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Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets

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Abstract

Objective: To test the theory of a U-shaped association between time from the first presentation of symptoms in primary care to the diagnosis (the diagnostic interval) and mortality after diagnosis of colorectal cancer (CRC).

Study Design and Setting: Three population-based studies in Denmark and the United Kingdom using data from general practitioner's questionnaires, interviewer-administered patient questionnaires, and primary care records, respectively.

Results: Despite variations in the potential selection and information bias when using different methods of identifying the date of first presentation, the association between the length of the diagnostic interval and 5-year mortality rate after the diagnosis of CRC was the same for all three types of data: displaying a U-shaped association with decreasing and subsequently increasing mortality with longer diagnostic intervals.

Conclusion: Unknown confounding and in particular confounding by indication is likely to explain the counterintuitive findings of higher mortality among patients with very short diagnostic intervals, but cannot explain the increasing mortality with longer diagnostic intervals. The results support the theory that longer diagnostic intervals cause higher mortality in patients with CRC.

Keywords: Delayed diagnosis; Waiting lists; Mortality; Colorectal cancer; Primary health care; Bias

1. Introduction

Survival rates for patients with colorectal cancer (CRC) in Denmark and the United Kingdom have lagged behind comparable European countries for decades [1]. Late diagnosis is believed to be an important contributor to this poor outcome [2,3]. Access to diagnostic and treatment facilities is universal and free in both countries, so it has therefore been hypothesized that the organization of medical care may account for some of the differences in outcomes [4].

Numerous studies of time to cancer diagnosis have reported counterintuitive results showing that CRC patients with short diagnostic intervals suffer higher mortality than the rest [5,6]. This so-called ''waiting time paradox'' is likely to stem from rapid investigation of patients who present with alarm symptoms or who are admitted to hospital as an emergency [7]. Most studies have assumed a monotonic (e.g., dichotomous or linear) association between the length of the diagnostic interval and mortality and may therefore have failed to observe that this paradox may be accompanied by an increased mortality with longer diagnostic intervals [8].

In 2011, the authors introduced spline regression to allow for a flexible association between the length of the diagnostic interval (defined as the time from first presentation of symptoms in primary care to diagnosis) and 3-year mortality in a cohort of Danish CRC patients. The authors found that the mortality rate fell with diagnostic intervals up to approximately 5 weeks and then increased significantly (a U-shaped association) [9]. The study relied on general practitioners (GPs) retrospectively ascribing a date to relevant milestones on the diagnostic pathway of each patient. Given the GPs' extensive knowledge of their patients, it was possible that the data collection was flawed by differential information bias.

The present article aims to ascertain whether the U-shaped association between the length of the diagnostic interval and mortality after diagnosis of CRC can be demonstrated for studies using other methods to collect information on dates.

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What is new?

- The major factor explaining the ''waiting time paradox'' (i.e., counterintuitive results showing that cancer patients with short diagnostic intervals suffer higher mortality than the rest) is confounding by indication owing to differentiated clinical triage.
- It takes place independently of the data source and thus represents a fundamental analytical problem for observational studies of delay and mortality in symptomatic cancer patients.
- By addressing confounding by indication, the article provides evidence for the theory that longer diagnostic intervals cause higher mortality in patients with colorectal cancer (CRC).
- The article thus supports efforts aimed at improving prognosis of CRC by shortening the clinical pathway.

2. Materials and methods

The authors analyzed data from three previously described population-based studies in Denmark and the United Kingdom. The Danish GP-based study used data from questionnaires sent to each patient's GP [9,10]. The Danish patient-based study used data from patient questionnaires administered by nurses at the hospital before surgery [11,12]. Finally, the English record-based study relied on data from a systematic coding of primary care records [13,14]. Details regarding the populations, designs, missing data, and follow-up are summarized in Table 1.

2.1. Setting

CRC is the most common cancer in Denmark and the third most common in the United Kingdom. In both countries, incidence rates have risen over the past three decades [15]. In 2000, the age-standardized (European) incidence rates were 59.9 and 58.0 for men, and 43.9 and 34.9 for women per 100,000 citizens in Denmark and the United Kingdom, respectively [16–18]. Approximately 90% of the CRC patients present to primary care with symptoms [11,19]. For patients diagnosed during 1995–1999, the age-standardized 5-year relative survival was 49.3% in Denmark and 50.5% in the United Kingdom [20].

2.2. Study populations

From each study, the authors included all newly diagnosed CRC patients older than 39 years. Subsequently, the study populations were restricted to the 88–91% of patients who had attended general practice before the cancer diagnosis. GP involvement was defined slightly differently in the three studies, which meant that the three studies deployed slightly different restriction criteria (Table 1).

2.3. Data collection

The authors were able to calculate the diagnostic interval in all included patients. However, owing to the different designs, the mechanisms for defining and identifying the relevant dates were different (Table 1). In the GP-based study, the GPs received questionnaires 2–4 weeks after the diagnosis and were asked to identify dates by using electronic patient files and hospital discharge letters. In the patient-based study, patients were asked before surgery to recall the date of first report of a CRC symptom to a doctor and the date of the decisive examination, which was then defined as the date of diagnosis. In the record-based study, four research assistants blinded to case or control status searched the medical records of 349 CRC patients and 1,744 controls for a range of symptoms and clinical features—some known to be independently associated with CRC. In this study, the date of diagnosis was defined as the date of positive histology.

2.4. Data on covariates

All studies included information on tumor site, gender, age at first presentation of symptoms, and tumor staging. Only the GP-based study used the TNM Staging System to classify CRC. These data were regrouped using a Dukes' staging classification: A (T1–2/N0/M0); B (T3–4/N0/M0); C (T1–4/N1–2/M0); and D (T1–4/N0–2/M1). The studies included additional data on emergency admissions and presenting symptoms (rectal bleeding, change in bowel habit, weight loss, and symptoms of pain). However, these variables varied too much in definition and/or coding to be included as covariates in the analyses.

2.5. Defining time and mortality

The study outcome was 5-year mortality after diagnosis. In the GP-based study, patients were followed from diagnosis to death or censoring. In the patient-based study, inclusion into the study depended on survival; therefore, patients were followed from interview to death or censoring. In the record-based study, patients were followed from diagnosis to death or censoring. Although deaths were routinely notified to the registry, the survivors were censored at the date of last hospital attendance to ensure all those apparently alive were in fact so.

2.6. Statistical analyses

Each study was analyzed separately and combined. The distributions of the diagnostic intervals differed between the three studies. The authors therefore combined the data by either allocating patients according to their study-specific diagnostic interval quartiles or by rescaling the diagnostic interval using the corresponding study-specific cumulative frequencies (see Fig. 1A).