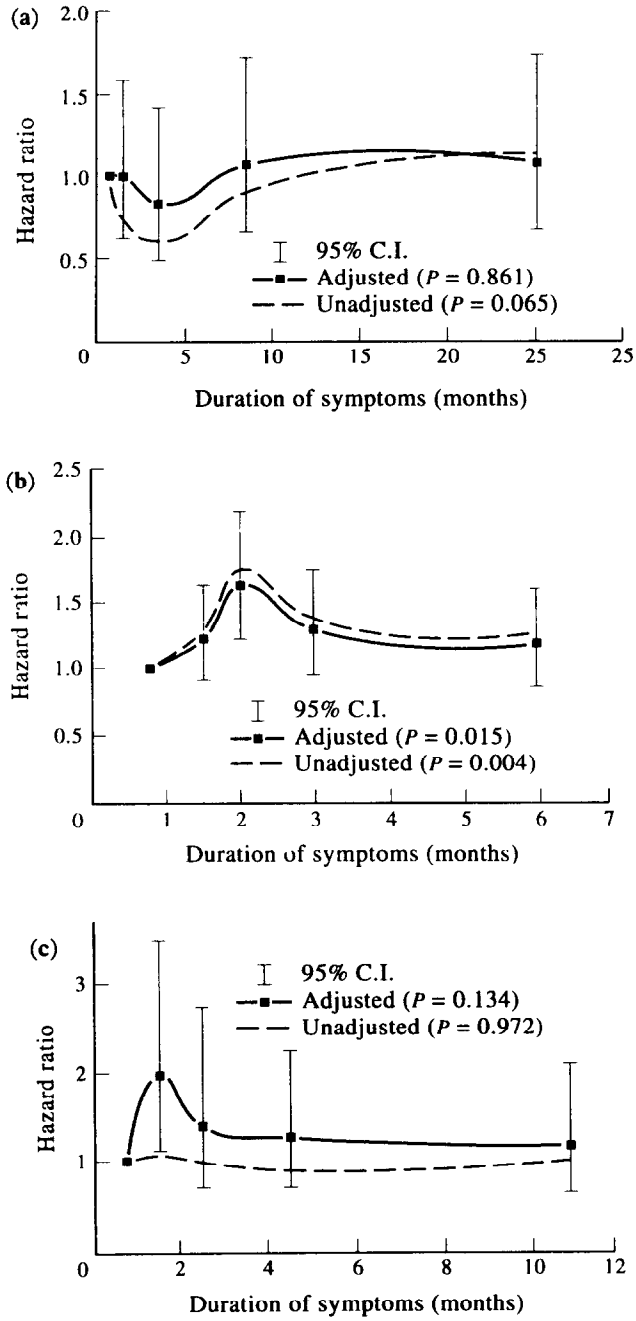

Figure 1. Risk function form of duration of symptoms on survival. (a) Breast cancer; (b) lung cancer; (c) rectal cancer.

SDI factor was statistically significant (improvement on fit: $P = 0.004$). While confidence intervals of quintiles 2 to 5 overlap, it should be noted that, as compared to subjects with SDI less than 1 month, subjects diagnosed at 2 months from their first sympton (third quintile) showed a 75% worse survival (HR = 1.75, $P < 0.001$) (model 2.2). The categorical variable still produced a significant improvement of fit ($P = 0.015$) in the age- and stage-adjusted model (model 2.4), showing the same form with a peak at 2 months ($P < 0.001$) and overlapping confidence intervals among quintiles 2 to 5. As can be seen in Figure 1b, the risk function for lung cancer is not linear; rather, an n-shaped function seems more appropriate. The inclusion of histology did not appreciably change the SDI results.

For rectal cancer, no effects of SDI were detected until the categorical variable was adjusted for age (linear) and stage (Table 3, model 3.4). Survival was seen to decrease with increasing tumour stage at diagnosis, and no effect of sex was observed. The inclusion of the categorical SDI variable marginally improved model fit ($P = 0.134$), the improvement being due to a significant increase in the HR associated with the 1–2 month SDI group (HR = 1.98, $P = 0.018$) (model 3.4). This change suggested that some relationship between categorical SDI and the covariates (age and stage) might exist. A test for interaction was, therefore, carried out and a significant interaction was found between stage and categorical SDI ($P = 0.037$) (Table 3, model 3.5). This interaction indicated that in rectal cancer the effect of SDI upon survival depends on tumour stage. The worst prognosis for those diagnosed with localised stage was at an SDI of 3–6 months (HR = 2.57, $P = 0.043$), whereas for cases diagnosed with regional tumour spread, the worst prognosis was seen in the group of 2–3 months SDI (HR = 7.12, $P = 0.053$) (as compared to the group with lowest SDI values). In the group diagnosed with a disseminated tumour, worst prognosis was in the SDI group of 2–3 months (HR = 2.91, $P = 0.280$), whilst significantly better survival was observed for the group of 3–6 months SDI (HR = 0.19, $P = 0.034$; Figure 1c). Caution always has to be taken in the interpretation of interaction as the subgroups may have few cases, possibly giving rise to unstable results. However, in spite of the low power associated with interaction tests, the overall test result was statistically significant (Table 3, 3.5), which suggests that in tumours of the rectum the risk function may differ among the stages (Figure 2).

