IMPLEMENTATION OF CANCER PATIENT PATHWAYS AND THE ASSOCIATION WITH MORE TIMELY DIAGNOSIS AND EARLIER DETECTION OF CANCER AMONG INCIDENT CANCER PATIENTS IN PRIMARY CARE

PhD dissertation

Henry Jensen

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PhD-student:
Henry Jensen, MHSc., The Research Unit for General Practice, Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark

Supervisors:
Professor Peter Vedsted, PhD, MD, The Research Unit for General Practice, Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark
Professor Frede Olesen, DrMedSci, MD, The Research Unit for General Practice, Department of Public Health, Aarhus University, Denmark
Associate Professor Marie Louise Tørring, PhD, MA, Section for Anthropology, Department of Culture and Society, Aarhus University, Denmark & The Research Unit for General Practice, Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark

External clinical advisor
Professor Jens Overgaard, PhD, MD, Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus C, Denmark

Assessment committee:
Head of Department Søren K. Kjærgaard, PhD, Lic. Med., Department of Public Health, Aarhus University, Denmark (Chairman)
Dr Georgios Lyratzopoulos, MD, FFPH, FRCP, MPH, DTM&H, Clinical Reader in Cancer Epidemiology, Health Behaviour Research Centre, Dept. of Epidemiology and Public Health, University College London, London, UK
Professor Mef Nilbert, MD, PhD, RCC South, Region Skåne & Institute of Clinical Sciences, Division of Oncology and Pathology, Lund University, Sweden

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This dissertation is based on data from three previous studies of time to diagnosis for incident cancer patients in Denmark. Two of these studies were undertaken as PhD studies: ‘Delay in the diagnosis of cancer’ was undertaken in 2004/05 and defended by Rikke Pilegaard Hansen in 2008 (1), while ‘Diagnosing cancer in a time of change – from delay to fast track’ was undertaken in 2007/08 and defended by Mette Bach Larsen in 2012 (2). The third study was a cross-sectional study on quality deviations and time to diagnosis which was carried out by the writer of this thesis in 2010 (3).
OUTLINE OF THE THESIS

Chapter 1 offers an introduction to the research area, including the concept of standardised patient pathways in Denmark (also known as fast-track diagnosis and treatment of cancer) and presents the hypotheses that form the basis of the present dissertation. The aim of the dissertation is presented at the end of this chapter.

Chapter 2 offers a brief description of setting, materials and methods used in the four studies of the thesis.

Chapter 3 offers a summary of the main results of the four studies.

Chapter 4 discusses the methods applied and the internal validity of the studies in terms of potential biases.

Chapter 5 offers a discussion of the results presented in the four studies.

Chapter 6 presents the conclusions.

Chapter 7 raises perspectives of relevance in future research.

Chapters 8 and 9 present English and Danish summaries.

The appendices contain the four papers that form the basis of this dissertation. The four papers will be referred to by their Roman numerals:

I. ‘Existing data sources for clinical epidemiology: Danish Cancer in Primary Care cohort’ (published in Clinical Epidemiology, July 2014).

II. ‘Diagnostic intervals before and after implementation of cancer patient pathways – a GP survey and registry based comparison of three cohorts of cancer patients’ (Published in B M C Cancer, April 2015).

III. ‘Tumour stages before, during and after implementation of standardised cancer patient pathways - a comparison between three cohorts of cancer patients diagnosed through a primary care route’ (submitted to British Journal of Cancer, February 2015).

ABBREVIATIONS

2WW  Two-Week-Wait
CaP   Cancer in Primary Care
CCI   Charlson Comorbidity Index
CI    Confidence Interval
CPP   standardised Cancer Patient Pathway
DCR   The Danish Cancer Registry
DI    Diagnostic Interval
DP    Diagnostic Pathway
GI    GastroIntestinal
GP    General Practitioner
ICD-10 The International Classification of Diseases, 10th revision
IQI   InterQuartile Interval
ISCED International Standard Classification of Education
NICE  The National Institute for Health and Care Excellence
NPR   The National Patient Registry
OECD  Organisation for Economic Cooperation and Development
OR    Odds Ratio
PAS   Patient Administrative System (Hospitals Discharge Registry)
PPV   Positive Predictive Value
PR    Prevalence Ratio
SE    Standard Error
StatDK Statistics Denmark
TNM   Tumor, Nodes, Metastasis
VPN   Virtual Private Network
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CHAPTER 1:

INTRODUCTION
The health-care management of cancer has seen considerable changes over the last two decades. At the turn of the century, repeated observations of lower survival rates of cancer in Denmark called for comprehensive cancer control plans. The first cancer plan was launched in 2000, a waiting time guarantee was introduced in 2001 and follow-up cancer plans emerged in 2005 and 2010 (4-7). During this time, many case stories on delayed cancer diagnosis and treatment received considerable interest in the Danish media. The reported delays did not only cause psychological distress, but also turned out to have fatal consequences for the patients. In the same period, the waiting times kept increasing (8-10), even though the clinicians increasingly discredited the waiting times (10;11).

In October 2007, the Danish government and the five Danish regions (i.e. the hospital owners) made a sudden “Agreement on acute action and clear information to cancer patients” (12). This new agreement required standardised cancer patient pathways (CPPs) for all patients with suspected cancer within a year (12). The ultimate aim of the CPPs was to improve the survival of cancer patients in Denmark by decreasing the waiting times. Other important aims were to improve patient satisfaction and limit psychological distress among cancer patients by reducing unnecessary and unproductive waiting times (11). When the CPPs had been formulated, each Region were allowed three months to implement the CPPs at local level (11).

This thesis evaluates the impact of the Danish CPPs by critically examining the key assumption behind the implementation; CPPs will improve the prognosis by more timely and earlier detection of cancer. Thus, the main aim of the present thesis is to find answers to the question: Does the implementation of Danish CPPs lead to more timely diagnosis and early detection of symptomatic cancer patients at a population level?
CANCER EPIDEMIOLOGY

Cancer is a widespread and hazardous disease. In 2012, the European incidence rate of cancer was 382 per 100,000 person years, and the mortality rate was 164.6 per 100,000 person years (13). The cancer incidence rate in Denmark was 452.9 for males and 330.1 for females, and the mortality rates were above the European average (13). Cancer alone accounted for 32% of all deaths in Denmark in 2012 (14). Despite improvements in cancer survival in Denmark (15;16), Danish cancer patients still have lower survival rates than patients in other Scandinavian countries and most Western European countries (13;16-18) (Figure 1.1).

![Figure 1.1: 5-year age-standardised survival rates in Denmark (red lines) from 1964 to 2012 compared to the other Scandinavian countries for men (left) and women (right) (16).]
POSSIBLE EXPLANATIONS FOR POOR SURVIVAL RATES

The lower survival rates for cancer patients in Denmark compared to other Scandinavian countries have been argued to be the result of differences in cancer registration, lifestyle, available treatment and time to final diagnosis and start of treatment (19).

The latter explanation relies on evidence that Danish cancer patients are diagnosed/treated at more advanced disease stages than patients in other countries (17;20-22). As tumours can be regarded to grow exponentially, early detection seems a crucial factor for the prognosis (23). Early detection may essentially be achieved in two ways: by screening or by ensuring more timely diagnosis of symptomatic cancer patients (i.e. shorter time intervals from the patient’s first presentation of symptoms in primary care until diagnosis of cancer). Earlier detection by more timely cancer diagnosis would affect the majority of cancer patients as more than 80% of all cancer patients are diagnosed after presenting symptoms to their general practitioner (GP) (24;25). It has long been unclear whether more timely cancer diagnosis brings favourable outcomes as much of the previous evidence is equivocal (26-31). Nevertheless, recent research indicates that it is reasonable to assume that expedited diagnosis of symptomatic cancer is likely to benefit the patients in terms of improved survival (32-35).

The time from first symptom presentation to initiated treatment of cancer is often divided into different interim intervals (Figure 1.2). Most studies have traditionally focused on one of these interim intervals at a time (e.g. patient, doctor or system interval), and the results show the length of the intervals vary and can be quite long (25;36-54). Yet, more emphasis has lately been put on the diagnostic interval as this interval encompasses the time spent in both primary and secondary care (38;41;42;55).
The association between long diagnostic intervals and higher mortality must be seen in light of the fact that the median interval from first symptom to treatment in Denmark was 98 days in 2004-05 (25). The system interval (Figure 2) takes up most of the time (median 55 days), partly due to unavoidable factors like consecutive processing of tests and test results (1;25). The consecutive test approach is suspected to lead to longer time intervals than a more contemporaneous test set-up due to longer processing time (10;57). Together with the increasing number of tests used for diagnosis, administrative challenges and capacity problems, the consecutive test approach has been argued to be a major cause of the longer waiting times experienced during the 1990s and up to the beginning of the new millennium (8;10).
STANDARDISED CANCER PATIENT PATHWAYS

The idea behind CPPs (i.e. uniform and more timely diagnosis of cancer patients) came from the UK. In 2000, the UK introduced more uniform procedures for cancer referral and diagnostic pathways. These included time limits for processing (58), and the UK introduced two-week wait referrals (2WW). This implied that GPs suspecting cancer were allowed to make ‘urgent’ referral of patients, which ensured that the patient would be seen by a specialist at a hospital within two weeks (59). To qualify for ‘urgent’ 2WW referral, the patient had to fulfil certain criteria outlined in the NICE cancer guideline no. 27 (59) (see Table 1.1 for guidelines on colorectal cancer).

CPPs were introduced in Denmark in 2007. The introduction was intended to improve the prognosis of Danish cancer patients by ensuring earlier detection of cancer by a more timely diagnosis of cancer through standardised and time-efficient diagnostic pathways (11). Danish CPPs for 32 cancer sites were implemented nationwide during 2008 and 2009 (6;9;11). The Danish CPPs consist of guidelines, including descriptions of selected alarm symptoms that may raise cancer suspicion, descriptions of medical procedures (mainly in the secondary health-care sector) and time frames for all phases (see Table 1.1 for guidelines on colorectal cancer). Patients can be referred to a Danish CPP when the clinician has ‘reasonable suspicion’ that cancer may be the final diagnosis on the basis of the alarm symptoms outlined in the CPP guidelines (11).
Table 1.1: Symptoms qualifying for ‘urgent’/fast-track referral for suspected colorectal cancer according to national guidelines (in Denmark and the UK) and time frames for different phases in the clinical cancer care pathway (59;60).

<table>
<thead>
<tr>
<th>Symptoms outlined in national guidelines for CPP/urgent referral</th>
<th>Danish CPP</th>
<th>UK (urgent referral / 2WW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients aged 40 years or more with at least one of the following symptoms:</td>
<td>All patients:</td>
<td></td>
</tr>
<tr>
<td>• rectal bleeding</td>
<td>• aged 40 years or more with rectal bleeding and changed bowel habits for at least 6 weeks</td>
<td></td>
</tr>
<tr>
<td>• change in bowel habit for four weeks</td>
<td>• aged 60 with either rectal bleeding or changed bowel habit for at least 6 weeks</td>
<td></td>
</tr>
<tr>
<td>• unexplained anaemia</td>
<td>• with right lower abdominal mass, irrespective of age</td>
<td></td>
</tr>
<tr>
<td>• and/or significant general symptoms (e.g. weight loss, stomach pain)</td>
<td>• unexplained anaemia according to sex specific criteria</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time frames of phases in the clinical cancer care pathway</th>
<th>9 days</th>
<th>14 days (2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral until first appointment at hospital/specialist</td>
<td>18 days</td>
<td>n.a.</td>
</tr>
<tr>
<td>First hospital visit until diagnosis</td>
<td>10 days (operation)</td>
<td>31 days*</td>
</tr>
<tr>
<td>Diagnosis until start of treatment (treatment interval (Figure 1.2))</td>
<td>14 days (radiotherapy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 days (chemotherapy)</td>
<td></td>
</tr>
<tr>
<td>Referral until start of treatment – overall time frame (‘system interval’ (Figure 1.2))</td>
<td>37 days (operation)</td>
<td>62 days</td>
</tr>
<tr>
<td></td>
<td>41 days (radiotherapy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 days (chemotherapy)</td>
<td></td>
</tr>
</tbody>
</table>

* Time from agreement on treatment plan (between patient and doctor) until start of treatment.

Other countries have also introduced different kind of CPPs, such as rapid or urgent referrals and fast-track systems (43;45;61;62). Even though the CPP content differs between countries, the fast-track systems all aim to improve the patients’ prognosis by a more timely diagnosis within a guaranteed timeframe.
One major difference between countries is that the Danish CPPs cover the entire time span from GP referral until end of treatment, whereas others mainly focus on the referral process from general practice to secondary care (e.g. 2WW in the UK). Yet, considerable similarities are also present, for instance regarding referral criteria and overall time frame (Table 1.1). Hence, the Danish CPPs can be seen as comparable to e.g. the 2WW in combination with the NICE guidelines that stipulate specific diagnostic and treatment modalities for cancer in the UK (e.g. NICE guideline no. 131 for colorectal cancer (63)).
ASSESSMENT OF THE IMPACT OF CPPS

As CPPs are aimed to improve the patients’ prognosis by ensuring earlier detection of cancer through more timely diagnosis (11), timely diagnosis and earlier detection will be the main foci of this thesis, and these will be more carefully defined below.

