

# Prevalence of cancer in Danish patients referred to a fast-track diagnostic pathway is substantial

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## ABSTRACT

**INTRODUCTION:** Danish patients diagnosed with cancer who present with unspecific signs and symptoms are diagnosed with unfavorable delay, which has led to the establishment of a national fast-track (cancer) pathway. The aim of this study was to estimate the prevalence of cancer and other diagnoses in patients referred to this programme at Aarhus University Hospital from general practitioners. Furthermore, we aimed to characterise the patient cohort, assess survival and estimate the predictive values of symptoms, signs and biochemical abnormalities.

**METHODS:** From 1 March 2011 to 31 December 2013, data of interest were consecutively collected from the electronic patient record by two medical doctors.

**RESULTS:** Overall, 18% (58/323) had cancer, but the prevalence decreased from 22% in 2011 to 16% in 2013. Haematological cancers and cancers originating from the digestive system were the predominant cancer diagnoses. Patients diagnosed with cancer unfortunately had a high mortality suggesting that we diagnose cancer in the late, non-curable stages. Patients referred to the fast-track pathway had a median of four symptoms, most commonly weight loss and fatigue. In one fourth of the patients, a final diagnosis was not reached at discharge. For the rest ( $n = 185$ ), gastrointestinal conditions, infectious and rheumatological diseases were most common. The predictive value of the presenting symptoms was poor. Age and biochemical markers considered as unspecific markers of cancer were better predictors. Anaemia was seen in 71% versus 34% of patients with/without diagnosed cancer, respectively.

**CONCLUSIONS:** Unspecific signs and symptoms that may be indicative of cancer represent a clinical challenge. A fast-track (cancer) pathway is a new option for patients not entitled to enter an organ-specific programme.

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In Denmark, fast-track cancer patient pathways (CPPs) were introduced by the Danish Health and Medicine Authority in 2007. The background for the implementation was documentation of an increased mortality in newly diagnosed cancer patients in comparison with comparable countries [1-4].

The national CPPs guidelines serve to standardise the cancer-diagnostic process with the overall aim of im-

proving the prognosis in Danish cancer patients. In 2009, a CPP for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP) was introduced because it was apparent that patients with unspecific symptoms were diagnosed with an unfavorable delay that may adversely impact treatment opportunities and survival.

On a national basis, it is estimated that approximately 20,000 annual patients will be referred to an NSSC-CPP, and preliminary data show that the prevalence of cancer in this cohort is 10-20% [5].

According to a guideline in the Central Denmark Region [6], the general practitioner (GP) ensures collection of a pre-defined minimum panel of blood and urine tests in patients with NSSC-CPP. Likewise, the GP refers and assesses the results of a computed tomography (CT) of the thorax, abdomen and pelvis prior to further evaluation and diagnostics at the hospital.

In March 2011, Aarhus University Hospital established a Diagnostic Outpatient Clinic (DOC) for NSSC-CPP.

The main purpose of our study was to estimate the prevalence of cancer and the distribution of other diagnoses in patients referred from the GP to the DOC due to NSSC. Furthermore, we wanted to characterise the patient cohort, assess survival and estimate the predictive value of symptoms, signs and biochemical abnormalities.

## METHODS

### Ethical aspects

The study was approved by the Danish Health and Medicine Authority (R.no: 3-3013-492/1/) and the Danish Data Protection Agency (R.no: 1-16-02-516-13), but did not need approval from the Regional Committee on Health Research Ethics.

### Patients

All ( $n = 323$ ) patients referred from GP to NSSC-CPP in the period from 1 March 2011 to 31 December 2013 were included. Before 23 August 2012, patients were identified manually and by the referring International Classification of Diseases code DZ031 (observation due to suspected cancer) and after 23 August 2012 by the specific cancer procedure code AFA01A.

