Non-specific symptoms and signs of cancer in general practice – access to investigation and diagnostic centres

PhD dissertation

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PREFACE
OUTLINE OF THE THESIS

Chapter 1 introduces the reasons for studying patients with non-specific symptoms and signs of cancer and presents the overall and specific aims of the thesis. The chapter also gives an introduction to primary health care and its role in early diagnosis of cancer as well as a short introduction to the concept of time intervals and time as a factor in cancer diagnosis. The initiatives toward timely cancer diagnosis are also presented; and thus the basic premises of the thesis are outlined. Chapter 2 presents the aims of the PhD study. In Chapter 3, the methods of the studies are described. Chapter 4 outlines the main results of the three studies. Chapters 5 to 7 present the three papers. Chapter 8 and 9 offers a general discussion of the methods used and the results presented in the articles. Chapter 10 summarises the main conclusions in relation to the aims. Chapter 11 describes the perspectives raised by the present research and offers ideas for future research. Chapter 12 is the English summary and Chapter 13 the Danish summary. Finally the appendix contain the invitation letter and questionnaires sent to the GPs.
THE THREE PAPERS OF THE THESIS

The PhD dissertation is based on the following papers, which will be referred to by their Roman numerals:

I. Ingeman ML, Ormstrup TE, Vedsted P 2014. Direct-access to abdominal ultrasonic investigation from general practice – the role in earlier cancer diagnosis (Published in Family Practice February 2015).


## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>2WW</td>
<td>2-Week Wait referral</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CPP</td>
<td>Cancer Patient Pathway</td>
</tr>
<tr>
<td>CPR</td>
<td>Central Person Register</td>
</tr>
<tr>
<td>CRN</td>
<td>Civil Registration Number</td>
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<tr>
<td>CRS</td>
<td>The Danish Civil Registration System</td>
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<tr>
<td>DCR</td>
<td>The Danish Cancer Registry</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HSR</td>
<td>Health Service Registry</td>
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<tr>
<td>IQI</td>
<td>Inter Quartile Intervals</td>
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<td>MLI</td>
<td>Mads Lind Ingeman</td>
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<tr>
<td>NHSR</td>
<td>Danish National Health Service Register</td>
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<td>NPR</td>
<td>The Danish National Patient Registry</td>
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<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>NSSC-CPP</td>
<td>Cancer Patient Pathway for patients with serious Non-Specific Symptoms and signs of Cancer</td>
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<tr>
<td>OC-US</td>
<td>Abdominal ultrasound performed in the filter-function of the NSSC-CPP</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PAS</td>
<td>The Patient Administrative System</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<td>PR</td>
<td>Prevalence Ratio</td>
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<td>PRR</td>
<td>Prevalence Rate Ratio</td>
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<tr>
<td>RIS</td>
<td>Radiology Information System</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>TO</td>
<td>Tina E. Omstrup</td>
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<tr>
<td>US</td>
<td>Abdominal ultrasound</td>
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CHAPTER 1:

INTRODUCTION
In many countries, general practitioners (GPs) act as the health-care system’s first line of contact providing medical advice and treatment to the general population\(^1\). In most of these countries, the GP also acts as a “gatekeeper” to diagnostic tests and to the secondary health-care system in general. This system effectively ensures that almost all citizens have a regular primary care doctor. During one year, about 85% of all citizens are in contact with their GP\(^2\), and most of the patients present with non-serious symptoms that the GPs manage on their own in approximately nine out of ten cases\(^3\). However, GPs regularly have to deal with situations in which there is a real, but very low, likelihood of a serious disease. A recent Danish study documented that in nearly 6% of all consultations in general practice, the GP had a suspicion of cancer or another serious disease, and 10% of these cases resulted in a serious diagnosis\(^4\). Even in the hands of a well-trained and experienced GP, the risk of missing cases of rare, but serious disease is always present\(^5\). Failure to accept any diagnostic risk will overload the health-care system and burden the patients with unnecessary worry and investigations\(^6\,\,7\). On the other hand, accepting too much risk leads to late diagnosis and missed cases\(^5\,\,8\). Cancer is one of the most important examples of serious disease, where it is particularly important and no less challenging for the GP to strike a balance between an expectant and an investigatory approach\(^9\,\,10\). Every year, a GP will have approximately one patient diagnosed with each of the four common cancers (lung, colon, breast and prostate)\(^11\,\,12\). Other cancers (except skin cancers) are less common and a GP will diagnose an ovarian cancer every 5 years on average, for example\(^13\). GPs therefore obtain little personal experience of cancer diagnosis although patients presenting symptoms that could represent malignancy are very common in general practice.
More than 98% of Danish citizens are registered with a GP. The average GP has approximately 1,600 patients listed, and the GP act as a ‘gatekeeper’ to ensure appropriate and timely flow of patients to the secondary health-care services. The remaining 2% of patients have chosen a health insurance which allows them to choose freely among all GPs and other practising specialists, but they have to pay part of the consultation charge themselves. All Danish residents are entitled to public health-care benefits and have free access to medical treatment in the primary health-care sector as well as in the secondary health-care sector. The Danish health-care system, where patients are listed at one specific primary care practice, favours interpersonal GP-patient continuity of care, which is highly valued by the patients. Danish GPs are often organised in practice units which on average have two GPs per unit in addition to nurses and secretaries. The GPs operate fully computerized administrative systems with computer-based patient records and digital submission of prescriptions and referrals to pharmacies, hospitals, etc. Over the past few years, a decrease in solo practices has been seen; in part because of the GP population’s age profile, with many GPs retiring and new GPs not wanting to practice alone.
Screening has been implemented in Denmark and many other Western countries for only three types of cancer: Two common ones, breast and colorectal, plus one rarer cancer, cervical. These screening programs have been shown to reduce mortality. Although cancer screening is important to early detection of some cancers, the majority of patients with cancer present with symptoms. Hence, a British study found that the UK colorectal screening programme identified only a minority of cancers, while the majority of cancer patients presented symptomatically to primary care. Screening programmes obviously cannot find all cancers in a population, e.g. each screening programme targets a particular age group, but cancers are also diagnosed outside the target age group. Furthermore, participation in screening programmes is less than 100%, and cancer might be overlooked in screening participants (screening programmes do not have 100% sensitivity).

Studies have shown that GPs are involved in the initiation of the diagnostic pathway in approximately 75% to 85% of all cancer patients. Thus, GPs play an essential role in referring patients with symptoms or signs of cancer for further investigation. This is often a difficult task because symptoms are diverse and develop over time as the cancer develops. Some symptoms of cancer are unspecific, e.g. fatigue, while others are more characteristic and distinctive – so-called cancer ‘alarm’ or ‘red flag’ symptoms. We define alarm symptoms as symptoms especially suspicious of cancer like rectal bleeding and haemoptysis. Alarm symptoms of breast, lung, colorectal and urinary tract cancer are common in the general population, and approximately 15% of the general population have experienced at least one of these cancer alarm symptom within the past 12 months. In Norwegian studies, warning signs of cancer were identified in 12.4% of GP consultations and, among these, the GPs suspected 24% to have cancer of which only 3.8% actually had cancer. GPs
are also faced with the clinical challenge that the positive predictive value (PPV) of even alarm symptoms of cancer has been found to be as low as 2-10% depending on age, gender and cancer type.\textsuperscript{12,36,42}

Two Danish studies showed that the GPs interpreted the initially presented symptoms as alarm symptoms in approximately 50% of cancer patients, and the rest of the cancer patients presented symptoms that were interpreted either as non-specific or as general symptoms.\textsuperscript{31,43} Patients with non-specific and general symptoms are frequent in general practice, and the PPV of cancer for these kinds of symptoms is much lower than it is for alarm symptoms.\textsuperscript{12,44}

The GP must judge the likelihood of critical disease, for example cancer, on the basis of several factors such as symptom presentation, physical examination, test results, knowledge of predisposing factors, age, gender as well as the GP’s clinical sense and experience. Furthermore, the GP has to deal with diagnostic uncertainty in many situations while still maintaining a high-quality gatekeeping function between the primary and secondary health-care system. In Denmark, patients need a referral from their GP to receive further medical examination or treatment in a hospital or by a specialist, unless they are admitted through the emergency services due to an accident or acute illness.

Patients are typically referred to diagnostic investigations like abdominal ultrasound (US) and chest x-ray through a waiting-list system, and the waiting time may vary from days to weeks in Denmark depending on the wording of the referral letter and the diagnostic department’s capacity. Many diagnostic departments have implemented direct-access to chest x-ray and other simple x-rays to shorten the waiting time. Recently, some diagnostic departments also implemented direct-access to US. Many cancer patients are not referred through the cancer patient pathways (CPPs)\textsuperscript{31,45,46} and this situation has spurred interest in setting up easy and fast avenues to relevant diagnostic investigations. Both
the UK and Denmark have introduced specific interventions, like open access to CT, to reduce waiting times\textsuperscript{47}. Furthermore, the Danish government has proclaimed that quick and easy access to relevant diagnostics is of high priority\textsuperscript{48}. This possibility for fast access to relevant diagnostic investigation could expedite the diagnosis of cancer, but it also holds a risk of overuse even though recent research refuted this in the context of direct-access to CT scan for suspected lung cancer patients\textsuperscript{49}. There is a lack of knowledge about the use and possible benefits of direct-access to diagnostic investigations for patients in need of quick clarification. In Paper I, we aim to describe patterns of use and cancer prevalence in patients referred by GPs who had the possibility to refer their patients directly to hospital-based US.

Johansen et al. (2012) documented how suspicion of cancer arose in general practice consultations and proposed four main ways of how GPs come to suspect cancer. These four ways include 1) practicing basic knowledge (e.g. alarm symptoms, knowledge of epidemiology), 2) displaying interpersonal awareness (e.g. knowing the patient), 3) acknowledging the patient’s or the GP’s own fear of cancer (e.g. the GP missed a certain type of cancer in another patient which trigger fear of missing it again) and 4) drawing on intuitive knowing/gut feeling\textsuperscript{50}. We define gut feeling in accordance with Stolper’s work as ‘a physician’s intuitive feeling that something is wrong with the patient although there are no apparent clinical indications for this, or a physician’s intuitive feeling that the strategy used in relation to the patient is correct although there is uncertainty about the diagnosis’\textsuperscript{51}. This gut feeling is reported by GPs in many European countries to be an important diagnostic tool, especially when GPs are faced with complicated, vague problems in situations of uncertainty that they have to solve at short notice\textsuperscript{51-53}. Thus, gut feeling is an important factor to consider when studying reasons for referral of patients in whom the GP suspects cancer.
During the past decade, the incidence of cancer has increased 34% for men and 22% for women. In total, 36,989 new cancer cases were diagnosed in 2012. For men, the most frequent cancer types are prostate, lung and colorectal cancer. For women, the most frequent cancer types are breast, lung and colorectal cancer. The elderly (>60 years) population accounts for approximately three quarters of new cancer diagnoses.

Cancer remains the leading cause of death in Denmark besides death from old age, and Danish cancer survival rates are relatively poor in comparison with those of many other European and Western countries. One reason for this may be more advanced stage of cancer at time of diagnosis among Danish cancer patients. Both delays from the onset of symptoms to the patient’s presentation to primary care and delays in the further referral pathway to the secondary health-care system seem to play important roles for the more advanced stages of cancer observed among Danish patients.
HEALTH CARE SEEKING PRIOR TO CANCER DIAGNOSIS

Studies of the diagnosis of cancer suggest that non-conclusive initial visits and a long waiting period for investigations to be performed are likely to delay the diagnosis\(^61,62\). A recent study found that during the 6 months leading up to diagnosis, Danish cancer patients started using more primary and secondary health care services than a reference population\(^63\). The first observed peak was in GP consultations, which is in accordance with previous studies documenting that cancer patients first contact their GPs\(^30,32\). Several studies have shown much variation in the number of GP consultations with cancer symptoms before they are referred to hospital for suspected cancer\(^64,65\). A questionnaire study on delay in the diagnosis of colorectal cancer found that patients with a long diagnostic delay had twice as many consultations before the cancer was diagnosed as patients without long delay\(^66\). To our knowledge, no studies have examined the number of consultations for cancer patients presenting with non-specific symptoms. As implied in a Danish study\(^31\), cancer patients with vague symptoms have a longer median time to diagnosis than patients with alarm symptoms. We lack knowledge of the factors causing this long diagnostic delay. Such knowledge may be acquired through the study of patients’ use of health-care services in the period before they are diagnosed. Furthermore, more detailed knowledge of these cancer patients’ use of primary and secondary health-care services before the time of diagnosis may allow us to better organise the supply of health-care resources and to potentially shorten the time to cancer diagnosis. This knowledge may also identify certain patterns in health-care use that can be used to better identify patients with a higher risk of cancer.
DEFINING TIME INTERVALS

The cancer pathway from first symptom presentation to initiated treatment of cancer is often divided into different time intervals. Previously, the term delay was used, but because of terminological confusion and little methodological rigor a standardised description has been offered (Figure 1.1). Three main time periods have been defined covering the whole period from the first symptom until treatment initiation: Patient interval refers to the time from the first symptom experienced by the patient until the first GP consultation; doctor interval refers to the time from the first symptom presentation to the GP until the initiation of an investigation of potentially cancer-related symptoms, and system interval refers to the time from the start of GP-initiated investigation until the start of treatment. Other time intervals of clinical importance are described in Figure 1.1. Among these intervals, the primary care interval refers to the time from the first presentation at the GP until the first referral to the secondary health-care system, which is the most important interval for this thesis. The primary care interval is very short for the majority of cancer patients, but a substantial primary care interval has been found for approximately one fourth of patients but this varies greatly.
Figure 1.1. Intervals in the cancer pathway

Olesen et al., (2009)70 Weller et al. (2012) 68
TIME AS A FACTOR IN CANCER DIAGNOSIS

Among the many elements related to cancer survival (quality of care, patient behaviour, treatment availability), data suggest that a long diagnostic interval in cancer diagnosis is an important factor and that it is related to poor 1-year survival rates\textsuperscript{56,61,70-73}; and there is growing evidence that a long diagnostic interval increases mortality\textsuperscript{74,75}. Paradoxically, numerous studies of time to cancer diagnosis report counterintuitive results showing that colorectal cancer patients with short diagnostic intervals suffer higher mortality than patients with longer diagnostic intervals\textsuperscript{76,77}. This so-called “waiting time paradox” is likely to be a result of more rapid investigation because severely ill patients present with serious alarm symptoms\textsuperscript{78}.

Nonetheless, existing literature is ambiguous as far as the true value of a long diagnostic interval is concerned\textsuperscript{77,79-87}. A recent review\textsuperscript{88} documented that there is variation between cancer types and that considerably more quality research is needed. Furthermore, The National Awareness and Early Diagnosis Initiative in England (NAEDI) supplement from 2015\textsuperscript{89} supports the focus on early diagnosis of cancer, but also underlines that further research is needed.

The importance of minimising the diagnostic interval lies not only in the possible effect on cancer stage and mortality, but also in the patient’s satisfaction with the GP and health-care in general\textsuperscript{90-92}.

Research has devoted much attention to the primary care interval although it is a comparatively short component in the overall, long diagnostic interval\textsuperscript{30,93-95}. Some studies found variation by gender, age and cancer site in the number of GP consultations prior to referral and in the length of the primary care interval\textsuperscript{96}. One of the most important factors associated with long diagnostic intervals is symptom misattribution or initial misdiagnosis\textsuperscript{62}. Other factors that may affect the length of the primary care interval include the GP’s or the patient’s
knowledge, the GP’s clinical skills, patient or GP beliefs, access to relevant investigations, constraining referral guidelines, and pressure to reduce referrals from general practice\(^9^7\). Simply assigning the responsibility of prolonged GP intervals to the GPs will not provide the explanation; nor will it give an indication of how best to intervene to improve health-care outcomes.

Factors in the secondary health-care system are primarily relevant during the interval between GP referral and final diagnosis (system interval), but they can also affect investigations in primary care and prolong the GP interval. Examples of such factors include waiting times for secondary health care, administrative delays and lack of integration between different levels of health-care\(^9^7\). Several studies show that waiting time for tests and lack of referral guidelines are among the most important issues related to prolonged system intervals\(^9^8,9^9\).
As a result of Danish cancer patients’ poor prognosis, political attention was drawn to waiting-lists in the Danish health-care setting, and the Danish government launched two comprehensive cancer plans in 2000\textsuperscript{100} and 2005\textsuperscript{101}. The implementation of the second cancer plan\textsuperscript{101} and the classification of cancer as an acute disease led to the introduction of standardised CPPs as a strategy to reduce waiting time for patients with a reasonable suspicion of cancer\textsuperscript{70}. In the autumn of 2007, multidisciplinary working groups chaired by the National Board of Health were established to describe the clinical pathway for each of the commonest cancers\textsuperscript{102}. Thus, CPPs were initiated for head and neck cancer, breast, colorectal and lung cancer from 1 April 2008; and within February 2010, CPPs were implemented for 34 types of cancers\textsuperscript{103}. Once the GP refers the patient urgently, all diagnostic and treatment procedures are organised as temporally and substantively well-defined processes where all relevant investigations and treatments are pre-planned and pre-booked within a given number of days. The aim of the CPP is to offer patients optimal diagnosis and treatment, thereby improving their prognosis and quality of life and reducing the insecurity that accompanies unwarranted delays.

The Danish CPPs and the equivalent initiative in the UK (2-week wait referral (2WW)) and the underlying practice guidelines focus on alarm symptoms of cancer\textsuperscript{104-106}, but they do not take into consideration that many cancer patients do not present with alarm symptoms and therefore do not benefit from these standardised pathways. The CPPs may shorten the diagnostic intervals for patients with alarm symptoms\textsuperscript{107-109}, but a recent Danish study demonstrated that only 40\% of all cancer patients benefitted from the implementation of alarm-symptom-based CPPs\textsuperscript{31}; and CPPs for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP) were therefore introduced. GPs can now refer patients with serious non-specific symptoms when they suspect
cancer and the nature of the alarm symptoms do not allow the GP to single out a specific CPP to which the patient should be referred.\textsuperscript{110}

Silkeborg Hospital developed and set up a diagnostic centre in 2009. This diagnostic centre was the forerunner of the NSSC-CPP and it permitted GPs to refer patients with serious, non-specific symptoms and signs of cancer or other serious disease to this centre. The NSSC-CPP was implemented on a nationwide scale as a separate CPP in 2011, and contrary to the referral criteria for the cancer-specific CPPs, the criteria for referral under this scheme were very broad\textsuperscript{111}, e.g. the GP’s mere suspicion of a patient being seriously ill is reason enough for referral. However, research into the patients referred to the NSSC-CPP is scarce. The second part of this thesis (Paper II and Paper III) characterises the referred patients and explores their contact to the GP and the diagnostic investigations leading up to referral.
In Denmark, GPs act as first line for unselected patients and as ‘gatekeepers’ regarding the secondary health-care system. Approximately 80% of all cancer patients initially present symptoms to their GP who therefore plays a central role in detecting cancer early.

Danish cancer patients have a relatively poor survival from cancer compared with citizens from many other European and Western countries. One reason may be that they have more advanced stages of cancer at the time they are diagnosed. Both delay from onset of symptoms to the patients’ presentation to primary care and delay in the further referral process to the secondary health-care system may partly explain Danish citizens’ more advanced stages of cancer when diagnosed.

Granting GPs direct-access to diagnostic investigations may expedite the diagnosis of cancer. There is a remarkable lack of knowledge of the GPs’ use of direct-access investigations and of the cancer prevalence among referred patients.

Concerns about the length of the diagnostic interval lay at the heart of the implementation of ‘fast-track’ cancer pathways which in the UK were introduced as the 2WW and in Denmark as the CPPs. In the beginning, the CPPs focused on alarm symptoms of cancer. A Danish study documented that only 40% of patients later diagnosed with cancer were referred to the alarm-symptom-based CPPs. Moreover, there is growing evidence that only half of all cancer patients initially presented with what the GPs characterised as alarm symptoms; the rest presented either non-specific or general symptoms and therefore the NSSC-CPP were introduced.
Knowledge about patients referred to the NSSC-CPP and their health-care-seeking behaviour may help us develop new effective strategies to shorten diagnostic intervals for cancer patients with non-specific symptoms and signs of cancer.
CHAPTER 2:

AIMS
The overall aims of this thesis were to gain insight into initiatives taken to ensure earlier diagnosis of patients presenting with serious, non-specific symptoms that could be cancer. This insight will be sought by exploring GPs’ use of direct-access to abdominal ultrasound (US), the characteristics of patients referred to the new cancer patient pathway for serious non-specific symptoms and signs of cancer (NSSC-CPP) and the patterns of pre-diagnostic health service utilisation of these patients.

The specific aims of this thesis were as follows:

1. To describe the patterns of use and estimate the cancer prevalence when providing Danish GPs with direct-access to hospital-based US (Paper I).

2. To describe the characteristics of patients referred from general practice to the Danish NSSC-CPP and to estimate the probability and distribution of cancers in this population (Paper II).

3. To investigate the rate of daytime GP face-to-face consultations, diagnostic investigations performed in general practice and diagnostic investigations in secondary care among cancer patients diagnosed through the NSSC-CPP. These figures were investigated 12 months prior to either date of cancer diagnosis or referral date to the NSSC-CPP. The results were compared with both a matched cancer reference group and a non-cancer NSSC-CPP reference group. (Paper III).
CHAPTER 3:

METHODS

This chapter describes the methods used in the thesis and papers. Table 3.1 gives an overview of the study design, the identification of the study population, inclusion methods, the data sources and the outcome measures for the three papers in the thesis. A more detailed description of the methods of the three different studies is given in Chapters 5-7 where the specific papers can be found.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study design</th>
<th>Study population</th>
<th>Inclusion methods</th>
<th>Data sources</th>
<th>Outcome measures</th>
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<tbody>
<tr>
<td>I</td>
<td>Descriptive/cross-sectional study</td>
<td>Patients (≥18 years) referred from a GP to US at the Department of Diagnostic Imaging, Vejle Regional Hospital 01.08.2009-31.01.2010</td>
<td>US listed in the local RIS at Vejle Regional Hospital</td>
<td>GP referrals, registers (DCR, CRS, NPR) and the local RIS at Vejle Regional Hospital</td>
<td>Symptoms and clinical findings</td>
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<td>The GP’s suspicion of cancer</td>
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<td>Cancer and non-cancer diagnoses</td>
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<tr>
<td>II</td>
<td>Descriptive/cross-sectional study</td>
<td>Patients (≥18 years) referred to the filter function at the NSSC-CPP at Aarhus or Silkeborg Hospital 07.03.2012-27.03.2013</td>
<td>Silkeborg: A unique digital marker on the battery of blood tests. Aarhus: A unique code on the NSSC-CPP CT-scan</td>
<td>Questionnaires completed by the GPs and registers (DCR, CRS, NPR and NHSR)</td>
<td>Symptoms, clinical findings and cancer diagnoses. Distribution of cancers according to referral characteristics, primary care interval, GP’s suspicion of cancer and gut feeling.</td>
</tr>
<tr>
<td>III</td>
<td>Matched comparative study</td>
<td>1. Cases: All cancer patients (≥18 years) referred to the filter function at the NSSC-CPP at Silkeborg Hospital 01.01.2011-31.12.2012 2. Cancer reference group: A matched group of ‘regular’ cancer patients 3. non-cancer NSSC-CPP reference group: All patients referred to the filter function at the NSSC-CPP not diagnosed with cancer</td>
<td>Patients included if they had either a specific US or a specific digital marker in the battery of blood tests taken. Both unique for the filter function Cancer patients were identified through the DCR</td>
<td>RIS Registers (DCR, CRS, NPR and NHSR)</td>
<td>Use of primary health care services (contacts and diagnostic tests) Use of selected diagnostic investigations performed at the hospital Cancer diagnoses</td>
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</table>

1 Abdominal ultrasound 2 The Radiology Information System 3 The Danish Cancer Registry 4 The Danish Civil Registration System 5 The National Patient Registry 6 Cancer Patient Pathway for patients with serious non-specific symptoms and signs of cancer 7 The National Health Services Register 8 When the GP selected the battery of blood tests, the digital markers are automatically added and registered when the GP sends the blood samples to Silkeborg Hospital
Paper I

Vejle Regional Hospital is part of Lillebaelt Hospital in the Region of Southern Denmark. The Department of Diagnostic Imaging at Vejle Regional Hospital provides services to approximately 190 GPs and 300,000 citizens. Direct-access to US on a day-to-day basis was introduced in 2006 and was originally implemented as a service to patients and GPs for any health-related reasons, irrespective of cancer suspicion. Usual waiting-list US, where the patient received a scheduled appointment, was continued nonetheless.

An electronic referral was forwarded to the Department of Diagnostic Imaging at Vejle Hospital if the GP found reason to order a US. In this referral, the GP listed the reasons for requesting the US and stated whether or not cancer was suspected. The US was performed by either a consultant radiologist, an experienced sonographer or a medical resident trained in US and supervised by an experienced supervisor (if necessary).

Patients referred to direct-access US could go to the hospital the same day as a number of examination rooms were reserved at the radiology department for direct-access US services.

At the time where the data collection started, the Department of Diagnostic Imaging at Vejle Regional Hospital was the only department offering the possibility of direct-access US. It would have been preferable to include patients from a hospital in the same Region like the rest of the present PhD project, but this was not possible. This is further discussed in Chapter 8.

Paper II and III

Aarhus and Silkeborg Hospitals are situated in the Central Denmark Region. All patients referred to the NSSC-CPP underwent a filter function consisting of a
battery of blood tests, urine test strip and diagnostic imaging. Diagnostic imaging consists of US (NSSC-CPP US) and a chest X-ray at Silkeborg Hospital or a CT scan (NSSC_CPP CT) with contrast of the chest, abdomen and pelvis at Aarhus Hospital. The diagnostic imaging was described by a radiologist; subsequently, the GP interpreted all test results and decided on any further diagnostic approach. This approach could be either watchful waiting or referral to a diagnostic centre for further investigations. If a specific disease or type of cancer was suspected, further diagnostic steps could involve referral to a medical specialist or another cancer-specific CPP (Figure 3.1).

A diagnostic centre is a medical unit with comprehensive facilities for diagnostic investigation, including easy access to expertise in a wide range of relevant medical specialties (e.g. oncology, gynaecology, gastro-enterological surgery, orthopaedics and radiology). NSSC-CPP patients referred to a diagnostic centre underwent further investigations on the basis of the presented symptoms and the clinical findings (e.g. blood tests, diagnostic imaging, endoscopies and biopsies). Based on these findings, the patient was either referred to a CPP for a specific cancer, to a specific hospital department or back to the GP.
Figure 3.1 The organisation of the cancer patient pathway for patients with serious non-specific symptoms and signs of cancer
STUDY POPULATION

Paper I
All adult (≥18 years) patients referred from general practice to US at the Department of Diagnostic Imaging at Vejle Regional Hospital, Lillebaelt Hospital, during the period from 1 August 2009 to 31 January 2010 were included in this study. Patient data were extracted from the local Radiology Information System (RIS), which keeps records of all radiological investigations performed at the hospital. We excluded patients receiving musculoskeletal or control US for malignant or benign disease and patients outside the catchment area of Vejle Regional Hospital, Lillebaelt Hospital.