Timely diagnosis
Time to diagnosis has been defined in different ways in the literature. In line with the latest recommendation, it will here be defined as the diagnostic interval (DI) (Figure 1.2) (56). It is implied that a shorter diagnostic interval is equivalent to a shorter clinical pathway and thus more timely diagnosis.

Earlier detection
Earlier diagnosis is defined as detection of cancer at an earlier stage (lower tumour stage). Yet, CPPs aim to improve the patient’s prognosis by improving the survival rates (11). However, cancer survival rates are also influenced by improvements in cancer treatment, new developments in treatment of comorbidity and lead time, which makes it difficult to conclude if a shorter time to diagnosis and treatment (and thereby a difference in the prognosis) is the result of CPP implementation or an effect of other factors. If the diagnostic criteria are stable over the study period, tumour stage may be considered a good indicator for the patient survival (64-66) and thus constitute an important and appropriate measure to evaluate the possible effect of CPPs on the prognosis.
EVIDENCE OF CPP IMPACT ON MORE TIMELY DIAGNOSIS AND EARLIER DETECTION

Timely diagnosis

Few studies have addressed the possible impact of CPPs on the length of the DI. The focus is primarily on a selected part of the DI and a specific cancer site, and some studies fail to include baseline measures (38;43;61;62;67-69). In addition, some studies are restricted to include only patients with predefined symptoms of cancer (55) or patients referred for a CPP (43). This inconsistency constitutes a problem because only about half of cancer patients initially present with well-defined symptoms of cancer that would allow direct access to a CPP (70;71). Despite these methodological drawbacks, studies overall conclude that the introduction of CPPs has led to more timely diagnosis in terms of shorter interim time intervals within the health-care sector.

A couple of studies have shown that patients who are not referred to a CPP have longer time intervals than CPP-referred patients (49;72). This led the authors to question the CPP strategy because it may hinder patients with vague or unspecific symptoms of cancer to obtain a more timely diagnosis. In fact, one of the studies found that implementation of the 2WW did not improve the overall time to diagnosis as cancer patients who were not referred to the 2WW experienced longer time to diagnosis than patients referred to the 2WW (72). Thus, although CPP implementation may reduce a specific time interval for a selected group of patients, it may not reduce the overall time to diagnosis for the whole group of cancer patients.

In conclusion, former studies indicate that the introduction of CPPs as a mean of securing more timely diagnosis seems to benefit only the selected group of patients who are referred to a CPP. At the same time, the CPP programme may be a considerable drawback for patients who do not qualify for CPP referral as
they may end up having longer diagnostic intervals than before the introduction of CPPs.

**Earlier detection**

There is a lack of evidence of the effect of CPP implementation on tumour stage at diagnosis for patients diagnosed through a primary care route. The evidence is limited to three studies; one found that CPP implementation was associated with a higher proportion of stage IV cancers among patients with head and neck cancers (38), one found that CPP implementation was associated with a higher proportion of Duke’s stage A tumours among colorectal cancers (44), and one found no difference in Duke’s staging and CPP referral among colorectal cancers (73). A fourth study on sarcoma patients found a reduction in tumour size across time after CPP implementation, which indicates a better prognosis, even though no staging nor grading were given (68). Thus, it is unclear whether CPP implementation achieves the goal of ensuring an overall earlier detection of cancer. Some cross-sectional studies show that tumour stages differ according to referral routes (CPP or not), but with conflicting results; one found more advanced stages of lung and ovarian cancers, and no difference among prostate cancer, while others find diverging results for colorectal cancer (45;49;62;74;75). This variation indicates that the level of disease might differ according to referral route.

In conclusion, studies on CPP implementation and stage outcome indicate that it remains unclear whether CPP implementation has led to earlier detection for the whole group of cancer patients diagnosed through a primary-care route. Furthermore, the level of disease may in itself be a confounder and may constitute an unacknowledged methodological problem, which challenges the testing of the effect of CPP implementation on earlier detection of cancer in symptomatic patients.
Selection of patients
Diagnosing cancer in primary care is difficult and complex. The GP must identify the few patients with cancer among the many patients with symptoms that might be a sign of cancer, but who are actually not ill (76). This is complicated by the fact that many cancer patients present with vague symptoms that are not suggestive of cancer disease (77). Even when the presenting symptoms are considered symptoms indicative of cancer, the positive predictive value of having cancer is low (78;79). As previously described, Danish GPs can refer patients to a CPP when a ‘reasonable suspicion of cancer’ is raised. Such suspicion must be based on a number of specific ‘triggers’ that are supposed to guide the GP in selecting appropriate patients for the CPP referral route. Yet, as ‘alarm’ symptoms and signs of cancer are based on cancer patients’ symptomatology when the diagnosis has already been established, this may raise concerns as to whether this guidance of the GP may rather encourage the GP to select only the patients who appear to be most sick for quicker diagnosis and treatment through a CPP referral route. Thus, the possible association between CPP implementation and a more timely diagnosis and earlier detection could also be affected by the GP’s selection of patients for CPP referral.

Indications for research
The previous studies which aim at assessing the impact of CPP implementation on more timely diagnosis and earlier detection may be hampered by the fact that the selection of patients for CPP referral is a non-random process based on the GP’s clinical assessments and decisions. Obviously, the chance of being selected for a CPP increases as the underlying disease evolves and produces more severe symptoms; this may be one of the reasons why tumour stage distributions differ between referral routes (CPP or not) (45;49;62;74;75). A recent British study found that patients who were referred and diagnosed within the time limits set out by the 2WW framework had higher tumour stages than other patients (80).
The non-random selection of patients for fast diagnostic evaluation seems to be constant across sector boundaries as the GP’s clinical assessment (in particular the GP’s interpretation of symptoms) may actively influence cancer trajectories after referral to the secondary-care sector and may thus affect the length of the diagnostic interval (81). Even so, no study has yet compared tumour stages by referral route before and after CPP implementation although such study may mitigate the confounding effect of clinical triage and provide us with a more clear impression of the actual effect of CPP implementation. The selection of patients with more severe disease for fastest diagnosis and treatment has also been said to be the cause of the so-called ‘waiting time paradox’; explaining why the fastest diagnosed patients have a higher mortality (32;34).

**Overall evidence**

The impact of CPPs on both the diagnostic interval (timely diagnosis) and tumour stage (earlier detection) is sparsely evidenced, as shown above. Yet, although the CPP implementation may have reduced a specific time interval for specific groups of cancer patients, it may not have reduced the overall time to diagnosis for all cancer patients; some groups might even end up having longer time to diagnosis after the CPP implementation. Furthermore, evidence of effects of CPP implementation on tumour stage may suffer from confounding by severity. This bias is the result of the selection process as CPP-referred patients per se are non-randomly selected on the basis on the severity of symptoms, which more or less reflects the underlying stage of disease (82). To reduce this bias, we need more comparisons of sub-groups of patients in order to consider the role of the GP’s interpretation of symptoms.
HYPOTHESES

On the basis of the sparse evidence outlined above, it is hypothesised that:

- CPPs in Denmark are mainly used for severely ill patients or patients with alarm symptoms of cancer.
- CPP implementation in Denmark has resulted in more timely diagnosis in terms of shorter DI, mainly for CPP-referred patients.
- CPP implementation in Denmark has resulted in earlier detection of cancer in terms of lower stage tumours, but not among CPP-referred patients.

To empirically test these hypotheses, we performed a study using three prior studies on time to diagnosis among incident cancer patients in Denmark; these three studies were carried out before, during and after the implementation of CPPs in Denmark (1-3). The three studies all used similar methods to identify patients and to collect and store data. The cohorts are based on a specific administrative area (Denmark), which may diminish some of the quality issues, that normally makes it hard to assess the quality of the provided health-care service as a whole. Yet, assessment of health-care performance is still methodologically challenging due to the heterogeneous mix of a wide range of cancers and different diagnostic and treatment modalities across various time periods. It is crucial that data are comparable, also across time and space (e.g. before and after a major health-care reform such as implementation of CPPs). Therefore, an important task of this project was to combine the three cohorts into one cohort without compromising the validity and the representativity of the data.
INTRODUCTION

AIMS OF THE THESIS

The overall aim of the present thesis was to investigate the impact of the introduction of CPPs on timely and early diagnosis among a cohort of incident cancer patients diagnosed through a primary-care route, with special attention towards the GPs use of the CPPs. This was done by analysing the associations between CPP implementation and both the DI and the tumour stage and by describing factors that predicted CPP use.

The overall aim was addressed through the following four specific aims set up for the underlying studies:

1. To investigate if it is possible to combine three cohorts of incident cancer patients so that the combined cohort comprised comparable data regarding early diagnosis of cancer in primary care across time and to describe the key characteristics of the combined cohort.

2. To compare the length of the DI in 2010 with the length of the DI before (2004/05) and during (2007/08) CPP implementation in Denmark for all incident cancer patients diagnosed through a primary-care route.

3. To compare tumour stages before and after CPP implementation in Denmark among incident cancer patients diagnosed through a primary-care route and also to investigate whether the GPs’ use of CPP referrals caused a different effect of CPP implementation.

4. To analyse if the GP’s suspicion of cancer predicted the choice of referral to a CPP and to analyse associations between choice of referral route and time to cancer diagnosis.
CHAPTER 2:

MATERIALS AND METHODS

This chapter describes the study population and the methods used to identify the included patients, and also the methods used in Papers I-IV.
The study population consists of three cohorts of incident cancer patients in Denmark. In the following, these three cohorts will be referred to as sub-cohorts 1-3. The three sub-cohorts were identified and data were collected in 2004/2005 (sub-cohort 1), 2007/2008 (sub-cohort 2) and 2010 (sub-cohort 3); each sub-cohort has been described in detail elsewhere (1-3). Although the three sub-cohorts had slightly different foci, they all centred on the timeliness of the diagnostic journey for cancer patients; from first onset of symptoms until the time of diagnosis. The three sub-cohorts were combined into one large study population in 2012-2013, referred to as the Danish Cancer in Primary Care (CaP) cohort (83). The CaP cohort forms the data basis for the present thesis, which comprises four scientific papers that all focus on patients from the CaP cohort.

The applied methods used to create the CaP cohort are presented in detail in Paper I. After the description of the CaP cohort, descriptions of the individual methods applied in the three remaining studies (Papers II-IV) will then follow. Table 2.1 gives an overview of the four studies regarding study design, study population, data sources and primary outcomes.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study design</th>
<th>Study population</th>
<th>Data source(s)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Descriptive / cross-sectional study</td>
<td>22,169 verified incident cancer cases aged ≥ 18 years and registered at a general practice</td>
<td>PAS, NPR, DCR, StatDK &amp; GPs’ medical records</td>
<td>Description of the study population in ‘the CaP cohort’</td>
</tr>
<tr>
<td>II</td>
<td>Ecological / comparative cohort study</td>
<td>12,558 verified incident cancer patients aged ≥ 18 years and registered at a general practice and attending general practice as part of their DP with complete information on length of DI</td>
<td>CaP cohort</td>
<td>Diagnostic interval (DI)</td>
</tr>
<tr>
<td>III</td>
<td>Ecological / comparative cohort study</td>
<td>7,725 verified incident cancer patients (with colorectal, lung, malignant melanoma, head and neck, upper gastrointestinal, gynaecological and urinary system cancer) aged ≥ 18 years registered at a general practice and attending general practice as part of their DP</td>
<td>CaP cohort</td>
<td>Clinical tumour stage: local, regional, distant, unknown or missing</td>
</tr>
<tr>
<td>IV</td>
<td>Cross-sectional study</td>
<td>3,823 verified incident cancer patients aged ≥ 18 years registered at a general practice and attending general practice as part of their DP with complete information on CPP use, GP symptom interpretation of presented symptoms and length of DI</td>
<td>CaP cohort: sub-cohort 3</td>
<td>Use of CPP &amp; association between use of CPP and DI</td>
</tr>
</tbody>
</table>

CaP = Cancer in Primary care, DCR = Danish Cancer Registry, DI = Diagnostic Interval, DP = Diagnostic Pathway, GP = General Practitioner, NPR = National Patient Registry, PAS = Patient Administrative System (hospital discharge registry), StatDK = Statistics Denmark
THE CREATION OF THE CAP COHORT: PAPER I

Paper I is a description of the establishment of the CaP Cohort (including the three sub-cohorts), which provides the data for Papers II-IV.

Setting

Denmark is a small kingdom with approximately 5.6 million inhabitants. The country is divided into five distinct geographical and administratively independent regions. The five Danish regions own and run the hospitals and buy services from primary care (including general practice) through collective contracts (84). Almost all Danish citizens (> 98%) are registered with a specific general practice, which they must consult for medical advice, except for cases of emergency. The Danish general practitioners (GPs) act as gatekeepers to the rest of the health-care system, including diagnostic investigations in secondary health-care, except for otorhinolaryngologists and ophthalmologists who can be accessed directly (84).