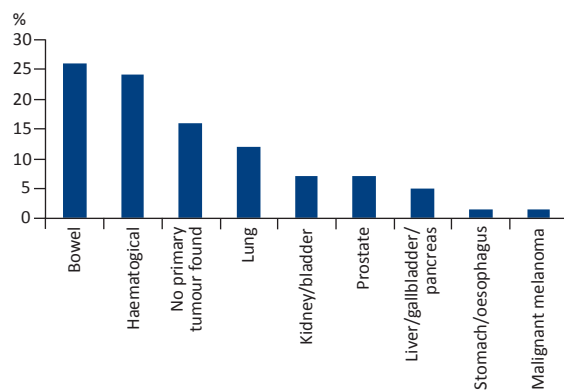
## ORIGINAL ARTICLE

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**FIGURE 1**

Distribution of type of cancer in the patients (n = 58) diagnosed with cancer in cancer patient pathways for patients with serious non-specific symptoms and signs of cancer.



### Procedure

All registered data were collected from the record by two doctors (LSB and BBJ). Prior to data collection, several meetings were held with the responsible senior doctors at DOC (SG and STK) to ensure reliability. The data of interest were consecutively collected from the referral and the electronic patient record, and laboratory results were identified in the record.

We evaluated the levels of plasma-ionised calcium ( $\text{Ca}^{2+}$ ), sedimentation rate (SR), haemoglobin (Hb) and alkaline phosphatase (ALP), as these are generally considered unspecific markers of cancer. If one or more of these markers were absent, the patient was excluded from the statistical analyses regarding biochemistry.

In the Diagnostic Unit, interdisciplinary teamwork is very important. The first day at the clinic, a doctor, a nurse, the patient and typically one or more relative(s) go through the patient's medical history. Subsequently, a physical examination is performed and in accordance with the guidelines published at [www.sundhed.dk](http://www.sundhed.dk) the ordered biochemistry and the computed tomography of the thorax, abdomen and pelvis are evaluated. Thereafter, an individual plan is prepared for the patient. (The photo was reproduced with acceptance from all four persons).



At the first visit in DOC, the clinician collects information on the symptoms from the patient by interview, and a focused physical examination is performed. This information was extracted from the patient file. The symptoms evaluated in the present study were unintended weight loss (> 2 kg), fatigue, decreased self-assessed performance, fever, pain, upper gastrointestinal symptoms, change in defecation, night sweats, and symptoms from the musculoskeletal system, central nervous system, cardiopulmonary system and urogenital system. The number of symptoms per patient was registered.

If the patient referred to DOC was diagnosed with cancer, no further diagnoses were given. In the group of patients without cancer, the outcome diagnosis(es) at end of the study was registered.

*Trial registration:* not relevant.

### RESULTS

#### Patients

A total of 327 patients were referred to NSSC-CPP at DOC. Four patients never showed up. This left 323 patients for the present study, distributed with 37 in 2011, 119 in 2012 and 167 in 2013. A total of 165 women and 158 men were included. The median time from first visit to diagnosis was ten days (range: 0-127 days). The median age in the entire group was 66 years (range: 18-91 years).

Only 62% of the patients without and 55% of the patients with diagnosed cancer were referred to a CT of the thorax, abdomen and pelvis by the GP. Of those referred, only a minority had the test performed prior to the first visit in the DOC.

In the group of patients diagnosed with cancer, subgroup analysis showed that only 21% of referred patients (n = 12) had the test performed prior to their first visit.

#### *Patients referred to cancer patient pathways for patients with serious non-specific symptoms and signs of cancer subsequently diagnosed with cancer (n = 58)*

The median age in the cancer cohort was 72 years (range: 24-91 years); 43% were women. A history of prior cancer from which they were considered cured was present in 21%.

In half of these patients, a relapse of previous cancer was diagnosed (two renal cell carcinomas, one malignant melanoma, one prostate cancer, one colon cancer and one lymphoma). The median time from first visit to a cancer diagnosis was assigned was 11 days (range: 0-37 days); 14 days for men and nine days for women. During the diagnostic process, 57% underwent colonoscopy and/or gastroscopy (67% of the women and 50% of the men).

### Prevalence and types of cancer

Two patients died before a final cancer diagnosis was made. One had a prostate-specific antigen > 900 microgram/l, whereas the other had multiple osteolytic bone lesions; they were interpreted as a prostate cancer and as “no primary tumour found”, respectively.

