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Mortality of patients examined at a diagnostic centre: A matched cohort study

Esben Næser[a,b,c,*], Henrik Møller[a,b,d], Ulrich Fredberg[c], Peter Vedsted[a,b,c]

[a] Research Unit for General Practice, Bartholins Allé 2, 8000 Aarhus C, Denmark
[b] Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
[c] Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Falkevej 1-3, 8600 Silkeborg, Denmark
[d] Cancer Epidemiology and Population Health, King's College London, Great Maze Pond, London SE1 9RT, United Kingdom

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ABSTRACT

Background: 'Diagnostic Centres' has been established to provide a diagnostic pathway for patients with non-specific, serious symptoms that could be cancer. As little is known about the prognosis, we aimed to 1) analyse mortality of patients examined at the diagnostic centre, stratified on diagnostic outcome (cancer, serious-non-malignant disease, or other/no diagnosis), and 2) compare mortality for cancer patients examined at the diagnostic centre with cancer patients diagnosed through other routes.

Method: Retrospective cohort study including 938 patients examined at the Diagnostic Centre, Silkeborg Regional Hospital, Denmark, during 2012–2014. Cancer patients examined at the diagnostic centre were matched (1:10) to a reference group of cancer patients diagnosed through other routes. Information on diagnosis, death, comorbidity and socioeconomic factors was obtained by linkage to national Danish registers. Mortality was assessed by Kaplan Meier mortality survival analysis and hazard ratios of death were estimated using Cox proportional regression analysis while adjusting for confounders.

Results: The 1-year cumulative mortality was 28% in cancer patients examined at the diagnostic centre. The hazard ratio of death was seven times increased in cancer patients compared to patients with other/no diagnosis. The hazard ratio of death was 0.91 (95% CI: 0.68; 1.22) in cancer patients examined at the diagnostic centre compared to cancer patients diagnosed through other routes.

Discussion: The mortality among cancer patients examined at the diagnostic centre was comparable to cancer patients diagnosed through other routes. The results indicate that cancer patients with non-specific serious symptoms do not have a worse prognosis than other cancer patients.

1. Introduction

Danish cancer patients have poorer survival compared to cancer patients in other Western-European Countries [1–3]. One possible explanation may be that Danish cancer patients are treated in later stages [4–6]. This may be due to delays in diagnostics [7]. Longer diagnostic intervals can lead to stage progression and poorer survival [8].

Internationally, several initiatives have been launched to improve cancer survival. In 2009, Silkeborg Regional Hospital developed an urgent referral pathway for non-specific serious symptoms, which was implemented throughout Denmark in 2011–2012 [9,10]. The implementation was supported by primary care studies suggesting that patients not presenting with alarm symptoms had longer diagnostic interval compared to patients presenting with alarm symptoms [11]. The urgent referral pathway for non-specific serious symptoms was part of the Danish three-legged cancer strategy and supplemented the urgent referral pathways for specific symptoms and signs [12]. The aim was to expedite cancer diagnosis by providing referral possibilities from general practice for patients with non-specific symptoms or signs that could be caused by serious disease. Guidance on which symptoms and signs that may cause the GP to suspect serious disease and refer to the pathway are described in the national guidelines [9].

The urgent pathway for non-specific serious symptoms was designed as a two-step approach [13,14]. First, the GP initiates the diagnostic workup based on the imaging results and a standardised panel of blood tests ("triage function"). Second, if relevant, the patient is

Abbreviations: CCI, Charlson Comorbidity index; DCR, Danish Cancer Registry; GP, general practitioner; IQI, Interquartile interval; NPR, National Patient Registry; Other/no-diagnosis, other or no diagnosis

* Corresponding author at: Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Falkevej 1-3, 8600 Silkeborg, Denmark.
E-mail address: esben.naeser@rm.dk (E. Næser).

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referred to the diagnostic centre, where a multidisciplinary team takes over the diagnostic responsibility for the patient [15]. The proportion of patients referred to a diagnostic centre after the triage function varies between 18% and 59% [13].

However, only little knowledge exists about the prognosis for patients examined at the diagnostic centre. One Danish study found a median survival of only 72 days among cancer patients suggesting that these patients may be cancer patients with the worst prognosis [16]. However, the study was small and did not include a comparison group of cancer patients diagnosed through other routes.

Thus, we need more precise knowledge about the prognosis when patients are referred to the diagnostic centre. The aim of this study was to 1) analyse mortality for patients examined at the diagnostic centre, stratified on diagnostic outcome and 2) compare mortality for cancer patients examined at the diagnostic centre with a matched reference group of cancer patients diagnosed through other routes.

2. Material and methods

2.1. Setting and organization of diagnostic pathway

All Danish citizens have free access to diagnostic services and treatment through the publicly funded health-care system. More than 98% of Danish citizens are registered with a GP, who they have to consult for medical advice. The GP act as gatekeeper to the more specialised part of the health care system, carrying out initial diagnostic investigations and referrals to secondary care as needed [17].

Each of the five Danish regions has at least one diagnostic centre and 21 diagnostic centres have now been established in Denmark. The Diagnostic Centre at Silkeborg Regional Hospital is situated in the Central Denmark Region, with a catchment area of approximately 177,000 residents aged 18 years or older.