Paper II
This paper includes patients (≥18 years) referred to the NSSC-CPP at Aarhus and Silkeborg Hospital during the period from 7 March 2012 to 27 March 2013. All patients who underwent the filter function were identified and included. At Silkeborg Hospital, the patients were identified by a unique digital marker on the battery of blood tests. When the GP selected the battery of blood tests, the digital marker was automatically added and registered. At Aarhus Hospital, we identified all patients who underwent the NSSC-CPP CT scan as this CT scan had a unique code.

Every fortnight, the patients were identified and linked to the county’s Health Service Registry (HSR) in order to identify each patient’s GP.

Some referrals to the NSSC-CPP were made from hospital departments and not from the GP. The GPs of these hospital-referred patients were contacted. However, the patients were only included in the study if their GP stated that they had been involved in the referral or diagnosis of the patient.
Paper III
First of all, the basis population of this paper was patients referred to the NSSC-CPP at Silkeborg Hospital in the years 2011-2012. To be included as the basis population, the patients needed to have part of the filter function performed. The inclusion was done by (1) Identifying patients who had the battery of blood tests taken and this was done by the unique digital marker as described in paper II. (2) Identifying patients who had the NSSC-CPP US performed. All US performed as part of the NSSC-CPP from 1 January 2011 were registered with a unique code. As seen in Paper III (Figure 2, page 103), there was a partial overlap between the two identified populations.

This paper includes three populations as described in Table 3.1.

As seen in Paper III (figure 3, page 104), 16 cases were excluded before the matching process. Six of the 314 cases could not be used in the matching procedure as they had not been living in Denmark for a full period of 24 months prior to the index date and four were not listed with a specific GP (health insurance group 2). Six of the cancer patients could not be used as these cancer patients were diagnosed with cancer in 2013 and register data regarding healthcare use were only available until 31 December 2012.

Therefore, cases were defined as the 298 cancer patients that could be used in the matching procedure as described above.

The two reference groups are described below.

Reference groups

We used incidence density sampling to create the cancer reference group.

To create the cancer reference group, ten randomly selected persons from a population registered with cancer were sampled per case. They were matched on region (Denmark has five regions and each region operates the hospital
service in that region), cancer type (ICD10), gender, date of cancer diagnosis (+/- 1 year) and date of birth. These references were alive and resident in Denmark and they were affiliated with a specific GP at the date of diagnosis/index date and throughout the full year preceding the referral to the cancer diagnosis. References could be sampled as references more than once for different cases, but only once for the same case. The use of incidence density sampling meant that a reference could also later be included as a cancer case.

The non-cancer NSSC-CPP reference group consisted of the patients referred to the NSSC-CPP without cancer 6 months after referral.

When comparing the cancer reference group with the cases, the index date was defined as the cases’ dates of cancer diagnosis. But when we compared the non-cancer NSSC-CPP reference group and the cases, the index date was the date of referral to the NSSC-CPP to ensure comparability between the reference group and the cases.

Furthermore, it was not possible to obtain ten references for all cases as some cancers were very rare, and this reduced the size of the cancer reference group by 50. In Paper III, the cancer reference group accordingly comprised only 2930 cases as opposed to 2980; Tables 1 and 3, Figures 3 and 4
The Radiology Information System

The Radiology Information System (RIS) is a computerized database used by radiology departments to store, manage and distribute patient radiological data and imagery\textsuperscript{113}. The system is generally used to track and schedule patients, report results and track images. The RIS complements the HIS (Hospital Information Systems) and is critical for efficient workflow to radiology practices. For Paper I, we used the RIS to retrieve data on the civil registration number (CRN) for patients in the inclusion period, referral and examination dates, the medical conclusion of the US and information about whether the patient was referred through direct-access or a waiting-list. For Paper III, we used the RIS to retrieve data on the CRN and the examination date for patients who underwent a US in the inclusion period.

LABKA

All hospital laboratories in the Central Denmark Region store their laboratory test results in a clinical laboratory information system called the LABKA\textsuperscript{114}. The LABKA system functions as a central routine diagnostic tool for medical doctors in all private clinics and hospital departments in Denmark. New laboratory test results are entered immediately and directly into the system, with automatic online updating and access to results for all relevant hospital personnel. Exceptions are some results from small and rapid point-of-care devices used by medical staff or patients themselves for instant analysis, e.g., International Normalised Ratio (INR), blood glucose, haemoglobin and C-reactive protein (CRP). For every digital marker and tumour marker panel, we retrieved who requested the blood test (GP or hospital), the CRN of the tested patient and test dates for the study populations in Paper II and Paper III.
The Danish Civil Registration System

Since 1968, all Danish citizens have been registered in the Danish Civil Registration System (CRS) and assigned a unique 10-digit CRN. The CRN contains information on date of birth, gender and a unique code identifying the individual. The register furthermore holds information about name, place of birth, place of residence, citizenship and marital status. The unique CRN can be linked to individuals across all national registries, including comprehensive registers containing health and socioeconomic data. We used this register along with several other registers to identify reference populations in Paper III.

The Patient Administrative Systems

All hospital contacts are registered in the Patient Administration Systems (PASs). Its purpose is to collect administrative information on hospital activities. The PAS comprises variables like the patient’s CRN, dates of admission and discharge, diagnoses classified according to the International Classification of Diseases (ICD-10), codes for undertaken procedures, the GP’s provider number and different additional codes. Of particular relevance for this study, the PAS comprises the additional code AZCA1. Certain diseases require a more detailed reporting, e.g. cancer. The AZCA1 code is required by law whenever a hospital ward is reporting a cancer diagnosis for the first time, assuring minimum regional differences. To provide data for the National Patient Registry (NPR), the hospitals are committed to update the PAS for the previous month by the 10th of each month and to report these data to the NPR.

The Danish National Patient Register

The Danish National Patient Register (NPR) was established in 1977. It is a national database unifying information from the five regional PASs. When data
are entered into the NPR, not all information is transferred, e.g. the GP provider number. The PAS is regional, whereas the NPR is run by the Danish Health and Medicines Authority (former National Board of Health) who carries out ongoing validation of the data from the PAS. Thus, both the PAS and the NPR are continuously updated. Since 2000, the NPR has served as the basis for the payment of public as well as private hospitals. Additionally, the NPR is used for medical research, mainly epidemiological studies and quality improvement studies and for identifying patients for various studies, even if this was not the main purpose of the NPR. The NPR holds information on a patient’s CRN, hospital department, dates of hospital admission and discharge, outpatient contact, treatment, waiting status, diagnosis (according to the ICD 10) and type of operation, examination, and treatment\textsuperscript{118}.

For Paper II, information on the patient’s cancer diagnosis was retrieved through the NPR after 31 December 2012 as data from the Danish Cancer Registry (DCR) were only available up to this date when we performed the data analysis.

The Danish Cancer Registry
The DCR was established in 1942 and is a national research register designed to collect and process data on incident cancer patients. It has been shown to be accurate and to have nearly complete registration of cancer cases. The registry contains information on the date of diagnosis, tumour topography, ICD10 diagnosis, morphology, stage and grade among others\textsuperscript{119}. Reporting to the DCR became mandatory in 1987. The DCR went through a modernisation from 2004-2008 in order to ensure future data quality\textsuperscript{119}. For several years, this caused considerable delay in data entry, and even today it is only possible to extract data from the DCR for the previous calendar year due to comprehensible quality control and validation\textsuperscript{11,117,119}. 
The DCR was used to identify cancer among included patients in Papers I and III and until 31 December 2012 in Paper II.

The Danish National Health Service Registry
The Danish National Health Service Register (NHSR) contains information about the activities of health care professionals contracted with the tax-funded public health-care system. These professionals are GPs, medical specialists, dentists, physiotherapists, psychologists, etc. The purpose of the register, which is within the remit of the Danish Health and Medicines Authority, is to document activities in primary health care for administrative use and to contribute to research in public health\textsuperscript{120}. The data in the register are generated through the GPs’ invoices to the Regional Health Administration. All general practices are computerised, and every week the practices forward electronic fee requests containing information about the citizens, the provider and the type of service to the Regional Health Administration which passes this information on to the National Board of Health. The strengths of the NHSR include completeness, size and a long follow-up period. However, reservations must be made regarding the validity of the register as no studies of this have been made\textsuperscript{120}. Data on the use of primary health care services (contacts and diagnostic procedures) were retrieved from this registry and used in Paper III.

Statistics Denmark
The Danish Integrated Database for Labour Market Research (IDA), which is run by Statistics Denmark\textsuperscript{121}, provides information on the educational level and marital status of the patients in Paper III. Data on each patient could be linked by using the patient’s CRN. Missing information on the registry-based variables

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ranged from 0% for the variables age, gender and diagnosis to 2.6% for data on educational level.\textsuperscript{122}
DATA FROM QUESTIONNAIRE

The questionnaire for the GPs was developed in the period from August 2011 to February 2012.

Development of questionnaire:

The themes of the GP questionnaire were identified on the basis of literature review, the clinical experience of the research group and experiences from similar studies using questionnaires in research performed at the Research Unit for General Practice, Aarhus University. The themes included: Patient symptoms, GP clinical and para-clinical findings, diagnostic pathway until referral, patients’ chronic diseases at referral, reasons for referral, the GPs’ estimation of the referred patients’ risk of cancer at referral and several questions regarding the GPs’ use of ‘Gut feeling’ (see further detail below).

Already existing questions were used whenever possible. Otherwise, ad hoc questions were constructed. The questions (“the item bank”) were carefully discussed within the research group and specific hypotheses were constructed for each topic. Much benefit was derived from contacts with GPs and researchers within the field.

We wrote two different cover letters; the first was a letter specifically for patients who were registered as referred by the GP; and second was a letter for patients who were registered as referred by a hospital department. The GPs of patients who were referred by a hospital department were asked to confirm their involvement in referring the patient. This was necessary as the hospital sometimes ordered the battery of blood tests even though it was the GP who actually had referred the patient.
Pilot testing

Even though most of the questions in the questionnaire were taken from existing and validated questionnaires, we performed a pilot test.

Cognitive semi-structured interviews were conducted with five GPs with research experience in this field in order to establish whether the questions in the questionnaire were comprehensible, meaningful and relevant in the context of general practice. We also intended to establish whether the response categories of the scales were sufficient and whether important concepts were understood correctly. Based on the interviews, adjustments were made to the questionnaire. The wording of some of the items was changed. In this way, we ensured a high level of content validity in relation to the research questions\textsuperscript{127}. To ensure as high construct validity as possible in the items regarding the GPs’ gut feeling, we paid special attention to these issues during the interviews.

After the adjustment, another pilot test was conducted among ten GPs without research experience.

Single items in the GP questionnaire

Symptoms

The GP was asked to indicate which of 21 listed symptoms the patients had at the time of referral; this question included the possibility of adding additional symptoms. The additional symptoms were classified by MLI according to the International Classification of Primary Care, Second edition (ICPC 2)\textsuperscript{128}.

Abnormal clinical and para-clinical findings

These findings included those of the GP’s abnormal findings during their clinical and para-clinical examination of the patient that were relevant at referral. In the questionnaire, 13 clinical and 3 para-clinical findings were
described with the possibility of adding additional findings. The additional clinical findings were classified by MLI according to the ICPC 2.

**Chronic diseases at referral**

In the questionnaire, 12 different chronic diseases were listed with the possibility of adding additional chronic disease. The GP was asked by MLI to state which chronic diseases the patient was diagnosed with at the time of referral. The additional chronic diseases were classified by MLI according to the ICD-10.

**Cancer risk at referral**

The GP was also asked to state his/her estimation of the patient’s risk of cancer from 0% to 100% at referral.

**GP interval**

The GP interval was measured by two questions. These questions were based on the Aarhus Statement and have previously been used in other projects at the Research Unit for General Practice. The first question requested information on the precise date of the first GP consultation with the patient concerning the symptoms that resulted in the referral of the patient. The second question asked for the precise date of referral to the NSSC-CPP; this information was not used in Paper II as we chose to use the date of the battery of blood tests from LABKA as the date of referral.

**Gut feeling**

Three items were developed to uncover the GPs’ use of gut feelings. The items were based on Stolper’s work on gut feeling. In item one, the GPs were
asked to rate the extent to which they had experienced a gut feeling in the consultation with the patient (degree of gut feeling was categorised into five possible levels from ‘no influence’ to ‘very high influence’). In item two, they were asked whether this feeling affected their decision to refer the patient to the NSSC-CPP. In item three, the GPs were asked to evaluate which factors contributed to the experience of any gut feeling.

Data collection

Patients were identified based on the algorithm described on page 140. The general practice where the patient was listed received an invitation letter, a questionnaire and a prepaid envelope within 2 weeks of the patient’s referral. The GP who had been responsible for the patient’s treatment and care was asked to fill out the questionnaire. GPs who did not respond to the questionnaire received a reminder after three weeks. The GPs received €16 as remuneration for each completed questionnaire. Each questionnaire was assigned a unique ID number enabling us to merge data from GPs and registries into one data file comprising all information on each patient.

Data entry

All returned questionnaires were coded by MLI according to a predefined coding manual. The predefined coding manual was a manual I made to ensure that all questionnaires were coded uniformly. Furthermore, it served as an instruction for the assistant who scanned all the returned questionnaires. The manual contained detailed instructions on how to code each question and how to approve the scanned questionnaires. To ensure proper scanning, the assistant was instructed to put aside a questionnaire when in doubt and these questionnaires were checked by me.
The questionnaires were electronically scanned and verified by use of the TeleForm® software, version 8.0. (Cardiff software Inc., San Marcos, CA, USA). A high accuracy has been documented for this procedure\textsuperscript{134}. However, a control procedure was performed to ensure no more than 1% error in the scanning and verification process. Fifty GP questionnaires were double-checked, and the error did not exceed 1% in the checked questionnaires.

Questionnaire data were then combined with register data to be used in Paper II.

For a short overview of data collection, see Table 3.2.
### Table 3.2 Overview of data collection in each of the three Papers (I,II,III)

<table>
<thead>
<tr>
<th>Registers</th>
<th>RIS</th>
<th>LABKA</th>
<th>Questionnaire</th>
<th>DCR</th>
<th>NPR</th>
<th>NHSR</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>- CRN on all included patients&lt;br&gt;- Date of investigation&lt;br&gt;- Direct-access or waiting-list US&lt;br&gt;- Data regarding the GP’s suspicion of cancer, symptoms and clinical findings from the text written in the GP’s referral&lt;br&gt;- Medical conclusion of the US including non-cancer diagnoses and information on cancer-suspicious findings seen on the US&lt;br&gt;- Referring GP/hospital department</td>
<td></td>
<td></td>
<td>- Cancer diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>- CRN on all included patients referred to the NSCC-CPP at Aarhus Hospital&lt;br&gt;- Date of investigation&lt;br&gt;- Referring GP/hospital department</td>
<td>- CRN on all included patients referred to the NSCC-CPP at Silkeborg hospital (digital marker on the battery of blood tests)&lt;br&gt;- Date of investigation&lt;br&gt;- Referring GP/hospital department</td>
<td>- Data to confirm that the GP had been involved in the referral&lt;br&gt;- Data regarding symptoms, abnormal clinical and paraclinical findings and chronic diseases at referral&lt;br&gt;- The GP’s estimation of the patient’s risk of cancer at referral&lt;br&gt;- Dates used in the estimation of the GP interval&lt;br&gt;- Data regarding the use and relevance of the GP’s gut feeling</td>
<td>- Cancer diagnosed before 31.12.2012&lt;br&gt;- Cancer diagnosed after 31.12.2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>-- CRN of all patient who underwent a specific US 01.01.2011-31.12.2012&lt;br&gt;- Date of investigation (used as inclusion date)</td>
<td>- CRN on all patients who underwent the battery of blood tests via a unique digital marker</td>
<td>- Cancer diagnosed before 31.12.2013&lt;br&gt;- Daytime use of general practice&lt;br&gt;- Use of diagnostic investigations in general practice&lt;br&gt;- Use of selected diagnostic investigations performed at a hospital: US, CT, Colonoscopy/sigmoidoscopy and thoracic X-ray&lt;br&gt;- Socio demographic data</td>
<td></td>
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</table>

1Civil registration number, 2Abdominal Ultrasound, 3Cancer Patient Pathway for patients with serious non-specific symptoms and signs of cancer, 4DCR-data were available for paper III as processing of data finished in June 2015.
DATA EXTRACTION

Data were analysed using STATA 12.0 (StataCorp LP, College Station, TX, USA).

Outcome Measures

**Paper I**

Data regarding cancer diagnosis (ICD-10) and date of diagnosis (defined as the first date of hospital admission after confirmation of cancer diagnosis) were retrieved from the DCR. We reported cancer diagnosed up to 3 and 6 months after the inclusion period and the prevalence of cancer where US gave rise to suspicion of cancer. The latter we used to calculate the prevalence rate and the PPV mentioned under statistical analyses, and these results were presented in the paper. Results using prevalence of cancer up to 3 and 6 months after US were also presented.

The GP’s cancer suspicion regarding each included patient was extracted from the GP referrals in the RIS and were categorised into suspicion or no suspicion of cancer.

Data on non-cancer diagnoses as well as clinical findings and on the patient’s symptoms listed in the GP referrals were also extracted from the RIS.

**Paper II**

Data regarding each patient’s cancer diagnosis were retrieved from the DCR. These data were available only until 31 December 2012. Cancer diagnoses made after this date were retrieved from the NPR until 6 months after the date of inclusion of the last patient.
Data on symptoms, GP’s suspicion of cancer, the GP’s gut feeling and clinical findings were extracted from the GP questionnaires (see Appendix 1, page 207). The primary care interval was calculated based on information from the GP questionnaire and the LABKA. The GP questionnaire provided information about the precise date of the first GP consultation with the patient concerning the symptoms that resulted in the referral of the patient.

The LABKA provided the registered date of the battery of blood tests and this was used as the date of referral to the NSSC-CPP.

*Paper III*

Data regarding each patient’s cancer diagnosis were retrieved from the DCR.

Data on primary health care services provided were retrieved from the NHSRT and included daytime contacts to the GP and diagnostic test performed at the GP. The codes are presented as they are classified by the GPs and as they are registered in the NHSRT.

All included contacts to the GP:

- 0101 Consultation
- 0411, 0421, 0431, 0441, 0451, 0461 Home visit
- 0105 Email consultation
- 0201 Telephone consultation

All included diagnostic test performed at the GP:

- Blood samples performed at the GP:
  - 7115 (Machinery blood count)
  - 7120 (C-reactive protein (CRP))
  - 7177 (Sedimentation rate (SR))
- 7108 (B-haemoglobin)

- Blood samples taken at GP but sent to the hospital for analysis
  - 2101

- Urinalysis
  - 7101 (U-stix)
  - 7189 (Urine sent to hospital for further analysis)
  - 7122 (Microscopic examination of urine)

- Lung function tests
  - 7183 (Peak flow)
  - 7113 (Extensive lung function test)
  - 7121 (Double lung function test with reversibility)

- Electrocardiogram (ECG)
  - 7156

Data on included hospital diagnostic investigations were retrieved from the NPR at statistics Denmark. The codes are presented as they are classified by the doctors and as they are registered in the NPR.

Overview of included hospital diagnostic investigations is listed here:

Colonoscopy/sigmoidoscopy
- KUJ32 Colonoscopy
- KUJ35 Colonoscopy with biopsy
- KUJ42 Sigmoidoscopy
- KUJ45 Sigmoidoscopy with biopsy
• KJFA15 Endoscopic polypectomy

Chest x-ray
• UXRC00 Chest

CT scan
• UXCA00 Cerebrum
• UXCB00 Neck
• UXCC00 Thorax
• UXCC60 Mediastinum
• UXCC75 Lungs
• UXCC77 High Resolution Lungs
• UXCD00 Abdomen
• UXCD10 Upper abdomen
• UXCD15 Lower abdomen
• UXCD20 Retroperitoneum
• UXCD40 Liver
• UXCD55 Pancreas
• UXCD60 Kidney
• UXCD75 Bladder
• UXCE10 Columna cervicalis
• UXCE20 Columna thoracalis
• UXCE30 Columna lumbalis

Ultrasonic investigations
• UXUD10 Abdomen
• UXUD11 Upper Abdomen
• UXUD15 Lower Abdomen
• UXUD20 Retroperitoneum
• UXUD40 Biliary system
• UXUD41 Pancreas
• UXUD61 Kidney
• UXUD70 Liver
• UXUD75 Bladder
STATISTICAL ANALYSIS

We applied 95% confidence intervals (95% CI) where relevant, and we regarded a probability of 5% or less as statistically significant. For each paper, data were analysed according to the specific aim.

Paper I

We used chi-square and Fisher’s exact tests to identify differences between groups. Wilcoxon rank-sum test was used to examine differences in waiting time.

The diagnostic value of the GP’s cancer suspicion was measured using the sensitivity, specificity, the PPV and the negative predictive value (NPV).

The prevalence ratio (PR) with the corresponding 95% CI was used to estimate differences between the prevalence of cancer where US gave rise to suspicion of cancer among patients with direct-access US and patients with waiting-list US. Furthermore, the PR was used to estimate associations between the GP’s cancer suspicion and a subsequent diagnosis of cancer.

Paper II

We used the chi-square (χ²) test and Wilcoxon rank-sum to test differences between participants and non-participants and to examine differences in primary care interval between patients with and without cancer. The primary care intervals are presented as medians, 75th and 90th percentiles.

The frequency of cancer was presented as prevalence in percentages (%). Associations between different characteristics and a subsequent cancer diagnosis were estimated with prevalence rate ratio (PRR) from a generalised linear
model, unadjusted and adjusted for age and gender, with the corresponding 95% CIs.

Paper III
Odds ratios (ORs) of having a GP contact, GP diagnostic tests or a diagnostic investigation performed at a hospital in the year before the index date (omitting the last month before) were calculated using a conditional logistical regression model to account for the matched design (Paper III, Table 3, page 108). When calculating OR between cases and non-cancer NSSC-CPP patients, logistic regression models were used as the non-cancer NSSC-CPP patients was not matched with the cases.

We calculated the incidence rate ratios (IRRs) for comparison of the monthly rates used in Figure 4 by using a negative binomial regression model and applying cluster robust variance estimation to account for heterogeneity between subjects. Included in the models were also a two-group effect of gender and marital status, a three-group effect of education and a linear effect of age (on the implied log scale).

As shown in a Danish study and in Paper III (Figure 4, page 107), cancer patients had a marked rise in contacts to their GP and in the number of diagnostic investigations the last month prior to diagnosis. This marked rise may hide any smaller differences otherwise seen 12 months prior to diagnosis. Therefore, when analysing the total number of contacts, tests and investigations, we chose to exclude the outcomes 1 month prior to diagnosis (Paper III, Table 3, page 108).
CHAPTER 4:

RESULTS IN SUMMARY

This chapter is a brief summary of the results of each paper in the thesis. A more detailed description of the results is presented in Chapters 5 to 7.

Table 4.1 Study results in Papers I-III

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Description of GP referrals to and use of direct access versus waiting list to US and cancer prevalence of the referred patients</td>
</tr>
<tr>
<td>II</td>
<td>Description of patients referred to the NSSC-CPP and distribution of cancer among these patients.</td>
</tr>
<tr>
<td>III</td>
<td>Health-care utilisation prior to referral to the NSSC-CPP and cancer diagnosis among patients referred to the cancer patient pathway for patients with serious non-specific symptoms and signs of cancer</td>
</tr>
</tbody>
</table>
In Paper I, 701 patients were included of whom 420 (59.9%) were referred to direct-access US and 281 (40.1%) to waiting-list US. The GPs suspected cancer in 10.2% of all patients referred to direct-access US and in 9.3% of all patients referred to waiting-list US (p=0.313).

Cancer was found in 19 (2.7%) of the referred patients within 6 months after the US investigation (16 in the direct-access group and 3 in the waiting-list group), and US gave rise to suspicion of cancer in 11 of these patients (57.9%). The most frequent cancer types were lung, colon and pancreatic cancers. The most frequent non-cancer diagnoses were cholecystolithiasis and steatosis. In total, 417 (59.5%) patients got one or more non-malignant diagnoses, and 265 (37.8%) patients were discharged without a diagnosis. None of the patients who received no diagnosis at the US developed cancer during the 6-month follow-up.

In 10 patients (2.4%) referred via direct-access, the US gave suspicion of their later verified cancer diagnosis. The association between the GP’s cancer suspicion (suspicion or no suspicion) and the subsequent diagnosis of cancer for patients referred to direct-access US showed a PR of 5.8 (95%CI: 1.7-19.9), while the PPV of the GP’s cancer suspicion was 9.3 (95%CI: 2.6-22.1).

In only one patient (0.4%) referred via the waiting-list did the US give rise to suspicion about the patient’s later verified cancer diagnosis.

Thus, the prevalence of cancer was higher among those in whom direct-access US gave rise to suspicion of cancer than among those who were referred to waiting-list US. This finding was, however, not significant (PR: 6.7 [95%CI: 0.85-52.0]). For those diagnosed with cancer within 3 and 6 months after US, we also found a higher prevalence of cancer among those in the direct-access group, and these findings were significant (See Paper I, Table 5, page 108).
The median waiting time from referral to performed US was 1 day (IQR: 1-4) for direct-access US and 16.9 days (IQR: 10-21) for waiting-list US (p<0.001).
In Paper II, 1278 completed GP questionnaires (73.8%) were returned, matching 1278 patients referred to the NSSC-CPP in Aarhus and Silkeborg Hospital. A total of 82 different symptoms and 51 clinical findings were identified from the GP questionnaires. There was wide variation in the number of symptoms per referral, and the most frequent symptoms were non-specific and vague symptoms, e.g. weight loss and fatigue. Only few symptoms were highly predictive of cancer, e.g. jaundice, dysphagia and neurological dysfunction; and most of these symptoms were rare (< 2% of patients), except lump/tumour which was present in almost 9% of the patients.

Six months after referral, 16.2% had a cancer diagnosis; the most common cancer types were lung cancer (17.9%), colorectal cancer (12.6%), haematopoietic tissue cancer (10.1%) and pancreatic cancer (9.2%).

The median primary care interval for patients diagnosed with cancer was 15 days; the 75 and 90 percentiles were 72 days and 130 days, respectively. The study population was too small to have the necessary statistical power to test differences in diagnostic interval between cancers; but breast, liver and biliary cancer patients seemed to have shorter than average primary care intervals, while patients with metastasis and cancer of the prostate, hematopoietic tissue, oesophagus, stomach and small intestine seemed to have longer than average intervals.

Patients presenting five symptoms at referral were more likely to have cancer than patients who presented only one symptom (adjusted PRR = 1.68 (95% CI: 1.06-2.65)). Patients presenting one or more clinical and/or paraclinical findings were more likely to have cancer than patient who had no findings at all.

59.0% of the patients from Silkeborg Hospital were referred to further examination at the diagnostic centre compared with 18.8% of the patients from
Aarhus Hospital. Patients who were not referred to further examination at a diagnostic centre were more likely to have cancer than those who were referred to further examination. However, this difference was only statistically significant in the group of patients from Silkeborg (Silkeborg: adjusted PRR = 1.62 (95% CI: 1.05-2.50); Aarhus: adjusted PRR = 1.22 (95% CI: 0.62-2.41)).