Overall, the prevalence of cancer in the cohort was 18% (58/323), declining from 22% in 2011 to 20% in 2012 and 16% in 2013. **Figure 1** illustrates the types of cancer diagnosed in the DOC in the study period. No breast cancers were found. In 16% (67% were men), no primary tumour was found. Of those, four declined further diagnostic procedures, one died during the diagnostic process, two were referred to palliative chemotherapy, and one patient had a too low performance state to allow further treatment or diagnostic procedures.

None of the patients with “no primary tumour found” had a CT available at the first visit. Among the 21% (n = 12) with an available description, 33% had gastrointestinal cancer, 25% haematologic cancer, 25% prostate cancer and 17% lung cancer.

### Symptoms and biochemistry

The median number of symptoms was four for women and five for men. At the first visit, 17% had pathological lymph node swelling. All patients were screened with Hb and ALP, 97% with Ca<sup>2+</sup> and 88% with SR. The number of patients with at least one abnormal blood test was 91%. For the four blood tests just mentioned, the frequency of abnormal blood tests was highest among men, this sex difference being most pronounced for ALP (60 versus 28%).

#### Patients without diagnosed cancer (n = 265)

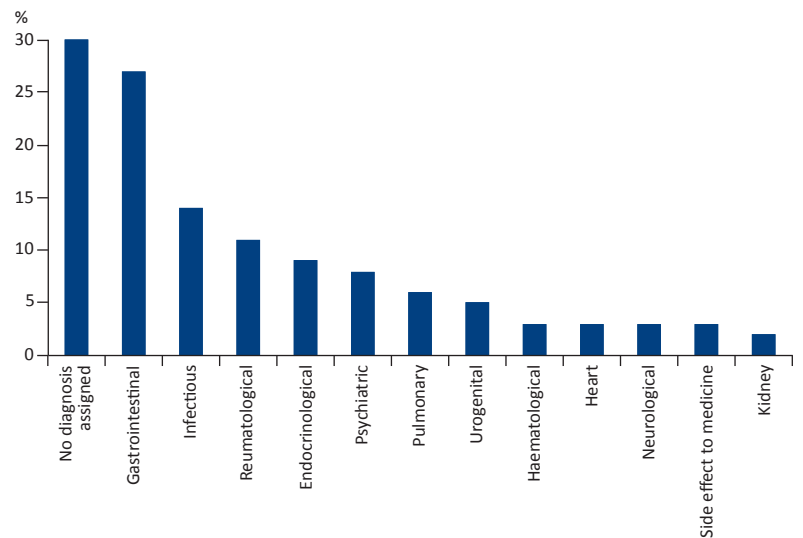
The median age of the subjects in whom we did not find cancer was 65 years (range: 18-88 years). Of these, 53% were women. The median time from the first visit to a diagnosis was reached was ten days (range: 0-127 days). At the first visit, 5% had pathological lymph node swelling. The median number of symptoms was four (range: 0-9). During the diagnostic process, 55% of the patients underwent colonoscopy and/or gastroscopy. 9% had a prior history of cancer from which they were cured.

#### Outcome diagnoses in patients without diagnosed cancer (n = 185)

In 80 patients, a final diagnosis explaining signs and symptoms was not reached at discharge from DOC. Among the rest, 251 diagnoses were made. Of those patients, an average of 1.4 diagnoses was assigned. **Figure 2** illustrates the distribution of diagnoses in the group of patients in whom we did not diagnose cancer. Patients found to have kidney disease had the shortest interval between referral and assignation of a diagnosis, whereas

**FIGURE 2**

Distribution of diagnoses in the group without diagnosed cancer.



a) Total > 100% because patients who were assigned with a diagnosis had 1.4 diagnoses on average.

patients with benign haematological disease had the longest interval (median four versus 13 days).

#### Biochemistry

For 236 patients (90%), Ca<sup>2+</sup>, SR, Hb and ALP were all available. In this group, 131 (56%) had at least one of four abnormal blood tests. There was no clear pattern regarding the distribution of the biochemical parameters among the different diagnoses.