Inclusion periods

The first sub-cohort included patients from 1 September 2004 to 31 August 2005 in the former Danish County of Aarhus (640,000 inhabitants), which now forms part of the Central Denmark Region (1). The second sub-cohort included patients from 1 September 2007 to 31 August 2008 in the Region of Southern Denmark (1.2 million inhabitants) and the Central Denmark Region (1.2 million inhabitants) (2). The third sub-cohort included patients from 1 May 2010 to 31 August 2010 from all over Denmark (3).

Identification of eligible patients

The procedure for identifying the patients for all three sub-cohorts have been described extensively elsewhere (1-3) and will only be briefly presented here.
The patients for each sub-cohort were identified by an algorithm that was developed in the beginning of this millennium and continuously improved. The basis of the algorithm was founded in the PhD study by Hansen and colleagues in 2004/05 (1). The algorithm started out as a monthly sampling, which showed to provide an incomplete cohort in 2007/08. A follow-up sample was then developed to ensure a complete cohort in 2007/2008 (85). The algorithm was hereafter further developed to sample patients monthly by incorporating late registered patients from previous months to ensure a complete cohort (85). The sampling algorithm displayed a positive predictive value of 97.9% (95%CI: 97.3;99.9) in 2007/2008 and 98.8% (95%CI: 98.5;99.1) in 2010 to identify cancer patients (85). Further details on the algorithm have been published elsewhere (85).

During the inclusion periods, data on consecutive cancer patients were identified through the regional Patient Administrative System (i.e. hospital discharge registry) and the Danish National Patient Register. Both registers hold similar information on e.g. dates of all inpatient and outpatient visits and discharge diagnoses classified according to the World Health Organization’s International Classification of Diseases, tenth edition (ICD-10) (86). These data sources allowed prospective inclusion of new cancer cases while excluding patients with previous cancer disease.

Core data for the CaP Cohort

In order to create a single combined cohort, core data from the three sub-cohorts were merged; these data included patient identifier, ICD-10 diagnosis, admission date, discharge date and hospital code. Patients from the three different sub-cohorts were identified through the Danish personal registration number (CPR), a unique 10-digit personal identification number assigned to all Danish citizens at birth or immigration, before combining all data into the CaP Cohort.
Patients were eligible for inclusion in the CaP cohort if 1) they were 18 years or older, 2) were registered at a Danish GP and 3) were diagnosed with a first-time diagnosis of cancer in a hospital registry or in the National Patient Registry. This resulted in identification of 22,739 patients. When combining the subcohorts, we verified the cancer diagnoses using data from the Danish Cancer Registry, which comprises information on all incident carcinoid tumours in Denmark since 1943 (87). Patients without a registered record in the Danish Cancer Registry or registered with other than an ICD-10 C-level diagnosis were deemed non-eligible and excluded from the CaP cohort. In total, 22,169 patients were eligible to be included in the CaP cohort (Paper I) (83).

**Additional data sources for the CaP cohort**

The CaP cohort was enriched with additional information from many different data sources such as GP questionnaires and patient questionnaires together with many nationwide registers such as the Danish Cancer Registry, the Danish National Patient Registry and information from Statistics Denmark. The patient questionnaires and the part of the register data that were not used in Papers II-IV are described in Paper I, but will otherwise not be described further in this dissertation.

**GP questionnaires**

Approximately 2-5 weeks after identification of patients in each sub-cohort, a questionnaire for each identified patient was sent to their GP. Non-responding GPs received a reminder (including a new questionnaire) after 3-5 weeks. The GPs received a remuneration of DKK 240 (approximately € 32) for participation in the first and second sub-cohorts, but no remuneration was received for participation in the third sub-cohort.

In all three GP questionnaires, the GPs were asked to provide a detailed description of the patient’s diagnostic pathway on the basis of their contemporaneously updated electronic medical records. Eleven items recurred
in all three GP questionnaires; these included milestone dates regarding first symptom presentation, initiation of diagnostic procedures, referral, diagnosis and start of treatment as defined in the Aarhus Statement (56). In all GP questionnaires, the GP was asked to declare if s/he had been involved in the patient’s diagnostic trajectory by ticking yes or no to the following question: ‘Were you/your general practice involved in diagnosing the cancer?’ These responses enabled us to identify the patients who, according to the GP, had been diagnosed through a primary-care route.

Nationwide registers

Registry data used for the CaP cohort were linked through the Danish CPR number. As the CPR number is generally registered alongside any personal data in all official registers in Denmark, using this CPR number allowed combination of data across registers at the personal level (88).

The Danish National Patient Registry contains information on all inpatient and outpatient visits to somatic hospitals in Denmark from 1972 and onwards (86). This registry was used to compute a modified Charlson Comorbidity Index (CCI) score according to Quan et al (89) by applying the publicly available Stata program (90). Two different CCIs were computed; one was based on the complete discharge history during the 10 years prior to the date of the first consultation with a GP (CCI at symptom presentation), and another was based on the complete discharge history during the 10 years before the date of the diagnosis (CCI at time of diagnosis).

The Danish Cancer Registry (DCR) contains information on all incident tumours diagnosed in Denmark since 1943 (87), including information on tumour stage, date of diagnosis and date of death. The DCR was used to obtain a validated date of diagnoses for all patients and to obtain tumour stage classifications according to the TNM classification system (T = size of original tumour, N = involved lymph nodes and M = distant metastasis). The date of
diagnosis recorded in this registry corresponds to the date of first contact (admission date) with the hospital department at which the cancer diagnosis was first registered as the primary cause of contact. If the patient was diagnosed by a private practicing specialist, the date of diagnosis corresponds to the date of the clinical diagnosis (91).

Statistics Denmark is not a registry in the literal sense, but an institution responsible for the maintenance of many different public registers with various information on citizens. Examples include educational level, income, housing conditions, citizenship and labour market affiliation (92). From Statistics Denmark, information on educational level and disposable household income was used to identify the educational level of each individual patient included in the CaP cohort in accordance with the International Standard of Education (ISCED) and to determine the level of the disposable household income of each individual patient included in the CaP cohort in accordance with the Organisation for Economic Cooperation and Development) (92;93).

**Statistical analyses**

To test for differences between groups due to drop-out, key clinical and basic characteristics were compared between patients listed with participating GPs and patients listed with non-participating GPs. This was done for both the entire CaP cohort and for each of the three sub-cohorts using non-parametric tests: Chi-square, Mann-Whitney and Kruskall-Wallis. A statistical level of \( p \leq 0.05 \) was considered significant in all analyses.

All statistical analyses were done with Stata® statistical software, version 13 (StataCorp LP, College Station, TX, USA).

**Ethics and approvals**

The study was approved by the Danish Data Protection Agency (file. no. 2009-41-3471).
According to Danish law and the Committee on Health Research Ethics of the Central Denmark Region, the study did not require approval by the National Committee on Health Research Ethics as no biomedical intervention was performed.

As the data include personal data, they are stored and maintained electronically at Statistics Denmark and can only be accessed via a secured virtual private network (VPN). All data have been anonymised at Statistics Denmark and can only be accessed by approved researchers operating under strict regulations to ensure that the data processing is performed in accordance with the approval granted by the Danish Data Protection Agency.
The three studies presented in Papers II-IV are all based on the CaP cohort (Table 2.1); setting, patient identification and data sources have been presented above. Therefore, these will not be described further.

However, as the studies in Papers II-IV consist of slightly different designs using different outcome and exposure variables and different statistical analyses, the methods applied in Papers II-IV will be described below for each separate paper.

Material and methods: Paper II

Design: This study was designed as an ecological study comparing diagnostic intervals among incident cancer patients who attended Danish general practice prior to the cancer diagnosis.

Study population: Patients from the CaP cohort aged 18 years or older with a first-time cancer diagnosis who was listed at a GP and who presented symptoms in general practice as the first part of their diagnostic journey. A total of 12,558 patients were analysed.

Data: The outcome was the diagnostic interval (DI). The DI was calculated by using the GP questionnaire to obtain the date of the patient’s first presentation of symptoms to the GP, while the Danish Cancer Registry was used to define the date of diagnosis. Exposure was defined as the sampling time of the three subcohorts according to the national CPP implementation: 2004/2005 = before CPP implementation (before), 2007/2008 = during CPP implementation (during) and 2010 = after CPP implementation (after). The ‘after’ group was subsequently reassigned to CPP-referred patients and non-CPP-referred patients based on information from the GP questionnaire. Confounders accounted for were gender, age, comorbidity, educational level and disposable income.
Materials and methods

Statistical analyses: Differences in diagnostic interval at different percentiles were estimated using the ‘QCOUNT’ procedure for the quantile regression analyses on the smoothed quantiles (94) as analyses on the smoothed quantiles are recommended for analyses of discrete (count) data (95). Confidence intervals were calculated using standard errors (SEs) estimated from 1000 repetitions bootstrap. Two adjusted models were considered: a model with no regard of referral route (overall trend) and a model with CPP-exposed patients divided into referral routes (trend by referral route). The implication of missing data of DI was investigated in best/worst case scenario sensitivity analyses.

Material and methods: paper III

Design: This study was designed as an ecological study comparing tumour stages before, during and after CPP implementation among incident cancer patients who attended Danish general practice prior to the cancer diagnosis.

Study population: Patients from the CaP cohort aged 18 years or older with a first-time cancer diagnosis, and who had a GP involved in diagnosis and diagnosed with colorectal, lung, malignant melanoma, head and neck, upper gastrointestinal, gynaecological or urinary system cancers. A total of 7,725 patients were analysed.

Data: The outcome, clinical tumour stage, was obtained from the DCR and based on the TNM classification system. Tumour stages for colorectal, lung, malignant melanoma and bladder cancers were categorised using established cancer-specific algorithms to categorise tumours with missing TNM components as either: local, regional, distant, unknown or missing (96-99). The TNM staging information for the remaining patients was categorised using the following principle: local (no positive lymph nodes or metastasis), regional (positive lymph nodes), distant (metastatic cancer), missing for patients without any T, N and M information, and unknown for the remaining cancers (83). The main exposure of interest was the sampling time of the three sub-cohorts according to
the CPP implementation: 2004/05 = before CPP implementation (before), 2007/2008 = during CPP implementation (during) and 2010 = after CPP implementation (after). The ‘after’ group was subsequently reassigned to CPP referred patients and non-CPP-referred patients based on information from the GP questionnaire (83). Confounders accounted for were gender, age, comorbidity, educational level and disposable income.

**Statistical analyses:** Complete case analyses were done. Differences in tumour stage distribution across implementation status of CPPs and between CPP-referred and non-CPP-referred patients were compared using Pearson Chi² test. Tumour stage was dichotomised into local vs. regional and distant combined. Logistic regression was used to estimate odds-ratios (ORs) to be diagnosed with a local tumour stage as a function of CPP implementation. Two adjusted models were considered: a model with no regard of referral route (overall trend) and a model with CPP-exposed patients divided into referral routes (trend by referral route). Model fit was assessed by Pearson goodness-of-fit test. The impact of selection bias and missing data of tumour stage was investigated by sub-analyses on all complete cases including patients with a non-participating GP (n=9,736) and by multiple imputation (n=12,346). Multiple imputations were done by a multivariate model with one-year survival, sex, age, comorbidity, income, educational background and cancer-site as predictors for missing and unknown tumour stage, missing educational level and income.

**Material and methods: paper IV**

*Design:* This study was designed as a population-based cross-sectional study of incident cancer patients who attended Danish general practice prior to the cancer diagnosis.

*Study population:* Incident cancer patients aged 18 years or more with an incident diagnosis of cancer (except for non-melanoma skin cancer) during 1
Materials and methods

May to 31 August 2010 and who had attended general practice as part of the cancer diagnosis. A total of 3,823 patients were analysed.

Data: Data on the GP’s symptom interpretation and the GP’s use of CPP referral were obtained in the GP-questionnaire used for the third sub-cohort in the CaP cohort. Information about the GP’s interpretation of the symptoms presented by the patient at the first consultation was collected by asking the GP: ‘How did you interpret the symptoms?’ Response options were: alarm symptoms suggestive of cancer (alarm), symptoms suggestive of any serious disease (serious), or vague symptoms not directly suggestive of cancer or other serious disease (vague). Thus, the category of alarm symptoms reflects the GP’s suspicion of cancer. The GP’s symptom interpretation was subjective and was not based on a pre-specified list of alarm symptoms. Information about the choice of referral for further investigation for cancer, i.e. whether or not the GP referred to a CPP, was collected by asking the GP: ‘Did you/your practice refer the patient to a cancer patient pathway?’ (yes/no). If no CPP referral had been made, the questionnaire focused on information about the patient’s referral to specialist care by asking the GP: ‘If you did NOT refer the patient using a cancer patient pathway, was cancer suspicion clearly stated in your first referral to a specialist/hospital?’ (Yes - specific cancer diagnosis, Yes – unspecific cancer diagnosis, No). This enabled us to classify the GP’s choice of referral route into the following four distinct categories: CPP, cancer obs. pro. but non-CPP, other, or unknown referral. The diagnostic interval was calculated by using the date of the patient’s first presentation of symptoms to the GP from the GP questionnaire and the date of diagnosis registered in the DCR.