The triage function at Silkeborg Regional Hospital consists of imaging and a standardized blood test panel [13,14]. The imaging includes thoracic X-ray and ultrasound of the upper and lower abdomen. A CT scan of chest, abdomen and pelvis is performed if considered relevant by the radiologist. The results of the investigations are returned to the GP within three working days, who GP decides on further diagnostic steps. If the triage function yields no obvious explanation for the patient's symptoms, the GP is advised to refer the patient to the diagnostic centre. After such referral, the diagnostic centre takes over the responsibility for the diagnostic workup of the patient [15]. At the diagnostic centre, patients undergo individual diagnostic programmes, based on the medical history and the results of investigations; these are developed in a close cooperation between relevant experts, and all medical specialties are represented in the Diagnostic Centre at Silkeborg Regional Hospital.

2.2. Study population and design

From a clinical database at Silkeborg Regional Hospital, we included 938 consecutive patients aged 18 years or more referred by their GP to the Diagnostic Centre at Silkeborg Regional Hospital, between 1 July 2012 and 30 September 2014. Using the unique Civil Registration Number, all patients were followed up for three months for the diagnosis of cancer, non-malignant disease, or other or no diagnosis (other/no diagnosis) in the Danish Cancer Registry (DCR) and the National Patient Registry (NPR), respectively [18–20]. In the cohort, 118 patients (12.6%) were diagnosed with cancer, 209 patients (22.3%) with a serious non-malignant disease and 611 patients (65.1%) with other/no diagnosis. The disease spectrum has been described in details in a previous study [15]. The most common malignant disorders were colorectal cancer (17.8%), lymphoma (14.4%), kidney cancer (10.2%) and lung cancer (9.3%). Serious non-malignant diseases were most frequently related to the medical specialties of rheumatology (18.2%), gastroenterology (14.8%), endocrinology (13.4%) and infectious diseases (9.1%). A list of the included serious non-malignant diseases is shown in Appendix A in Supplementary material.

Each cancer patient examined at the diagnostic centre was matched with ten reference cancer patients based on cancer type (ICD-10 code), sex, date of birth (+/− 5 years), and year of diagnosis (+/− 1 year). Individuals could be selected as reference in several matching strata. Reference patients residing in the Central Denmark Region were affiliated with a specific GP at the day of diagnosis and had not been referred for any diagnostic centres within three months of the date of diagnosis. It was not possible to obtain ten reference patients for each exposed cancer patients, as some cancer types were rare. This reduced the number of reference patients by 77 patients.

When we compared patients examined at the diagnostic centre based on diagnostic outcome, the index date was assigned as date of first visit at the diagnostic centre. When we compared cancer patients examined at the diagnostic centre with the reference group of cancer patients, the index date was assigned as the date of registered cancer diagnosis in the DCR.

Dates of death and migration were obtained from the Danish Civil Registration System [18]. All patients were followed until death, migration or until the end of follow up (31 December 2015), whichever occurred first.

2.3. Covariates

Socioeconomic information in the index year was collected from Statistics Denmark. We grouped level of education into "low" (≤10 years of education), "medium" (11–15 years of education) and "high" (> 15 years of education) in accordance with the International Standard Classification of Education (ISCED) [21]. Marital status was categorised into "married or cohabiting" or "living alone". Disposable income was defined as the Organisation for Economic Cooperation and Development (OECD) adjusted household income [22]. We grouped disposable income in three groups: the lowest 25%, the middle 50% and highest 25%. Labour market affiliation was categorised as "working", "retired or receiving pension" or "out of workforce."

The Charlson Comorbidity Index (CCI) was computed for each patient using complete hospital history as recorded in the NPR during the preceding 10 years before the index date [23,24]. When comparing cancer patients examined at the diagnostic centre with the reference group of cancer patients, the CCI was computed using hospital history up to three months before the date of registered cancer diagnosis in the DCR to eliminate the risk of any influence of registered diagnosis related to the diagnostic work up for cancer. We grouped level on patients comorbidity into "None" (index score 0), "Moderate" (index score 1 and 2), "High" (index score 3 or more).

Tumour stage distribution was divided into three categories: local (no positive lymph nodes or metastasis), regional (positive lymph nodes) or distant (metastatic cancer) combined, or missing on the basis of the TNM classification obtained from the DCR.

2.4. Statistical analysis

The outcome in the data analysis was all-cause mortality. The cumulative mortality was calculated as the probability that a patient would die in the period from first visit to the end of each yearly interval, separately for each diagnostic outcome (cancer, serious non-malignant disease, or other/no diagnosis). The mortality rate was calculated as the number of deaths that occurred per person-year at risk in each yearly interval. We used a Cox proportional hazards model to produce hazard ratios (HRs) of all-cause mortality in the three patient groups. The model was adjusted for sex, age (continuous), CCI, educational level and marital status.

Chi-squared and Wilcoxon rank sum tests were used to test differences between cancer patients examined at the diagnostic cancer and the reference group of cancer patients. We used the log rank test to