#### “No diagnosis found, n = 80”

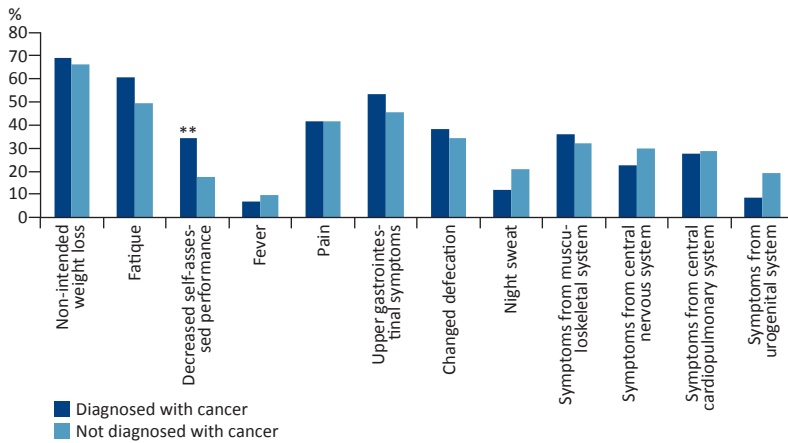
The number of symptoms, duration of the diagnostic process, mortality and the proportion undergoing colonoscopy and/or gastroscopy were similar in the groups with and without a non-cancer outcome diagnosis. The only distinct difference was less biochemical abnormalities in the latter group. However, 45% had at least one of four abnormal blood tests, anaemia (6%), increased SR (25%), elevated ALP (16%) and hypercalcaemia (3%).

#### Comparison of symptoms, biochemistry and mortality in patients with and without diagnosed cancer

**Figure 3** compares the prevalence of symptoms in the group of cancer patients (n = 58) and patients without diagnosed cancer (n = 265). In both groups, the median number of symptoms was four. Non-intended weight loss, fatigue and upper gastrointestinal symptoms were dominating in both groups, but seemingly higher in patients who were subsequently diagnosed with cancer. A decreased self-assessed performance state was a stronger predictive, but a less frequent, sign.

**FIGURE 3**

Comparison of symptoms in the group of patients referred to cancer patient pathways for patients with serious non-specific symptoms and signs of cancer with and without diagnosed cancer.

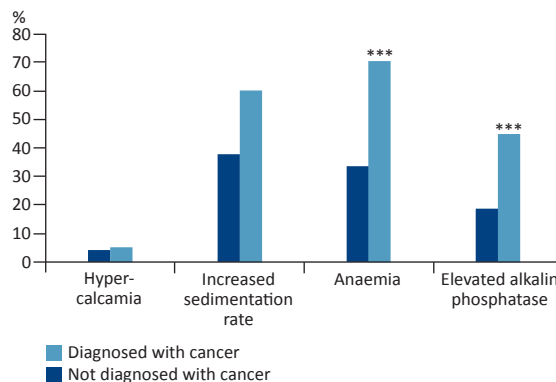


\*\* $p < 0.01$ .

**FIGURE 4**

Prevalence of selected biochemical abnormalities that are generally considered unspecific markers of cancer in the group with and without cancer.

\*\*\* $p < 0.001$ .



**Figure 4** compares selected cancer biomarkers in the cohort when separated into those with and without a cancer diagnosis. As illustrated, biochemical parameters were more predictive of a subsequent cancer diagnosis than the presenting symptoms in the cohort. Anaemia had a particular high predictive value (71% versus 34%), but none of the described parameters were specific for a subsequent diagnosis of cancer.

The mortality in the patients who were diagnosed with cancer was very high; thus, more than half of these patients were dead one year after their diagnosis (median 72 days). By comparison, 97% of patients without diagnosed cancer were alive in February 2014.

## DISCUSSION

We found an overall prevalence of cancer of 18% in patients referred to the DOC. This prevalence decreased

over the study period, from 22% in 2011 to 16% in 2013. Our data indicate that the prevalence of cancer in the DOC will probably decrease more over time when the GPs become more familiar with the NCCS-CPP. A continuing decrease in the prevalence of cancer in patients with unspecific signs and symptoms referred to NCCS-CPP to a level similar to the organ-specific CPPs (5-10%) has been considered an indicator of success [7].