Statistical analyses: The likelihood of patients to be referred to a CPP was estimated as a function of GP symptom interpretation by calculating the prevalence ratios (PRs) using Poisson regression as the outcome was expected to be frequent [35]. Furthermore, the associations between GP symptom interpretation and diagnostic interval and between use of CPP and diagnostic
interval were calculated using the ‘QCOUNT’ procedure for quantile regression analysis on the smoothed quantiles (94) as we considered the outcome to be count data (discrete) (95). Confidence intervals were calculated using standard errors (SEs) estimated from 1000 repetitions bootstrap. The analyses were adjusted for patient gender, age, comorbidity, educational level, disposable income and region of residence and for patient clusters at GP level.

**General considerations for all three CaP Cohort studies: papers II-IV**

*Ethics and approvals*

The study was approved by the Danish Data Protection Agency (file no. 2009-41-3471).

According to Danish law and the Committee on Health Research Ethics of the Central Denmark Region, the study did not require approval by the National Committee on Health Research Ethics as no biomedical intervention was performed.

As the data include personal data, they are stored and maintained electronically at Statistics Denmark and can only be accessed via a secured virtual private network (VPN). All data have been anonymised at Statistics Denmark and can only be accessed by approved researchers operating under strict regulations to ensure that the data processing is performed in accordance with the approval granted by the Danish Data protection Agency.

*Level of statistical significance and software used*

A statistical level of $p \leq 0.05$ was considered significant in all analyses. All analyses were done using Stata® statistical software, version 13 (StataCorp LP, College Station, TX, USA).
CHAPTER 3:

SUMMARY OF RESULTS

This chapter offers a brief presentation of the results of the studies seen in perspective of the aims of the dissertation. A detailed presentation of the results is given in the four papers (appendix).
KEY CHARACTERISTICS OF THE DANISH CANCER IN PRIMARY CARE (CAP) COHORT (AIM 1)

In total, 22,739 incident cancer cases were identified. In 570 (2.5%) of these cases, the diagnosis could not be verified by the DCR (Figure 3.1). Cases that could not be verified ranged across the three sub-cohorts from 2.3% to 3.9%. In 4,603 (21%) of the 22,169 verified cases, GPs did not respond to the questionnaires, resulting in a GP participation rate of 79.2%. The GP participation rate varied between the sub-cohorts from 85.7% to 73.8% (Table 3.1).

Response analyses

Included patients listed with participating GPs did not differ from patients listed with non-participating GPs in regard to 1-year survival, comorbidity or educational level. However, patients listed with participating GPs were more likely to be women, to be younger, to have a higher disposable income, to have more regional or distant spread of tumours, and were also more likely to have breast cancer and less likely to have prostate cancer than patients listed with non-participating GPs (Table 3.1).

In the first sub-cohort (before CPP implementation), patients with participating GPs were more likely to be diagnosed with lung cancer and to have a lower 1-year survival rate, but this group did not differ in age or disposable income from patients listed with non-participating GPs. In the second sub-cohort (during CPP implementation), patients with participating GPs were more likely to be diagnosed with colorectal cancer, but this group did not differ from patients listed with non-participating GPs in regard to age, tumour stage or disposable income (Table 3.1).
Figure 3.1: Patient flow for each sub-cohort and the CaP cohort in total (far right). Note: c* = C01 - C99, except C44, according to the 10th edition of the International Classification of Diseases (ICD-10).
Table 3.1: Patient characteristics by general practitioner (GP) response for all sub-cohorts and for the combined CaP cohort (far right).
LENGTH OF THE DIAGNOSTIC INTERVAL BEFORE AND AFTER CPP IMPLEMENTATION (AIM 2)

From the CaP cohort, all 17,566 cases with a response from a GP were eligible. In total, 13,785 (78.5%) patients had consulted their GP as part of their diagnostic pathway. We obtained information for 12,558 patients on the diagnostic interval (DI), and these data were used for the analyses.

Diagnostic interval across time
The median DI was statistically significantly shorter across time: 49 (interquartile interval (IQI): 24;96) days before, 35 (IQI: 16;78) days during and 32 (IQI: 14;73) days after CPP implementation. The DI was also shorter across time when adjusted for sex, age, comorbidity, educational level and income; the median DI was 14 (95%CI: 11;16) days shorter during than before CPP implementation and 17 (95%CI: 15;19) days shorter after than before CPP implementation (Table 3.2).

Diagnostic interval across time by referral route
The DI was significantly longer for the non-CPP referred group than for the CPP-referred group in 2010 (p<0.001). For the CPP-referred group, the adjusted median was 23 (95%CI: 21;25) days shorter than for all patients combined before CPP implementation. For the non-CPP referred group, the adjusted median DI was 9 (95%CI: 7;12) days shorter than for all patients combined before CPP implementation. At the 90th percentile, the DI for the non-CPP referred group was similar (6 (95%CI: -66;77) days shorter) to the DI for all patients combined before CPP implementation (Table 3.2).

For the CPP-referred group, the adjusted median DI was 15 (95%CI: 12;17) days shorter than for all patients during the CPP implementation. For the non-CPP referred group, the adjusted median DI was 4 (95%CI: 1;7) days longer than
for all patients during CPP implementation (Table 3.2). The results were similar across cancer sites, although not statistically significantly at all percentiles.

**Sensitivity analyses**

The results of the sensitivity analyses were similar when using best-/worse-case scenarios.
Table 3.2: Estimated differences in diagnostic interval (DI) during and after CPP implementation compared to before, measured in calendar days, (Model 1). Furthermore, estimates are shown according to referral route after implementation: to a CPP route (after-CPP) or not (after-no CPP) (Model 2).

Estimates with 95% confidence intervals (95%CI) are displayed for the 25th, the 50th, the 75th and the 90th percentiles. Bold estimates indicate statistical significance at p=0.05 level or less (N=11,640).

<table>
<thead>
<tr>
<th>Percentile</th>
<th>During vs. before</th>
<th>After vs. before</th>
<th>After-CPP vs. before</th>
<th>After-no CPP vs. before</th>
<th>After-CPP vs. during</th>
<th>After-no CPP vs. during</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95%CI)</td>
<td>Estimate (95%CI)</td>
<td>Estimate (95%CI)</td>
<td>Estimate (95%CI)</td>
<td>Estimate (95%CI)</td>
<td>Estimate (95%CI)</td>
</tr>
<tr>
<td>25th</td>
<td>-7 (-8; -5)</td>
<td>-10 (-11; -8)</td>
<td>-12 (-13; -11)</td>
<td>-6 (-8; 5)</td>
<td>-8 (-9; 7)</td>
<td>0 (-2; 1)</td>
</tr>
<tr>
<td>50th</td>
<td>-14 (-16; -11)</td>
<td>-17 (-19; -15)</td>
<td>-23 (-25; -21)</td>
<td>-9 (-12; -7)</td>
<td>-15 (-17; -12)</td>
<td>4 (1; 7)</td>
</tr>
<tr>
<td>75th</td>
<td>-22 (-27; -16)</td>
<td>-27 (-34; -20)</td>
<td>-46 (-51; -41)</td>
<td>-11 (-21; -1)</td>
<td>-32 (-37; -28)</td>
<td>10 (1; 19)</td>
</tr>
<tr>
<td>90th</td>
<td>-53 (-76; -30)</td>
<td>-44 (-65; -23)</td>
<td>-110 (-153; -67)</td>
<td>-6 (-77; 66)</td>
<td>-80 (-126; -34)</td>
<td>48 (-49; 145)</td>
</tr>
</tbody>
</table>

Model 1 reference: before group, female, 45 years of age, colorectal cancer, no comorbidity, high disposable income and high educational level.

Model 2 = model 1, but with 'after group' split by referral route (CPP).

*Adjusted for gender, age, cancer site, comorbidity, educational level and disposable income.
From the CaP cohort, we identified 12,346 cases diagnosed with colorectal cancer, lung cancer, malignant melanoma, cancer of head and neck, upper gastrointestinal (GI) cancer, gynaecological cancer or cancer in urinary system. Among the 9,816 cases with a participating GP, the GP reported to be involved in diagnosing the cancer in 7,725 (78.7%) cases. These 7,725 patients were used for the primary analyses.

**Tumour stage distribution overall**

The tumour stage distribution did not differ across time for all cancers combined (p=0.494), nor for the individual cancer types. However, proportions of missing and unknown tumour stages differed statistically across time for all cancers combined (P<0.001) and for colorectal, lung, head and neck cancers as well as for gynaecological cancers. The tumour stage distributions did not differ between CPP and non-CPP referred patients; neither for all cancers combined, nor for any of the seven investigated specific cancer types.

**Localised tumour across time**

For all cancers combined, the odds ratio (OR) of having local cancer was 0.88 (95%CI: 0.73;1.06) after CPP implementation compared to before (Table 3.3). The likelihood of having local cancer was higher after CPP implementation compared to before for malignant melanoma and head and neck cancers, although these ORs were not statistically significant. Lung cancer patients had an OR of 0.62 (95%CI: 0.41;0.94) of having local cancer after CPP implementation compared to before (Table 3.3).
Table 3.3: Odds ratios (ORs) for incident cancer patients diagnosed through a primary care route of having local cancer during and after CPP implementation compared to before CPP implementation.

<table>
<thead>
<tr>
<th></th>
<th>During</th>
<th>Adjusted²</th>
<th>After</th>
<th>Adjusted²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw (95%CI)</td>
<td>Adjusted¹</td>
<td>Raw (95%CI)</td>
<td>Adjusted¹</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.98 (0.72;1.33)</td>
<td>0.96 (0.69;1.34)</td>
<td>0.89 (0.64;1.23)</td>
<td>0.84 (0.59;1.19)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.91 (0.65;1.29)</td>
<td>0.89 (0.62;1.28)</td>
<td>0.64 (0.43;0.96)</td>
<td>0.62 (0.41;0.94)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1.16 (0.65;2.07)</td>
<td>1.18 (0.65;2.13)</td>
<td>1.41 (0.75;2.68)</td>
<td>1.59 (0.82;3.10)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>1.09 (0.62;1.91)</td>
<td>1.10 (0.61;2.00)</td>
<td>1.60 (0.88;2.91)</td>
<td>1.65 (0.88;3.10)</td>
</tr>
<tr>
<td>Upper GI</td>
<td>0.69 (0.44;1.10)</td>
<td>0.66 (0.40;1.09)</td>
<td>0.79 (0.48;1.30)</td>
<td>0.73 (0.43;1.24)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>0.95 (0.60;1.50)</td>
<td>1.08 (0.67;1.73)</td>
<td>0.90 (0.55;1.47)</td>
<td>0.91 (0.55;1.53)</td>
</tr>
<tr>
<td>Urinary system</td>
<td>0.71 (0.43;1.19)</td>
<td>0.77 (0.44;1.36)</td>
<td>0.92 (0.52;1.62)</td>
<td>0.80 (0.43;1.48)</td>
</tr>
<tr>
<td>Total</td>
<td>0.88 (0.77;1.02)</td>
<td>0.93 (0.78;1.10)</td>
<td>0.90 (0.77;1.04)</td>
<td>0.88 (0.73;1.06)</td>
</tr>
</tbody>
</table>

¹Adjusted for sex, age, cancer site, comorbidity, educational level and household income.
Localised tumour across time by referral route

For all cancers combined, an OR of 0.77 (95%CI: 0.62;0.94) of having local cancer was found for CPP referred patients compared to the total group of patients before CPP implementation (Table 3.4).

Table 3.4: Odds ratios (ORs) for incident cancer patients diagnosed through a primary care route of having local cancer shown by referral route (CPP-referred or non-CPP referred) compared to all patients before CPP implementation.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>CPP-referred</th>
<th>Non-CPP referred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw</td>
<td>Adjusted¹</td>
</tr>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.83 (0.56;1.24)</td>
<td>0.81 (0.53;1.24)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.62 (0.37;1.03)</td>
<td>0.60 (0.35;1.01)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1.23 (0.55;2.78)</td>
<td>1.34 (0.57;3.18)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>1.35 (0.59;3.10)</td>
<td>1.34 (0.54;3.30)</td>
</tr>
<tr>
<td>Upper GI</td>
<td>0.77 (0.37;1.58)</td>
<td>0.68 (0.31;1.46)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>0.61 (0.31;1.19)</td>
<td>0.60 (0.30;1.21)</td>
</tr>
<tr>
<td>Urinary system</td>
<td>0.75 (0.37;1.52)</td>
<td>0.67 (0.32;1.43)</td>
</tr>
<tr>
<td>Total</td>
<td><strong>0.78 (0.64;0.94)</strong></td>
<td><strong>0.77 (0.62;0.94)</strong></td>
</tr>
</tbody>
</table>

¹Adjusted for sex, age, cancer site, comorbidity, educational level and household income
Localised tumours between referral routes

For all cancers combined, CPP referred patients tended to be less likely than non-CPP referred patients to be diagnosed with localised cancer (OR=0.81 (95%CI: 0.65;1.01) (p=0.066) (Figure 3.2).