A strong association was found between the GP’s assessment of the estimated cancer risk at referral and the patient later being diagnosed with cancer. Furthermore, the patients were more likely to have cancer if the GP had reported ‘strong’ or ‘very strong’ gut feeling compared with ‘no’ gut feeling at referral (Paper II, Table 4, page 80).

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**PAPER III**

In Paper III, 2210 patients referred to the NSSC-CPP in Silkeborg were included. 314 (14.2%) were diagnosed with cancer within 6 months. After further exclusion (Paper III, Figure 3, page 104), we defined 298 of these cancer patients as our cases and compared them with two different reference populations: (1) a cancer reference group and (2) a non-cancer NSSC-CPP reference group (Paper III, Figure 4, page 107 and Table 3, page 108).

When comparing cases and the cancer reference group, we found a significant increase in the cases’ number of GP contacts, GP diagnostic tests and hospital diagnostic investigations the last 2 months prior to diagnosis. Furthermore, cases were more likely than cancer references to have more than one hospital diagnostic investigations 12 months prior to diagnosis (excluding the last month prior to diagnosis).

When comparing cases and the non-cancer NSSC-CPP reference group, we found cases to have a significantly lower number of GP contacts. Additionally,
2-8 months prior to diagnosis, cases had slightly lower rates of GP diagnostic tests than the non-cancer NSSC-CPP reference group, and there was a slight increase in the number of GP diagnostics tests the last month prior to referral. Cases had significantly higher rates of hospital diagnostics than non-cancer NSSC-CPP references in the month prior to referral but fewer diagnostics 2-12 months prior to referral but not all months were significant. Additionally, cases were more likely to have no hospital diagnostic investigations at all compared with non-cancer NSSC-CPP references.
CHAPTER 5:

PAPER I
Health Service Research

Direct-access to abdominal ultrasonic investigation from general practice—the role in earlier cancer diagnosis

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Abstract

\textbf{Background.} Abdominal ultrasound (US) is a safe and low-cost diagnostic tool for various abdominal symptoms. Direct-access to US from general practice has been suggested as a feasible option to promote earlier cancer diagnosis because abdominal cancer often presents with non-specific and vague symptoms, and the exact location may be difficult to identify on the basis of symptoms alone.

\textbf{Objective.} To describe patterns of use and cancer prevalence in referred patients when providing Danish GPs with direct-access to hospital-based US.

\textbf{Methods.} In an observational study, GPs were given the opportunity to either refer patients directly to US or through a waiting-list at Vejle Regional Hospital in Denmark; 701 patients were included between 1 August 2009 and 31 January 2010. Data were retrieved from the local Radiology Information System, GP referrals and the Danish Cancer Registry.

\textbf{Results.} GPs refer 60\% of all patients to direct-access US. Cancer was diagnosed in 19 (2.7\%) of the referred patients within 6 months after the US investigation. US gave rise to the suspicion of cancer in 11 of these patients (57.9\%); 10 of these had been referred to direct-access US. At least one non-malignant diagnosis resulted from US in 59.5\% of the cases, while 37.8\% of the cases had no final diagnosis.

\textbf{Conclusion.} The findings in this study might indicate that GPs refer patients assessed to have a higher risk of cancer through direct-access US. The finding was statistically non-significant, and further research is required to confirm this result.

\textbf{Key words:} Denmark, diagnosis, diagnostic imaging, general practice, neoplasms, ultrasonography.

Introduction

Cancer is a serious and common disease with increasing incidence (1). In many countries, cancer is currently the most frequent cause of death (1). Cancer patients in the UK and Denmark are particularly vulnerable; they have a poorer prognosis than patients in other Western countries (2), and Danish cancer patients are generally treated at more advanced disease stages than other populations (3,4). All these challenges call for new insights that may offer potential for more effective and earlier diagnosis of cancer and thereby also ensure better cancer outcome in the future.

Rapid and adequate referral is valued by most patients when symptoms have been presented to the health care system (5). Previous studies have found that 80–85\% of all cancer patients initially present symptoms to their GP (6,7), but many present with unspecific or uncharacteristic symptoms (6,8). Cancer patients have been found to
have much more contact to their GP 3 months before diagnosis, for some cancers even earlier (9). A possible explanation could be that early symptoms are less manifest and tend to mimic symptoms of frequently seen benign diseases (10,11).

Abdominal cancers, primary or metastatic, often present with non-specific, vague and otherwise frequent symptoms, and the exact location may be difficult to identify on the basis of symptoms alone (12). Abdominal symptoms cause ~5% of all GP consultations (9,13). The positive predictive values (PPVs) of abdominal symptoms for cancer are low; yet the frequency of ‘low-risk-but-not-no-risk’ symptoms and signs are high (10). Thus, direct-access to rational investigations is crucial for efficient and early diagnosis (14).

Abdominal ultrasound (US) is a safe and low-cost diagnostic tool for patients with various abdominal symptoms (14,15). However, the delay for a waiting-list US is often weeks to months in Denmark, depending on the wording of the referral and the capacity of the diagnostic unit. Direct-access to US has been discussed as a feasible option to promote earlier cancer diagnosis. This possibility for quick investigation could expedite the diagnosis of cancer, but also holds a risk of US overuse.

The aim of this study was to describe the patterns of use and estimate the cancer prevalence when providing Danish GPs with direct-access to hospital-based US.

Methods
We performed an observational cross-sectional study on patients referred to US from general practice. The GP could choose between referring to direct-access or to waiting-list US. The data for the study were collected at Vejle Regional Hospital, which has a catchment area of 300,000 and ~190 GPs.

Organization of US access
Danish GPs act as gatekeepers to specialized hospital-based health care, including cancer-specific investigations. Direct-access to US on a day-to-day basis was introduced in 2006 at Vejle Regional Hospital. It was originally implemented as a service for patients with health-related issues, irrespective of cancer suspicion, and as an opportunity for the GP to achieve fast clarification of a patient with possible serious disease. For both direct-access US and waiting-list US, the results were sent to the GP who subsequently decided on further diagnostic steps. If further diagnostic investigations were evidently needed (e.g. because of suspicion of cancer), these investigations were planned immediately by the radiologist in close cooperation with either the patient’s GP or a medical specialist at the hospital.

An electronic referral was forwarded to the Department of Diagnostic Imaging at Vejle Hospital if the GP found reason to order a US. In this referral, the GP listed the reasons for requesting the US and stated whether or not cancer was suspected. The US was performed by either a consultant radiologist, an experienced sonographer or a medical resident trained in US and supervised by an experienced supervisor (if necessary).

Patients referred to direct-access US could go to the hospital immediately as a number of examination rooms were reserved at the radiology department for direct-access US services. Patients referred to waiting-list US were not allowed to use this day-to-day-service and had to wait for the scheduled time provided by the hospital.

There were no restrictions or instructions to the GP regarding which patients to refer to the direct-access US, except that referred patients were required to fast for 4 hours before the US.

Study population
A retrospective review was performed on all adult (≥18 years) patients referred from general practice to US at the Department of Diagnostic Imaging at Vejle Regional Hospital between 1 August 2009 and 31 January 2010. In Denmark, US referral is decided by the GP who can refer any patient estimated to benefit from this investigation. Patient data were extracted from the Radiology Information System (RIS), which keeps records of all radiological investigations at the hospital. We excluded patients receiving musculoskeletal or control US for a malign/benign disease and patients outside the catchment area.

A total of 729 patients were referred to US in the inclusion period; 25 patients were excluded because of previous cancer, and three additional patients were excluded for other reasons. Overall, 701 eligible patients were included in the study (Fig. 1).

Data
RIS data included the patient’s unique Danish civil registration number, referral and examination dates, the medical conclusion of the US and information as to whether the patient was referred through direct-access or waiting-list.

From the GP referrals, we extracted information about each GP’s cancer suspicion (suspicion or no suspicion), the clinical findings and the patient’s symptoms.

Data regarding cancer diagnosis (ICD-10) and date of diagnosis (defined as the first date of hospital admission after confirmation of cancer diagnosis) were retrieved from the Danish Cancer Registry (16). We reported cancer diagnosed up to 3 and 6 months after the inclusion period; 25 patients were excluded because of previous cancer, and an additional 17 patients were excluded due to cancer outside the catchment area.

Figure 1. Flow chart of patient inclusion, US referrals and GP cancer suspicion.
Statistical analyses
Chi-square and Fisher’s exact tests were used to identify differences between groups. Wilcoxon rank-sum test was used to examine differences in waiting time. Statistical significance was inferred at P value ≤0.05.

The diagnostic value of the GP’s cancer suspicion was measured using the sensitivity and specificity, the PPV and the negative predictive value.

The prevalence ratio (PR) with 95% confidence intervals (95% CI) was used to estimate differences in the prevalence of cancer among direct-access US and waiting-list US. Further, the PR was used to estimate associations between GP’s cancer suspicion and subsequent diagnosis of cancer.

Stata v.11 was used for the analyses.

Results
Of all 701 patients, 420 (59.9%) were referred to direct-access US and 281 (40.1%) to waiting-list US. The GPs suspected cancer in 10.2% of all patients referred to direct-access US and in 9.3% of all patients referred to waiting-list US (P = 0.313).

Referred patients had a mean age of 51.9 years (SD: 17.4, range: 18–95), and 35.7% of the referred patients were men. No age differences were found between men and women (52.5 versus 51.6, P = 0.741). No statistically significant differences were found in gender or age distribution between direct-access and waiting-list US.

Table 1 shows the symptoms and clinical findings that were most frequently stated in the GPs’ referrals; abdominal pain (74.5%) and abnormal liver blood tests (14.4%) were the two most frequent causes of referral.

Table 2 shows the cancer types diagnosed up to 6 months after the US and non-cancer diagnoses discovered by the US. Cancer was found in 19 (2.7%) of the referred patients within 6 months after the US investigation. US gave rise to suspicion of cancer in 11 of these patients (57.9%); more details regarding these cancers can be found in Table 3. The most frequent cancer types were lung, colon and pancreatic cancers. The most frequent non-cancer diagnoses were

Table 1. Symptoms or clinical findings stated in the GP referral (divided into direct-access US and waiting-list US)

<table>
<thead>
<tr>
<th>Symptom or clinical finding</th>
<th>Direct-access US (n = 420)</th>
<th>Waiting-list US (n = 281)</th>
<th>Total (n = 701)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>321 (76.4%)</td>
<td>201 (71.5%)</td>
<td>522 (74.5%)</td>
</tr>
<tr>
<td>Abnormal liver blood samples</td>
<td>63 (15.0%)</td>
<td>38 (13.5%)</td>
<td>101 (14.4%)</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>58 (13.8%)</td>
<td>26 (9.3%)</td>
<td>84 (12.0%)</td>
</tr>
<tr>
<td>Weight loss†</td>
<td>43 (13.4%)</td>
<td>25 (8.9%)</td>
<td>68 (9.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (9.1%)</td>
<td>27 (9.6%)</td>
<td>65 (9.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (8.6%)</td>
<td>12 (4.3%)</td>
<td>48 (6.8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (6.7%)</td>
<td>8 (2.9%)</td>
<td>36 (5.1%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>6 (1.5%)</td>
<td>2 (0.7%)</td>
<td>8 (0.1%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>58 (13.8%)</td>
<td>43 (15.3%)</td>
<td>101 (14.4%)</td>
</tr>
</tbody>
</table>

*Patients may present more than one symptom or clinical finding.
†Weight loss is indicated as a clinical sign in the referral (no specific definition).

Table 2. Cancer diagnosed up to 6 months after the US and non-cancer diseases diagnosed for direct-access US and waiting-list US, respectively

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Direct-access US (n = 420)</th>
<th>Waiting-list US (n = 281)</th>
<th>Total (n = 701)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4 (1.0%)</td>
<td>0 (0%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>3 (0.7%)</td>
<td>0 (0%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2 (0.5%)</td>
<td>0 (0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1 (0.2%)</td>
<td>2 (0.7%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Oesophageal cancer</td>
<td>1 (0.2%)</td>
<td>1 (0.4%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Hepatic cancer</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Malignant neoplasm of abdomen</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>All cancers†</td>
<td>16 (3.8%)</td>
<td>3 (1.1%)</td>
<td>19 (2.7%)</td>
</tr>
<tr>
<td>Non-cancer diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystolithiasis</td>
<td>81 (19.3%)</td>
<td>48 (17.1%)</td>
<td>129 (18.4%)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>64 (12.9%)</td>
<td>41 (14.6%)</td>
<td>105 (15.0%)</td>
</tr>
<tr>
<td>Gallbladder polyp</td>
<td>30 (7.1%)</td>
<td>9 (3.2%)</td>
<td>39 (5.6%)</td>
</tr>
<tr>
<td>Cystis hepur</td>
<td>12 (2.9%)</td>
<td>12 (4.3%)</td>
<td>24 (3.4%)</td>
</tr>
<tr>
<td>Spleenomegaly</td>
<td>8 (1.9%)</td>
<td>7 (2.5%)</td>
<td>15 (2.1%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>5 (1.2%)</td>
<td>5 (1.8%)</td>
<td>10 (1.4%)</td>
</tr>
<tr>
<td>Hernia</td>
<td>3 (0.7%)</td>
<td>5 (1.8%)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>3 (0.7%)</td>
<td>2 (0.7%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>All non-cancer diagnoses†</td>
<td>307</td>
<td>206</td>
<td>513</td>
</tr>
<tr>
<td>Patients with non-cancer diagnosis</td>
<td>270 (64.3%)</td>
<td>166 (59.1%)</td>
<td>436 (62.2%)</td>
</tr>
<tr>
<td>Patients with no diagnosis</td>
<td>150 (35.7%)</td>
<td>115 (40.9%)</td>
<td>265 (37.8%)</td>
</tr>
</tbody>
</table>

*All cancers excluding non-melanoma skin cancer.
†Some patients had more than one non-cancer diagnosis; therefore percentage is not shown.
cholelithiasis and steatosis. In total, 417 (59.5%) patients got one or more non-malignant diagnoses, and 265 (37.8%) patients were discharged without a diagnosis. None of the patients who were given no diagnosis were diagnosed with cancer at the 6-month follow-up.

Among patients referred to direct-access US, we identified 10 patients in whom the performed US gave rise to suspicion of cancer; the prevalence of cancer in these cases was thus 2.4% (Table 4). The association between the GPs' cancer suspicion and the subsequent diagnosis of cancer for patients referred to direct-access US showed a PR of 5.8 (95% CI: 1.7–19.), while the PPV of the GPs’ cancer suspicion was 9.3 (95% CI: 2.6–22.1).

Among patients referred to waiting-list US, we identified only one patient in whom the performed US gave rise to suspicion of cancer; the prevalence of cancer in these cases was thus only 0.4%. As the statistical precision of this finding is very low, further results will not be presented.

For patients suspected of cancer after having the US, direct-access US was associated with a higher prevalence of cancer than waiting-list US. This finding was, however, not statistically significant [PR: 6.7 (95% CI: 0.85–52.0)]. For patients diagnosed with cancer within 3 or 6 months after having the US, we also found a higher prevalence of cancer among patients in the direct-access group; these findings were statistically significant (see Table 5).

The median waiting time from referral to performed US was one day (Interquartile range [IQR]: 1–4) for direct-access US and 16.9 days (IQR: 10–21) for waiting-list US (P < 0.001).

**Discussion**

**Main findings**

In this study, we examined patients referred from their GP to either direct-access or waiting-list US. We identified 11 patients in whom the US raised suspicion to their later verified cancer diagnosis. Out of this group, patients referred through direct-access were more likely to have cancer than patients referred through waiting-list, but these data were not statistically significant. Nevertheless, this finding may indicate that GPs generally refer patients assessed to have a higher risk of cancer through direct-access US. This hypothesis was also confirmed by our analyses showing that cancer was often found within 3 and 6 months, and these findings were statistically significant (see Table 5). Yet, further research is needed to confirm our findings.

The GP-reported cancer suspicion (no suspicion or suspicion) was similar in the two different types of US referrals and, therefore, cannot explain the found difference in cancer prevalence. As seen in Tables 1 and 2, no substantial differences were found between the two types of US referrals in regard to symptoms, clinical findings and non-cancer diagnoses. A further subdivision of the GPs cancer suspicion (e.g. small, medium, strong, very strong) may explain some of this difference, but the observed difference in cancer prevalence may also be explained by the intensity and/or acuteness of presented symptoms in combination with the GP’s ‘gut feeling’ or ‘cancer intuition’. Unfortunately, this study does not provide any detailed insight into the GP’s cancer suspicion nor into the GPs’ criteria for choosing direct-access.

The reason why some GPs decided to refer patients suspected of cancer to the waiting-list US instead of the direct-access US is unknown, but it might be related to the level of the GP’s initial suspicion of cancer or unawareness among the GPs of the possibility of direct-access US.

The performed US gave rise to suspicion of cancer in more than half of the diagnosed cancer patients; this suspicion included both primary cancer and metastasis (Table 4). This result implies that the performed US failed to identify cancer in >40% of the patients who were later diagnosed with cancer. The study design does not allow us to conclude whether these missed cancers could and should have been found. Although GPs rarely use an US as the only diagnostic investigation, it is relevant to question if an US was the most appropriate diagnostic tool for investigation of cancer in the referred patients, and this issue should be addressed in future studies.

It is not known whether the 16-day median difference in waiting time between the two types of US referrals has had any influence on the stage of cancer at diagnosis. However, when the US forms part of a longer diagnostic path before the final cancer diagnosis is established, the combined waiting time of all performed investigations might be of influence. One in three patients received no diagnosis after US investigation and returned to general practice, but none of these patients developed cancer during the 6-month follow-up.

The findings suggest that further qualitative work is required, in particular on the decision-making process among GPs about referral to direct-access US and on the patient’s experience. More research on health economics perspectives are also called for, specifically studies of costs and benefits of providing this service.
Cancer diagnosed within 6 months
Cancer diagnosed within 3 months
US gave suspicion of cancer

prevalence of gallstone disease among women (two to three times
high number of women might be explained by the generally higher
tribution has formerly been identified in a similar study (17). The
abdominal symptoms.
tool for determining the right management strategy for patients with
cancer in general practice, but may also serve as an important
diagnostic imaging; US may not only shorten the diagnostic interval
for cancer identified by an initial US. et al. (18) found that 17% of ovarian can-
tection. US has also been found to play an important role in the diagnosis
specialist and permitted swift reassurance of patients in general prac-
tice; in particular, we lack knowledge about the use of direct-access

Comparison with other studies
Limited research focuses on patients referred to US from general prac-
tice; in particular, we lack knowledge about the use of direct-access
US in the diagnosis of cancer. Speets et al. (17) found that the GPs’
patient management strategy changed for 64% of patients after upper
abdominal US. Furthermore, they found that upper abdominal US
substantially reduced the number of subsequent referrals to a medical
specialist and permitted swift reassurance of patients in general prac-
tice. US has also been found to play an important role in the diagnosis
of ovarian cancers; Barret et al. (18) found that 17% of ovarian can-
cers were identified by an initial US.

These findings stress the importance of quick access to relevant
diagnostic imaging; US may not only shorten the diagnostic interval
for cancer in general practice, but may also serve as an important
tool for determining the right management strategy for patients with
abdominal symptoms.

One-third of the patients in our study were men; this gender dis-
tribution has formerly been identified in a similar study (17). The
high number of women might be explained by the generally higher
prevalence of gallstone disease among women (two to three times
higher than for men), gallstone being the most common diagnosis in
both our study and in other US studies (13,17). Further, the suspi-
cion of gynaecological cancers in women also plays a role.

Many European countries have, as Denmark, a strong primary
sector acting as first line in the health care system (19). Our study
indicates that GPs may benefit from having direct-access to US in se-
condary care for patients in need of quick clarification. However, a
possible side-effect could be that easy access to one kind of medical
examination with a negative result might increase the risk of delaying
the final diagnosis by other medical examinations, e.g. colonoscopy
for suspicion of colon cancer. Our findings confirm that the GPs are
able to identify patients with the highest risk of cancer and that the
GPs also refer these patients to the direct-access US.

Conclusion
The examined patients were referred from their GP to either direct-
access US or waiting-list US. The performed US gave rise to the suspi-
cion of cancer in more than half of the diagnosed cancer patients, and
this suspicion included both primary cancer and metastasis. The US
raised suspicion of cancer in 11 patients who were later diagnosed with
cancer. Among these, patients referred through direct-access were more
likely to have cancer than those referred through waiting-list. This find-
ing might indicate that GPs refer patients assessed to have a higher risk
of cancer through direct-access US. As the finding was non-significant,
further research is needed to confirm and expand these findings.

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alone are responsible for the content and writing of the paper.

Declaration
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the Novo Nordisk Foundation. The sponsors were not involved in any part of the
study.
Ethical approval: according to Danish law, approval by the National
Committee on Health Research Ethics was not required as no biomedical
intervention was performed. The study was approved by the Danish Data
Protection Agency (j. no: 2011-231-0115).
Conflict of interest: the authors report no conflicts of interest.

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CHAPTER 6:

PAPER II
The Danish cancer pathway for patients with serious non-specific symptoms and signs of cancer—a cross-sectional study of patient characteristics and cancer probability

Mads Lind Ingeman¹,²,³*, Morten Bondo Christensen¹, Flemming Bro¹, Søren T. Knudsen⁴ and Peter Vedsted¹,²

Abstract

Background: A Danish cancer pathway has been implemented for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP). The initiative is one of several to improve the long diagnostic interval and the poor survival of Danish cancer patients. However, little is known about the patients investigated under this pathway. We aim to describe the characteristics of patients referred from general practice to the NSSC-CPP and to estimate the cancer probability and distribution in this population.

Methods: A cross-sectional study was performed, including all patients referred to the NSSC-CPP at the hospitals in Aarhus or Silkeborg in the Central Denmark Region between March 2012 and March 2013. Data were based on a questionnaire completed by the patient’s general practitioner (GP) combined with nationwide registers. Cancer probability was the percentage of new cancers per investigated patient. Associations between patient characteristics and cancer diagnosis were estimated with prevalence rate ratios (PRRs) from a generalised linear model.

Results: The mean age of all 1278 included patients was 65.9 years, and 47.5 % were men. In total, 16.2 % of all patients had a cancer diagnosis after six months; the most common types were lung cancer (17.9 %), colorectal cancer (12.6 %), hematopoietic tissue cancer (10.1 %) and pancreatic cancer (9.2 %). All patients in combination had more than 80 different symptoms and 51 different clinical findings at referral. Most symptoms were non-specific and vague; weight loss and fatigue were present in more than half of all cases. The three most common clinical findings were ‘affected general condition’ (35.8 %), ‘GP’s gut feeling’ (22.5 %) and ‘findings from the abdomen’ (13.0 %). A strong association was found between GP-estimated cancer risk at referral and probability of cancer.

Conclusions: In total, 16.2 % of the patients referred through the NSSC-CPP had cancer. They constituted a heterogeneous group with many different symptoms and clinical findings. The GP’s gut feeling was a common reason for referral which proved to be a strong predictor of cancer. The GP’s overall estimation of the patient’s risk of cancer at referral was associated with the probability of finding cancer.

Keywords: Fast-track, Neoplasm, General practice, Diagnosis, Cancer symptoms, Denmark

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Background
Cancer is the most common cause of death in Denmark and many other countries. One in five of all citizens in the developed world will die from cancer [1]. British and Danish cancer patients experience poorer cancer survival rates than patients from other western countries [2, 3]. Differences in public cancer awareness, health-care seeking behaviour, diagnostic pathways and treatment options have been suggested as important contributing factors [3]. Studies indicate that early diagnosis of cancer is important for improving the prognosis [4, 5]. The health care system must, therefore, provide medical services for prompt cancer diagnosis.

The majority of patients with cancer have a symptom-atic presentation of the disease [6]. Symptoms are often diverse and may evolve over time as the cancer develops. In many health systems, general practitioners (GPs) form the first line of health care and provide medical advice to an unselected group of people. At the same time, GPs often act as ‘gatekeepers’ to ensure appropriate and timely flow of patients into the more specialized health services [7]. Thus, general practice plays a central role in diagnosing cancer [8–10]. Furthermore, the use of general practice has been shown to increase significantly several months before a patient is diagnosed with cancer [11]; this indicates an open ‘diagnostic window’.

To reduce the length of the diagnostic interval, several countries have implemented urgent referral cancer pathways [9, 12, 13] for patients with clinical suspicion of cancer [14]. In the UK, such pathway was introduced as the 2-week wait referral (2WW) system [15]. The first Danish Cancer Patient Pathways (CPPs) for diagnosis and treatment of suspected cancer were implemented in 2008; these are specific clinical pathways for several of the most common cancers/cancer sites [14, 16]. Once the GP refers the patient to a CPP, all diagnostic and treatment procedures will be promptly organised in well-defined processes; all relevant clinical investigations and treatments will be planned and booked within a given number of days. The aim of the CPP is to offer patients optimal diagnosis and treatment, which may ultimately improve their prognosis, and to provide better quality of life by reducing the insecurity that tends to accompany unwarranted delays.

Alarm symptoms of cancer and the related practice guidelines [17] are the primary focus of both the Danish and the British pathways [18, 19]. This approach may result in shorter diagnostic intervals [20] for patients with specific alarm symptoms. However, only approx. 40 % of all cancer patients seem to have benefitted from the implementation of the CPPs based on alarm symptoms as demonstrated by British and Danish studies [21, 22]. This is due to the fact that only half of cancer patients initially present symptoms classified as alarm symptoms by the GP [8, 21], findings from the UK indicate similar figures [20]. As a consequence of these findings, additional CPPs were implemented in Denmark in 2011 for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP) [23]. These provided the Danish GPs with the opportunity to refer patients with serious non-specific symptoms for further diagnostic workup if cancer is suspected although no alarm symptoms (qualifying for specific CPP routes) are present [24]. However, the consequences of this urgent referral modality are not known at present. In particular, more information is needed on i) which patients are referred, ii) which factors constitute the basis of the referral and iii) whether or not the investigated patients have cancer.

This paper aims to describe the characteristics of patients referred from general practice to the Danish NSSC-CPP and to estimate the probability and distribution of cancers in this population.

Methods
We performed a cross-sectional study including all patients aged 18 years or more who were referred to the NSSC-CPP at the hospitals in Aarhus or Silkeborg in the Central Denmark Region between 7 March 2012 and 27 March 2013. All identified patients were followed up for six months for the diagnosis of cancer.

Setting and NSSC-CPP organisation
All Danish residents are entitled to tax-financed public health-care benefits with free access to health care. More than 98 % of Danish citizens are registered with a specific general practice. The GPs act as gatekeepers to the rest of the health-care system, except for emergencies [25]. During one year, 85 % of the Danish population is in contact with general practice.

All patients referred from their GP to the NSSC-CPP underwent a filter function comprising three components: a battery of blood tests, a urine test and diagnostic imaging. The diagnostic imaging consisted of an abdominal ultrasound and a chest X-ray performed at Silkeborg hospital and a CT scan (with contrast) of chest, abdomen and pelvis performed at Aarhus University Hospital. The results of the diagnostic imaging were first assessed by a radiologist, and the GP subsequently interpreted all test results in combination and decided on further diagnostic steps to be taken. Such steps could be either watchful waiting or referral to a diagnostic centre for further investigations. If a specific disease or type of cancer was suspected, further steps could also involve referral to a medical specialist or another cancer-specific CPP (Fig. 1).