DISCUSSION

As in other studies [7–17, 21–25, 35–37], the duration of symptoms was found to bear a weak relationship with tumour stage and with survival. Out of the seven sites studied, only the breast showed tumour extension at diagnosis to be significantly influenced by SDI, and only in lung and rectal cancers did it have some relationship with prognosis; neither relationship was linear, and for rectal cancer, it was complexly related with tumour stage.

A main purpose of diagnosing cancer early is to enhance the effectiveness of treatment. Although therapy for lung cancer is often relatively ineffective, results indicate a somewhat worse survival for patients who reported an SDI of 2 months as compared to patients diagnosed within the first month from symptom onset. A possible explanation may be that clinical lead-time bias increases apparent survival for those who have a shorter SDI. If this were the case, reducing such interval would not

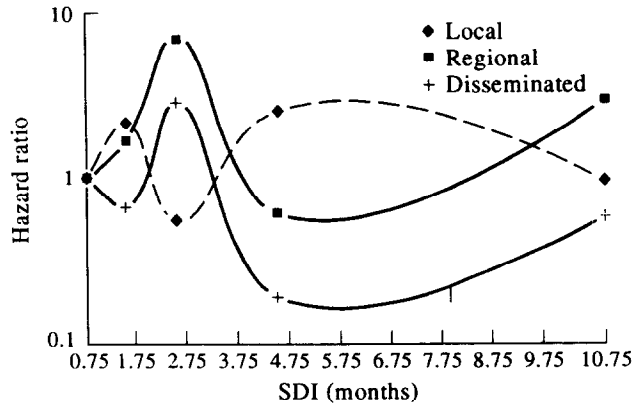

Figure 2. Risk function form in rectal cancer by tumour stage at diagnosis.

actually increase the average chance of survival in a given group of patients. Several studies of lung cancer screening programmes [38–40] showed no benefit, and it was estimated that to detect three quarters of cases by screening (advancing diagnosis by 6 months) would require complete participation in a twice-yearly programme. Even this rate of compliance would reduce mortality only very slightly [41]. In contrast, breast cancer screening programmes have been effective in several contexts [1–6]. However, evidence on the benefit of detecting early symptomatic disease is weaker [6, 10, 42, 43]; for example, Elwood and Moorehead found women with breast cancer with a short SDI to have better survival than those with a long interval, but comparison of the two groups within stage categories showed no clinically or statistically significant differences [18]. It is indeed unfortunate that two fundamentally distinct meanings are sometimes given to the term "early detection": (a) detecting tumours with limited spread through screening an asymptomatic, defined population, and (b) advancing the diagnosis in mostly symptomatic patients who consult a health professional in a clinical setting [5, 6, 44]. The fact that analyses of screening results have produced valuable estimations of the pre-clinical phases and of the natural history of disease [45, 46] raises the question of whether studies on the duration of symptoms could also contribute to these aims, as suggested by some authors [18, 27].

As in any hospital-based study, interpretation of stage-unadjusted results must take into account that some patients self-refer to the hospital emergency department; if such individuals tended both to underestimate the duration of their symptoms—as compared to patients with programmed referral—and to present with more disseminated disease, a beneficial (inverse) effect of SDI upon survival could be missed. Although many studies included patients admitted to hospital through the emergency department, few addressed the influence this may have had on results [12, 47–49]. However, whereas limitations of hospital-based tumour registries are well documented [28, 50], such data bases did yield excellent analyses on diagnostic delay [17–19]. Our registry data come from clinical records, a very common source in this area of inquiry. In theory, the possibility exists for non-random delays in treatment onset to have biased results; the registry is currently updating information on the diagnosis to treatment interval, and results will be reported in due course.

Because the entire sample was already symptomatic at diagnosis, the results must not be taken to suggest that screening programmes are ineffective, nor to cast doubts on the value of speeding up diagnosis in individuals. From a medical point of view, there is a responsibility to diagnose and promptly treat individuals presenting with symptoms. Efforts to increase cancer screening and prevention should focus on helping health professionals indentify and overcome practice barriers [51, 52]. In particular, delays in diagnosis and treatment caused by failures in the organisation of hospitals and the primary care system must be lessened [23]. Cancer prognosis is largely influenced by factors already operating in the subclinical phases of the illness, and by clinical decisions like the type of treatment; such decisions commonly depend less on the duration of symptoms than on biological and clinical variables (e.g. histology, tumour spread). Certainly, results of this study are in line with other evidence disputing the notion that advancing clinical diagnosis will have a significant impact on the mortality experience of a given community. However, great prudence is needed in extrapolating to individuals the results stemming from groups of patients whose help-seeking and diagnostic processes are always heterogeneous [23]. As stated by Polissar and colleagues, "a lack of association between duration [of symptoms] and survival for a population does not necessarily imply that shortening a duration for a single individual will have no effect on survival."[11]