In our setting, the most predominant cancer diagnoses included cancers originating from the digestive and haematological systems. Thus, the relative proportion of these cancers were much higher than the relative proportion in the general population [8]. Haematological cancers and cancers from the digestive system are rarely detectable on the primary CT; hence, several, successive examinations are required for diagnosing. Furthermore, those types of cancer present fairly specific symptoms, and are associated with more consultations [9].

More than half of all patients referred to NCCS-CPP underwent colonoscopy and/or gastroscopy, but no differences in the group with and without diagnosed cancer was found (57% versus 55%).

As expected, patients diagnosed with cancer were older than patients without diagnosed cancer (median 72 years versus 65 years), and more patients had previously been treated for cancer (21% versus 9%). The prevalence was highest in men (57%), which is consistent with data from the literature [10].

Patients referred to NCCS-CPP constitute a heterogeneous group characterised by many unspecific symptoms. In organ-specific CPPs, patients typically present with 1-2 symptoms [11] compared with four symptoms in the present study. In our study, the predominant symptoms were weight loss and fatigue, but these symptoms were not predictive of a later cancer diagnosis.

Biochemical abnormalities (elevated SR, anaemia and increased ALP) were better predictors of cancer than the above-mentioned symptoms, although they were not specific. Thus, in more than half of the patients without a subsequent diagnosis of cancer, at least one of the four blood tests was outside the normal range. Surprisingly, we found no differences between the two groups in terms of the proportion of patients with hypercalcaemia. However, the number of patients with this finding was small, which makes it difficult to draw a definite conclusion.

The most prevalent outcome diagnoses in the group of patients not diagnosed with cancer (82%) were gastrointestinal, infectious and rheumatological diseases. However, in a fourth of the patients, the signs and symptoms disappeared and/or we did not reach a definite diagnosis.

Too many patients did not have an available (and interpreted) CT at the first visit, but this proportion will

hopefully decrease when the GPs become more familiar with the algorithm.

Our study highlights the role of the GP as a “gate-keeper”, who decides which patients are eligible for further diagnostic evaluation. A total of 85% of initial cancer diagnostics takes place in general practice [11], and it is estimated that GPs suspect cancer in 6-8% of all consultations [5, 12-14]. Approximately 90% of newly diagnosed cancers are detected owing to symptoms, [15, 16], and only half of these initial symptoms are considered alarm symptoms [11, 14].

It seems impossible to make a clear-cut guideline on the referral of patients to NCCS-CPP. The biochemical parameters (especially anaemia) as well as age are somewhat useful predictors. There is a need for an active strategy that is applicable to the group of patients with unspecific signs and symptoms indicative of cancer. Even though it is remarkably difficult to confirm [17, 18], it is credible that an early diagnosis will lead to an improved outcome. Unfortunately, the high mortality in our cohort suggests that we diagnose cancer in the late, non-curable stages in the NCCS-CPP. Because patients referred to the unit present general symptoms typically seen in late stages of cancer, this might be expected, which complicates comparison with other CPPs. Despite this, referring more patients based on less stringent criteria may be a strategy for improving the outcome for these patients.

### Strengths and weaknesses

A major strength of the study is the fact that there was no drop-out. Furthermore, the outcome diagnoses were based on a medical assessment ensuring reliability. A number of advantages and disadvantages are associated with obtaining information from patient files. Importantly, there is no recall bias. On the other hand, some of the obtained information may be difficult to interpret since it was not obtained specifically for the purpose of this study.

### CONCLUSIONS

Patients referred for NCCS-CPP represent a heterogeneous group with several unspecific symptoms. Overall, 18% has cancer, and the mortality is high. A patient with unspecific signs and symptoms that may be indicative of cancer represents a diagnostic challenge. The NCCS-CPP is a new option for the GP when the patient is not entitled to enroll in an organ-specific CPP, and hopefully the prognosis will improve over time.

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In the article “Prevalence of cancer in Danish patients referred to fast track diagnostic pathway is substantial” by Bislev et al. Dan Med J 2015;62:(9):A5138 Figure 4 has been replaced on 1st December 2015.

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