A diagnostic centre is a medical unit with comprehensive facilities for diagnostic investigation, including easy access to expertise in a wide range of relevant medical
specialties (e.g. oncology, gynaecology, gastroenterological surgery, orthopaedics and radiology). NSSC-CPP patients referred to a diagnostic centre must undergo further investigations on the basis of presented symptoms and clinical findings (e.g. blood tests, diagnostic imaging, endoscopies and biopsies). Based on the findings, the patient is either referred to a CPP for a specific cancer, to a specific hospital department or back to the GP.

The Danish medical services are divided into five regions, and each of these regions must have at least one diagnostic centre. Approx. 15 centres have so far been established in Denmark.

Identification of patients
All patients who underwent the filter function were identified and included. In the Silkeborg catchment area, eligible patients were identified by a digital marker on the battery of blood tests. At the hospital in Aarhus, all patients receiving CT scans as part of the filter function were identified with a particular code.

The unique civil registration number (CRN), which is assigned to all Danish citizens, links the medical records at the personal level across the Danish national registries [26]. Newly identified patients were extracted every two weeks, and we linked these data to the Health Service Registry (HSR) in the Central Denmark Region to identify the GP of each of the included patients.

Some referrals to the NSSC-CPP were made from hospital departments. To ensure inclusion of only relevant patients, we sent a letter to the GPs of the patients who were referred from the hospital to clarify whether the GP had been involved in the referral of this particular patient.

In total, 1899 referrals (1837 unique patients) were identified. We decided to consider two referrals of the same patient as two separate events if six or more months had passed between the referrals.

A total of 167 (8.0 %) referrals were excluded for the following reasons: same patient referred within six months (51 referrals), patient under 18 years (eight referrals), cancer within one year prior to current referral (41 referrals), recurrence of known cancer (15 referrals), questionnaire rejected and returned by the GP for various reasons, e.g. retirement of the referring GP (52 referrals). In total, 1732 referrals were included in the study (Fig. 2).

Data collection
A pilot-tested paper questionnaire was sent to the GP of the identified patient no more than two weeks after inclusion of the patient in the study. This procedure was followed for all included patients. Non-respondents received a reminder after three weeks. In general practices with more than one GP, we asked the GP who was most familiar with the patient to complete the questionnaire. Participating GPs were remunerated for each completed questionnaire (DKK 121 corresponding to approx. EUR 16).

The GPs provided information regarding the patient’s symptoms, known chronic diseases and estimated risk of cancer at referral in addition to clinical findings, abnormal diagnostic test results and level of the GP’s ‘gut feeling’ (understood as clinical intuition) regarding possible serious disease. Furthermore, the date of the first symptom presentation to the GP/practice was reported.

Symptoms were defined as presence or absence of 21 specified symptoms at the time of referral, with the option to add other symptoms that were not listed. As far as possible, all symptoms were classified according to the International Classification of Primary Care, second edition (ICPC-2) [27]. Clinical findings were defined as the GP’s abnormal findings during the clinical examination of
Diagnostic test results were defined as diagnostic tests that were considered abnormal and highly relevant for the overall pathological picture at the time of referral. In accordance with Stolper’s work, we define gut feeling as ‘a physician’s intuitive feeling that something is wrong with the patient, although there are no apparent clinical indications for this, or a physician’s intuitive feeling that the strategy used in relation to the patient is correct, although there is uncertainty about the diagnosis’ [28].

In line with the Aarhus Statement [13], the primary care interval was defined as the time from the patient’s first symptom presentation at the GP/practice until referral to the NSSC-CPP. To ensure accurate data, we used the registered inclusion date as the referral date, i.e. the electronically registered date at which the filter function had been ordered.

Data regarding each patient’s cancer diagnosis were retrieved from the Danish Cancer Registry (DCR) [29–31]. These data were available only for the period until 31 December 2012. Cancer diagnoses made after this date were retrieved from the National Patient Registry (NPR) until six months after the date for inclusion of the last patient. The identification of incident cancers from the NPR has proven to be reliable as 95 % of the cancer diagnoses are displayed after four months and with high validity [32]. The date of diagnosis in the NPR was defined as the first date of the hospital admission at which the cancer diagnosis was confirmed in the DCR. If the patient was diagnosed with ICD-10 codes C760–C800.

![Fig. 2 Referrals and patient inclusion for the NSSC-CPP](image-url)
(i.e. malignant neoplasm’s of ill-defined, other secondary and unspecified sites), we searched and replaced this code with a more cancer-specific diagnostic code if the diagnosis had been made no more than two months after the date at which the cancer incidence had first been registered.

Data collection regarding referral for further examination at the diagnostic centre at the hospital in Aarhus did not start until 1 August 2012. Thus, the data collection for the data shown in Table 4 started nearly five months later than the data collection from the hospital in Silkeborg.

**Statistical analyses**

We used chi-square ($\chi^2$) test and Wilcoxon rank-sum test to identify differences between participating and non-participating GPs, to examine variations in the primary care interval between patients with and without cancer and to calculate the prevalence ratio (PR) in Table 5. The primary care intervals are presented as medians as well as 75 and 90 percentiles.

Cancer probability is presented as the percentage of included patients who were diagnosed with a new cancer within six months after the referral date. Associations between different patient characteristics and subsequent cancer diagnosis were estimated with prevalence rate ratios (PRRs) from a generalised linear model, both unadjusted and adjusted for age and gender, including 95 % confidence intervals (95 % CIs).

The statistical significance level was 0.05 or less. No alterations were made regarding missing data on presence or no presence of cancer. Stata statistical software v. 11 was used for the analyses.

**Ethics and approval**

The study was approved by the Danish Data Protection Agency (j.no: 2011-41-6118) and the Danish Health and Medicines Authority (j.no: 7-604-04-2/301). This study needed no approval from the Danish National Committee on Health Research Ethics.

**Results**

**Study population**

A total of 1278 completed GP questionnaires (73.8 %) were returned and included in the analyses (Fig. 2). Five patients were included twice. No significant differences were found between referrals from participating GPs and non-participating GPs concerning hospital distribution, gender, age or probability of cancer diagnoses (Table 1).

**Patient characteristics**

The mean age of patients included in the analyses was 65.9 years (sd: 14.7, range: 18–99), and 47.5 % were men. The most frequent chronic diseases at referral were hypertension, chronic lung disease and diabetes (Table 1).

A total of 82 different symptoms and 51 clinical findings were identified from the GP questionnaires (data not shown). The median number of symptoms was 3.0. Non-specific symptoms were the most predominant of all registered symptoms; weight loss and fatigue were both present in more than half of all referrals (Table 2). Symptoms associated with the highest probability of

| Table 1 Characteristics of patients referred from participating GPs and from all included referrals |
|---------------------------------------------------------------|-----------------------------------------------|
| Variable                              | Referrals from participating GPs n = 1278 | All referrals including non-responders n = 1732 |
|                                      | n    | %     | N    | %     |
| **Hospital**                           |      |       |      |       |
| Silkeborg                             | 705  | 55.2  | 927  | 53.5  |
| Aarhus                                | 573  | 44.8  | 805  | 46.5  |
| **Sex**                               |      |       |      |       |
| Female                                | 671  | 52.5  | 821  | 52.6  |
| Male                                  | 607  | 47.5  | 911  | 47.7  |
| **Age**                               |      |       |      |       |
| Mean (Range, SD)                      | 65.9 | 18–98 | 66.1 | 18–98 |
| Age groups                            |      |       |      |       |
| 18-39 years                           | 70   | 5.5   | 90   | 6.2   |
| 40-54 years                           | 179  | 14.0  | 234  | 16.1  |
| 55-69 years                           | 441  | 34.5  | 481  | 33.0  |
| 70-79 years                           | 345  | 27.0  | 368  | 25.3  |
| ≥80 years                             | 243  | 19.0  | 282  | 19.4  |
| **Cancer**                            |      |       |      |       |
| Yes                                   | 207  | 16.2  | 277  | 16.0  |
| No                                    | 1071 | 83.8  | 1455 | 84.0  |
| **Chronic diseases at referral**      |      |       |      |       |
| Hypertension                          | 355  | 27.8  | -    | -     |
| Chronic lung disease                  | 216  | 16.9  | -    | -     |
| Diabetes                              | 153  | 12.0  | -    | -     |
| Ischaemic heart disease               | 142  | 11.1  | -    | -     |
| Chronic joint or rheumatic disease    | 134  | 10.5  | -    | -     |
| Light to medium mental disorder       | 125  | 9.8   | -    | -     |
| Osteoporosis                          | 79   | 6.2   | -    | -     |
| Apoplexy                              | 69   | 5.4   | -    | -     |
| Moderate to severe mental disorder    | 67   | 5.2   | -    | -     |

*Data based on returned questionnaires and therefore exclusively on participating GPs
cancer were jaundice (42.9 %), dysphagia (36.7 %), neurological dysfunction (35.3 %) and lump/tumour (26.9 %) (Table 2).

The three most common clinical findings were affected general condition (35.8 %), the GPs’ gut feeling (22.5 %) and abdominal findings (13.0 %). The highest probability of cancer was found for enlarged lymph nodes (27.3 %), neurological findings (26.7 %), the GPs’ gut feeling (24.0 %) and abdominal findings (21.1 %) (Table 2).

Abnormal diagnostic test results were primarily related to blood samples and diagnostic imaging, and no single diagnostic test result was associated with a particularly high probability of cancer.

### Cancer and primary care interval

After six months, 16.2 % of all patients had a cancer diagnosis. The most common cancer types were lung cancer (17.9 %), colorectal cancer (12.6 %), hematopoietic tissue cancer (10.1 %) and pancreatic cancer (9.2 %) (Table 3). In comparison, the most common cancer types in Denmark in general for men are prostate cancer, lung cancer, colon cancer and urinary tract cancer, while the most common types for women are breast cancer, lung cancer, colon cancer and malignant melanoma.

The median primary care interval for patients diagnosed with cancer was 15 days; the 75 and 90 percentiles were 72 days and 130 days, respectively. Breast, liver and biliary cancer patients seemed to have shorter than average primary care intervals, while patients with metastases or cancer of the prostate, hematopoietic tissue, oesophagus, stomach or small intestine seemed to have longer primary care intervals than all other patients (Table 3). However, the study population was too small to provide any statistical precision for these estimates.

Men generally had a significantly higher probability of cancer than women when referred (adjusted PRR = 1.32 (95 % CI: 1.03-1.70)) (Table 4). A more detailed overview of symptoms and clinical findings found to be highly predictive of cancer is presented in Additional file 1.

### Cancer probability in different referral groups

Referred patients with five symptoms had a significantly higher probability of having cancer than patients referred with only one symptom (adjusted PRR = 1.68 (95 % CI: 1.06-2.65)) (Table 4). The presence of one or more clinical and/or diagnostic test results implied a significantly higher probability of finding cancer (Table 4).

Patients from Aarhus constituted 44.8 % of the referrals. These patients had a significantly higher probability of cancer than the patients referred to the hospital in Silkeborg (although not in the adjusted analysis) (Table 4).

In total, 59.0 % of the patients from Silkeborg were referred to further examination at the diagnostic centre compared to 18.8 % of the patients from Aarhus. A higher probability of cancer was found among patients who had not been referred to further examination compared to patients who had been referred. However, this difference was only statistically significant in the group of patients from Silkeborg (Silkeborg: adjusted PRR = 1.62 (95 % CI: 1.05-2.50); Aarhus: adjusted PRR = 1.22 (95 % CI: 0.62-2.41)).

The number of chronic diseases and the length of the primary care interval showed no significant associations with the probability of cancer (Table 4).

A strong association was found between the GP’s assessments of estimated cancer risk at referral and the probability of finding cancer (Table 4).

### Table 2 Symptoms, abnormal clinical findings and abnormal diagnostic test results among included patients at referral

<table>
<thead>
<tr>
<th>Symptoms at referral</th>
<th>Total (n = 1269)</th>
<th>Patients with cancer n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>671 (52.5 %)</td>
<td>104 (15.5 %)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>642 (50.2 %)</td>
<td>102 (15.9 %)</td>
</tr>
<tr>
<td>Pain</td>
<td>468 (36.6 %)</td>
<td>86 (18.4 %)</td>
</tr>
<tr>
<td>Nausea</td>
<td>352 (27.5 %)</td>
<td>65 (18.5 %)</td>
</tr>
<tr>
<td>Malaise</td>
<td>314 (24.7 %)</td>
<td>59 (18.8 %)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>174 (13.6 %)</td>
<td>29 (16.7 %)</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>137 (10.7 %)</td>
<td>24 (17.5 %)</td>
</tr>
<tr>
<td>Excessive sweating</td>
<td>128 (100 %)</td>
<td>15 (12.5 %)</td>
</tr>
<tr>
<td>Cough</td>
<td>114 (8.9 %)</td>
<td>15 (13.2 %)</td>
</tr>
<tr>
<td>Lump/tumour</td>
<td>108 (8.5 %)</td>
<td>29 (26.9 %)</td>
</tr>
<tr>
<td>No symptom</td>
<td>33 (2.6 %)</td>
<td>7 (21.2 %)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal clinical findings at referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected general condition</td>
</tr>
<tr>
<td>GP’s ‘gut feeling’</td>
</tr>
<tr>
<td>Abdomen</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Extremity</td>
</tr>
<tr>
<td>Lungs</td>
</tr>
<tr>
<td>Lymph node</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Joints</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal diagnostic test results at referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sample at GP</td>
</tr>
<tr>
<td>Blood sample at hospital</td>
</tr>
<tr>
<td>Diagnostic imaging</td>
</tr>
<tr>
<td>Urine sample</td>
</tr>
</tbody>
</table>

Cancer and primary care interval

After six months, 16.2 % of all patients had a cancer diagnosis. The most common cancer types were lung cancer (17.9 %), colorectal cancer (12.6 %), hematopoietic tissue cancer (10.1 %) and pancreatic cancer (9.2 %) (Table 3). In comparison, the most common cancer types in Denmark in general for men are prostate cancer, lung cancer, colon cancer and urinary tract cancer, while the most common types for women are breast cancer, lung cancer, colon cancer and malignant melanoma.

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Cancer probability in different referral groups

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Patients from Aarhus constituted 44.8 % of the referrals. These patients had a significantly higher probability of cancer than the patients referred to the hospital in Silkeborg (although not in the adjusted analysis) (Table 4).

In total, 59.0 % of the patients from Silkeborg were referred to further examination at the diagnostic centre compared to 18.8 % of the patients from Aarhus. A higher probability of cancer was found among patients who had not been referred to further examination compared to patients who had been referred. However, this difference was only statistically significant in the group of patients from Silkeborg (Silkeborg: adjusted PRR = 1.62 (95 % CI: 1.05-2.50); Aarhus: adjusted PRR = 1.22 (95 % CI: 0.62-2.41)).

The number of chronic diseases and the length of the primary care interval showed no significant associations with the probability of cancer (Table 4).

A strong association was found between the GP’s assessments of estimated cancer risk at referral and the probability of finding cancer (Table 4).
The GPs’ estimations were generally higher than the actual probability of cancer. The probability of cancer was higher if the GP had reported ‘strong’ or ‘very strong’ compared to ‘no’ gut feeling. Furthermore, GP gut feeling showed an association with the four most common clinical findings (weight loss, fatigue, affected general condition and abnormal blood sample) for patients diagnosed with cancer (Prevalence ratio: 1.50 (95 % CI: 0.82-2.75)) (Table 5).

Discussion
Main findings
NSSC-CPP referred patients were a heterogeneous group with over 80 different symptoms, 51 different clinical findings and wide variations in number of symptoms per referral. The most frequent symptoms were non-specific and vague symptoms, which are also very frequent reasons for consultations in general practice [33]. The term ‘non-specific symptom’ is used as opposed to specific alarm symptoms as non-specific symptoms are not necessarily indicative of a specific cancer type, but may suggest several cancers or other diseases. Only a few symptoms were highly predictive of cancer; most of these were rare (<2 % of patients), except for lump/tumour which was present in almost 9 % of the patients. The GP’s estimation of the patient’s risk of cancer at referral showed an expected correlation with the actual probability of cancer. However, it should be noted that the GP’s estimated risk was almost twice the size of the actual probability of cancer.

The overall probability of cancer was 16 %. Cancer was found more often in men than in women, which might be explained by the fact that breast cancer often presents with an alarm symptom [34]. In addition, referred men tended to have a higher probability of cancer than referred women [35, 36].

Affected general condition was the most common clinical finding and the GP’s gut feeling was another important clinical finding, which also showed a high probability of cancer (24.0 %). As seen in Table 4, little influence of gut feeling was less predictive of cancer than no influence, which may be because some patients have clear symptoms where gut feeling has minor importance. Nonetheless, an association was found between the most common findings and gut feeling, as shown in Table 5. These findings indicate that more research is needed to further explore the role of gut feeling in early diagnosis of serious disease. Our study did not allow identification of the specific components of this gut feeling, but it seems to embrace several clinical aspects that in combination increase the patient’s probability of cancer.

The primary care interval for all cancer patients diagnosed in this study was markedly longer than the interval found in previous studies [37, 38]. The long primary care trajectory before referral underlines the complexity

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Numbers (% of all cancers)</th>
<th>Median (days)</th>
<th>75 percentile</th>
<th>90 percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer patients</td>
<td>207 (100 %)</td>
<td>15</td>
<td>72</td>
<td>130</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>37 (17.9 %)</td>
<td>19.5</td>
<td>77.5</td>
<td>127</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>26 (12.6 %)</td>
<td>11</td>
<td>56</td>
<td>110</td>
</tr>
<tr>
<td>Hematopoietic tissue cancer</td>
<td>21 (10.1 %)</td>
<td>19</td>
<td>85</td>
<td>278</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>19 (9.2 %)</td>
<td>7</td>
<td>22</td>
<td>51</td>
</tr>
<tr>
<td>Oesophagus, stomach and small intestine cancer</td>
<td>17 (8.2 %)</td>
<td>32.5</td>
<td>88</td>
<td>130</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>13 (6.3 %)</td>
<td>8</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Liver and biliary system cancer</td>
<td>11 (5.3 %)</td>
<td>7</td>
<td>49</td>
<td>80</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>11 (5.3 %)</td>
<td>35</td>
<td>69</td>
<td>168</td>
</tr>
<tr>
<td>Metastasis</td>
<td>11 (5.3 %)</td>
<td>51</td>
<td>100</td>
<td>345</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>10 (4.8 %)</td>
<td>53</td>
<td>131.5</td>
<td>357</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>5 (2.4 %)</td>
<td>21</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>Cervix, ovarian and uterus cancer</td>
<td>4 (1.9 %)</td>
<td>29</td>
<td>69.5</td>
<td>96</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>4 (1.9 %)</td>
<td>125</td>
<td>79</td>
<td>135</td>
</tr>
<tr>
<td>Soft tissue cancer</td>
<td>4 (1.9 %)</td>
<td>36.5</td>
<td>79</td>
<td>99</td>
</tr>
<tr>
<td>Unspecified cancer</td>
<td>4 (1.9 %)</td>
<td>123</td>
<td>365</td>
<td>365</td>
</tr>
<tr>
<td>Lip, oral and pharynx cancer</td>
<td>2 (1.0 %)</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>2 (1.0 %)</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Other cancers*</td>
<td>6 (2.9 %)</td>
<td>34</td>
<td>74</td>
<td>108</td>
</tr>
</tbody>
</table>

*Ill-defined digestive organ cancer: larynx cancer, chest cavity cancer, sternum cancer and clavicle cancer, penis cancer and testicle cancer
### Table 4: Distribution of referrals, cancer probability, crude PRR and adjusted PRR according to referral characteristics, primary care interval, GP’s suspicion of cancer and GP’s gut feeling

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Referrals (%)</th>
<th>Probability of cancer (%)</th>
<th>Crude PRR for cancer (95% CI)</th>
<th>Adjusted PRR for cancer (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>1278 (100%)</td>
<td>207 (16.2%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silkeborg</td>
<td>705 (55.2%)</td>
<td>101 (14.3%)</td>
<td>1.29 (1.01-1.66)</td>
<td>1.22 (0.95-1.56)</td>
</tr>
<tr>
<td>Aarhus</td>
<td>573 (44.8%)</td>
<td>106 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Referral to further examination at diagnostic centre</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silkeborg Yes</td>
<td>415 (59.0%)</td>
<td>49 (11.8%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>No</td>
<td>289 (41.0%)</td>
<td>52 (18.0%)</td>
<td>1.64 (1.05-2.50)</td>
<td>1.62 (1.05-2.50)</td>
</tr>
<tr>
<td>Aarhus Yes</td>
<td>75 (18.8%)</td>
<td>12 (16.0%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>No</td>
<td>325 (81.2%)</td>
<td>63 (19.4%)</td>
<td>1.26 (0.64-2.48)</td>
<td>1.22 (0.62-2.41)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>671 (52.5%)</td>
<td>95 (14.2%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Male</td>
<td>607 (47.5%)</td>
<td>112 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39 years</td>
<td>70 (5.5%)</td>
<td>3 (4.3%)</td>
<td>0.96 (0.26-3.51)</td>
<td>0.95 (0.26-3.49)</td>
</tr>
<tr>
<td>40-54 years</td>
<td>179 (14.0%)</td>
<td>8 (4.5%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>55-69 years</td>
<td>441 (34.5%)</td>
<td>80 (18.1%)</td>
<td>4.06 (2.00-8.22)</td>
<td>4.01 (1.98-8.12)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>345 (27.0%)</td>
<td>73 (21.2%)</td>
<td>4.73 (2.33-9.60)</td>
<td>4.76 (2.35-9.64)</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>243 (19.0%)</td>
<td>43 (17.7%)</td>
<td>3.06 (1.91-8.21)</td>
<td>3.31 (1.90-8.15)</td>
</tr>
<tr>
<td><strong>Patients with previous cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1134 (88.7%)</td>
<td>186 (16.4%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>144 (11.3%)</td>
<td>21 (14.6%)</td>
<td>0.89 (0.59-1.35)</td>
<td>0.80 (0.52-2.20)</td>
</tr>
<tr>
<td><strong>Symptoms at referral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (1.8%)</td>
<td>6 (26.1%)</td>
<td>1.96 (0.92-4.15)</td>
<td>1.88 (0.89-3.95)</td>
</tr>
<tr>
<td>1</td>
<td>240 (19.0%)</td>
<td>32 (13.3%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>276 (21.9%)</td>
<td>31 (11.2%)</td>
<td>0.84 (0.53-1.34)</td>
<td>0.82 (0.52-1.29)</td>
</tr>
<tr>
<td>3</td>
<td>278 (22.0%)</td>
<td>47 (16.9%)</td>
<td>1.27 (0.84-1.92)</td>
<td>1.26 (0.84-1.91)</td>
</tr>
<tr>
<td>4</td>
<td>206 (16.3%)</td>
<td>38 (18.5%)</td>
<td>1.38 (0.90-2.13)</td>
<td>1.38 (0.90-2.12)</td>
</tr>
<tr>
<td>5</td>
<td>118 (9.3%)</td>
<td>27 (22.9%)</td>
<td>1.72 (1.08-2.72)</td>
<td>1.68 (1.06-2.65)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>122 (9.7%)</td>
<td>28 (18.9%)</td>
<td>1.41 (0.87-2.30)</td>
<td>1.35 (0.83-2.18)</td>
</tr>
<tr>
<td><strong>Clinical findings at referral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>147 (3.3%)</td>
<td>9 (6.1%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>580 (52.4%)</td>
<td>80 (13.8%)</td>
<td>2.25 (1.16-4.82)</td>
<td>1.98 (1.02-3.84)</td>
</tr>
<tr>
<td>2</td>
<td>297 (26.9%)</td>
<td>67 (22.6%)</td>
<td>3.68 (1.89-7.18)</td>
<td>3.04 (1.56-5.92)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>82 (7.4%)</td>
<td>19 (23.2%)</td>
<td>3.78 (1.80-7.98)</td>
<td>3.25 (1.55-6.81)</td>
</tr>
<tr>
<td><strong>Diagnostic test results at referral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>187 (17.1%)</td>
<td>13 (7.0%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>565 (51.7%)</td>
<td>98 (17.4%)</td>
<td>2.50 (1.34-4.34)</td>
<td>2.16 (1.24-3.77)</td>
</tr>
<tr>
<td>2</td>
<td>267 (24.4%)</td>
<td>41 (16.4%)</td>
<td>2.21 (1.22-4.01)</td>
<td>1.95 (1.07-3.53)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>75 (6.9%)</td>
<td>13 (17.3%)</td>
<td>2.49 (1.21-5.13)</td>
<td>2.28 (1.14-4.66)</td>
</tr>
<tr>
<td><strong>Number of chronic diseases at referral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>295 (24.5%)</td>
<td>50 (17.0%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>403 (33.5%)</td>
<td>62 (15.4%)</td>
<td>0.91 (0.65-1.28)</td>
<td>0.73 (0.52-1.02)</td>
</tr>
<tr>
<td>2</td>
<td>286 (23.5%)</td>
<td>48 (16.8%)</td>
<td>0.99 (0.69-1.42)</td>
<td>0.71 (0.49-1.02)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>220 (18.2%)</td>
<td>34 (15.5%)</td>
<td>0.91 (0.61-1.36)</td>
<td>0.63 (0.42-0.95)</td>
</tr>
<tr>
<td><strong>Primary care interval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>723 (56.6%)</td>
<td>117 (16.2%)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1-2 months</td>
<td>156 (12.2%)</td>
<td>20 (12.8%)</td>
<td>0.79 (0.51-1.23)</td>
<td>0.81 (0.52-1.26)</td>
</tr>
<tr>
<td>2-3 months</td>
<td>79 (6.2%)</td>
<td>16 (20.3%)</td>
<td>1.25 (0.78-2.00)</td>
<td>1.31 (0.82-2.07)</td>
</tr>
<tr>
<td>3-4 months</td>
<td>52 (4.1%)</td>
<td>12 (23.1%)</td>
<td>1.43 (0.85-2.41)</td>
<td>1.42 (0.85-2.39)</td>
</tr>
<tr>
<td>4-5 months</td>
<td>29 (2.3%)</td>
<td>6 (20.7%)</td>
<td>1.28 (0.62-2.66)</td>
<td>1.36 (0.67-2.76)</td>
</tr>
<tr>
<td>5-6 months</td>
<td>17 (1.3%)</td>
<td>3 (17.7%)</td>
<td>1.10 (0.39-3.09)</td>
<td>1.26 (0.47-3.39)</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>222 (17.3%)</td>
<td>33 (14.9%)</td>
<td>0.92 (0.64-1.31)</td>
<td>0.90 (0.64-1.29)</td>
</tr>
</tbody>
</table>
of diagnosing these patients, but also stresses the need for quick and easy access to diagnostic investigations [39], including earlier referral by the GP despite non-specific symptoms.