We shall not expand here on the conceptual model of SDI outlined in previous works [23, 27, 53]. Two points are yet in order. Firstly, it has long been recognised [6, 11–13, 17, 18, 22, 24, 37, 44, 53–55]—though perhaps as often forgotten—that a significant proportion of tumours presenting shortly after symptom onset may be highly aggressive and, more generally, that the biological characteristics of the tumour interact with patients promptness in seeking medical attention, and with the effectiveness of the health system in achieving a diagnosis [23, 53]. Slower growing and less aggressive tumours may exist for longer in the presence of the patient's awareness without prompting action than do rapidly growing, aggressive neoplasms [44]. This being so, the latter tumours would reduce the variability in the time at which patients refer themselves to medical attention. Our results provide support for that hypothesis: the observed variance of SDI for breast cancer, a neoplasm of relatively low virulence, was over 20 times that of lung cancer. Even within a given site, tumour and patient behaviours interact. One textbook on cancer reads: "[Lung] epidermoid carcinomas tend to grow more slowly and remain localised longer than the other cell types. They more often grow in larger bronchi, producing symptoms of airway obstruction and thus bringing these patients to the physician earlier than the other forms of lung cancer." [56].

Secondly, measuring duration of symptoms is a trying challenge, mainly because patients may often not recall accurately their onset; once again, this was acknowledged long ago [7–9, 57–64]. It seems unlikely that a differential bias favouring any specific subgroup occurred in our study, but we cannot rule out that non-differential measurement errors might have obscured a relationship between SDI and survival. It is unquestionable that more accurate measures of the SDI components are needed. In particular, it may seem that estimates based on one symptom are too crude, and that it would be more meaningful to do so in terms of the total number of symptoms [11] or of a set of initial symptoms which together indicate symptomatic disease onset [10, 47, 48, 64, 65]. In such frame of thought, detailed patient interviews aided by structured questionnaires and additional data from a variety of sources could accurately estimate the duration of symptomatic illness. However, focusing on measurement issues may not suffice: a substantial reconceptualisation of the meaning of the duration of symptoms appears to be warranted [66–71].

In conclusion, treating the duration of symptoms as a discrete variable with several levels, and assuming *a priori* no specific function form, enabled us to rule out that the risk function was linear and, therefore, to recommend that studies of diagnostic delay do not represent SDI in multivariate models as a linear, continuous term. Failure to consider the non-linear effect of SDI may partly explain previous inconclusive findings. Nonetheless, studies that did treat the duration of symptoms as a discrete variable also found conflicting, mostly negative results as far as the relationship with survival is concerned [11–16, 19–21]. Studies analysing more complex sets of factors, processes and forms of the SDI function are needed. Whether they will uncover a significant impact upon survival remains an open question.

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Prognostic Significance of pS2 Protein Expression in Pulmonary Adenocarcinoma

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In the present study, pS2 protein expression in pulmonary adenocarcinoma was investigated on paraffin-embedded sections obtained from 170 patients. 28 (16%) patients showed varying degrees of pS2 protein expression in the cytoplasm of tumour cells, as detected by immunohistochemical staining with anti-pS2 protein antibody. There was a significant association between pS2 protein expression and larger tumour size, and the acinar or bronchiolo-alveolar subtype. However, no significant correlations between pS2 protein status and the other clinicopathological factors, i.e. T-factor, N-factor, stage and histological differentiation, were shown. In contrast to breast cancer, patients with pS2-positive pulmonary adenocarcinomas had a significantly worse prognosis than those with pS2-negative pulmonary adenocarcinomas; this was true for stage I patients, as well as for all patients. Multivariate analysis showed that pS2 protein expression was a discriminating variable in overall survival. These findings suggest that pS2 protein status is a possible prognostic indicator in pulmonary adenocarcinoma.

Key words: pulmonary adenocarcinoma, pS2 protein, immunohistochemistry, prognosis
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INTRODUCTION

THE pS2 GENE was originally isolated by Chambon and co-workers [1] as a gene whose transcript, including mRNA of about 600 nucleotides [2], has been shown to be directly regulated by oestrogen in the human breast cancer cell line, MCF-7. The 5′ flanking sequence of the gene includes an oestrogen-inducible promoter [3]. The pS2 gene contains a single open reading frame encoding an 84 amino acid long secretory protein [2], whose function is still unknown. Recent studies, using a cDNA probe for pS2 mRNA and specific antibodies against the pS2 protein, have shown that pS2 is predominantly expressed in oestrogen receptor-positive breast tumours [4–10]. These findings in breast