



## 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.

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## 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.<sup>1–4</sup> 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.<sup>5–8</sup> Many studies illustrating this paradox take the results to show that there is no association between delay and mortality and find the results reassuring.<sup>9–11</sup> 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.<sup>12,13</sup> 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).<sup>14–17</sup> 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.<sup>18</sup> 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.<sup>19</sup>

### 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.<sup>18</sup> 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

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