The higher probability of cancer among patients not referred to further examination at a diagnostic centre may be explained by the separation of patients with specific cancer findings through the filter function; these patients are referred to specific CPPs or other pathways and not to the diagnostic centre. This indicates that the filter function prior to the referral to the diagnostic centre is useful. However, some patients who were terminated by the GP without further examination (watchful waiting) may actually have had a cancer or another serious disease. The present study did not gain insight into this issue, and further research in this area is needed.

The lower percentage (18.8 %) of referrals from the hospital in Aarhus to further examination at the diagnostic centre might partly be explained by the use of an initial CT scan, which may be more effective as a diagnostic instrument and thus may reduce the need for referral to further diagnostic workup. However, it could also be false assurance as no difference was found in the proportions of cancer between non-referred patients and patients referred to the diagnostic centre in Aarhus. Furthermore, the NSSC-CPP at the hospital in Silkeborg had been implemented several years before the NSSC-CPP in Aarhus. This difference may also have affected the number of GPs who chose to refer to the diagnostic centre.

**Strengths and weaknesses of the study**

A major strength of this study is the prospective design, which allowed us to include all patients referred to the NSSC-CPP and not only already diagnosed cancer patients. Although we included patients prospectively, the questionnaires were sent out retrospectively, and this may have introduced recall bias. To minimise recall bias, we posted our questionnaire to the GP no more than two weeks after inclusion of the patient, and the diagnostic workup for many patients had not been finished by the time the GP received the questionnaire. This also minimized possible information bias as the GPs did not know the results of the referral for many of the patients. Further data on this potential recall bias were not available. Lack of complete information in some questionnaires might have introduced information bias, but this is unlikely to have influenced the estimated probability of cancer or the reported clinical findings.

The register data are considered precise and valid as the cancer information in the DCR was registered prospectively. The DCR has an almost complete registration of all Danish cancer data and has been shown to be accurate [29]. We used the NPR to identify cancer patients

### Table 4 Distribution of referrals, cancer probability, crude PRR and adjusted PRR according to referral characteristics, primary care interval, GP’s suspicion of cancer and GP’s gut feeling (Continued)

| GP’s estimation of patient’s risk of cancer at referral | 0-20% | 21-40% | 41-60% | 61-80% | 81-100% | 448 (36.8%) | 195 (16.0%) | 314 (25.8%) | 155 (12.6%) | 104 (8.6%) | 36 (8.0%) | 24 (12.3%) | 47 (15.0%) | 41 (26.5%) | 52 (50.0%) | 622 (43.1-890) | 530 (362-776) |
| Did gut feeling influence the decision of referral? | No | 287 (24.6%) | 46 (16.0%) | 1 (ref) | 1 (ref) |
| | A little | 224 (19.2%) | 25 (11.2%) | 0.66 (0.39-1.11) | 0.65 (0.38-1.10) |
| | Some | 425 (36.4%) | 63 (14.8%) | 0.91 (0.60-1.38) | 0.86 (0.56-1.31) |
| | Much | 182 (15.6%) | 43 (23.6%) | 1.62 (1.02-2.58) | 1.55 (0.97-2.48) |
| | Very much | 50 (4.3%) | 17 (34.0%) | 2.70 (1.39-5.25) | 2.57 (1.31-5.05) |

*Adjusted for age and gender

GP: General Practitioner

### Table 5 Association between GP gut feeling and the four most common findings in cancer patients

<table>
<thead>
<tr>
<th>Four most common findings*</th>
<th>At least one</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPs’ gut feeling</td>
<td>Yes</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>109</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>38</td>
<td>207</td>
</tr>
</tbody>
</table>

Prevalence ratio: 1.50 (95 % CI: 0.82-2.75)

*Weight loss and fatigue (two most common symptoms), affected general condition (most common clinical finding) and abnormal blood sample at GP (most common abnormal diagnostic test result)
diagnosed in 2013, and this method of identifying cancer patients has been reported to have an accuracy of 95% after four months [32]. The introduced misclassification is considered to be non-differential.

The GP response rate is comparable to similar studies using GP questionnaires [34, 37] and must be considered high, which limits potential selection bias. Still, non-responding GPs may have had patients with special characteristics although a non-response analysis revealed no differences between patients of participating GPs and patients of non-participating GPs.

Although ‘gut feeling’ is a well-known and common phenomenon among GPs [28], this notion may have introduced a problem regarding the construct validity as it is uncertain whether GPs regard ‘gut feeling’ in the same way. Furthermore, ‘gut feeling’ can be difficult to separate from e.g. the GP’s estimation of the patient’s risk of cancer in this study design. The association between gut feeling and the four most common findings indicates that gut feeling is often seen in combination with other findings. Further sub analysis showed that no symptoms, clinical findings or abnormal diagnostic test results were stated in the medical records for only 11 of the patients; none of these patients were registered with a GP gut feeling. Furthermore, the fact that the probability of cancer appeared higher with no gut feeling (compared to little gut feeling) indicates that presence of clear signs of cancer does not generally prompt activation of gut feeling. Our results warrant further studies into the importance of ‘gut feeling’ in early detection of cancer.

Comparison with other studies
Bosch et al. [40] published a paper on referrals from GPs to a quick diagnostic unit (QDU) similar to the one described in this paper, but their aim was different from ours. The study showed that 30% of the patients referred directly to the QDU had cancer compared to the 16% found in our study. Data from the UK have shown that 11% of the patients referred to the ordinary urgent referral pathways were diagnosed with cancer [22]. Apart from the study by Bosch et al. [40], we are unaware of any published studies examining and quantifying GP referrals to NSSC-CPPs and related outcomes.

An earlier study confirmed that action should be taken when the GP suspects serious disease as these patients have a high risk of a new diagnosis of cancer or another serious disease within 2 months [41]. Furthermore, Hamilton has also highlighted the importance of the GP’s suspicion [6]. Our study adds to this evidence within primary care diagnostics.

Jensen et al. [21] documented that only 40% of the Danish cancer patients were referred to a ‘cancer specific’ CPP. This finding stresses the importance of providing the GPs with diagnostic tools like the NSSC-CPP as well as direct access to diagnostic investigations [39, 42, 43].

Conclusions
This study documents that 16.2% of all patients referred through the Danish NSSC-CPP because of non-specific serious symptoms had cancer. Patients referred to the NSSC-CPP were a heterogeneous group with many different symptoms and clinical findings. The GP’s gut feeling was a common clinical finding which was a strong predictor of cancer. Likewise, the GP’s assessment of the patient’s risk of cancer at referral was also strongly associated with the actual probability of finding cancer.

Additional file
Below is the link to the electronic supplementary material.

Additional file 1: Symptoms and abnormal clinical findings highly predictive of cancer.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
MLI participated in the design of the study, drafted the GP questionnaire, performed the data analysis and drafted the manuscript. PV conceived the study, contributed to the drafting of the GP questionnaire, the data analysis and the interpretation of results as well as the revision of the manuscript. MBC and FB contributed to the design of the study, the GP questionnaire and the revision of the manuscript. STK contributed to the design of the study, the data collection at the hospital in Aarhus and the revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements
We thank the contributing GPs for their time and effort with completing the questionnaire. We also thank the personnel at the hospitals in Aarhus and Silkeborg for providing the data used to include the relevant patients for this study. Data manager Kaare Rud Flanup is also acknowledged for his substantial assistance with the data retrieval from the Danish national registries.

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References
19. Almind Praksis i Aarhus, Aarhus University; 2010.
### Appendix 1. Symptoms and abnormal clinical findings highly predictive of cancer

<table>
<thead>
<tr>
<th>Symptoms at referral</th>
<th>Total (n=1269)</th>
<th>Patients with cancer n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of hunger</td>
<td>3 (0.2%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Paralysis/limb weakness</td>
<td>4 (0.3%)</td>
<td>2 (50.0%)</td>
</tr>
<tr>
<td>Neurological symptom</td>
<td>18 (1.4%)</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>14 (1.1%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>22 (1.7%)</td>
<td>9 (40.9%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>30 (2.4%)</td>
<td>11 (36.7%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>9 (0.7%)</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>Tingling fingers/feet/toes</td>
<td>6 (0.5%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Joint symptom</td>
<td>7 (0.6%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Memory loss</td>
<td>7 (0.6%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>35 (2.8%)</td>
<td>9 (27.7%)</td>
</tr>
<tr>
<td>Lump/tumor</td>
<td>107 (8.4%)</td>
<td>29 (27.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical findings at referral</th>
<th>Total (n=1269)</th>
<th>Patients with cancer n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone soreness</td>
<td>3 (0.2%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>3 (0.2%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Icterus</td>
<td>10 (0.8%)</td>
<td>5 (50.0%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>2 (0.2%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>Abnormal finding in mamma</td>
<td>6 (0.5%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (0.5%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (0.2%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Level of conscience</td>
<td>13 (1.0%)</td>
<td>4 (30.8%)</td>
</tr>
<tr>
<td>Neurological finding</td>
<td>29 (2.3%)</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>Abnormal lymph glands</td>
<td>43 (3.4%)</td>
<td>11 (25.6%)</td>
</tr>
<tr>
<td>GP's gut feeling</td>
<td>287 (22.6%)</td>
<td>73 (25.4%)</td>
</tr>
<tr>
<td>Exploratio rectalis</td>
<td>8 (0.6%)</td>
<td>2 (25.0%)</td>
</tr>
</tbody>
</table>
CHAPTER 7

PAPER III
Use of primary care and hospital services prior to cancer diagnosis among patients with serious non-specific symptoms and signs of cancer: a matched comparative study

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Abstract

Background: Cancer Patient Pathways (CPPs) for specific cancers have been implemented in Denmark since 2008. Studies have documented that only 40% of patients with cancer are diagnosed through these urgent referral pathways, probably because only half of all Danish cancer patients initially present with ‘alarm symptoms’ of cancer. These findings have prompted the implementation of a CPP for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP) and the establishment of ‘diagnostic centres’ in Denmark. We aimed to investigate the patterns in use of primary care and hospital services in the year preceding cancer diagnosis among cancer patients diagnosed through the NSSC-CPP.

Methods: We conducted a matched comparative study of cases defined as cancer patients identified through the NSSC-CPP at the diagnostic centre at the regional hospital in the Danish town of Silkeborg in the period 2011-2012. The reference groups were a matched group of cancer patients and a group of NSSC-CPP referred patients who were not diagnosed with cancer. The main outcomes were rates of daytime GP face-to-face consultations, diagnostic tests performed by the GP and diagnostic investigations completed at a hospital during the 12 months before either date of cancer diagnosis or NSSC-CPP referral.

Results: We found an increase in healthcare seeking and for diagnostic activity in both general practice and at the hospital 2-4 months prior to diagnosis among cases compared to the matched cancer reference group. Non-cancer patients referred to the NSSC-CPP had more contacts to general practice than referred patients who were later diagnosed with cancer.

Conclusions: The results indicate that the use of primary care and hospital services prior to cancer diagnosis among patients with serious non-specific symptoms and signs of cancer is higher than among cancer patients in general. The markedly increased use of general practice among NSSC-CPP referred
patients without cancer indicates that a group of patients who are frequently seen in general practice are referred to the NSSC-CPP, probably to rule out serious disease.

Keywords: Fast-track; Neoplasm; Primary care; Diagnosis; Cancer symptoms; Denmark
Introduction

Cancer is a common disease and is the leading cause of death in Denmark[1]. Danish cancer patients have relatively poor survival rates compared to many other countries[2, 3]. One reason could be that many cancers are not diagnosed and treated until they have developed into more advanced stages of disease[2, 3]. Delayed diagnosis of some cancers may result from late presentation of symptoms[2, 4-6], and delayed diagnosis of cancer has been found to have a negative effect on mortality[7-9].

Urgent referral cancer pathways have been implemented in many countries[10-12] due to concerns about the length of the diagnostic interval[12-14]. In the UK, the 2-week wait (2WW) referral pathway for earlier diagnosis of suspected cancer was introduced in 2000[15]. In Denmark, a number of different Cancer Patient Pathways (CPPs) have been implemented from 2008 and onwards[16, 17]. The clinical practice guidelines for the CPPs[18] were initially based on symptoms indicative of cancer (alarm symptoms)[19, 20]. Studies have, however, documented that only 40% of the patients who have later been diagnosed with cancer were identified through these CPPs[21, 22]. Moreover, only half (49%) of all Danish cancer patients initially present with symptoms characterized by the GP as alarm symptoms; the rest of the patients present with non-specific or general symptoms[21, 23]. Recent findings from the UK indicate the same trend[24]. In an attempt to identify more patients with early stages of cancer, a new CPP was introduced in Denmark in 2011 for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP)[25-27]. At the same time, a number of national diagnostic centres were established.

In Denmark, general practitioners (GPs) act as the first line of health care. They provide medical advice to an unselected group of citizens, but they also act as gatekeepers to ensure appropriate and timely flow of patients into the specialised health-care services[28].
A Danish study showed that cancer patients start to have increased use of primary and secondary health-care services than a reference group six months prior to their final cancer diagnosis[29]. Prior studies of GPs’ use of investigations have primarily dealt with performance of tests[30] and their efficiency[31, 32]. A recent English study found that, for certain cancers, investigations in primary care were associated with later referral for specialist assessment[33].

However, no studies have investigated the use of health-care services prior to diagnosis among cancer patients presenting with non-specific symptoms. Such knowledge may help provide faster diagnosis for this group of patients if specific patterns of health-care use can be identified.

We aimed to investigate the rate of daytime GP face-to-face consultations, diagnostic investigations performed in general practice and diagnostic investigations in secondary care among cancer patients diagnosed through the NSSC-CPP. These figures were investigated 12 months prior to either date of cancer diagnosis or referral date to the NSSC-CPP. The results were compared with both a matched cancer reference group and a non-cancer NSSC-CPP reference group.

Material and methods

Study design, setting and study population

We conducted a matched comparative study of all cancer patients identified through the NSSC-CPP at the hospital in Silkeborg in the Central Denmark Region for the period 2011-2012. The reference groups were 1) a matched cancer reference group and 2) a reference group consisting of patients referred to the NSSC-CPP who were not diagnosed with cancer.

Organisation of the NSSC-CPP
All Danish residents have free access to health care; the national health-care system is publicly funded, primarily through taxation. More than 98% of Danish citizens are registered with a specific general practice. The GPs act as gatekeepers to the rest of the health-care system, except for emergencies[34]. During one year, 85% of the Danish population is in contact with general practice.

All patients referred from their GP to the NSSC-CPP underwent a filter function comprising three components: a battery of blood tests, a urine test and diagnostic imaging. The diagnostic imaging consisted of an abdominal ultrasound (US) and a chest X-ray performed at Silkeborg hospital. The results of the diagnostic imaging were first assessed by a radiologist, and the GP subsequently interpreted all test results in combination and decided on further diagnostic steps to be taken. Such steps could be either watchful waiting or referral to a diagnostic centre for further investigations. If a specific disease or type of cancer was suspected, further steps could also involve referral to a medical specialist or another cancer-specific CPP (Figure 1).

The Danish medical services are divided into five regions. Each region operates the hospital service in that region and must have at least one diagnostic centre. Approx. 15 centres have so far been established in Denmark.

A diagnostic centre is a medical unit with comprehensive facilities for diagnostic investigation, including easy access to expertise in a wide range of relevant medical specialties (e.g. oncology, gynaecology, gastroenterological surgery, orthopaedics and radiology). NSSC-CPP patients referred to a diagnostic centre underwent further investigations on the basis of presented symptoms and clinical findings (e.g. blood tests, diagnostic imaging, endoscopies and biopsies). Based on the findings, the patient is then either referred to a CPP for a specific cancer, to a specific hospital department or back to the GP.

Patient identification
All patients who underwent the filter function in Silkeborg Hospital catchment area during 2011 and 2012 were identified and included. Eligible patients were identified by a digital marker on the battery of blood tests or by a unique code on the US performed as part of the filter function. Figure 2 shows the flow of patients. Among these patients, 56.3% had both the battery of blood tests and US performed, 30.8% had only the battery of blood tests and 12.9% had only the US performed.

In total, 2256 patients were identified (Figure 2), and 46 referrals (2.0%) were excluded for different reasons: patients under 18 years of age (n=8), cancer diagnosis within one year prior to referral (n=35) and relapse of known cancer (n=3). Of the remaining 2210 patients, 314 (14.2%) were diagnosed with cancer within six months after NSSC-CPP referral.

Before creating the cancer reference group 16 cancer patients were excluded for various reasons (Figure 3): Six cancer patients were not included because these persons had not been living in Denmark for a full period of 24 months prior to the index date, and four were not listed with a specific GP. Six cancer patients were not included because they were diagnosed with cancer in 2013, and register data regarding their health-care use were available only until 31 December 2012.

Cases

Cases were defined as the 298 cancer patients that could be used in the matching procedure when creating the cancer reference group (Figure 3).

Reference groups

We used incidence density sampling to create the cancer reference group.

The cancer reference group was established by sampling ten randomly selected persons from a population registered with cancer per case. They were matched on region, cancer type (ICD-10 coding), gender, date of cancer diagnosis (+/- one
year) and date of birth. These reference persons were alive, resident in Denmark and affiliated with a specific GP at the date of diagnosis/index date and throughout the two full years preceding the referral leading to the cancer diagnosis. It was not possible to obtain ten reference persons with cancer to all cases as some cancer types were very rare. This reduced the size of the cancer reference group by 50, which explains why the number of patients in the cancer reference group shown in Table 1 and Figure 4 and the number used in Table 3 and Figure 3 is 2930 and not 2980.

References could be sampled more than once for different cases, but only once for the same case. The use of incidence density sampling meant that a reference could also later be included as a cancer case[35].

The non-cancer NSSC-CPP reference group consisted of patients referred to the NSSC-CPP without having a cancer diagnosis six months after referral.

When we compared the cancer reference group with the cases, the index date was defined as the date of cancer diagnosis for each of the included cases. However, when we compared the non-cancer NSSC-CPP reference group with the cases, the index date was defined as the date of referral to the NSSC-CPP to ensure comparability between this reference group and the cases.

**Outcome measures**

The main outcomes were rates of daytime contacts to the GP, diagnostic tests performed by the GP and diagnostic investigations performed at a hospital. Information on health-care utilisation was collected for the 24 months prior to the index day (date of either cancer diagnosis or referral). The outcomes are shown as mean numbers per month (Figure 3) and as proportions of persons with contacts, tests and investigations during the 12 months prior to the index date (excluding the last month) (Table 3). As many cancer patients had a marked increase in contacts to their GP and more diagnostic investigations performed during the last month immediately before the diagnosis[29] (Figure 3), we
excluded this last month in the analyses shown in Table 3 as inclusion of these data could have reduced any small differences seen during the 12 months prior to the diagnosis.

Primary health-care services

All primary health-care services provided to citizens in Denmark are registered in the Danish National Health Insurance Service Register (NHSR) with specific codes together with the patient’s unique civil registration number (CRN). All entered registrations are based on fee-for-service reimbursement of health contractors in primary health care (i.e. GPs), and data in the NHSR are thus very complete[36]. The NHSR provided data on both daytime contacts and on diagnostic tests performed in general practice 24 months prior to the index day. Daytime GP contacts included consultations, home visits, e-mails and telephone consultations, whereas preventive consultations and vaccinations performed by GPs were not included. Diagnostic tests performed in general practice included blood tests (CRP test, differential blood count, haemoglobin measurement and blood samples sent from the GP to a laboratory), urine tests (urine test by stick, microscopy of urine and urine culture), pulmonary function tests and electrocardiography (ECG). Although some tests might not be relevant to cancer, we chose to include all performed tests.

Diagnostic investigations and register data

As a measure of hospital diagnostic investigations, we included performed US, CT scans, thoracic X-rays and colonoscopies/sigmoidoscopies performed on the patients 12 months prior to the index date. All these investigations may be part of a diagnostic process initiated by a GP, either directly or via referral to a medical consultant. From the National Patient Register (NPR), we obtained data on the number of US, CT scans, thoracic X-rays and colonoscopies/sigmoidoscopies performed at the hospital. Diagnostic investigations of both discharged and non-discharged patients were included.
For all NPR variables, only one event per category was included per day due to the complexity of the registrations in this registry.

Data on age, gender and country of residence were obtained from the Danish Civil Registration System. The demographic and socioeconomic variables included marital status and highest level of education; the latter was categorised according to the International Standard Classification of Education (ISCED)[37].

Cancer data

Data on the cancer diagnoses of the NSSC-CPP referred patients and the cancer reference group were retrieved from the Danish Cancer Registry[38-40].

Statistical analyses

Odds ratios (ORs) for having a GP contact, GP diagnostic tests or a diagnostic investigation performed at the hospital in the year prior to the index date (except the last month) were calculated using a conditional logistical regression model to account for the matched design (Table 3). When comparing cases with the non-cancer NSSC-CPP patients, logistic regression models were used because the non-cancer NSSC-CPP patients were not matched with cases like the cancer reference group.

For comparison of the monthly rates of health-care use (shown in Figure 4), the incidence rate ratios (IRRs) were calculated by using a negative binomial regression model and applying cluster robust variance estimation to account for heterogeneity between subjects[41]. A two-group effect of gender and marital status, a three-group effect of education and a linear effect of age (on the implied log scale) were included in the models.

The statistical significance level was 0.05 or less. All data were analysed using the statistical software Stata 12.0 (StataCorp LP, TX, USA).

Ethics and approval
The study was approved by the Danish Data Protection Agency (j.no: 2011-41-6118) and the Danish Health and Medicines Authority (j.no: 7-604-04-2/301). According to Danish law, approval by the National Committee on Health Research Ethics was not required as no biomedical intervention was performed.

Results
Cases and references were comparable (Table 1) although cases were statistically significantly older (mean=70.8 years) than NSSC-CPP non-cancer patients (mean=64.5 years) (p<0.001). The study included a total of 2210 patients referred to the NSSC-CPP of whom 314 (14.2%) were diagnosed with cancer within six months after referral and 302 (13.7%) within three months after referral. The most common cancers were lung cancer (21.3%), hematopoietic tissue cancer (14.3%) and colorectal cancer (11.8%) (Table 2).

Findings in cancer reference group

Daytime contacts to the GP
Two months prior to diagnosis, cases had a higher rate of daytime GP contacts than the cancer reference group (Figure 4a). In the twelve months (except the last month) prior to diagnosis, no significant differences were found in the distribution of GP contacts between cases and the cancer reference group, except that cases were less likely to have no contacts (Table 3).

Diagnostic tests performed by the GP
Two months prior to diagnosis, cases had significantly higher rates of diagnostic tests performed by the GP than the cancer reference group; a slight increase was observed in the cases already 10-12 months before the diagnosis (Figure 4a).

Diagnostic investigations at the hospital
Cases had significantly higher rates of diagnostic investigations performed at the hospital than the cancer reference group; this increase was found already from four months before the diagnosis (Figure 4a). The cases were also more likely to have more than one diagnostic investigation performed at the hospital 12 months before the diagnosis than the cancer reference group (Table 3).

**Findings in the non-cancer NSSC-CPP reference group**

*Daytime contacts to the GP*

During all months (except for the last month before diagnosis), cases had a significantly lower monthly rate of daytime contacts to primary care than the non-cancer NSSC-CPP reference group (Figure 4b) and (Table 3).

*Diagnostic tests performed by the GP*

Cases had slightly lower rates of diagnostic tests performed by the GP during 2-8 months before the diagnosis than the non-cancer NSSC-CPP reference group. A slight increase was found in the last month before the referral (Figure 4b). Cases had less diagnostic tests performed by the GP than the non-cancer NSSC-CPP reference group (Table 3).

*Diagnostic investigations at the hospital*

Cases had significantly higher rates of diagnostic investigations at the hospital compared to the non-cancer NSSC-CPP reference group in the month before the referral (Figure 4b). Cases were more likely to have no diagnostic investigations performed at all than the non-cancer NSSC-CPP reference group (Table 3).

**Discussion**

Within six months after referral to the NSSC-CPP, 314 patients (14.2%) were diagnosed with cancer. 298 cancer patients could be used as cases because 16 patients were excluded (Figure 3). Cases consulted their GP and were
investigated both in general practice and at the hospital more frequently than the cancer reference group during the two to four months before the diagnosis. Furthermore, a higher proportion of the cases had diagnostic tests performed by the GP and diagnostic investigations at the hospital during the four months before the diagnosis. In conclusion, this indicates that the cancer patients diagnosed through the NSSC-CPP had a longer diagnostic path in general practice than ‘regular’ cancer patients. At the same time, they were also referred to diagnostic investigations at the hospital earlier than anticipated. The available data did not allow us to conclude whether this could be explained by e.g. false negative results or inappropriate investigations. These findings suggest that further research is needed to explore the decision-making process and the chosen diagnostic investigations used.

In contrast to these findings, the NSSC-CPP referred patients without cancer had more contacts to general practice (except for the last month before the referral) than cases. This increase was seen already two years before the diagnosis (data not shown). This pattern could be explained by referral of ‘frequent attenders’ or patients with complex morbidities to the NSSC-CPP as these patients generally have high rates of GP consultations and secondary health-care use[42, 43]. The NSSC-CPP non-cancer patients thus seem to constitute a group of patients with a steady higher health-care use at least two years prior to referral, and they are also significantly younger on average than cases.

**Strengths and weaknesses of the study**

A major strength of this study was that we included a matched cancer reference group as this design allowed us to compare the cases with a population of ‘regular’ cancer patients.

Another strength was that the inclusion of all patients referred to the NSSC-CPP enabled us to study the differences between NSSC-CPP referred patients with and without cancer.
Danish register data is generally regarded as complete and valid. Information on nearly all cancers is registered prospectively in the Danish Cancer Register (DCR), and the records have formerly been shown to be accurate\cite{44}. Furthermore, the information on health-care services provided in general practice is considered valid because these registrations is also used for remuneration purposes\cite{36}.

By matching references and cases according to gender, age and regional area in addition to matching according to cancer type in the cancer reference group, we limited possible confounding by these factors. Moreover, cases and their matched references were comparable regarding educational level and marital status, which also reduced potential bias. Nevertheless, the results might have been influenced by residual confounding, such as comorbidity, but the significance of this is considered minimal.

A limitation of this study was the lack of information on the patients’ reasons for requesting a consultation with the GP and the contents of the consultations. Furthermore, the results of the diagnostic tests performed by the GP and the diagnostic investigations at the hospital were not available.

**Comparison with other studies**

Our finding of an increased consultation frequency in general practice before the cancer diagnosis is consistent with a study by Christensen et al.\cite{29}, which showed increasing consultation rates prior to cancer diagnosis, and a recent study by Wang et al.\cite{45} on gender differences in consultation patterns among cancer patients. These two studies included all types of cancer patients, while our study focused on cancer patients presenting with serious non-specific symptoms and signs of cancer.

Lyratzopoulos et al.\cite{46} have documented that the number of pre-referral consultations has construct validity as a measure of the primary-care interval.
Development of interventions to reduce the number of pre-referral consultations may help improve the timeliness of cancer diagnosis. This issue constitutes a priority for future early-diagnosis initiatives and research projects. It also seems appropriate to explore the use of the NSSC-CPP and the diagnostic centres and further develop these two initiatives accordingly. This is particularly important because all cancer patients have different pre-diagnostic pathways. Although urgent referral schemes already exist for several specific types of cancer, our study shows that many cancer patients are diagnosed through the urgent pathway for serious non-specific symptoms of cancer.