![Figure 3.2: Odds ratio with 95% confidence limits to have local cancer among CPP referred patients compared to non-CPP referred patients. Values below 1 indicate CPP referred patient are less likely to have more localised cancer than non-CPP referred patients.]

Sensitivity analyses

The sensitivity analyses, which were conducted to test whether GP non-response or missing data altered the results, showed no changes in results.
From the CaP cohort, all 5,581 cases from 2010 (sub-cohort 3) with a response from the GP were eligible. In total, 4,101 patients had consulted their GP as part of their diagnostic pathway. We obtained complete information for 3,823 of these patients on diagnostic interval, CPP use and GP’s symptom interpretation, and these data were used for the analyses.

**GP’s symptom interpretation and CPP use**

In 48.2% of the cases, the GP interpreted the patient’s symptom as an ‘alarm’ symptom, and ‘vague’ in 32.3% of the cases, with variation across cancer sites. The GP used CPPs in 1,426 (37.3%) of all cases, with variation across cancer sites (Table 3.5).

**Association between GP’s symptom interpretation and CPP use**

Referral to a CPP was less likely among patients with symptoms interpreted by the GP as ‘vague’ symptoms (PR=0.53 (95%CI: 0.48;0.60)) and among patients with symptoms interpreted by the GP as ‘serious, but not indicative of cancer’ (PR=0.40 (0.34;0.48) (Table 3.6). Only the GP’s symptom interpretation was statistically significantly associated with CPP referral across all cancer sites, except for malignant melanoma for which no association was found (Table 3.6).
Table 3.5: Number and percentages of how the GP interpreted the patient’s presenting symptoms and of GPs’ use of CPP referrals shown by cancer site and total (N=3,823).

<table>
<thead>
<tr>
<th>GP’s symptom interpretation</th>
<th>Colorectal n (%)</th>
<th>Lung n (%)</th>
<th>Melanoma n (%)</th>
<th>Breast n (%)</th>
<th>Prostate n (%)</th>
<th>Other n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alarm</td>
<td>298 (48.7)</td>
<td>148 (31.2)</td>
<td>121 (53.3)</td>
<td>419 (80.9)</td>
<td>264 (47.5)</td>
<td>592 (41.2)</td>
<td>1,842 (48.2)</td>
</tr>
<tr>
<td>Serious</td>
<td>127 (20.8)</td>
<td>162 (34.2)</td>
<td>9 (4.0)</td>
<td>27 (5.2)</td>
<td>59 (10.6)</td>
<td>362 (25.2)</td>
<td>746 (19.5)</td>
</tr>
<tr>
<td>Vague</td>
<td>187 (30.6)</td>
<td>164 (34.6)</td>
<td>97 (42.7)</td>
<td>72 (13.9)</td>
<td>233 (41.9)</td>
<td>482 (33.6)</td>
<td>1,235 (32.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Referral mode</th>
<th>Colorectal n (%)</th>
<th>Lung n (%)</th>
<th>Melanoma n (%)</th>
<th>Breast n (%)</th>
<th>Prostate n (%)</th>
<th>Other n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Patient Pathway (CPP)</td>
<td>222 (36.3)</td>
<td>193 (40.7)</td>
<td>82 (36.1)</td>
<td>324 (62.5)</td>
<td>220 (39.6)</td>
<td>385 (26.8)</td>
<td>1,426 (37.3)</td>
</tr>
<tr>
<td>Cancer obs – no CPP</td>
<td>108 (17.6)</td>
<td>79 (16.7)</td>
<td>76 (33.5)</td>
<td>92 (17.8)</td>
<td>199 (35.8)</td>
<td>369 (25.7)</td>
<td>923 (24.1)</td>
</tr>
<tr>
<td>Other</td>
<td>262 (42.8)</td>
<td>174 (36.7)</td>
<td>61 (26.9)</td>
<td>83 (16.0)</td>
<td>114 (20.5)</td>
<td>613 (42.7)</td>
<td>1,307 (34.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (3.3)</td>
<td>28 (5.9)</td>
<td>8 (3.5)</td>
<td>19 (3.7)</td>
<td>23 (4.1)</td>
<td>69 (4.8)</td>
<td>167 (4.4)</td>
</tr>
</tbody>
</table>
Table 3.6: Patient’s likelihood of CPP referral initiated by the GP expressed as adjusted prevalence ratios (PRs) by cancer site and patient clusters at GP level. Estimates marked in bold were statistically significant at the minimum level of p<0.05 (N = 3,672).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table provides the adjusted prevalence ratios (PRs) for patients referred to CPP by gender and cancer site. The estimates marked in bold are statistically significant at the p<0.05 level. The table includes data for various cancer sites such as colorectal, lung, and breast, as well as other categories. The total column represents the combined data across all cancer sites and genders.
Associations between GP’s symptom interpretation and DI and between CPP use and DI

The overall median DI was 32 days (interquartile interval (IQI): 14;73), and this differed statistically significantly among both GP symptom interpretation (p<0.001) and GP referral modes (p<0.001). The adjusted DI was longer when the GP did not suspect cancer and also when the GP did not refer to a CPP. Symptoms interpreted as ‘vague’ displayed the strongest association with the DI, e.g. the median DI was 34 (95% CI: 28;41) days longer than the DI for patients with symptoms interpreted by the GP as ‘alarm’ symptoms (Table 3.7). The additional DI associated with the GP’s interpretation of symptoms as ‘vague’ was approximately twice as long as the additional DI associated with non-CPP referral (Table 3.7).
Table 3.7: DI in calendar days displayed by GP’s symptom interpretation and referral mode.

<table>
<thead>
<tr>
<th>Referral mode</th>
<th>Unknown</th>
<th>179 (286-643)</th>
<th>30 (179.9)</th>
<th>190 (103-300)</th>
<th>3 (1-7.4)</th>
<th>1 (1-2.2)</th>
<th>1.24 (1-2.3)</th>
<th>1.24 (1-2.3)</th>
<th>1.24 (1-2.3)</th>
<th>1.24 (1-2.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other reasons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer delay - no CPP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Point estimates marked in bold are statistically significant at minimum level of p>0.05 (N = 2787).

Implementation of Cancer Patient Pathways and more timely diagnosis and earlier detection of cancer.
CHAPTER 4:

DISCUSSION OF METHODS

The overall aim of this thesis was to examine the overall assumption behind the CPP implementation, i.e. that CPPs lead to more timely diagnosis and earlier detection of symptomatic cancer patients at population level, by comparing outcomes across time. This was done using two different observational designs; a cross-sectional design in Papers I and IV and an ecological design in Papers II and III. This chapter addresses the strengths and weaknesses of the four papers and critically evaluates how study design, bias and random errors might have affected the findings.
STUDY DESIGN

Ecological design

Paper II and III’s used an ecological design, which infers a risk that the associations observed between CPP implementation and the DI and tumour stage are coincidental associations (100;101). In the present papers, other factors over the time span of this study may have caused the DI to decrease and the tendency of local tumour stage to worsen. To reduce the risk of coincidental associations, the second sub-cohort in Papers II and III was used to divide the analytic period into two distinct time periods.

The use of sub-cohort 2 showed that the DI was shorter already before the full implementation of CPPs. Thus, causality between CPP implementation and more timely diagnosis of cancer seems unlikely. Yet, alternatively, the possible effect of CPPs on the DI should be understood as a combination of at least two things: an organisational change (starting in October 2007) with focus on time to diagnosis and the actual standardised cancer pathway (CPP guideline). Likewise, the use of sub-cohort 2 showed that the tendency of a lower likelihood of more localised cancer was also observed before the full implementation of CPPs, and this contradicts causality between CPP implementation and differences in localised tumour stages. Yet, the possible impact of CPPs on tumour stage may alternatively be understood as a combination of, at least, three things: stage migration over time and the two reasons outlined above for DI: an organisational change with focus on time to diagnosis and the actual CPP (guideline).

Cross-sectional design

The use of a cross-sectional design in Paper IV to seek aetiological information on the use of CPP referral is considered to be appropriate, provided that the exposures occurred prior to the referral and were constant during the entire study period (100). All register-based variables in Paper IV are considered valid.
as they have been prospectively recorded. The GP’s interpretation of symptoms is also considered trustworthy, although it was reported retrospectively, as the interpretation was based on prospectively recorded symptoms in the GP’s electronic medical record. Thus, the criteria for seeking aetiological information in a cross-sectional study design seem to have been fulfilled.
SELECTION BIAS

Incomplete identification of cancer patients, geographical differences or missing data could cause selection bias in all papers.

Identification of patients
A predefined algorithm to consecutively identify patients in population-based hospital discharge registries and the Danish National Patient Register (85) was used in combination with the Danish Cancer Registry to verify the diagnosis. This procedure ensured high sensitivity and reduced selection bias. The Danish health care system is almost uniformly organised across different geographically and administratively independent regions. This organisation allowed the merging of the three sub-cohorts into one, although they originated from different geographical locations (regions) in Denmark and thus belonged to different subsets. In fact, the case-mix of the sub-cohorts resembles the case-mix in the DCR of a given year (1:85). This indicates that the identified incident patients in the CaP Cohort are representative of incident cancer patients in Denmark at the time when the patients were identified. Yet, as the geographical locations (regions) of sub-cohorts 1 and 2 were subsets of the third sub-cohort, a non-random selection was still present in the identification process. This non-random selection had no effect on the outcomes as sensitivity analyses restricted to the same geographical region showed similar results in Papers II and III. Thus, any potential bias related to the identification process seems to have only little influence on the results.

Non-response
The GPs did not respond to the questionnaires for 20.8% of the patients. This non-response was non-random between the cohorts and may have been associated with the tumour stage and the length of the DI. It is believed that some of the non-participating GPs may not have been involved in diagnosing
cancer. This would potentially be the case for a substantial and increasing number of cases across time, e.g. those who were diagnosed through the national screening programme for breast cancer or accidental findings as a consequence of better imaging equipment. Nevertheless, some GPs might have chosen not to participate because they retrospectively believed that they had caused undue delays in diagnosing cancer. Yet, there is no reason to believe that GPs became more or less inclined to participate over time because of fear of having caused undue delay. Hence this non-random selection is unlikely to have biased the difference in DI across time observed in Paper II. Likewise, there is no reason to suspect variations in the GPs’ willingness to participate among the subgroups in Paper IV. Therefore, the non-random selection procedure is not expected to bias the difference in DI found between the subgroups in Paper IV.

Missed data
Non-random selection of patients for analyses due to missing data seemed more likely among patients in sub-cohort 2 in Paper II and in sub-cohort 1 in Paper III; patients in sub-cohort 2 in Paper II had more missing DIs, and patients in sub-cohort 3 in Paper III had more missing/unknown tumour stages. In Paper II, this was attempted accommodated by performing best/worst case sensitivity analyses. In Paper III, missing data was tried accommodated by multiple imputation. All performed sensitivity analyses displayed similar results to the main analyses, indicating that the effect of this selection bias was minimal.
INFORMATION BIAS

In the four papers, information bias may have arisen from misclassification of the study subjects (i.e. cancer diagnoses, GP involvement), the exposures (GP’s symptom interpretation, GP’s CPP use), the outcomes (the dates encompassing the diagnostic interval, tumour stage) or the confounding variables (in particular comorbidity, educational level and household income).

Overall
One of the major strengths of the present studies lies in their use of population-based designs, which was possible due to the tax-funded uniform health care system in Denmark. A further strength lies in the use of prospectively updated national registries with high data validity, e.g. DCR, NPR and registries upheld by Statistics Denmark (86-88;92). These data sources enabled to control for important confounding factors, such as comorbidity, educational level and household income. Furthermore, the DCR enabled validation of the patients’ diagnosis, which ensured high sensitivity and specificity of the cancer diagnoses and reduced the risk of misclassification and related potential information bias due to precise identification of study subjects.

Questionnaire data
A specific problem, which applies to all studies in the field on more timely diagnosis, is that time and time points are difficult to measure accurately retrospectively. In particular, it may be difficult to pinpoint the exact date of the first symptom presentation, especially for cases with long time intervals. Yet, this recall bias was reduced by using the GPs’ prospectively updated electronic medical records. Even so, the retrospective nature of the questionnaires holds the risk that the GPs may have misinterpreted the date of first presentation of symptoms for some of the cases. Hence, the date of first symptom may erroneously be mixed up with the first time that a GP considered presented
symptoms as a marker of cancer or other serious disease. This could lead to an underestimation of the actual length of the DI in Paper IV and hence underestimate the associations between the GP’s interpretation of symptoms and the DI. However, the risk of misclassification of the date of symptom presentation is considered equal among all three sub-cohorts and consequently will not bias the observed differences of DI across time in Paper II.

**Registry data**

Although registry data are generally considered very valid because of the prospective data collection method which is unrelated to the objective of this study, information bias cannot be entirely ruled out. In the studies of this thesis, information bias may particularly have arisen from misclassification of the date of diagnosis and misclassification of tumour stages.