Jensen et al.[21] documented that only one in three of all Danish cancer patients were referred to a CPP for a specific type of cancer. This finding stresses the importance of providing the GPs with additional diagnostic tools, such as the NSSC-CPP and direct access to relevant diagnostic investigations[26, 47-49].

Conclusions
We identified increased diagnostic activity in both general practice and at hospitals during the two months prior to a cancer diagnosis when we compared cases to a matched reference group of cancer patients. This might indicate that the cancer patients diagnosed through the NSSC-CPP had a longer diagnostic path in general practice than ‘regular’ cancer patients. At the same time, the cases were also referred to diagnostic investigations at the hospital earlier than ‘regular’ cancer patients. Furthermore, we found a marked higher use of primary health care among NSSC-CPP patients without cancer compared to cases. This pattern could be explained by referral of ‘frequent attenders’ or patients with complex morbidities to the NSSC-CPP.

Further research is needed to explore the decision-making process and the chosen diagnostic investigations used among patients with serious non-specific symptoms.
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Competing interests

The authors declare that they have no competing interests.

Author contributions

MLI participated in the design of the study, performed the data analysis and drafted the manuscript. PV conceived the study, contributed to the data analysis and the interpretation of results as well as the revision of the manuscript. MBC and FB contributed to the design of the study and the revision of the manuscript. All authors read and approved the final manuscript.

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Figure 1. Organisation of the Danish NSSC-CPP

- **GP refers patient to NSSC-CPP**
- **Filter function:**
  - Battery of blood tests
  - Abdominal ultrasound and chest X-ray (Silkeborg) or CT scan (Aarhus)
- **GP receives test results and determines further diagnostic steps**
- **GP still suspects cancer or serious disease**
  - Referral to diagnostic centre for further investigations
- **GP suspects specific cancer type or other serious disease**
  - Referral to specific urgent referral cancer pathway or medical specialist

No reason for further diagnostics
- Watchful waiting in general practice
Figure 2. Flow chart of inclusion of NSSC-CPP patients

Abbreviations: NSSC-CPP = Cancer Patient Pathway for patients with serious Non-specific Symptoms and Signs of Cancer; OC ultrasound: Abdominal ultrasound performed as part of the filter function of the NSSC-CPP
Figure 3. Flow chart of excluded cases when creating the cancer reference group

314 cancer patients diagnosed within six months

16 patients excluded:
- Lived outside DK 2 years before diagnosis (6)
- Not registered with a GP 2 years before diagnosis (4)
- Diagnosed with cancer in 2013 (6)

Cases: 298 patients

Cases matched 1:10 via registers
(50 references missing as all cases could not be matched 1:10)

Cancer reference group: 2930 patients
### Table 1. Descriptive data for all cases and reference groups

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Cancer reference group</th>
<th>Non-cancer CPP reference group</th>
<th>NSSC-CPP reference group</th>
</tr>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>298</td>
<td>100</td>
<td>2930</td>
<td>100</td>
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<tr>
<td><strong>Gender</strong></td>
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<td>Female</td>
<td>129</td>
<td>43.3</td>
<td>1268</td>
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<td><strong>Age</strong></td>
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<tr>
<td>Mean</td>
<td>70.8 years</td>
<td>70.7</td>
<td>64.5 years</td>
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<td>(range, SD)</td>
<td>(38-96, 10.1)</td>
<td>(20-95, 9.8)</td>
<td>(18-98, 14.7)</td>
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<tr>
<td><strong>Age groups</strong></td>
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<td>18-54 years</td>
<td>17</td>
<td>5.7</td>
<td>177</td>
<td>6.0</td>
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<td>55-69 years</td>
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<td>35.9</td>
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<td>70-79 years</td>
<td>120</td>
<td>40.3</td>
<td>1163</td>
<td>39.7</td>
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<td>≥80 years</td>
<td>54</td>
<td>18.1</td>
<td>492</td>
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<td><strong>Marital status</strong></td>
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<td>63.2</td>
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<td>1078</td>
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<td><strong>Education</strong></td>
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<td>Basic(&lt;10 years)</td>
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<td>46.3</td>
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<tr>
<td>Short(10-15 years)</td>
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<td>39.5</td>
<td>1179</td>
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<tr>
<td>Long(&gt;15 years)</td>
<td>42</td>
<td>14.2</td>
<td>358</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Abbreviations: NSSC-CPP = Cancer Patient Pathway for patients with serious Non-specific Symptoms and Signs of Cancer; SD = Standard Deviation
Table 2. Type of cancer diagnosed in NSSC-CPP referred patients

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Number of cancers</th>
<th>% of all cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer patients</td>
<td>314 (100%)</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>67 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic tissue cancer</td>
<td>45 (14.3%)</td>
<td></td>
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<tr>
<td>Colorectal cancer</td>
<td>37 (11.8%)</td>
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<tr>
<td>Pancreatic cancer</td>
<td>30 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>25 (8.0%)</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>16 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>15 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>14 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Oesophagus and stomach cancer</td>
<td>12 (3.8%)</td>
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<tr>
<td>Liver and biliary system cancer</td>
<td>11 (3.5%)</td>
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<tr>
<td>Bladder cancer</td>
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<tr>
<td>Cervix, ovarian and uterus cancer</td>
<td>7 (2.2%)</td>
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<td>Lip, tongue and tonsil cancer</td>
<td>4 (1.3%)</td>
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<tr>
<td>Malign melanoma</td>
<td>6 (1.9%)</td>
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<tr>
<td>Testicle cancer</td>
<td>4 (1.3%)</td>
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<td>Brain cancer</td>
<td>3 (1.0%)</td>
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<tr>
<td>Soft tissue cancer</td>
<td>3 (1.0%)</td>
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<tr>
<td>Non-specified cancer</td>
<td>6 (0.6%)</td>
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<tr>
<td>Nose cancer</td>
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<td>Extremity cancer</td>
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<tr>
<td>Penis cancer</td>
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<tr>
<td>Thyroid gland cancer</td>
<td>1 (0.3%)</td>
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</tbody>
</table>

Abbreviations: NSSC-CPP = Cancer Patient Pathway for patients with serious Non-specific Symptoms and Signs of Cancer
Figure 4. Activities 12 months prior to cancer diagnosis (Figure 4a) or referral date (Figure 4b)

Upper part of each figure: rates of daytime contacts, diagnostic tests performed in general practice and selected diagnostic investigations performed at the hospital (mean per month) for NSSC-CPP patients with cancer and reference group 12 months prior to diagnosis/index day. Lower part of each figure: incidence rate ratios (IRR) with 95% confidence intervals (95%CIs).

Figure 4a Cases compared to cancer reference group

Figure 4b Cases compared to non-cancer NSSC-CPP reference group

Abbreviations: NSSC-CPP = Cancer Patient Pathway for patients with serious Non-specific Symptoms and Signs of Cancer; GP= General Practitioner
Table 3. Proportions of persons with contacts to their GP, diagnostic tests performed by the general practitioner and diagnostic investigations at a hospital 12 months prior to the index date (except the last month). Adjusted* analyses comparing diagnostic activity between cases and references

<table>
<thead>
<tr>
<th>GP Contacts</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>2.0</td>
<td>144</td>
<td>4.9</td>
<td>0.40 (0.18-0.93)</td>
<td>11</td>
</tr>
<tr>
<td>1-5</td>
<td>73</td>
<td>24.5</td>
<td>735</td>
<td>25.1</td>
<td>0.96 (0.72-1.27)</td>
<td>86</td>
</tr>
<tr>
<td>6-10</td>
<td>80</td>
<td>26.9</td>
<td>702</td>
<td>24.0</td>
<td>1.17 (0.90-1.55)</td>
<td>81</td>
</tr>
<tr>
<td>11-20</td>
<td>78</td>
<td>26.1</td>
<td>827</td>
<td>28.2</td>
<td>0.88 (0.67-1.16)</td>
<td>73</td>
</tr>
<tr>
<td>&gt;20</td>
<td>61</td>
<td>20.5</td>
<td>522</td>
<td>17.8</td>
<td>1.21 (0.89-1.65)</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GP diagnostics</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>74</td>
<td>24.8</td>
<td>951</td>
<td>32.5</td>
<td>0.67 (0.50-0.89)</td>
<td>97</td>
</tr>
<tr>
<td>1-2</td>
<td>87</td>
<td>29.2</td>
<td>734</td>
<td>25.0</td>
<td>1.23 (0.94-1.60)</td>
<td>87</td>
</tr>
<tr>
<td>3-4</td>
<td>53</td>
<td>17.8</td>
<td>466</td>
<td>15.9</td>
<td>1.10 (0.79-1.51)</td>
<td>46</td>
</tr>
<tr>
<td>&gt;4</td>
<td>84</td>
<td>28.2</td>
<td>779</td>
<td>26.6</td>
<td>1.12 (0.85-1.48)</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital diagnostics</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
<th>Cases</th>
<th>References</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>188</td>
<td>63.1</td>
<td>1955</td>
<td>66.7</td>
<td>0.83 (0.64-1.07)</td>
<td>241</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>8.7</td>
<td>398</td>
<td>13.6</td>
<td>0.63 (0.42-0.96)</td>
<td>29</td>
</tr>
<tr>
<td>&gt;1</td>
<td>84</td>
<td>28.2</td>
<td>577</td>
<td>19.7</td>
<td>1.65 (1.25-2.18)</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: NSSC-CPP = Cancer Patient Pathway for patients with serious Non-specific Symptoms and Signs of Cancer; OR = odds ratio; CI = confidence interval; GP = General Practitioner

*ORs are adjusted for age, gender, marital status and education
References


19. Clinical Governance Research and Development Unit (CGRDU), Department of Health Sciences, University of Leicester; 2005


CHAPTER 8:

DISCUSSION OF METHODS
INTERNAL VALIDITY

Design

The present thesis deploys two different designs to reach its aims:

1. A cross-sectional study design (Papers I and II)
2. A matched comparative design (Paper III)

Cross-sectional study design

Paper I was designed as a cross-sectional study with inclusion of patients referred from general practice to US at the Department of Diagnostic Imaging at Vejle Regional Hospital. The outcome measures were (1) whether the US gave rise to suspicion of cancer and (2) the number of cancers diagnosed 3 and 6 months after inclusion. It might be argued that the US counts as an exposure (in a statistical meaning) because we report cancer diagnosed also after 3 and 6 months, but since a cancer diagnosis can take months to be established, even though it was present at the time of the US, we needed this time frame to ensure that all relevant cancer patients were, indeed, diagnosed.

A strong alternative to the cross-sectional design could have been a randomised controlled trial, and such a trial might have been possible by block-randomising the GPs (randomising the GPs in the same practice together). As is often the case within health services research, this was not possible because the possibility of direct-access US was already available and had been implemented for all GPs in the Vejle Hospitals catchment area.

Paper II was designed as a cross-sectional study in which we included patients referred to the NSSC-CPP at the hospitals in Aarhus and Silkeborg, and data were collected retrospectively via postal questionnaire filled in by the patient’s GP. This design made it possible to retrospectively collect data on the milestones in each patient’s referral pathway. We were able to obtain data regarding presenting symptoms, clinical and abnormal diagnostic test results, the GP’s
suspicion of cancer at the time of referral and the influence of the GP’s gut feeling. Furthermore, the design allowed data to be obtained regarding the date of the first GP consultation about the symptoms that resulted in the patient’s referral. The date of the GP’s referral to the NSSC-CPP was also registered, but this date was not used in this study as we had complete data regarding the referral date from the clinical laboratory at Silkeborg Hospital and from the Department of Diagnostic Imaging at Aarhus Hospital. Asking the GPs retrospectively concerning dates in order to be able to calculate the length of the GP interval increases the risk of recall bias. A prospective collection of information on daily symptoms and diagnostic processes in a large follow-up study could decrease the risk of introducing recall bias. On the other hand, it would hardly have been feasible to use a prospective design because GPs only encounter few new cancer patients every year; and while cancer is more frequently suspected, referral to a NSSC-CPP remains a relatively rare event.

The use of a retrospective questionnaire survey is associated with certain limitations pertaining to the collection of clinical information about issues that are not noted in the patient’s medical record, e.g. information on the GP’s gut feeling and the GP’s assessment of the patient’s risk of cancer at referral. An interview study may have shed more light on the use of important diagnostic tools and may have produced deeper insight into the diagnostic work-up process in general practice. Audits and thorough scrutiny of the medical records could also have been useful. However, such study designs demand large amounts of resources and did not fit the financial setting of the present PhD study.

**Matched comparative design**

In Paper III, cases were defined as patients with cancer diagnosed within 6 months of being referred to part of the filter-function of the NSSC-CPP at Silkeborg Hospital in the period 2011-2012. The two reference groups were (1) a
cancer reference group matched on region, cancer type (ICD10), gender, date of cancer diagnosis(+/- one year) and date of birth.; and (2) a non-cancer NSSC-CPP reference group consisting of the patients referred to the NSSC-CPP not diagnosed with cancer within 6 months after referral. The design hereby resembles the design of a case-control study. The utilisation of primary health care services and diagnostic hospital investigations was studied 12 months prior to diagnosis and referral, and cases were compared with the two reference groups. Primary health care services were consultations and diagnostic tests performed at the GP and were considered a proxy for symptom presentation in primary care 12 months prior to diagnosis. The strength of this design lies especially in the inclusion of a large number of references in the cancer reference groups, which ensured an adequate robustness of the study’s estimates.

The incidence density sampling of the reference group allowed us to estimate the probability of having contact with general practice in a background population of ‘ordinary’ cancer patients. The inclusion of ten matched reference persons per case minimised the risk of confounding.

The registries from which data were drawn held no accessible information on the reason for the patients’ or the reference patients’ encounters or diagnostic investigations. Thus, one weakness in this part of the study was the lack of an opportunity to describe why patients consulted their GP. However, analysis of the use of clinical tests at the GP and any hospital investigations afforded us with reasonable insight into whether the GP had made any further clinical examinations and thereby obtained information, even if indirect, on the reason for the encounter.

Inclusion method

**Paper I**

We included all patients referred to US at the Department of Diagnostic Imaging, Vejle Regional Hospital. We excluded patients receiving
musculoskeletal or control US for a malignant/benign disease. These patients were excluded for two reasons; first, because we wanted to look only at abdominal US and, second, because we wanted to look at patients referred from GPs with a diagnostic aim and not for the purpose of control for an already known disease. Furthermore, we excluded patients outside the catchment area of Vejle Regional Hospital, Lillebaelt Hospital, because the Department of Diagnostic Imaging believed that these patients differed from the patients referred from GPs in the catchment area as the Department of Diagnostic Imaging at Vejle Hospital is the only hospital to offer direct-access US in the region; moreover, the services offered by the Department are highly appreciated, which might encourage GPs from outside the catchment area to refer some of their patients to diagnostic work-up at Vejle Regional Hospital. The referral of these non-catchment area patients to Vejle Hospital rather than to the hospitals within their own residential catchment area could indicate that they were facing a higher risk of cancer than the standard patient referred. As Vejle Hospital offers a faster access (direct-access) to a US than the other hospitals in the region, GPs outside Vejle Hospital’s catchment area might refer patients with a higher risk of cancer to this hospital, wanting these patients to have a US as quickly as possible.

Paper II

In Paper II, we included patients referred to the NSSC-CPP at both Aarhus and Silkeborg Hospitals from 7 March 2012 to 27 March 2013.

At Aarhus Hospital, we included patients who underwent the NSSC-CPP CT scan as this CT scan has a unique code. This registration process was used in an internal registration process at the Department of Diagnostic Imaging and it was considered valid. It was not possible to obtain data to validate this registration, which could have contributed to the strength of the study.
At Silkeborg Hospital, we included patients identified via a specific digital marker that was automatically added when the GP or the hospital department selected the battery of blood tests to be performed. As this digital marker was unique, the specificity of this method was very high.

The sensitivity of the digital marker was, however, problematic for several reasons. Firstly, the digital marker was only part of the battery of blood tests from 3 December 2010, but the battery of blood tests was introduced earlier in 2010. Therefore, the general practitioners had to install the latest version of the battery of blood tests on their local computer system because the digital marker was not part of the previous version of their computer systems. To ensure that all GPs installed the latest version of the battery of blood tests, we sent out a special newsletter through the local GP organisation and arranged a local meeting for GPs in the Silkeborg Hospital catchment area informing GPs about this as well as the optimal use of the NSSC-CPP. Secondly, it was possible to de-select blood samples which, unfortunately, included de-selection of the digital marker from the standardised battery of blood tests in the GP’s local computer system, possibly causing missed patients. Unfortunately, there were no valid ways of checking the amount of missed patients as the we could not access the GPs’ computer systems to verify which version of the standardised battery of blood tests were installed.

In this way, we were sure to include patients who had the battery of blood tests taken, but we might have missed eligible patients for the above-mentioned reasons.

**Paper III**

The study populations in Paper II and Paper III are partly overlapping as some of the patients from the NSSC-CPP at Silkeborg Hospital were included in both studies. In Paper III, we included patients referred to part of the filter-function
Discussion of Methods

of the NSSC-CPP at Silkeborg Hospital in the period 2011-2012. The digital marker on the battery of blood tests described in Paper II was used as well as a uniquely coded US (OC-US) to ensure inclusion of all patient who had either the battery of blood test or the US performed as part of the filter function (Chapter 3, table 3.1, page 32 and figure 3.1, page 35).

We included all patients who underwent part of the filter function (Paper III, Figure 2, page 103). A total of 56.3% of the included patients had both the OC-US and the battery of blood test performed, whereas 30.8% had only the battery of blood test and 12.9% only the OC-US. The reason for the percentage of patients only included by the OC-US may be due to the sensitivity problems of the digital marker mentioned in Paper II. The reasons for the relative large percentage of patients who did not have the OC-US performed are more uncertain. One possibility could be that the GPs use the battery of blood tests as a screening method before actually referring the patient to the full filter function. Furthermore, the results of the blood samples could explain the patient’s symptoms and the patient might therefore need no further diagnostic work-up and the OC-US were cancelled.

Information regarding cancer prevalence, gender and age in the inclusion groups can be seen in Table 8.1 below. Notice that this table contains all included patients after exclusions (as presented in Paper III (Figure 2, page 103) and not only patients used in the matching process.

According to Tsang C et al (2013)\textsuperscript{137}, approximately 14% of cancer patients in England are diagnosed through emergency admission; and it is well-known that the proportion of cancers presenting as emergency admission cases is higher for some types of cancer than for others (http://www.nclin.org.uk/publications/data_briefings/routes_to_diagnosis). It is unsure if these findings from the UK setting can be extrapolated to Danish
cancer patients. Nonetheless, it is, indeed, likely as studies have shown that approximately 90% of Danish cancer patients primarily present symptoms to their GP. Patients diagnosed with cancer in the context of an emergency presentation are not included in Papers II and III. Even so, it is hypothesized that among such patients, only few will present with non-specific symptoms; still, this issue will have to be addressed in future studies.
### Table 8.1. Descriptive data on all included patients organised by method of inclusion

<table>
<thead>
<tr>
<th></th>
<th>All included patients</th>
<th>Patients included in both groups</th>
<th>Patients included only by the battery of blood test</th>
<th>Patients included only by the OC-US</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2210</td>
<td>100</td>
<td>1249</td>
<td>100</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>314</td>
<td>14.2</td>
<td>181</td>
<td>14.5</td>
</tr>
<tr>
<td>No</td>
<td>1896</td>
<td>85.8</td>
<td>1068</td>
<td>85.5</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1177</td>
<td>53.3</td>
<td>588</td>
<td>47.1</td>
</tr>
<tr>
<td>Male</td>
<td>1033</td>
<td>46.7</td>
<td>661</td>
<td>52.9</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>65.4 years</td>
<td></td>
<td>65.2 years</td>
<td></td>
</tr>
<tr>
<td>(range, SD)</td>
<td>(18-98, 14.3)</td>
<td></td>
<td>(19-97, 13.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-54 years</td>
<td>458</td>
<td>20.7</td>
<td>255</td>
<td>20.4</td>
</tr>
<tr>
<td>55-69 years</td>
<td>769</td>
<td>34.8</td>
<td>444</td>
<td>35.6</td>
</tr>
<tr>
<td>70-79 years</td>
<td>585</td>
<td>26.5</td>
<td>344</td>
<td>27.5</td>
</tr>
<tr>
<td>≥80 years</td>
<td>398</td>
<td>18.0</td>
<td>206</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Abbreviations: OC-US = Abdominal ultrasound performed as part of the NSSC-CPP  SD = Standard deviation
Validity of the GP questionnaire

No pre-designed questionnaire was available, so the questionnaire had to be developed by the research group. However, many questions and definitions from earlier surveys were used, which enhances the validity of the questionnaire. The questions regarding symptoms and clinical findings were carefully discussed with researchers in the field and with GPs. This approach served to optimize the content validity of the questionnaire127.

The content validity of the GP questionnaire was assessed among two groups of GPs (see Chapter 3, page 40). The GPs filled out the questionnaire, and cognitive interviews were conducted to assess the GPs’ understanding of the questionnaire. This assessment revealed no difficulties in the GPs’ understanding of the items and concepts in the questionnaire. In this setting, we also tested the sufficiency of the questions and their appropriateness for patients referred with non-specific symptoms of cancer via cognitive interviews (construct validity)127.

For most items in the questionnaire, a test against a golden standard (criterion validity) made no sense as no such true values could be found. The majority of the items used in Paper II were factual and single items127. The use of latent variables would have required psychometric tests, such as item-response analyses and factor analyses, to ensure the construct validity127,138.

Processing of the questionnaire data

To ensure high quality in the questionnaire data, MLI coded the questionnaires guided by a predefined coding strategy, and the coding was double-checked before the questionnaires were scanned. A single research assistant scanned and verified all the questionnaires. The quality of this procedure was checked and
found satisfactory as there was no more than 1% error between the scanned and the verified data.

Selection bias
Different parts of the study may have introduced a risk of selection bias due to the procedures used for selecting the population for investigation or due to non-response. The inclusion of patients in the three papers is extensively discussed above.

In Paper I, it is important to note that the aim of this study was not to test if direct-access US was better than waiting-list US, but simply to report how the GPs used the opportunity to use direct-access US. Naturally, there will be a selection of more ill patients in the direct-access group which was underlined by the fact that most cancers were found in the direct-access group (84.2% after 6 months).

In Paper II, the GP response rate was high (73.8%) and no significant differences were found between referrals from participating GPs and non-participating GPs concerning the patients’ gender, age or probability of cancer diagnoses.

In Paper III, 16 cases (NSSC-CPP patients diagnosed with cancer) were excluded before the matching process. Six of the 314 cases could not be used as they had not been living in Denmark for a full period of 24 months prior to the index date, and four were not listed with a specific GP (health insurance group 2). Six of the cancer patients could not be used as these cancer patients were diagnosed with cancer in 2013 and register data regarding hospital diagnostics were only available until 31 December 2012. Furthermore, it was not possible to obtain ten references for all cases as some cancers were very rare, and this reduced the size of the cancer reference group by 50. This explains why the numbers shown in Paper III (Tables 1 and 3, Figure 3) is 2930 and not 2980.
Except for these exclusions, complete information was available on the primary health care use and hospital diagnostics of all included cases and references. No loss to follow-up occurred. All in all, selection bias seems as an unlikely explanation for our findings.

Cases and the cancer reference group were comparable regarding age, marital status and education (Paper II, Table 1, page 105).

Cases were statistically significantly older (70.4 years) than the NSSC-CPP non-cancer references (64.6 years; \( p<0.0001 \)), but there was no significant difference in distribution of gender. As there is an increase in daytime contact to general practice and health care utilisation\(^\text{139,140}\) with increasing age, the observed age difference will underestimate the larger use of health care seen in the non-cancer NSSC-CPP reference group.

Information bias

Information bias arises when the information collected is incorrect. Confounding factors or misclassification of exposure and outcome can cause such errors\(^\text{141,142}\).

The below section discusses information bias in the registries and the questionnaires.

The registries

Concerns regarding information bias were minimal in Paper I. Registration errors do occur, yet most likely non-differentially.

The date of diagnosis was obtained from the prospectively registered DCR, which minimises the information bias. However, these data were only available until 31 December 2012 when we performed the analysis of data for Paper II.
In Paper II, cancer diagnoses registered after 31 December 2012 were retrieved from the NPR until 6 months after the date of inclusion. This approach to classify incident cancer from the NPR is well-known, and the method has proven to be efficient as 95% of the cancer diagnoses are displayed after 4 months. The date of cancer diagnosis from the NPR was defined as the first date of the hospital admission at which the cancer diagnosis was confirmed. If the patient was diagnosed with ICD-10 codes C760 – C800 (i.e. malignant neoplasms of ill-defined, other secondary and unspecified sites), we searched and replaced this code with a more cancer-specific diagnostic code if such a diagnosis had been made no more than 2 months after the first cancer diagnosis was registered.

The questionnaires

The retrospective nature of the questionnaire-based study (Paper II) makes it prone to recall bias. Recall bias will affect the accuracy of the data (e.g. dates and clinical information), and aspects regarding accuracy may be particularly relevant for the reported date of the first GP consultation with the patient concerning the symptoms that resulted in the referral. To minimise recall bias, the questionnaire was sent to the identified patient’s GP no more than 2 weeks after the patient had been included in the study. Furthermore, as each GP only refers few patients to a cancer patient pathway, the GP is likely to remember these patients, which minimises recall bias as well.

By including referrals from hospital specialists, we introduced a potentially large lead time as we have no information regarding the time between the visit at the GP and the referral time (inclusion) from the hospital specialist. This time lead could be weeks or months and it may give rise to a more profound recall bias in this patient group.

The GP interval was analysed in this questionnaire and measured by two questions in line with the current guidelines as described in Chapter 3. The first
question requested the precise date of the first GP consultation with the patient concerning the symptoms that resulted in the patient’s referral. The second question asked for the precise date of referral to the NSSC-CPP; this information was not used in Paper II where we chose to use the date of the battery of blood tests from the LABKA as the date of referral to minimise bias and avoid missing data. Although this may have underestimated the length of the GP interval, the blood tests are typically sent from general practice to the clinical laboratories and registered on a daily basis.

The GPs were encouraged to consult their electronic patient files when completing the questionnaire to reduce potential information bias. Nearly all Danish GPs have electronic patient files144.

Confounding

In Paper I, we found no statistically significant differences in either gender or age distribution between direct-access and waiting-list US. The observational nature of the study implies that we cannot assess the precise effect of the US as other investigations may have been performed before or after the US. A potential confounder could be that the difference in cancer seen between direct-access US and waiting-list US derived from different GPs using either direct-access or waiting-list referrals. Future studies should include analysis of referring GPs as well as more patients and hospitals to ensure better statistical precision and generalisability.

In Paper II, we described the frequency of symptoms, clinical and abnormal diagnostic test results for all referred patients and for patients diagnosed with cancer without doing any further stratification. A larger study would allow these findings to be stratified by gender which would be preferable as there are gender-specific cancers and possibly other differences in e.g. health care utilisation prior to cancer diagnosis and referral to a CPP.
In Paper III, the effect of confounding by age, gender, type of cancer and geography was eliminated via random selection of the cancer reference population having the same gender, cancer and region as the cases as well as approximately the same age. As there is a slight difference in age distribution between the cases and cancer reference group (Paper II, Table 1, page 105), there might still be residual confounding here. Furthermore, we matched the patients on region (Central Denmark Region) which is a large geographical region. This could result in residual confounding as patients from a large city (e.g. Aarhus) may have different ways of contacting their GP, and this could affect our results. A larger nation-wide study could be useful in reducing this confounding and in improving the generalisability of the results.

In the statistical analyses, we adjusted our estimates to control for the influence of known confounders by using the multivariate analysis as described under statistical analysis and precision below. However, the possibility of residual confounding by factors not accounted for, e.g. pre-existing co-morbidity, cannot be excluded in this study.

Statistical analysis and precision
The waiting time from referral to performed US (Paper I) and GP intervals (Paper II) was not normally distributed, and some intervals were very long. All time intervals were calculated as medians rather than means to prevent overestimation which would arise if the mean of the GP intervals included the extremes.

In Papers I and II, PRs and PRRs were preferred to ORs because the use of ORs would tend to overestimate the associations as the prevalence of the outcome measure was high. In this case, ORs can sometimes be very high (20-40ish) or very low (0.05ish) and difficult to interpret, especially for a clinician. ORs can
be a good approximation of the risk ratio in cross-sectional and case-control studies and they are probably best in the latter when having rare events\textsuperscript{148}. To make our estimates of the associations in our studies more understandable and truer to the real change in the probability, we used PR/PRR. Furthermore, when using an OR, CIs have a tendency to widen as the prevalence of the outcome measure rises.

Even though we presented the GP intervals in Paper II, we refrained from further analysis of this interval as the study population was small and too small to test differences. The primary care intervals were presented as medians as well as 75 and 90 percentiles for each cancer type.

In Paper III, the monthly rates of daytime contacts and diagnostic tests at the GP and hospital diagnostic investigations were calculated for the cases and for the two reference groups. Some patients are frequent attenders in general practice, and the 10\% most attending patients seem to account for 30-50\% of all contacts\textsuperscript{149}. Previous studies have shown that social, economic and psychological factors influence consulting behaviour\textsuperscript{150-153}. The variability of recurrent events (e.g. consultations) is often greater than expected by the standard Poisson distribution, which could lead to an over-dispersion\textsuperscript{136}. By using the negative binominal regression model\textsuperscript{154}, we sought to account for the heterogeneity between subjects\textsuperscript{136}. A two-group effect of gender and marital status, a three-group effect of education as well as a linear effect of age (on the implied log-scale) were included in the models. ORs of having a contact, GP diagnostic test or hospital diagnostic investigation were calculated using a conditional logistical regression model to account for the matched design. In cases vs the non-cancer NSSC-CPP reference group, logistic regression models were used as these groups were not matched; in these analyses, we also adjusted for age and gender.
GENERALIZABILITY

In Paper I, we explored the use of direct-access US at Vejle Regional Hospital. The generalizability of this paper is questioned by the observational nature of the study and the fact that we included only one diagnostic unit in the region of Southern Denmark. The results need to be confirmed in future studies that include diagnostic units from different regions of Denmark. Since the data collection for this study of direct-access to US and other diagnostic imaging has been implemented throughout Denmark, this could enhance the generalizability of our results. As mentioned in Chapter 3, we decided to perform this research in the Region of Southern Denmark. It would have been preferable to have included patients from a hospital in the same region as the rest of my research, but this was not possible as no hospital in the Central Denmark Region offered direct-access to US. Furthermore, the direct-access to US had already been introduced in 2006 at Vejle Regional Hospital and it was therefore regarded as well-implemented.

The population living in the Southern Denmark region counts 1.2 million of the 5.6 million Danes. This makes this region the third largest of the five Danish regions population-wise. The region consists of 33 municipalities in the southern part of Jutland and Funen and its acreage and population size are comparable to the Central Denmark Region which is the setting for the rest of my research. At the time, Vejle Regional Hospital served an area of 300,000 people. Whether the two regions and especially the uptake of Vejle hospital and other Danish hospitals are comparable is uncertain; and as mentioned above, further studies should include a larger part of Denmark.

In Papers II and III, we included patients referred to the NSSC-CPP at Silkeborg and Aarhus Hospital (Paper II) and Silkeborg Hospital (Paper III). Although the
inclusion criteria and the set-up of the NSSC-CPP are almost identical throughout Denmark, we cannot conclude that our findings are representative of Danish patients referred to the NSSC-CPP. The Danish health care system is organised almost uniformly across regions, but regional differences might exist and larger studies including more patients and diagnostic centres are needed to ensure the generalizability of our results.

Extrapolation of our findings in Papers I-III to other countries requires careful consideration of differences in the organisation of health-care. The extrapolation will at least need a similar health-care organisation where the GP acts as a gatekeeper to specialised health care and where GPs have similar access to diagnostic investigations.
CHAPTER 9:
DISCUSSION OF RESULTS

This chapter contains a discussion of the main results of the three papers comprising the thesis. The results will be discussed in relation to the aims of the three individual papers and in relation to the results of other studies.
In this study, we examined patients referred from their GP to either direct-access or waiting-list US. When considering the group of patients where US raised suspicion of cancer and where cancer was later confirmed, patients referred directly to US were more likely to have cancer than patients referred via a waiting list. This finding may indicate that GPs prefer to refer patients estimated to have a higher risk of cancer via direct-access US, but the finding was non-significant. When looking at cancer diagnosed after 3 and 6 months, the difference between the direct-access and waiting-list referral was significant (Paper I, table 4, page 67). We chose to report PPV and PR of cancer where US raised suspicion of cancer; but because US often is part of a longer diagnostic trajectory, it is also relevant to report diagnosed cancers within 3 and 6 months after the US.

US triggered suspicion of cancer in more than half of the later diagnosed cancer patients, and this suspicion concerned primary cancer as well as metastasis (Paper I, table 5, page 68). Another way to interpret this result is that more than 40% of the patients later diagnosed with cancer were missed by the US. Whether these missed cancers ought to have been found cannot be concluded with the present study design. GPs seldom use a US as a solitary diagnostic tool; still, it is relevant to question if US is, indeed, the most appropriate diagnostic investigation to use in the referred group of patients if cancer is suspected.

More than one in five of the diagnosed cancers were lung cancers. This is not surprising considering the high frequency of this type of cancer. Furthermore, symptoms of lung cancer may mimic symptoms from the upper abdomen, tend to have non-specific and vague symptoms, and have frequently metastasised upon diagnosis. One in three patients received no diagnosis and returned to general practice without further diagnostic investigations; none of these patients were diagnosed with cancer during the 6-month follow-up. We do
not know what is the additional value of US in patients in whom no or non-relevant abnormalities were found, or if the results of abdominal US changed management decisions or had an effect on the outcome of the patient’s illness.

For each separate patient referral, the GPs stated on the referral forms if they had or did not have suspicion of cancer. Comparing the GPs’ statements about this suspicion, we observed no significant differences between patients referred via direct-access and patients referred via waiting-list. Consequently, the differences seen in cancer prevalence cannot be explained in this way.

A more detailed subdivision of the GPs’ suspicion for cancer may have provided more insight into a possible correlation between the level of suspicion and the cancer prevalence. As reported in Paper II, we found an interesting, strong association between the GP’s assessment of the cancer risk at referral and the prevalence of later, verified cancer diagnosis in patients referred to the NSSC-CPP. The observed difference in cancer prevalence between the different ways of referral may partly be explained by the intensity or acuteness of symptoms in combination with the GP’s ‘gut feeling’ or ‘cancer intuition’. Unfortunately, this study does not provide insight into the more detailed level of GPs’ cancer suspicion or into the GPs’ criteria for choosing direct-access. There were no substantial differences in symptoms, clinical findings or non-cancer diagnoses between the two approaches to US referral. It is well known that a cancer suspicion may be presented ‘between the lines’ rather than stated explicitly; and in this design, we cannot rule out that we missed referrals where the GP had a cancer suspicion. In any event, this would underestimate the ‘effect’ of the GP’s suspicion of cancer as referrals in which the GP actually had a cancer suspicion were assigned to the ‘no suspicion of cancer group’.

The reason why some GPs decided to refer patients whom they suspected had cancer to waiting list US is unknown, but we speculate whether this decision might be related to the GP having only a weak suspicion of cancer in this group.
or whether it may be due to lack of knowledge of the rather new possibility of
direct-access US.

It is questionable whether the median difference in waiting time between the
two approaches to US referral of 16 days has any influence on the stage of
cancer\textsuperscript{156}, but the combined waiting time may have some relevance because US is
often part of a longer diagnostic path before a cancer diagnosis is established.
The most important outcome of a more expedited cancer diagnosis is, of course,
increased survival. However, we also need to acknowledge other outcomes like
patient evaluation and health economic issues, and that a mean/median value
covers an underlying distribution which implies that some patients waited
considerably longer than the mean/median time reported here.

Research focused on patients referred to US from general practice is scarce and
focuses mainly on the appropriateness of the GP’s referrals\textsuperscript{157,158}; in particular,
we lack knowledge about the use of direct-access US in the diagnosis of cancer.
Speets et al. found that GPs’ patient management strategies changed in 64\% of
patients after an upper abdominal US had been performed\textsuperscript{159}. Furthermore, they
found that upper abdominal US substantially reduced the number of
subsequent referrals to a medical specialist and permitted swift reassurance of
patients in general practice. US has also been found to play an important role in
the diagnosis of ovarian cancers; Barret et al. found that 17\% of ovarian cancers
were identified by an initial US\textsuperscript{160}.

These findings stress the potential benefits of quick access to relevant diagnostic
imaging; US may not only shorten the diagnostic interval for cancer diagnosis in
general practice; it may also serve as an important tool for determining the right
management strategy for patients with abdominal symptoms. On one hand,
direct-access US may induce further referrals if the US does not produce
diagnostic findings matching the patient’s symptoms or appearance. On the
other hand, a possible side effect could be that easy access to one kind of
medical examination with a negative result could increase the risk of delaying the final diagnosis by other medical examinations, e.g. colonoscopy for suspicion of colon cancer.
In this study, we documented that patients referred to the NSSC-CPP formed a heterogeneous group. They presented with various, different symptoms and clinical findings and with a wide variation in the number of symptoms per referral. The most frequent symptoms were non-specific and vague, i.e. symptoms that are common reasons for encounter in general practice\textsuperscript{44}. Few symptoms were highly predictive of cancer, and most of these were very rare among the included patients (Paper II, additional file 1, page 83). All in all, patients referred to the NSSC-CPP had very diverse characteristics, which underlines the diagnostic challenge these patients constitute for the GPs\textsuperscript{8,9}.

As expected, the GP’s estimation of the patient’s risk of cancer at referral correlated with the actual probability of having cancer. An earlier study confirmed that action should be taken when the GP suspects serious disease\textsuperscript{4}; and Hamilton et al also highlighted the importance of the GP’s suspicion\textsuperscript{26}. Our study adds to this evidence within primary care diagnostics. However, it should be noted that the GP’s estimated risk at referral was almost twice as high as the actual risk of being diagnosed with cancer. This overestimation of the patient’s risk of cancer may reflect lack of knowledge of the very low PPV for cancer when the patient’s symptoms are non-specific and vague. But, it may also indicate that the referral threshold of these patients is too high and that GPs need to readjust their referral threshold for cancer suspicion.

Jensen et al.\textsuperscript{31} documented that only one in three of the Danish cancer patients had been referred to a ‘cancer-specific’ CPP. This finding stresses the importance of providing the GPs with diagnostic tools like the NSSC-CPP as well as providing direct-access to diagnostic investigations\textsuperscript{49,161-165}.

The primary care interval for all cancer patients diagnosed in this study was longer than the primary care interval found in previous studies\textsuperscript{30,96}. But the
results were also in accordance with earlier findings of a prolonged diagnostic interval for patients who had symptoms that the GPs interpreted as vague. The long primary health care path before referral underlines the complexity of diagnosing these patients, but it also stresses the need for quick and easy access to diagnostic investigations and the importance of the GP’s early referral, even where symptoms are non-specific.

The reason why fewer patients (18.8%) were referred from the hospital in Aarhus to further examination at the diagnostic centre compared with Silkeborg (59%) may be that an initial CT scan was used at Aarhus Hospital. The CT scan may be more effective than US as a diagnostic instrument and it may offer higher sensitivity. Compared with the chest X-ray and US performed at Silkeborg hospital, the initial CT scan in Aarhus hospital may have helped the GP refer more patients to a cancer-specific CPP or a medical specialist, and, possibly, the CT scan may convince the GP to use watchful waiting more often. Furthermore, the NSSC-CPP was implemented at the hospital in Silkeborg several years prior to the NSSC-CPP in Aarhus, which may have affected how many GPs chose to refer to further diagnostic investigations at the diagnostic centre. Implementation of guidelines like a CPP takes time.
In this study, we documented that within 6 months after referral to the NSSC-CPP, 14% of the patients were diagnosed with cancer. These cancer patients consulted their GP and were investigated in primary care and at hospital more frequently than the cancer reference group during the 2-4-month period preceding diagnosis. The growing use of health care services just before diagnosis is hardly unexpected as it reflects the more frequent contact to primary care leading up to the diagnosis\textsuperscript{63}. The use of hospital investigations for cases compared with the cancer reference group rose in the 4-month period preceding diagnosis. The same tendencies were seen in number of consultations and diagnostic tests in primary care in the months before diagnosis, but the trend was not as evident. This was surprising as we would have expected that a rise in contacts and test in general practice would precede the rise in hospital investigations.

All in all, this indicates that cancer patients diagnosed through the NSSC-CPP had a longer diagnostic path at the GP than ‘regular’ cancer patients; but at the same time, they were referred earlier to diagnostic investigations at the hospital.

As the number of consultations is associated with increased time from presentation to referral\textsuperscript{96}, it is crucial to minimize these as much as possible. Furthermore, 20% of cancer patients visit their GP with relevant symptoms three or more times before referral and about 80% of patients with multiple consultations had at least one diagnostic test—twice the proportion of patients who were referred after a single consultation\textsuperscript{64}.

The question is if this reflects an avoidable delay or it reflects that diagnostic difficulty and the need for investigation of poorly differentiated symptoms in primary care are reasons for multiple consultations\textsuperscript{171}.
These findings underscore the need for further qualitative work to explore GPs’
decision-making about referral to diagnostic investigations and the NSSC-CPP
as we may expect that some patients may benefit from an earlier referral to the
NSSC-CPP.

The non-cancer reference group had more frequently contact to general practice
than cases, except in the month prior to referral. In fact, this difference was seen
2 years prior to diagnosis. This finding may be explained by ‘frequent attenders’
or by patients having complex morbidities being referred to the NSSC-CPP
because they may pose an insurmountable diagnostic challenge for the GP\textsuperscript{172,173}.

Health care-seeking behaviour varies, and estimates in the present study were
given as average numbers. Some patients have a high threshold for health care-
seeking, while others have a low threshold. Previous studies have shown that
social, economic and psychological factors as well as gender influence
consulting behaviour\textsuperscript{150-152,174}.

Studies have shown that most cancer patients are seen in primary care before
their diagnosis\textsuperscript{63,175}, and our results underpin that the cancer patients diagnosed
through the NSSC-CPP increase their number of contacts to primary health care
before their diagnosis.
Non-specific symptoms and signs of cancer in general practice - access to investigation and diagnostic centres
CHAPTER 10:

MAIN CONCLUSIONS
Referring to the aims of the thesis stated in Chapter 2 and based on the findings in the three studies, the following conclusions may be drawn:

Paper I
The findings in this study suggest that GPs refer patients whom they estimate have a high risk of cancer via direct-access US rather than via a waiting-list system, but the finding was non-significant and demands further research to be confirmed. Furthermore, a significant difference in waiting time of median 16 days was found between direct-access and waiting-list US. It is questionable if this difference has any influence on the stage of cancer at diagnosis, but US is often part of a longer diagnostic path, and the combined waiting time for various diagnostic investigations may be of influence.

Paper II
This study documents that 16.2% of patients referred via the NSSC-CPP were diagnosed with cancer. Patients referred to the NSSC-CPP formed a heterogeneous group with various, different symptoms and clinical findings. This testifies to the diagnostic challenge these patient pose for the GP. The GP often had a gut feeling about cancer, and the GP’s ‘gut feeling’ was a strong predictor of cancer. Likewise, the GP’s assessment of the patient’s risk of cancer at referral was strongly associated with the actual probability of being diagnosed with cancer, although the GPs in general overestimated the risk for the group.

Paper III
NSSC-CPP cancer patients’ health care-seeking behaviour became more active, and the diagnostic activity in general practice and at hospitals increased 2-4 months prior to their diagnosis compared with a matched reference population of cancer patients. Overall, the results indicate that the GPs refer these patients to diagnostic investigations at a hospital earlier than cancer patients in general,
but it is possible that referral to the NSSC-CPP could have taken place at an even earlier time.

Furthermore, we observed a markedly higher use of primary health care among non-cancer NSSC-CPP patients than among cancer NSSC-CPP patients. This indicates that a group of patients seen more frequently in general practice are referred to the diagnostic centre to rule out serious disease.
CHAPTER 11:

PERSPECTIVES
In the first part of this thesis (Paper I), we report that GPs seem to use the possibility of direct-access US to refer patients with a high risk of cancer compared with patients referred to an ordinary waiting-list. Further research into the effect of granting GPs the possibility of direct-access to US and diagnostic investigations in general is needed. It would be very interesting to explore whether the use of direct-access diagnostic investigations ensures earlier diagnosis of cancer and other serious diseases. Further research could also include a qualitative study of GPs’ decision-making processes regarding direct-access to US and other diagnostic investigations. Furthermore, a health economic study of the costs and benefits when providing this service to GPs is needed as is more qualitative work on patients’ experience of direct-access US.

The second part of this thesis (Papers II and III) primarily describes the pre-referral characteristics of patients referred to the NSSC-CPP and the health care-seeking behaviour of NSSC-CPP patients later diagnosed with cancer. This part illustrates that increased health care-seeking behaviour predates cancer diagnosis in patients referred to a CPP with serious non-specific symptoms and signs of cancer compared with cancer references.

Such findings call for more granulated clinical studies including deeper case studies on incident NSSC-CPP cancer patients and relevant references in order to try to find more distinct combinations of early cancer-predictive clinical symptoms, signs and patterns in health care-seeking behaviour.

This research should also seek to document the NSSC-CPP cancer patients’ survival rates compared with a matched group of standard cancer patients. Further studies concerning the optimal combination of diagnostic imaging and blood samples in the initial ‘filter function’ are also important and should be investigated in large multi-centre studies.

Furthermore, research is needed regarding serious non-cancer diseases diagnosed among NSSC-CPP patients because these diseases most likely occur
frequently, and their diagnosis and treatment is important to the work otherwise performed by the diagnostic centres. Preliminary results from the diagnostic centre in Silkeborg show a high frequency of especially rheumatic diseases.

The GP’s gut feeling is barely addressed in this thesis, but our findings underline the importance of this “sixth sense”, or clinical intuition; likewise, there is growing evidence that gut feeling clearly helps clinicians in their daily work5,51,52,176,177. Further research is needed to improve our understanding of the positive and negative influences of this gut feeling regarding both referral and diagnosis of cancer patients – especially among cancer patients with non-specific symptoms and signs of cancer where the GPs are faced with a special clinical challenge to single out the few patients having cancer among the many presenting these frequent symptoms in general practice. Qualitative research is probably the most suitable method to further examine this complex phenomenon.

Lyratzopoulos et al (2013)96 found that the number of pre-referral consultations has construct validity as a measure of the primary care interval. Further research is needed to identify any possible excess of consultations and diagnostic investigations prior to referral to the NSSC-CPP171. Development of interventions to reduce the number of pre-referral consultations and diagnostic investigations may help improve the timeliness of cancer diagnosis and may be a priority for early diagnosis initiatives and research.

The needed future research should have a clinical focus as argued above. However, it should also address evidence-based ways of organising health care services in the most appropriate way, making the GP able to strike the balance between timely referral and diagnosis of patients with serious disease and at the same time maintaining a high-quality gate-keeper function to ensure acceptable referral rates to the secondary health-care system.
In 2009 Olesen et al described the initiatives to reduce delays in cancer diagnosis in Denmark. Since then, the focus on early diagnosis of cancer in Denmark has been to create comprehensive support for the GPs’ different tasks in diagnosing cancer including the diagnosis of patients with non-specific and vague symptoms of cancer as described in a recently published paper. To improve and optimise this strategy, more research and evidence-based implementation strategies are needed. The effectiveness and efficiency of the NSSC-CPP and direct access to diagnostic investigations should also be further investigated. Intervention studies are needed to test whether there is an effect on survival, quality of life, health economy and patient evaluation. In addition to all the needed research, it is important to ensure the practical implementation of new initiatives by educating the GPs and by building capacity of diagnostic investigations and diagnostic centres, to make new strategies succeed.

Whether our results can be extrapolated to countries with similar gatekeeper systems is unsure and depends on the exact organisation of health care and especially on the GPs’ access to diagnostic investigations and the organisation of the diagnostic centres.
CHAPTER 12:

ENGLISH SUMMARY
Introduction

The majority of patients with cancer have a symptomatic presentation. The symptoms are often diverse and evolve over time as the cancer develops. In many countries, including Denmark, GPs form the first line of health-care services; they provide medical advice to an unselected group of citizens and also act as ‘gatekeepers’ to ensure appropriate flow of patients in need of specialised care into the secondary health-care system. Thus, the GP plays a central role in diagnosing cancer.

Several countries have implemented national cancer patient pathways (CPPs) to reduce the length of the diagnostic interval for patients with ‘alarm’ symptoms and specific clinical symptoms that may indicate certain types of cancer. The dilemma is that only half of all cancer patients present with symptoms which the GP would describe as ‘alarm’ symptoms. Therefore, the GPs need further diagnostic opportunities. A CPP for patients with serious non-specific symptoms and signs of cancer was implemented in Denmark in 2012. At the same time, some hospitals started to provide direct-access to several diagnostic investigations for patients referred directly from GPs.

Aims

The overall aim of this thesis was to gain insight into initiatives taken to ensure earlier diagnosis of patients presenting with serious non-specific symptoms that could be signs of cancer. This insight was obtained by exploring GPs’ use of direct-access to abdominal ultrasound (US), the characteristics of patients referred to the new cancer patient pathway for serious non-specific symptoms and signs of cancer (NSSC-CPP) and the patterns of pre-diagnostic health service utilisation among these patients.
Methods

Three different studies were conducted:

1. a cross-sectional study of patients referred from their GP to either direct-access US or waiting-list US, 2. a cross-sectional study (based on questionnaire data from participating GPs) describing patients referred to the NSSC-CPP at the hospitals in Aarhus and Silkeborg, and 3. a matched comparative study of contact patterns of NSSC-CPP cancer patients during daytime, diagnostic tests in general practice, and diagnostic investigations at a hospital 12 months prior to their cancer diagnosis.

Results

In the first part of the thesis (paper I), we examined patients referred from their GP to either direct-access or waiting-list US. We identified 11 patients in whom the US raised suspicion of their later verified cancer diagnosis. Among these patients, we found that the patients referred via direct-access were more likely to have cancer than those referred via the waiting-list. Although this finding was statistically non-significant, it indicates that the GPs make appropriate use of the direct-access to US.

Our findings suggest that the opportunity for GPs to refer to direct-access US entails potential for earlier diagnosis of cancer. We found a significant median difference of 16 days in the waiting time between direct-access and waiting-list US, but it is unsure whether this difference may influence the stage of cancer at diagnosis. However, we know that US often forms part of a long diagnostic path, and the total waiting time for the combined diagnostic investigations may be of influence.

The second part of the thesis (papers II and III) documents that 14-16% of the patients referred to the NSSC-CPP were diagnosed with cancer. Patients referred
to the NSSC-CPP were a heterogeneous group with various symptoms and clinical indications. This finding underlines the diagnostic challenge that these patients tend to pose for the GP.

The GP’s gut feeling was a common clinical finding and a strong predictor of cancer. Likewise, the GP’s assessment of the patient’s risk of having cancer at referral was strongly associated with the actual probability of finding cancer.

Furthermore, cancer patients diagnosed via the NSSC-CPP consulted their GP more often and were also investigated in general practice and at the hospital more frequently two to four months prior to their cancer diagnosis compared to a cancer reference group. The use of hospital investigations for cancer patients diagnosed via the NSSC-CPP rose four months prior to diagnosis compared to the cancer reference group. This indicates that cancer patients diagnosed via the NSSC-CPP had a longer diagnostic path in general practice than ‘normal’ cancer patients, but it also suggests that these cancer patients were referred to diagnostic investigations at the hospital at an earlier stage.

In addition, there was considerably higher use of primary health-care services among non-cancer NSSC-CPP patients compared to cancer NSSC-CPP patients. This finding probably indicates that a group of patients who are frequently seen in general practice for various symptoms are referred to the NSSC-CPP to rule out serious disease.

Conclusion and perspectives

The findings regarding direct-access US described in the first part of this thesis warrant confirmation in future studies. In particular, there is a need for further qualitative work exploring the decision-making of the GPs when referring to direct-access US. Likewise, we need more qualitative studies of the patients’ experience with direct-access US. More research on health economics
perspectives are also called for, specifically studies of costs and benefits of providing direct-access to diagnostic investigations. Nevertheless, our findings indicate that direct-access US may be a potentially strong tool for ensuring faster diagnostic clarification of patients with unspecific symptoms, and it seems the GPs know how to select the right group of patients who are at high risk of having cancer.

The second part of this thesis illustrates increased health-care seeking behaviour before cancer diagnosis in patients referred to an NSSC-CPP. Such finding calls for further detailed clinical studies, including thorough case studies on incident NSSC-CPP cancer patients to identify more distinct combinations of early clinical symptoms and signs that may predict cancer and related patterns in health-care seeking behaviour.

Future research should have a clinical focus, as also argued above, but should also explore evidence-based ways of organising health-care services in the most appropriate way to ensure that the GP will be able to strike the balance between timely referral and diagnosis of patients with serious disease and yet maintain the gatekeeper role with reasonable referral rates to the secondary health-care system.
CHAPTER 13:

DANSK RESUME
Baggrund

Flere lande har indført nationale kræftpakker for at afkorte længden på de diagnostiske intervaller for patienter med såkaldte “alarm”-symptomer på kræft og patienter med symptomer på bestemte typer af kræft. Det store dilemma er, at det kun er cirka halvdelen af alle kræftpatienter, der præsenterer symptomer, som lægen vil kategorisere som “alarm”-symptomer på kræft. Derfor skal den praktiserende læge have flere muligheder for hurtig udredning ved mistanke om kræft hos de patienter, der kommer med symptomer, som ikke passer med henvisningskriterierne for en specifik kræfttype. I Danmark blev der i 2012 indført en ny kræftpakke for patienter med alvorlige uspecifikke symptomer på kræft. Samtidig har de praktiserende læger i tiltagende grad fået mulighed for at henvise patienter via åben adgang (uden om den almindelige venteliste) til en række diagnostiske undersøgelser på hospitalerne, heriblandt ultralydsskanning af maveregionen.