Misclassification of the date of diagnosis is suspected to be present in Papers II and IV as the official date of diagnosis from the DCR was used. The DCR states the first date of contact to a hospital ward as the date of diagnosis in the record, but most diagnoses are verified after this date, mostly at a multidisciplinary team meeting at the hospital during the time of admission. Thus, the use of the DCR’s date of diagnosis would underestimate the length of the DI. This is considered to be non-differential in both Papers II and IV as it is suspected that the potential underestimation of DI is not associated with the CPP implementation in Paper II or the exposal subgroups in Paper IV. Thus, deviations in the date of diagnosis would tend to underestimate the differences in the DI in both Papers II and IV.

Misclassification of tumour stages may be present in Paper III for three reasons: data entry errors in the DCR, misclassification of tumours (local, regional or distant) and registration time of tumour stage (at diagnosis or treatment). Misclassification of stages is believed to be non-differential, as it should not depend on the implementation status of CPPs, and thus would tend
to underestimate the ORs in Paper III. Bias due to registration time may however be differentiated, as more patients have their tumour staged at diagnosis across time, which have led us to underestimate the ORs presented. Likewise, it is believed that misclassifications due to data entry errors would underestimate the ORs presented, as data entry errors should be lower across time, as the modernisation of the DCR finalised (91).
CONFOUNDING

The estimates were controlled for effects of age, sex, comorbidity, educational level and income in Papers II-IV. However, the estimates of the associations found could still be affected by residual, unmeasured or unknown confounding in all studies.

Handling of confounding in the studies

The modified Charlson’s Comorbidity Index by Quan et al (89) was used to control for comorbidity. This comorbidity index was originally developed to predict one-year mortality of hospitalised patients based on hospital chart review (102). As the studies did not use survival as outcome, it may be questionable if Charlson’s Comorbidity Index can fully adjust for the effect of comorbidity in the present studies. When controlling for comorbidity, no major change in the estimates was observed; this finding argues against the presence of residual confounding.

In Papers II and III, adjustment for age was done as a linear term centred at 45 years of age to avoid residual confounding of age. In Paper IV, age was included as a categorical variable to simplify the output, but a sensitivity analysis with age as a linear term found no changes in the estimates reported.

Using overly broad categories of either educational level or income could also have introduced residual confounding. When controlling for these possible confounders, almost no changes to the estimates were observed, which argues against the presence of residual confounding. Using overly broad categories of referral in Papers II-IV (e.g. not to divide CPP referrals into specific CPPs) could also have caused residual confounding. Sub-categorisation of CPPs could have mitigated this problem, but it was chosen not to perform this procedure in order to avoid reducing the statistical precision of the study.
Confounding by severity

A particular challenge that could compromise the interpretation of study results, especially in observational studies, is confounding by severity (103). Confounding by severity is a case of confounding by indication in which the disease severity or the perception of disease severity are important (100;103). Confounding by severity should be regarded as a confounder as it correlates with CPP use (exposure) and constitutes a risk factor for both long DIs and severe tumour stage (outcome). Confounding by severity is suspected to stem from the GP’s interpretation of symptoms as this symptom interpretation is merely a subjective perception of the severity of the patient’s illness. Confounding by severity seems a likely explanation for the observed shorter DIs among CPP-referred patients compared to non-CPP referred patients in Paper IV and for the finding of lower likelihood of local tumour stage among CPP-referred patients compared to non-CPP referred patients in Paper III. A further discussion of factors that may cause confounding by severity is presented in the next chapter in the section 'Underlying Mechanisms of the results'.
OUTCOMES AND STATISTICAL METHODS

Outcomes
In Papers II and IV, the DI was used as outcome. The DI was calculated by using factual dates from the patient’s medical record and the DCR. The distribution of the DI was highly right-skewed. This skewness of the DI data infers a challenge when the goal is to compare cohorts or subgroups. Differences in skewed data can generally be analysed only by using non-parametric methods, but these methods cannot adjust for the case-mix, which is essential here as the identified differences in Papers II & IV may otherwise have been caused by differences in the case-mix. This problem can be overcome in two ways: by categorisation of the DI or by quantile regression, which is a fairly novel method in medical research.

Categorisation of the DI could essentially be done in two ways. You can substitute the DI with the number of contacts prior to diagnosis, or you can categorise/dichotomise the DI. Using the number of contacts as a substitute for the factual DI rests on the hypothesis that the higher number of pre-diagnostic consultations, the longer the patient had to wait for the diagnosis (50;104). This may be inappropriate as an outcome in aetiological studies as it may introduce some misclassifications of outcome. These misclassifications would stem from patients being assigned non-randomly to the categories (e.g. one patient may need two contacts to be examined, while another patient may incidentally have three contacts due to different diseases). This may lead to confounding and make it difficult to spot real and clinical relevant differences between subgroups/sub-cohorts. This was a particular risk in Papers II and IV and was the reason why this approach was found inappropriate in these two studies. Categorisation of the factual DI into two or more categories would constitute the same problem.
Statistical methods applied

In order to overcome the issues outlined above, quantile regression (105;106) was used to estimate associations between the different exposures and the DI in Papers II and IV. Quantile regression can be used for non-normally distributed data (105;106) if the outcome is continuous and monotone (no ties). This was not the case in Papers II and IV as the DI was considered to be discrete of nature and comprised many ties. Yet, it has been shown that quantile regression is still valid for discrete data with ties if jitter is inferred during the calculations (95). Therefore, as recommended by Cameron and Trivedi (105), a procedure written by Miranda was adopted for performing quantile regression on discrete data by using Stata statistical software (94).

In Paper IV, associations were estimated using Poisson regression with robust variance which considered the clustering of patients within each general practice. This method was used because it provides estimates as prevalence ratios (PR) in cross-sectional studies, which can be interpreted as relative risk (107). This procedure was preferred to e.g. logistic regression, which instead provides odds ratios (ORs) as ORs would have overestimated the relative risk due to the high proportion of CPP referrals (107).

Logistic regression was used in Paper III to estimate the associations between CPP implementation and local tumour stage. Logistic regression was deemed more suitable in Paper IV as this enabled the use of multinominal logistic regression in the multiple imputation, which may account for some of the selection bias due to missing tumour stages inherent in the study (see selection bias).
STATISTICAL PRECISION AND POWER

It could be problematic to rely exclusively on a two-tailed p-value of 0.05 or less to define the statistical significance in the three regressions methods used in this thesis. This is especially true when considering the large sample sizes, which tend to increase the likelihood of falsely rejecting the null hypothesis (type II error). Therefore, 95% confidence intervals (CIs) were provided for all estimates to reflect the degree of precision. The degree of precision also needs to be evaluated together with the sample sizes in the studies, which were defined by the previous studies.

Study power
A priori power calculations showed that the studies in Papers II and IV had a power of more than 96% to detect differences of 5% or more in the DI. This indicated high statistical precision, but also held a risk of falsely rejecting the null hypotheses of no difference in DIs. Yet, the difference in DI was larger than 5%, which explains why the actual risk of type II errors was low in Papers II and IV.

In the study in Paper III, a priori power calculations showed that 292 patients were needed to detect a 10% change in the proportion of local cancer with a power of 90%. The proportional changes of localised tumours were lower than 10%, and this indicates that the non-significant results in Paper III may be due to low statistical power and hence may be prone to type I error.
GENERALISABILITY

The CaP Cohort combined a national cohort with a regional cohort and a county cohort. Owing to the large sample size and the fact that each cohort was found to correspond to the overall population in terms of gender, age and diagnoses (1,85), the combined cohort can be considered to be representative of incident cancers in Denmark during the investigated period of time. Although small regional differences might exist, the study population is sufficiently large to reduce the effect of any differences. In fact, sub-analyses of a geographical subset (region) in Papers II and III showed similar results as the main analyses indicated that the effect was similar across regions. Nevertheless, the effect of CPP implementation will obviously also depend on the local context.

Extrapolation of the results in the present thesis to other countries and health care systems will require careful consideration of various differences in the health care systems, e.g. financing, levels of gatekeeping and population demographics (e.g. age distribution) and cultural differences. A prerequisite for extrapolation to other settings is the presence of a primary health care sector in which the GP acts as a gatekeeper to the specialised healthcare/hospitals. Within this setting, the effect of CPP implementation will also depend on at least two health care related factors: the use of CPPs among GPs and the organisation of CPPs at hospital level.
CHAPTER 5:

DISCUSSION OF RESULTS

As pointed out in the introduction, only a few studies have estimated the impact of CPP implementation on the diagnostic interval (DI) and on tumour stage at diagnosis. These studies offer only little evidence of how the CPPs may influence cancer outcomes. The results of the four papers in this thesis are new in the sense that they study possible relations between CPP implementation and more timely diagnosis and earlier detection, while they address important design-dependent issues of bias, and analytical approaches to estimate changes in the length of the diagnostic interval.

In this Chapter, I will discuss the findings and the possible underlying mechanisms of the present studies by relating the results to previous studies.
CANCER IN PRIMARY CARE COHORT (AIM 1)

In Paper I, the aim was to set up the Danish Cancer in Primary Care (CaP) cohort to support epidemiological and health services research within the field of cancer diagnosis. The three sub-cohorts of the CaP cohort were established by using a predefined algorithm to identify newly diagnosed cancer patients in discharge registries at the time of the creation of the three sub-cohorts (1;85). The discharge register data of the identified patients were later combined with questionnaire data from both the patient and the GP, and these were finally combined with personal level register data. In this way, we were able to gather in-depth information about the cancer diagnostic pathways in near-real-time and in a timely manner (1;85).

The main focus when setting up the CaP cohort was to ensure that the data was valid. This focus required the questionnaire response rates to be high, the use of valid register data and also presupposed that the case-mix of the identified patients was representative of all Danish incident cancer patients at the time of data collection. On the basis of the descriptive and comparative analyses of the combined data, we found the CaP cohort/database to be a valid source of information and representative of the source population. This results from, that the cohorts reached a completeness of 60% in the first month after the first admission data and 90% in the second month for breast, colorectal and lung cancers and malignant melanoma (85). Furthermore, by comparing the basic characteristics of the three cohorts with national data from Danish Cancer Registry, we found high correspondence with regard to positive predictive values for sampling incident cancer patients (85) and comparable case mix (1;85). Thus, we believe that the identified patients are representative of the source population and that the observed differences (in e.g. gender, age, sites and stage distribution) among identified patients across sub-cohorts reflect true differences in the three source populations (Paper I).
Many local databases and cohorts of incident cancer patients exist, and many of these contain relevant data for research within the field of early cancer diagnosis (38;51;55;61;62;67;68;78;108). Nevertheless, comparing these is not easy because the cohorts are often sampled in different ways and based on different sources of information. The CaP cohort is the only known existing cohort with concurrent data at different time points from both GPs and patients in combination with valid data at the personal level from national registries, such as income, education and comorbidity. Thus, the CaP cohort is unique and can serve as a source for epidemiological and health services research within the field of cancer diagnosis, also for future studies.
Paper II is the first study to explore differences in the full DI before and after CPP implementation for all cancer types in Denmark, while previous studies in Denmark have been restricted to single cancer sites or the secondary care interval \( (11;38;54;67-69;109;110) \). The finding that the DI was lower after than before CPP implementation is comparable to a large UK study on the implementation of the NICE guidelines \( (55) \), two Danish studies on head and neck cancer \( (38;69) \) and a Danish study on sarcomas \( (68) \). The UK study was the only of the three to account for case-mix. The estimates of decrease in DI across time reported by the UK authors were lower than the DI differences found in Paper II. This variation is most likely caused by the lack of accounting for the right skewed DI data in the UK study \( (55) \) as this will underestimate the findings \( (106) \). The UK study and one of the Danish studies on head and neck cancer acknowledge that causality between CPPs and DI may not exist due to the ecological design used in their studies \( (38;55) \), but this is not acknowledged in the other two studies, which increases the risk of ecological fallacy in these studies \( (68;69) \). Yet, both of the two Danish studies on head and neck cancer argue that the DI dropped rapidly after CPP implementation, but Lyhne et al did not provide the data on this essential issue \( (38) \), while Sorenson et al reported a statistically significant drop in the time interval from before CPP implementation to the period just prior to and at the start of CPP implementation \( (69) \). Probst et al argued that the secondary care interval (Figure 1.2) decreased abruptly after CPP implementation, but most cancers displayed a drop in the secondary care interval already from 2006 until 2007, as seen in their Table 1, when no CPPs were implemented \( (11) \). For example the median secondary care interval for head and neck cancer dropped from 57 days in 2006 to 44 days in 2007 \( (11) \). Another finding by Larsen et al based on Sub-cohort 2 of
the CaP cohort showed that the secondary care interval declined steadily from before CPP implementation until the beginning of CPP implementation; this trend was found for all hospitals, including the regional hospital in Vejle (‘Vejle Amts Sygehus’), which had already implemented CPPs for colorectal, lung, breast and gynaecological cancers several years before the national CPP implementation (54;111). Larsen et al argued that factors other than CPP implementation seem to have had a positive impact on the secondary care interval. These results are comparable to the findings in Paper II, which reports that the largest DI difference (drop) was observed from 2004/2005 to 2007/2008 when the CPPs were not yet fully implemented. Therefore, these findings question whether the shorter DI across time can be attributed to the effect of implementing CPP guidelines alone.

A number of changes in policy, clinical practice and health care investments may have contributed to the observed changes in DI across time. The CCP implementation was just one of many new initiatives following the second Danish cancer plan, which also included a major expansion of radiotherapy facilities (6). The effect of CPPs on the DI should thus be understood as a combination of at least two things: an organisational change with increased focus on time to diagnosis, starting with the “Agreement on acute action and clear information to cancer patients” announced by the Danish government in October 2007 (12), and the actual implementation of standardised cancer pathways (CPPs). The shorter DIs in 2007/2008 may also be ascribed to a ‘Hawthorne’ effect (112) and/or that local leaders, clinicians and other healthcare personnel may have started to streamline the diagnostic trajectories already before the official CPP implementation in 2008/2009. The ‘Hawthorne’ effect may also explain why the time interval in the study by Sorenson et al was slightly higher in 2011 than in 2007/2008 (69) or it may be that the introduction of CPP guidelines may have a ‘side effect’. The definition of eligibility for CPP referral inevitable also holds a risk of defining a group of patients who are
deemed to be at high risk of experiencing longer diagnostic intervals. This may partly explain the finding of longer time to diagnosis across time for non-urgently referred patients reported by Potter et al in 2007 (72).

The study in Paper II was the first known study to compare DI across time at different percentiles across time while adjusting for case-mix. Therefore, the study was also the first to show that the lower DI across time was more profoundly seen among the patients who waiting the longest, e.g. a 27-day shorter DI for the 25% who waited the longest and a 44-day shorter DI for the 10% who waited the longest. This may have major impact on the prognosis for both patients with long DIs and at a population level, as it is reasonable to assume that expedited diagnosis of symptomatic cancer is likely to benefit the patients in terms of improved survival (32-35). In fact, a recent study on colorectal cancer patients treated at a small hospital in Denmark showed a decrease in the secondary care interval from 28 to 22 days and an increase in the long-term survival from 61.1% to 72.6% across the time of the CPP implementation (109).

The finding that CPP referred patients have a shorter DI than non-CPP referred patients at all percentiles (compared to all patients diagnosed before the implementation) may be the result of the GPs interpretation of severity, i.e. the GP’s interpretation of presented symptoms, as this interpretation may considerably influence the cancer trajectories in the secondary-care sector (81). These findings might also, at least in part, explain why many studies have shown that CPP referred patients experience shorter DIs (or part of it) than non-CPP referred (49;50;52;55;72;80). The present thesis finds that non-CPP referred patients had slightly lower DI across time. This contrasts the finding reported by Potter et al in 2007, who concluded that non-urgently referred patients generally have prolonged time to diagnosis after the introduction of the 2WW (72).
Paper III is one of the first studies to compare tumour stage before and after CPP implementation for patients diagnosed through a primary-care route. Until now, only three studies exist on single cancer sites (38;44;73), but none of these provided adjusted estimates for localised tumours after CPP implementation compared to before. Nevertheless, our study’s results are in line with those reported in a UK study on colorectal cancer by Zafar et al, who found no differences in Dukes’ staging after CPP implementation (73). The other two studies found opposite results. Lyhne et al found higher proportions of stage IV cancers after CPP implementation for patients with head and neck cancers (38), and Cerdan-Santacruz et al found a higher proportion of Dukes’ stage A tumours after CPP implementation for patients with colorectal cancers (44). One can only speculate why these studies have different findings. The most plausible explanations, beside a true effect, are inter-study differences in stage migration, data sources, lack of study power and differences in the time horizon of the study. The only study to report earlier detection across time was the study by Cerdan-Santacruz et al, who compared outcomes over a 25-year time horizon. Their results are likely to reflect general key changes in patient awareness and help-seeking behaviour rather than the effect of a relatively recent CPP implementation. The study by Zafar et al included only 148 patients, and their findings may thus be a type II error due to the low power of their study, which was also a problem in Paper III of the present thesis. The study by Lyhne et al showed results similar to Paper III, although different data sources were used. Lyhne et al used the clinical database DAHANCA of the Danish Head and Neck Cancer Group (38) to obtain tumour stage instead of the DCR, which was the source of information for the study on tumour stage in Paper III. The similar results reported by Lyhne et al and in Paper III indicate that a tendency towards
less local cancer may be evident across the time in question in Denmark. Changes in diagnostic procedures and upgrading of the Danish imaging equipment (e.g. more multi-slice CT scanners and MRI technology) prompted by the Danish Cancer Plan II of 2005 (6) are likely explanations for this finding.

The comparison of localised tumours between CPP referred patients and all patients before CPP implementation was the first of its kind. Hence, the finding of lower odds to be diagnosed with local tumour stage for CPP referred patients after CPP implementation (compared to all patients before) was also the first of its kind. Yet, some previous cross-sectional studies found no differences in tumour stages between referral routes for some cancers. Results are ambiguous (45;49;62;74;75), which may again pertain to methodological issues like study size and data source of tumour stages. It is striking that the findings in Paper III are relatively consistent in the sense that all estimates, although statistically insignificant, indicate that CPP referred patients are less likely to have localised tumours than non-CPP referred patients. This finding may be explained by confounding by severity stemming from a selection of a certain patient group referred to the urgent CPP route as many alarm symptoms may be signs of a more advanced disease.
Paper IV is the first study to explore the use of CPP in primary care for all cancers in Denmark. The finding that 37% of all patients are referred to a CPP is comparable to the reported use of 2WW in the UK (40;52;72;113-115). The reasons for this may be that the criteria behind the ‘reasonable suspicion of cancer’ is too specific to target the symptomatology of the patients seen in general practice; up to 60% of cancer patients do not present with alarm symptoms (70;71). This issue has also been raised as a concern in the UK (52;115). If the primary focus is directed towards a predefined checklist of symptoms and guidelines, we may disregard the fact that the clinical triage in primary care is two-sided: the GP is expected to spot (and refer) the seriously ill patients, but the GP is also expected to prevent healthy people from getting unnecessary examinations at the hospitals (76).

To our knowledge, only one former study by Dviwedi et al has estimated adjusted DIs at different percentiles, but the authors did not adjust for cancer suspicion nor for the case-mix (42). Hence, our study is the first to quantify the associations between cancer suspicion and the DI at different percentiles while also accounting for the case-mix. Even so, our finding of an overall (unadjusted) median DI of one month is similar to the findings of other studies (25;41;42;49;52).

Lack of ‘cancer suspicion’ by the GP was found to decrease the likelihood of CPP referral and influence the DI considerably more than the actual use of CPP, in particular among patients with vague symptoms. This finding may be the consequence of the GP’s clinical triage. Hence, the difference found in the DI among several different categories of patient symptoms may stem from confounding by severity (103).
UNDERLYING MECHANISMS OF THE RESULTS

In Papers II and IV, CPP referred patients were found to have faster diagnosis than non-CPP referred patients. Nevertheless, CPP referred patients were still found in Papers III and IV to be more ill as they had more severe symptoms (alarm symptoms of cancer) and lower likelihood of localised cancer. These findings are likely to be caused by confounding by severity. If we bear in mind that confounding by severity is a case of confounding by indication (103), the findings of ‘more timely diagnosis although not earlier detection of cancer’ diagnosis among CPP referred patients mirrors the so-called ‘waiting time paradox’, which is argued by Tørring et al to ‘stem from the inherent difference in prognosis of patients given different medical priority’ (116).

This similarity seems feasible as GPs are trained to act in accordance with guidelines and to refer patients with high-risk symptoms to secondary care (76). Thus, it seems that CPP implementation underpins the selection of the ill patients for faster (more timely) diagnosis. This may also explain why the fastest diagnosed (CPP-referred) patients are less likely to have localised cancer after CPP implementation when compared to all patients before CPP implementation and to non-CPP referred patients. Recently, Forrest et al argued that the patient’s performance status is a main explanatory factor in determining who is diagnosed and treated most promptly: the lower performance status, the higher the likelihood of being diagnosed and treated within time targets. This led Forrest et al to argue that confounding by severity of the disease (referred to as the ‘sicker quicker’ effect in their study) was the major reason for their similar findings in post-primary care (80).
If the severity of symptoms is assumed to act as a confounder on the relation between CPP use and tumour stage (Figure 5.1), it would also imply that the finding in Paper III of lower likelihood to be diagnosed with local cancer among CPP referred patients (than the total group before) may be biased. As it is not possible to identify the patients who would have been referred to CPPs in 2004/2005 and 2007/2008 if the CPPs had been implemented at the time, it is likely that the CPP-eligible patients would have had a tendency to have more advanced tumour stages before and during the CPP implementation. Therefore, this specific finding of more advanced tumour stage across time for CPP-referred patients, which was found in Paper III, seems likely to be caused, at least in part, by confounding by severity. This is substantiated by the findings in Papers III and IV, which show that CPP referred patients are more likely to have the most severe (alarm) symptoms of cancer and also tend to have worse tumour stages. This is in line with the finding by Forrest et al (80).

It has been postulated that a ‘fast-track’ system may disadvantage a large group of patients who do not present warning signs of cancer (114;115) as the ‘fast track’ tends to infer prolonged time to diagnosis because these patients may not present the ‘right’ symptoms stated in the guidelines to qualify for urgent referral. This may be used to argue that the CPP (and 2WW) approach to

![Figure 5.1: Hypothesised relations between CPP use, tumour stage and severity of symptoms](image)
faster diagnosis is perhaps not the best starting point of the diagnostic trajectory for all cancer patients. Yet, as the longer time to diagnosis among patients referred outside the urgent referral system may be the result of bias due to missing information on referral route before CPP implementation, this raises a principal problem; if the results are biased, we cannot trust the results showing that only CPP referred patients have gained shorter DI from CPP implementation, as found in Paper II, because non-CPP referred patients may also have gained a shorter DI from the CPP implementation. However, the difference in DI between CPP and non-CPP referred patients is more likely to reflect the clinical triage of patients as the GP is not only expected to identify the really ill patients, but the GP is also expected to prevent healthy people from getting unnecessary examinations at the hospitals (76).
In view of the aims of this thesis (chapter 1), several conclusions can be drawn, and these will be outlined in the following.
COMBINATION OF THREE COHORTS INTO ONE (AIM 1)

A unique cohort (referred to as the CaP cohort) has been created and presented. The CaP cohort consists of three datasets of newly diagnosed cancer patients and comprises questionnaire and register data. The CaP cohort can be used for epidemiological and health services research within the field of early cancer diagnosis, with careful attention to potential bias.

MORE TIMELY DIAGNOSIS OF CANCER (AIM 2)

The diagnostic interval for the five most common cancers and for all cancers combined in Denmark was lower after CPP implementation (2010) than before CPP implementation (2004/2005). The largest difference was seen from before to during CPP implementation (2007/2008), and this finding may indicate that the CPP implementation alone cannot have caused the observed lower diagnostic interval across time.

CPP referred patients had the largest difference in diagnostic interval across time, whereas non-CPP patients had only a slightly lower diagnostic interval across time. This may be an expression of bias caused by missing information on the GP’s selection of referral route before CPP implementation.

EARLY DETECTION OF CANCER (AIM 3)

No clear tendencies of earlier detection of cancer were observed for a range of cancer types after the national implementation of CPPs in Denmark in 2008; no difference was found in tumour stage distribution, and no higher likelihood of being diagnosed with localised cancer was found. These finding may be due to stage migration over time as a consequence of better diagnostic procedures and lack of study power.

CPP referred patients were less likely to be diagnosed with localised tumours after CPP implementation compared to all patients before. This group of
patients was also borderline statistically significant less likely to be diagnosed with localised cancer than non-CPP referred patients. This finding may be biased by the GP’s selection of severely ill patients for CPP referral.

**GP USE OF CPP REFERRALS (AIM 4)**

GPs suspected cancer more often than they referred to a CPP, and patients were less likely to be referred to a CPP if their symptoms were not interpreted as an ‘alarm’ symptom of cancer. When the patient’s symptoms were interpreted by the GP as ‘vague’, this was associated with an additional DI approximately twice that of not referring a patient to a CPP route. This indicates that the GPs tend to refer only a selected group of patients with severe symptoms to faster diagnosis by CPPs.

**OVERALL CONCLUSION**

In light of the discussion of methods and results, the results indicate that confounding by severity is likely to explain the findings of more timely diagnosis and lower likelihood of localised cancer among the CPP referred patients. This conclusion is mainly reached because the severity of symptoms is the main predictor for the GP to refer a patient to a CPP. However, confounding by severity cannot explain the overall improvement of more timely diagnosis and the lack of difference in localised cancer across time, why both of these findings are evident. Yet, causality may not exist between implementation of CPP guidelines and more timely diagnosis and earlier detection of cancer across time. In conclusion, the present thesis indicates that other unmeasured factors are likely to cause these findings and that CPPs should only be seen as part of a larger reformation of the cancer care pathway in Denmark.
Implementation of Cancer Patient Pathways and more timely diagnosis and earlier detection of cancer
CHAPTER 7:

FUTURE RESEARCH
The results of this thesis call for further research in several areas. As studies of early detection of symptomatic cancer, in particular observational studies, tend to suffer from confounding (by severity), future research should apply this knowledge in the interpretation of new findings to better identify the underlying mechanisms of the results to avoid misinterpretation.

The thesis results show that the overall diagnostic interval was shorter for all cancers already in 2007/2008 when Danish CPPs were only partly implemented, and this finding calls for more comprehensive monitoring of the diagnostic interval. It may be hypothesised that the early decrease in the diagnostic interval was partly caused by a ‘Hawthorne’ effect, which would diminish over time. This may indicate that the shorter diagnostic interval observed will not be maintained, for example five years after CPP implementation. A new monitoring study should categorise patients according to the GPs use of CPPs and thus ensure that the results are not affected by confounding by severity. Such a study is already in the pipeline as a new similar cohort of incident Danish cancer patients with colorectal, lung, breast and ovarian cancers diagnosed in 2013 and 2014 will be combined with the CaP cohort, and hereby serve as the foundation for this new study.

The thesis identified that more timely diagnosis was observed, although no earlier detection of cancer was found across time. This finding calls for further research to find out whether this result may also apply to survival as it has been shown that the survival rates for Danish cancer patients have improved across the period of the CPP implementation (15;109). However, survival rates are also positively affected by a more uniform and precise pre-therapeutic tumour staging because it enables a more appropriate treatment modality. Hence, future survival analysis should also consider the stage-specific survival rates to explore if the overall improvement in survival rates is consistent across tumour stages.

The thesis also found that no overall change in localised tumour stage was identified across time. As this finding may be due to insufficient power to detect
an improvement, this finding also calls for further research. A large study may further investigate this finding by using the same or a refined analytical approach to e.g. national data from the Danish Cancer Registry or one of the many Danish clinical cancer databases.

Three in four cancer patients were found to be diagnosed through a primary care route. This calls for further studies of the diagnostic trajectory in primary care to explore the clinical triage in the early steps of a cancer diagnosis. Such research could target the underlying reasoning behind the GPs’ use of CPP referral as other factors than just ‘alarm’ symptoms seem to influence the use of CPP referral.

Non-CPP referred patients and patients with vague symptoms were found to have longer diagnostic intervals. This together with other findings that cancer patients in general have increasing attendance rates in general practice several months before their diagnosis (50;57;104;108;117) invite further research into alternative routes to diagnosis, such as direct access to tests, to ensure that the GP is provided with better tools for assessment of cancer risk.
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Implementation of Cancer Patient Pathways and more timely diagnosis and earlier detection of cancer
ENGLISH SUMMARY
Introduction
Cancer is a common hazardous disease worldwide. In Denmark, the incidence is above the average in Europe and other Scandinavian countries and the survival rates are lower than many other countries. The lower survival rates for cancer patients in Denmark have been argued to result from differences in cancer registration, lifestyle, treatment options and prolonged time to final diagnosis and start of treatment.

Cancer Patient Pathways (CPPs) have been introduced in some European countries to promote more timely diagnosis and earlier detection of cancer, despite a paucity of evidence. Denmark implemented CPPs in 2008/09 after an “Agreement on acute action and clear information to cancer patients” from October 2007. The general assumption behind the Danish CPPs is that they should improve the prognosis by more timely diagnosis and earlier detection of symptomatic cancer patients.

Aims
The overall aim of the present thesis was to investigate the impact of the introduction of CPPs on timely diagnosis and early detection of symptomatic cancer among a cohort of incident cancer patients diagnosed through a primary-care route, with special attention towards the GPs’ use of the CPPs.

Material and methods
Three cohorts of incident cancer patients (before (2004/05), during (2007/08) and after (2010) CPP implementation in Denmark) were used to create the Cancer in Primary care (CaP) Cohort, comprising questionnaire data from GPs linked to registry data on the personal level (Paper I).

Data from the CaP Cohort was used in three studies (Papers II-IV): 1) a comparison of the length of the diagnostic interval (DI) between the three subcohorts in an ecological study design, 2) a comparison of tumour stages between the three sub-cohorts in an ecological study design and 3) an estimation of
associations between patient characteristics, GP’s symptom interpretation and the use of CPP referrals in a cross-sectional study design.

Differences in DI between sub-cohorts were analysed using quantile regression. Tumour stage was dichotomised into local vs. other and analysed using logistic regression with cohort time as the main predictor. Poisson regression analysis was used to estimate associations between patient characteristics, GP’s symptom interpretation and the use of CPP referrals.

**Main results**

In total, 22,169 out of 22,739 incident cancer patients from the three cohorts were eligible for inclusion in the CaP Cohort. The GP responded to the questionnaire in 17,566 (79.2%) of the cases and reported to be involved in diagnosing the cancer in 13,800 (78.6%) of these 17,566 cases.

The diagnostic interval (DI) was analysed for 12,558 complete cases of the 13,800 patients with GP involvement. The median DI was 49 days before CPP implementation and was 14 (95%CI: 11;16) days shorter during and 17 (95%CI: 15;19) days shorter after CPP implementation. Compared to before CPP implementation, the median DI was 23 (95%CI: 21;25) days shorter after CPP implementation for CPP referred patients and 9 (95%CI:7;12) days shorter for non-CPP referred patients.

Tumour stages across time were analysed for 7,725 complete cases of the 9,816 patients diagnosed with one of seven cancer types and with a GP involved in the diagnostic process. Local cancer was 0.88 (95%CI: 0.73;1.06) times less likely after than before CPP implementation. Across time, CPP referred patients were less likely to be diagnosed with local cancer after than before CPP implementation (OR=0.77 (0.62;0.94)), whereas non-CPP referred patients were just as likely as before CPP implementation (OR=0.96 (0.80;1.14)). CPP referred patients tended to be less likely to have localised tumours than non-CPP referred patients (OR=0.81 (95%CI: 0.65;1.01)).
The use of CPP referral was analysed for 3,823 complete cases of 4,101 patients with GP involvement after CPP implementation. The GPs used a CPP referral in 37.3% of all cancer cases, with variations across cancer types. GPs were less likely to refer a patient to a CPP when the patient presented vague symptoms compared to a patient with alarm symptoms; prevalence ratio: 0.53 (95%CI: 0.48;0.60).

**Discussion and conclusion**
Although the DI was shorter after than before CPP implementation, no favourable development in tumour stage across the time of CPP implementation could be observed. It is questionable whether the lower DI seen across time can be fully ascribed to implementation of CPP guidelines as the largest difference in DI was seen from before to the period just prior to and during the beginning of CPP implementation.

CPP referred patients had shorter DIs compared to all patients before CPP implementation and also compared to non-CPP referred patients. In addition, CPP referred patients were less likely to be diagnosed with localised cancers across time and also compared to non-CPP referred patients, which is likely to be caused by confounding by severity as GPs are more likely to refer patients with more severe symptoms to the CPP during the clinical triage.

However, confounding by severity cannot explain the overall improvement across time in timely diagnosis and the lower likelihood of being diagnosed with localised cancer across time. Yet, due to the ecological study design causality may not exist between CPP guidelines and changes in both DI and tumour stages across time. The results of the thesis indicate that other unmeasured factors are likely to have contributed to the more timely diagnosis, yet not earlier detection, of symptomatic cancer across time among cancer patients diagnosed through a primary care route.
DANSK RESUME
**Introduktion**

Kræft er en relativt hyppig sygdom med en høj dødelighed på verdensplan. I Danmark er incidensraterne for kræft højere end gennemsnittet i Europa og de øvrige nordiske lande, og overlevelsesraterne er lavere. Den lavere overlevelse blandt kræftpatienter i Danmark er blevet tilskrevet forskelle i kræftregistrering, livsstil, tilgængelige behandlingsformer samt længere tid til diagnose og behandling.

Pakkeforløb for kræft (kræftpakker) er blevet introduceret i nogle europæiske lande for at sikre hurtigere diagnose og tidligere opsporing af kræft, selvom evidensen bag disse pakkeforløb stadig er mangelfuld. Danmark indførte kræftpakker i 2008/09 som følge af Regeringens og Danske Regioners “Aftale om gennemførelse af målsætningen om akut handling og klar besked til kræftpatienter” i oktober 2007. Overordnet bygger de danske pakkeforløb for kræft på antagelsen om, at kræftpatienters overlevelse kan forbedres ved at sikre hurtigere diagnose og tidligere opsporing af kræft blandt symptomaticke kræftpatienter i Danmark.

**Formål**

Afhandlingens formål er at undersøge pakkeforløb for kræfts indvirkning på tiden til diagnosen og på tidligere opsporing af kræft blandt symptomaticke førstegangskræftpatienter, der præsenterede symptomer hos en praktiserende læge inden diagnosen, med fokus på den praktiserende læges brug af kræftpakker.

**Materiale og metode**

Data fra CaP-kohorten blev brugt i tre studier (Artikel II-IV). I Artikel II sammenlignes længden af det diagnostiske interval (DI) mellem tre sub-kohorter i et økologisk studiedesign. I Artikel III sammenlignes tumorstadier mellem de tre sub-kohorter i et økologisk studiedesign, og i Artikel IV analyseres sammenhænge mellem patientkarakteristika, den praktiserende læges symptomtolkning og lægens brug af kræftpakker i et tværsnitsstudiedesign.

Resultater
I alt blev 22.169 ud af 22.739 patienter inkluderet i CaP-kohorten. Den praktiserende læge responde rede på et spørgeskema for 17.566 (79,2 %) af patienterne. Lægen angav at være involveret i diagnosen i 13.800 (78,6 %) af de 17.566 patienter.

DI blev analyseret for 12.558 ud af de 13.800 patienter, hvor den praktiserende læge var involveret i udredningen. Det mediane DI var 49 dage før indførelsen af kræftpakkerne og var henholdsvis 14 (95% CI: 11; 16) dage kortere under og 17 (95% CI: 15; 19) dage kortere efter indførelsen af kræftpakkerne. Patienter, som blev henvist til kræftpakker i 2010, havde et median 23 (95% CI: 21; 25) dages kortere DI end før indførelsen af kræftpakkerne. Patienter, der ikke blev henvist til kræftpakker i 2010, havde et median 9 (95% CI: 7; 12) dages kortere DI end før indførelsen af kræftpakker.

Tumorstadier blev analyseret for 7.725 ud af de 9.816 patienter, som blev diagnosticeret med én af syv kræfttyper, hvor den praktiserende læge var involveret i udredningen. Risikoen udtrykt for at blive diagnosticeret med en lokal tumor ved odds var 0,88 (95% CI: 0,73; 1,06) gange lavere end før indførelsen af kræftpakkerne. Patienter, som blev henvist til kræftpakker i 2010, havde mindre tilbøjelighed for at blive diagnosticeret med en lokal tumor (OR = 0,77 (0,62; 0,94)). Patienter, der ikke blev henvist til kræftpakker i 2010, havde en uændret sandsynlighed ift. før indførelsen af kræftpakkerne (OR = 0,96 (0,80; 1,14)). Patienter, som blev henvist til kræftpakker, tenderede mod at have lavere
sandsynlighed for at blive diagnosticeret med lokal tumor ift. patienter, der ikke blev henvist til en kræftpakke (OR = 0,81 (95% CI: 0,65; 1,01).

**Diskussion og konklusion**

Selvom det diagnostiske interval var lavere efter indførelsen af kræftpakkerne, kunne der ikke observeres nogen positiv udvikling i tumorstadier i samme periode. Den største forskel (fald) i DI blev observeret fra 2004/05 til tiden lige før og i begyndelsen af indførelsen af selve kræftpakkerne. Derfor er det uvist, om det kortere DI henover tid kan tilskrives indførelsen af selve kræftpakkerne.

Patienter, som blev henvist til kræftpakker, havde kortere DI både i forhold til alle patienter før kræftpakkerne samt sammenlignet med patienter, som ikke blev henvist til en kræftpakke. Samtidig var de patienter, som blev henvist til kræftpakker, mindre tilbøjelige til at have en lokal tumor både over tid og sammenlignet med patienter, der ikke blev henvist til en kræftpakke, hvilket sandsynligvis ”confounding by severity”. Dette fænomen opstår som følge af, at den praktiserende læge synes mere tilbøjelig til at henvise patienter med de mest alarmerende symptomer til kræftpakkerne.

”Confounding by severity” kan dog ikke forklare den overordnede forbedring af tiden til diagnosen og den lavere sandsynlighed for at have lokal tumor over tidsperioden. Grundet brugen af det økologiske studiedesign i analyserne kan ændringerne over tid skyldes andre faktorer. Resultaterne indikerer, at andre umålte faktorer sandsynligvis har bidraget til den kortere tid til diagnose og at der ikke var forskel i sygdomsstadie set over tidsperioden blandt kræftpatienter som startede deres udredning i almen praksis.