Formål
Formålet med første del af denne ph.d.-afhandling var at få mere viden om de praktiserende lægers brug af åben adgang til ultralydsskanning af maveregionen og udbredelsen af kræft blandt de henviste patienter. Formålet med anden del af ph.d.-afhandlingen var at opnå mere viden om de patienter,
som bliver henvist til kræftpakken for uspecifikke symptomer, herunder læge-søgningsadfærden op til diagnosen hos de patienter, som endte med at få en kræftdiagnose.

Metode
Tre forskellige studier blev gennemført i forbindelse med dette ph.d.-projekt: 1. et tværsnitsstudie af de patienter, som blev henvist fra deres egen læge til ultralydsskanning af maveregionen (enten via åben adgang eller venteliste), 2. et tværsnitsstudie (baseret på data fra en spørgeskemaundersøgelse blandt praktiserende læger), som beskriver de patienter, der blev henvist via kræftpakken for uspecifikke symptomer og udredt gennem enten Aarhus Sygehus eller Regionshospitalet Silkeborg og 3. et komparativt studie, der beskriver henvendelser til og diagnostiske undersøgelser hos den praktiserende læge blandt de kræftpatienter, der blev diagnosticeret gennem kræftpakken for alvorlige uspecifikke symptomer, og de diagnostiske undersøgelser, der blev udført på hospitalerne i løbet af de sidste tolv måneder før kræftdiagnosen.

Resultater
I den første del af afhandlingen (artikel I) undersøgte vi de patienter, som blev henvist fra egen læge til ultralydsskanning af maveregionen enten via åben adgang eller venteliste. Resultaterne fra skanningen gav anledning til mistanke om kræftsygdom hos 11 patienter, som senere i forløbet fik en kræftdiagnose. Studiet viste også, at de patienter, som blev henvist via åben adgang, havde en større risiko for at have kræft end de patienter, som blev henvist via venteliste. Selvom dette resultat ikke er statistisk signifikant, vidner det om, at de praktiserende læger forstår at bruge tilbuddet om åben adgang hensigtsmæssigt.
Resultaterne tyder på, at praktiserende lægers mulighed for at henvise til ultralydsskanning via åben adgang kan være med til at afkorte udredningsforløbet for kræft. Vi fandt en statistisk signifikant gennemsnitlig forskel i ventetiden på 16 dage mellem åben adgang til ultralydsskanning og adgang via venteliste. Det er uvist, om denne forskel har haft indflydelse på sygdomsstadiet på diagnosetidspunktet. Men da ultralydsskanning ofte udgør en del af et længere udredningsforløb, kan den samlede ventetid for alle de diagnostiske undersøgelser potentielt have indflydelse på sygdomsstadiet (på diagnosetidspunktet).

Andel del af afhandlingen (artikel II og III) viser, at 14-16 % af de patienter, som blev henvist via kræftpakken for uspecifikke symptomer, blev diagnosticeret med kræft. De henviste patienter udgjorde en blandet gruppe med mange forskellige symptomer og kliniske fund, hvilket tyder på, at denne gruppe af patienter er en stor diagnostisk udfordring for den praktiserende læge.

Den praktiserende læges mavefornemmelse blev ofte anvendt som en del af udredningen og viste sig også at være en stærk markør for kræft. Desuden viser resultaterne, at den praktiserende læges vurdering af patientens risiko for at have kræft på henvisningstidspunktet stemte godt overens med den reelle sandsynlighed for senere at blive diagnosticeret med kræft.

Yderligere viser studiet, at de patienter, som blev diagnosticeret via kræftpakken for uspecifikke symptomer, også kontaktede deres egen læge oftere og fik foretaget flere undersøgelser både hos egen læge og på hospitalet i to til fire måneder op til kræftdiagnosen (sammenlignet med en referencegruppe med kræft). Forbruget af hospitalsundersøgelser viste sig at stige fire måneder før selve kræftdiagnosen hos de patienter, som blev udredt via kræftpakken for uspecifikke symptomer (sammenlignet med en referencegruppe med kræft). Alt i alt tyder meget på, at de kræftpatienter, som blev udredt via kræftpakken for uspecifikke symptomer, havde et længere diagnostisk forløb i almen praksis end
gennemsnitlet af alle kræftpatienter. Samtidig ser det dog ud til, at denne patientgruppe også blev henvist til udredning på hospital på et tidligere tidspunkt i forløbet.

Da vi så nærmere på de patienter, som blev udredt via kræftpakken for uspecifikke symptomer, viste det sig, at forbruget af ydelserne i almen praksis var højst hos de patienter, som ikke fik en kræftdiagnose (sammenlignet med de patienter, som fik en kræftdiagnose). Denne forskel var tydelig allerede 24 måneder før henvisning til kræftpakken. Det kan tyde på, at en gruppe af patienter, som kommer ofte i almen praksis med diffuse symptomer, henvises af den praktiserende læge til udredning via kræftpakken for at udelukke mulig alvorlig sygdom.

Konklusion og perspektiver

Afhandlingens resultater om åben adgang fra almen praksis til ultralydsskanning af maveregionen bør bekræftes yderligere i fremtidige studier. Der er særligt behov for kvalitative studier, som kan se nærmere på de faktorer, som udgør den praktiserende læges beslutningsgrundlag vedrørende henvisning til ultralydsskanning via åben adgang. Der er også brug for kvalitative studier af patienternes oplevelse af muligheden for henvisning til ultralydsskanning via åben adgang. Derudover bør der forskes mere i de sundhedsøkonomiske perspektiver ved modellen, særligt omkostninger og fordele ved at udbyde en sådan service.

Trods behovet for yderligere forskning på området viser afhandlingens resultater, at den åbne adgang til ultralydsskanning af maveregionen potentielt kan medvirke til at afkorte det diagnostiske forløb. Resultaterne viser også, at de praktiserende læger synes at være gode til at finde de patienter, som har en stor risiko for at have kræft, og at få dem henvist via den åbne adgang til ultralydsscanning.
Andel del af afhandlingen viser, at de patienter, der henvises til kræftpakken, ofte har et øget forbrug af sundhedsydelser i perioden op til diagnosen. Flere kliniske studier, herunder grundige case-studier af kræftpatienter, der er blevet udredt via kræftpakken, vil måske kunne bidrage til at få identificeret, om der findes helt bestemte kombinationer af tidlige kliniske tegn på sygdom og deraf følgende lægesøgningsadfærd, som måske kan varsle kræft på et tidligere tidspunkt i sygdomsudviklingen.

Fremtidig forskning inden for dette område bør også fokusere på at finde de mest optimale måder at organisere sundhedssystemet på. Den praktiserende læge skal have muligheden for at henvise relevante patienter til undersøgelser via åben adgang uden ventetid og skal samtidig beholde ”gate-keeper”-funktionen, så sygehussystemet ikke overbebyrdes.
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Non-specific symptoms and signs of cancer in general practice - access to investigation and diagnostic centres

GP INVITATION LETTER

Kære [GP_Navn],

Vi vil gerne prøve at forbedre diagnoseen for cancer ved at give patienter en adgang til en ny diagnoseudviklings-proces. Derfor er vi glad for at udtale dig i det efterfølgende. For en del patienter kan det være nødvendigt at have en adgang til en diagnoseudviklings-proces, og vi vil gerne give dig denne adgang.

Vedr. [P_Fornavn], [P_Efternavn], [P_ernavn]

[Signature]

Med venlig hilsen - på proteingruppen vejne

[Name]

[Position]

[Institution]

[Address]

[Website]

[Phone]

[Email]
Vi tillader os at sende dette spørgsmål til dig, hvor du har henviset nødsagende patient til kræftpraksen "alvorlig sygdom, der kunne være kræft (alderet cancer)".

Almen praksis spiller en vigtig afgørende rolle i diagnostikken af mere end 80 % af alle kræfttilfælde. Det er ofte en vanskelig klinisk udfordring at finde de patienter, der skal henvises til udfordring, blandt de mange med merebenævnte symptomer og sygdomme. Den medarbejder i dette projektilleger os ny verd til denne vanskelige diagnostiske proces.

Vedr. [Fornavn] [Efternavn], [F. nr.

Vi vil bede dig give nogle kliniske oplysninger om det præhospitalforløb for patienten, hvis i er flere læger i praktik, bedes relevant udfyldt af den læge, der før var involveret i sygdomsforløbet op til tidspunktet for henvisningen.


Vi vil hæde dig returaf spørgeskemaer som det muligt. Der er naturligvis friwilligt at deltage. Vi tillader os at sende dig en plakat, hvis vi ikke har modtaget spørgeskemaet inden tider. Alle oplysninger anonymiseres og behandles forverts. Alle deltageres læger vil blive informeret om undersøgelses samtale resultater, som også vil blive begrænset efteruddannelses og til forbedring af de diagnostiske tilbud til almen praksis.

Du er velkommen til at ringe eller mailde til undersøgelse, hvis du har spørgsmål eller kommenterer.

På forhånd tak for hjælp!

Med venlig hilsen – på projektgruppens vegne

[Underskrift]

Mads Lind Jørgensen, specielge i almen medicin, phd-studerende
Forskningsprojektet, for Almen Praksis i Aarhus. Tlf 26 70 01 89/97 16 77 21 e-mail: Madsjansen@almaas.dk

Peder Vendskov, læge, ass. forskningsleder, professor, phd.
Førstegangspraksis, praksisleder læge, forskningsleder, professor, dr.med.
Norden Bondo Christensen, praksisleder læge, særdeles forsker, phd.

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Secretary: Phone: +86 40 32 02 00 | Fax: +86 40 32 02 01 | E-mail: canc@almalab.dk | Web: www.cap-med.dk

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Non-specific symptoms and signs of cancer in general practice – access to investigation and diagnostic centres

Date: 19/11/2011

Kvinde

Vi henvendte os til dig for at prøve igen for at hente dig deltag i en undersøgelse af det prækliniske diagnosticeringsforløb hos en klinisk patient, der blev henvist til undersøgelse via lægeoversigtet "alvorlig system, der kunne være kraftigt dysfunktionelt". Du vil ikke have hørt fra mig, eller er du kendt til at huske mig igen. Hvis du eller andre har udført eller akademisk været spærget i lægen, skal du bare sende dem brev rigt, og så findes derefter i udelukkelsens.

Dette fra angiveligt dyren på, at det måtte er lager på angiveligt der har besøgt lægen. Darfor er det muligt at du ikke har været involveret i hvert andet af patienten. Hvis du ikke har haft mulighed om brug af det aktuelle forløb har denne patient du ikke udførte spærget i lægen. Vi vil dog høre dig om et overrakt i nødvolde helse og sende denne note til et i vedligeholdt marknadsfor, spærget i lægen kan konsulteres.

Ja/nej har ikke haft mulighed om spærget i det aktuelle forløb hos denne patient og derfor kan spærget i lægen ikke udføres.

Men praksis giver en betydelig rolle i diagnosticerings af mere end 50 % af alle kliniske områder. Det er et af vigtige områder i undersøgelsens del i præklinisk praksis. Der er derfor en betydelig mulighed for, at de patienter, der ikke har haft mulighed om spærget i lægen, skal den 

Vide. P. Foranvendes "P. Efstrands, "P. og". P. og

Vi vil have dig give nogle klare oplysninger om det prækliniske diagnosticeringsforløb for patienten. Hvis der foreligger tanke om præklinisk praksis, bedes tænket omhvervet i undersøgelsens del i præklinisk praksis.

Undersøgelsen er godkendt af Kommunedirektør og Landhedsbyrådene og i PEAS og Godes undlad vedrørende

Målgruppens og dele af undersøgelsen, er en del af undersøgelsens del i præklinisk praksis.

Alle dele om undersøgelsen er anonymiseret og behandles fortroligt. Alle deltagende læger vil blive informeret om undersøgelsens mål

Vi vil høre dig om et spærget i vedligeholdet marknadsfor, er du i træt om noget, er du velkommen til at stille

På forhåndtik for hjælpen.

Med respekt hilsen – på præklinisk praksis

Mads Limbo Lyngman, specialister i intern medicin, ph.d., meterne

Forfatteren: Mads Lang Poulsen, Aarhus Universitets Hospital, TIL 26 70 01 88 71 16 79 71 e-mail: mads.lang@alma.au.dk.

Peter Vedel, læge, ass. forskningsleder, professor, ph.d.

Pål Høy, seniorlæge, læge, forskningsleder, professor, ph.d.

Mads Lisbo Christensen, professor, læge, seniorforsker, ph.d.
Kære lægerne i Rådvalg:

Vi henviste os til dig for at par uger siden for at høre dig delage i en undersøgelse af det praksisbaserede forløb hos en konkret patient, der blev henvist til udredning via kræftpakken "dværgsyndrom, der kunne være kraft (okkult cancer)"). Da vi ikke har hort fra dig, tillader vi os hermed at kontakte dig igen. Hvis du allerede har udfyldt og afsendt vores spørgeskema, skal du bare smide dette brev væk, da i så fald undersøgelse er udført.

Almen praksis spiller en helt afgørende rolle i diagnostikken af mere end 80% af alle kræftvæltnings. Der er ofte en vanskelig klinisk udforståelse at finde de patienter, der skal henvises til udredning, blandt de mange med mere høffelige symptomer og sygdomme. Din medvirken i dette projekt giver os ny viden om denne vanskelige diagnostiske proces.

Vedr. [Fornavn] [Efternavn], [Fyrarne]

Vi vil have dig give nogle kliniske oplysninger om det praksisbaserede forløb for patienten. Hvis I er flere læger i praksis, bedes stemmet udfyldt af den læge, der i praksis har involveret sig i patientens forløb og til tidspunktet for henvisning.

Undersøgelsen er godkendt af Danmarks sundhedsstyrelse og ILO og DIAMs uddigt vedvarende Multi-praksisundersøgelse samt arbejdet og støttet af Findmors- og Inderskovlænkesenteret i Region Midtjylland. Deltagelse i undersøgelsen er bevilget med en modolog (nr. 12.12.2) i praksis spørgeskema.

Alle oplysninger anonymiseres og behandles forsvarligt. Alle deltagende læger vil blive informeret om undersøgelses mål og resultater.

Vi vil have dig returnere spørgeskemaet i vedlagte frakkerede svarbrev. Er du i tvivl om noget, er du velkommen til at kontakte os.

På forhånd tak for hjælpen.

Med venlig hilsen, – på projektgruppens vegne

[Signatur]

[Adresse]

[Telefonnummer]

[Email]

[Sted, dato]

[Underskrift]

[Adresse]

[Telefonnummer]
Kæftpakken for alvorlig sygdom, der kunne være kæft

Forskningsenheden for Almen Praksis
Aarhus Universitet
Projektansvarlig Mads Lind Ingeman, speciallæge i almen medicin

Forskningsenheden for Almen Praksis
Aarhus Universitet
Bartholins Allé 2
8000 Århus C

Tlf. 87 16 71 21
E-mail: mads.ingeman@alm.au.dk
Kreftpakken for alvorlig sygdom, der kunne være kæft.

Dette spørgeskema vedrører forløbet for patienten anført i følgebrevet, som du/din praksis har henvist til pakken “alvorlig sygdom, der kunne være kæft”.

Hvis I er flere læger i praksis, vil I bede om, at den læge, der primært var involveret i sygdomsforløbet frem mod henvisningen, udfylder skemaet.

Den første del af spørgeskemaet omhandler tidspunktet, hvor du henviste patienten til pakken “alvorlig sygdom, der kunne være kæft”.

1. Hvilken dato henviste du patienten til pakken “alvorlig sygdom, der kunne være kæft”?
   
   [ ] Dag: [ ] Måned: [ ] Årstal:

   [ ] Ved ikke

2. Hvad var afgørende for, at du henviste denne patient?
   (Set gerne flere krydsier)

   [ ] Patientens anamnese
   [ ] Pårørendes fortælling
   [ ] Den objektive undersøgelse
   [ ] Blodprøvensvar
   [ ] Anden paraklinisk undersøgelse
   [ ] Manglende bedring af symptomer
   [ ] Forværring af symptomer
   [ ] "Mavefornemmelse/forenemmelse af at noget var galt
   [ ] Andet:

   [ ] Forbeholdt kodning

3. Hvor stor risiko for kæft, udtrykt i procent, vurderede du på henvisningstidspunktet, at denne patient havde?

   [ ] [ ] %

   (0 % = ingen risiko, 100 % = helt sikkert kæft)
Kørfpakken for alvorlig sygdom, der kunne være kræft.

Vi spørger nu om symptomer og objektive fund ved henvisningen. Først symptomer.

4. Hvilket(t) symptom(er) var til stede ved henvisningen?
   Hvis patienten havde symptomer, som ikke er nævnt på listen, bedes du skrive disse under "Andet".
   (NB: Vi spørger om objektive fund i næste spørgsmål.)

   (Sæt gerne flere krydser)
   □ Ingen symptomer
   □ Tæthed
   □ Sømme
   □ Hovedpine
   □ Vægttab
   □ Ægte svæt tendens
   □ Fieber
   □ Utoilshed
   □ Smerter
   □ Appetitløshed/valme
   □ Udfyldning/knude
   □ Andenæd
   □ Hoste
   □ Blodigt opspyt
   □ Synkebesvær
   □ Ændring af afværingsmønster
   □ Blod i afværningen
   □ Besværet vandladning
   □ Blod i urinen
   □ Unormal blodning fra underliv
   □ Ændring af modermærke
   □ Sår

   □ Andet:  ____________________________________________
   □ Andet:  ____________________________________________
   □ Andet:  ____________________________________________
   □ Andet:  ____________________________________________
   □ Andet:  ____________________________________________

   (Forbeholdt kodning)
5. Abnorme fund på henvisningstidspunktet

Sæt kryds, hvis der var abnorme fund - sæt kryds i "Intet patologisk fund" nederst på siden, hvis der ikke var abnorme fund:

(Sæt gerne flere krydser)

Objektive fund:

☐ Almentilstand
☐ Bevidsthedsniveau
☐ Neurologi
☐ Lymphknudestatus
☐ Hjerte
☐ Lung
☐ Mammae
☐ Abdomen
☐ Expl. rectalis
☐ Ekstremtæter
☐ Hud
☐ Led
☐ "Meveformemmelse"/formemmelse af at noget var galt
☐ Andet: ________________________________

Parakliniske undersøgelser:

☐ Biokemisk undersøgelse foretaget i egen klinik
☐ Biokemisk undersøgelse foretaget på hospital/hos speciallæge
☐ Bildediagnostisk undersøgelse

☐ Andet: ________________________________

☐ Intet patologisk fund
6. Hvilke kroniske sygdomme havde patienten ved henvisning til pakken "alvorlig sygdom, der kunne være kraft"?

(Sæt gerne flere krydser)

- Tidligere cancer. Hvilken: ____________________________
- Hypertension
- Iskærmisk hjertesygdom
- Apopleksi
- Diabetes
- Stofskiftelavelse
- KOL, bronkitis, emfysem eller astma
- Allergi
- Artritis eller reumatisk sygdom
- Osteoporose
- Lettere psykisk lidelse (let/moderat depression, let angst mv.)
- Psykisk sygdom (svær depression, udtalt angst, skizoafnem, bipolar lidelse mv.)
- Andet: ____________________________________________

- Ingen - gå venligst videre til spørgsmål 8
- Ved ikke - gå venligst videre til spørgsmål 8

7. Havde patientens forudgående kroniske sygdom nogen betydning for henvisning til pakken "alvorlig sygdom, der kunne være kraft"?

(Sæt gerne flere krydser)

- Nej, ingen betydning
- Ja, jeg så an, længere end jeg ellers ville have gjort, for jeg henviste patienten
- Ja, jeg lavede nogle undersøgelser/tast, for jeg henviste patienten
- Ja, jeg henviste hurtigere til pakken, end jeg ellers ville have gjort
- Ved ikke
8. Var der forhold, som du mener, var medvirkende til at forlænge udredningsforløbet i praksis eller forsinkede henvisning til pakkeforløbet?

☐ Patienten var ikke kendt af dig/praksis forud for dette udredningsforløb
☐ Patienten var "for kendt" af dig/praksis
☐ Patienten havde sproglige og/eller kulturelle vanskeligheder
☐ Patienten havde svært ved at udtrykke sig klart
☐ Patienten havde flere konkurrerende sygdomme
☐ Patienten havde et misbrug (alkohol, uforbrændende stoffer eller medisin)
☐ Patienten havde tenderer til at komme i praksis med småting
☐ Patienten havde tilbøjelighed til at udvide somatiserende afdærf
☐ Patienten blev oplevet som besværlig
☐ Patienten havde ikke tid til dig/praksis
☐ Patienten var for skrabelig (fysisk, psykisk eller mentalt) til at skulle gennemgå et udredningsforløb
☐ Patienten var for gammel til et udredningsforløb
☐ Patienten var for ung til at have kæft
☐ Ventetid på undersøgelser
☐ Falsk negative svar på undersøgelser

☐ Andet. Venligst uddyb:

☐ Ingen af ovenstående
☐ Ved ikke/ikke relevant

Forbeholdet lovgivning

De næste spørgsmål drejer sig om den såkaldte "mavefordommelse".

Mavefordommelse forstås her som en læges intuitive fordomme af, at noget er gået med patienten, selv om der ikke er tydelige kliniske tegn på dette, eller som en læges intuitive fordomme af, at den anvendte strategi i forhold til patienten er korrekt, selvom der er usikkert om diagnosen.

9. Var din mavefordommelse medvirkende til din beslutning om at henvisse patienten?

☐ Slet ikke - gå venligst videre til spm. 12
☐ I ringe grad
☐ I nogen grad
☐ I høj grad
☐ I meget høj grad
☑ Ved ikke - gå venligst videre til spm. 12
10. Hvilke forhold havde indflydelse på, at du havde en "maveformemmelse" ved denne patient?
   (Sæt gerne flere krydser)
   □ Den aktuelle sygehistorie (anamnesen)
   □ Patientens udseende/der fysiske fremtoning
   □ Det samlede kliniske indtryk
   □ Dit kendskab til patienten
   □ Patientens og/eller de pårørende bekymring
   □ Tidligere erfaringer med en lignende sygehistorie ("mønstergenkendelse")
   □ Andet. Venligst uddyb: ____________________________

   _____________________________________________
   _____________________________________________
   _____________________________________________
   _____________________________________________
   _____________________________________________
   _____________________________________________

Næste del af spørgeskemaet handler om perioden, fra patienten første gang henvendte sig med symptomer, der senere førte til henvisning til pakken "alvorlig sygdom, der kunne være kraft".

Svar venligst så nøjagtigt som muligt ud fra journalnotater og din hukommelse. Hvis du ikke kan angive præcise datoer/valigheder, giv da så præcist et skøn som muligt.

12. Efter dit bedste skøn, hvilken dato henvendte patienten sig første gang i praksis i det forløb, der senere førte til henvisning til pakken "alvorlig sygdom, der kunne være kraft"?
   ✓_____ - ✓_____ - 20___
   □ Ved ikke

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### Kræftpakken for alvorlig sygdom, der kunne være kræft.

13. Hvilke symptomer havde patienten ved første henvendelse, og hvor længe havde de stået på?

Hvis patienten havde symptomer, som ikke er nævnt på listen, bedes du skrive disse under "Andet symptom".

(Sæt gerne flere krydser)

<table>
<thead>
<tr>
<th>Varighed af symptom ved første henvendelse: (antal uger)</th>
<th>Varighed af symptom ved første henvendelse: (antal uger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Træthed</td>
<td>☐ Hoste</td>
</tr>
<tr>
<td>☐ Smiddeth</td>
<td>☐ Blodig opslyt</td>
</tr>
<tr>
<td>☐ Hovedpine</td>
<td>☐ Synkebesvær</td>
</tr>
<tr>
<td>☐ Vægttab</td>
<td>☐ Åndring i afføringsmønster</td>
</tr>
<tr>
<td>☐ Øget sværesentens</td>
<td>☐ Blod i afføringen</td>
</tr>
<tr>
<td>☐ Føber</td>
<td>☐ Besværet vandlådning</td>
</tr>
<tr>
<td>☐ Utilpasched</td>
<td>☐ Blod i urinen</td>
</tr>
<tr>
<td>☐ Smertor</td>
<td>☐ Unormal blødning fra underliv</td>
</tr>
<tr>
<td>☐ Appetitløshed/kvalme</td>
<td>☐ Åndring af moderne mærke</td>
</tr>
<tr>
<td>☐ Udfyldning/knude</td>
<td>☐ Sår</td>
</tr>
<tr>
<td>☐ Andet symptom</td>
<td></td>
</tr>
</tbody>
</table>

Angiv symptom: __________________________________________ Forbeholdt kode

☐ Andet symptom

Angiv symptom: __________________________________________ Forbeholdt kode

☐ Andet symptom

Angiv symptom: __________________________________________ Forbeholdt kode

☐ Andet symptom

Angiv symptom: __________________________________________ Forbeholdt kode
14. Blev der i verksat undersøgelse i forløbet, før du henviste til pakken "alvorlig sygdom, der kunne være kæft"?
(Sæt gerne flere krydsør)

<table>
<thead>
<tr>
<th>Øgede resultatet en evt. kæftmisanke?</th>
<th>Foretaget dato?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Ja</td>
<td>Nej</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Blodprøver 1.
- Blodprøver 2.
- Urinundersøgelse (Stix, mikroskopi, dyrkning mv.)
- Biopsi, cytologisk undersøgelse mv.
- Røntgenundersøgelse
- Ultralydscanning
- Endoskopisk undersøgelse
- Henvisning til praktiserende speciallæge
- Henvisning til sygehus (ekskl. kæftpakker)
- Henvisning til en organspezifikk kæftpakke

Andet, skriv venligst hvad:

- 20

Andet, skriv venligst hvad:

- 20

- Ingen
### 16. Hvad fik dig/praksis til første gang at overveje, at det kunne være kæft eller anden alvorlig sygdom?

(Obs: Forskelligt fra spørgsmål 2 hvor vi spurte, hvad der var afgørende for, at du henviste patienten)

Set gerne flere krysser

- Patientens fortælling
- Pårærendes fortælling
- Den objektive undersøgelse
- Blodprøvninger
- Manglende bedring af symptomer
- Forværring af symptomer
- "Mavefølelse"/følelse af at noget var galt
- Andet. Venligst uddyb:

  —

  **Forbeholdt kodings**

### 17. Hvordan vil du karakterisere dit kendskab til patienten før aktuelle sygdom?

- Meget godt
- Godt
- Nogenlunde
- Minimelt
- Kendske ikke patienten (første kontakt)

### Inside del af spørgeskemaet spørger vi om enkelte grundlæggende informationer om dig

#### 18. Hvilken stilling har du i praksis?

- Fast læge i praksis med ydernummer (inkl. delegyderummer)
- Afhastningsamanvendelse eller vi kan for praktiserende læge
- Uddannebeslægtede (gå venligst videre til spørgsmål 21)

#### 19. Hvor mange års ancienitet har du som speciallæge i almen medicin?

- **År**

#### 20. Hvad er dit køn?

- Mand
- Kvindel
21. Du er velkommen til at skrive her, hvis du har øvrige kommentarer:


