Childhood cancer in primary care
– from symptom to treatment

PhD dissertation

Jette Møller Ahrensberg

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PhD student:

MD, Jette Møller Ahrensberg, The Research Unit for General Practice, Danish Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark

Supervisors:

Professor, MD PhD, Peter Vedsted, The Research Unit for General Practice, Danish Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark
Consultant, Dr.Med.Sci., Henrik Schrøder, Department of Pediatrics, Aarhus University Hospital, Denmark
Professor, Dr.Med.Sci., Frede Olesen, The Research Unit for General Practice, Danish Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark
MD, PhD, Rikke Pilegaard Hansen, The Research Unit for General Practice, Danish Research Centre for Cancer Diagnosis in Primary Care, Department of Public Health, Aarhus University, Denmark

Assessment committee:

Consultant, MD, PhD, Mette Nørgaard, Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (Chairman)
Ass. Professor, MD, PhD, Hans Thulesius, Landstinget Kronoberg, Unit for Research and Development, Växjö, Sweden
Consultant, MD, Dr. Med., Karsten Nysom, Section of Paediatric Haematology and Oncology, Copenhagen University Hospital, Copenhagen, Denmark

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MY MOTIVATION

During my first years as a resident, I worked at departments of paediatrics and anaesthesiology. I liked the challenge and the action of my daily work and took part in the diagnosis and treatment of patients suffering from severe and life-threatening diseases. Years later, during my specialist training and my work in general practice, the challenging aspects of working in a low prevalence setting in the frontline of medical care as gatekeeper to the secondary healthcare system became clear to me. I decided to look further into the general practitioner’s role in the diagnosis of a rare and severe disease, namely childhood cancer.

ACKNOWLEDGEMENTS

A large number of individuals have contributed in making this PhD study process such a pleasant and rewarding experience. First and foremost, I wish to express my sincere gratitude to my supervisors Peter Vedsted, Henrik Schrøder, Rikke Pilegaard Hansen and Frede Olesen for their guidance and support throughout the research process. All my supervisors have offered timeless, very constructive feedback and have all critically and meticulously reviewed my papers and my work. My main supervisor Peter Vedsted has inspired me deeply and throughout the whole process shown his enthusiasm for working with cancer diagnostics in primary care. I am so very grateful to you, Peter. I am also most grateful to Henrik Schrøder for giving me access to the data from the DCCR and to Karen Møller Ottesen for her assistance in preparing the data from the DCCR. I wish to thank Rikke for helping me in the construction of the questionnaires and for her friendly way in guiding me; and I wish to thank you, Frede, for always reminding me of what general practice is all about.

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Finally, I am totally indebted to my friends and my family: to my mother for always having been a tremendous support. Last, but not least, my most sincere and deepest gratitude goes to my beloved Mogens and our three daughters Nanna, Ida and Emma Dicte - for all your love and all the joy you bring into my life.

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PREFACE
OUTLINE OF THE THESIS

This PhD thesis is based on the project “Childhood malignancies. From symptom to treatment.” The project was carried out during my time as a research fellow at the Research Unit for General Practice, Aarhus University and the Section for General Practice, Department of Public Health, Aarhus University.

The gatekeeper function of general practice and the concept of time intervals in the pathway from symptom to treatment in cancer diagnosis are introduced in Chapter 1 which also offers a brief introduction to the epidemiology of childhood cancer. Chapter 2 presents the aims of the PhD study. Chapter 3 describes the study design, the data sources, the development of questionnaires and the data collection. The main results of the four studies are presented in Chapter 4, and Chapters 5 to 8 present the four papers. Chapters 9 and 10 offer a general discussion of the methods used and the results presented in the articles. Chapter 11 presents the main conclusions and implications. Chapter 12 describes the perspectives raised by the present research and offers ideas for future research. Chapter 13 is the English summary, and Chapter 14 is the Danish summary. The last chapters contain the references and appendix (I-IV).
This PhD thesis is based on the following papers, which will be referred to by their Roman numerals:

I. “Use of primary care during the year before childhood cancer diagnosis: a nationwide population-based matched comparative study”

II. “The initial cancer pathway for children - one fourth wait more than three months”

III. “Presenting symptoms in primary care for children with cancer”

IV. “Childhood cancer and factors associated with the diagnostic interval. A nationwide population-based cohort study”.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DCCR</td>
<td>The Danish Registry of Childhood Cancer</td>
</tr>
<tr>
<td>DCR</td>
<td>The Danish Cancer Registry</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CRN</td>
<td>Civil registration number</td>
</tr>
<tr>
<td>CRS</td>
<td>The Danish Civil Registration System</td>
</tr>
<tr>
<td>DI</td>
<td>The diagnostic interval (from first presentation in general practice to diagnosis)</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>NHSR</td>
<td>The National Health Service Registry</td>
</tr>
<tr>
<td>ICD-10</td>
<td>The International Classification of Diseases, 10th revision</td>
</tr>
<tr>
<td>IQI</td>
<td>Interquartile interval</td>
</tr>
<tr>
<td>OOH</td>
<td>Out of hours</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Q (Parent)</td>
<td>Questionnaire for parents</td>
</tr>
<tr>
<td>Q (GP)</td>
<td>Questionnaire for GPs</td>
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<td>PR</td>
<td>Prevalence ratio</td>
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CHAPTER 1:  
INTRODUCTION
The vast majority of Danish children are ‘fit and healthy’, and most symptoms and episodes of illness in childhood are short and self-limiting [1,2]. During a two-week period, 20% of children under sixteen and 40% of infants have symptoms or feel sick. Colds, bellyache and headache are common complaints [2]. The majority of illnesses are dealt with by parents, while the professional health care system is involved in approximately 10-20% of cases [3,4]. Some symptoms are more likely than others to trigger health care seeking [4,5]. In Denmark, general practice is the front line in the national healthcare system, and the general practitioner (GP) has a core function in singling out the few very sick children among the many suffering from less threatening diseases. The risk of severe and life-threatening diseases in primary care is low, yet real [3].

This thesis outlines the process toward cancer diagnosis in childhood, one of the rare and severe diseases that GPs and paediatricians fear to overlook.
Cancer is, next to accidents, the second most common cause of childhood death in developed countries [6-8]. The total incidence of childhood cancer varies little throughout the world. In Europe, approximately 1 in 5-600 children develop a malignant disease before the age of fifteen [9]. In Denmark (59,000 births in 2011) [10]), 150-160 children are diagnosed with cancer annually [11], meaning that 1 in 400-450 Danish children are diagnosed with cancer before the age of fifteen. A minor part of childhood cancers are caused by genetic factors [11,12], but the aetiology of most childhood cancers remains unknown [11]. Childhood cancers differ markedly from adult cancers in their nature, distribution and prognosis [13]. Carcinomas are most common in adult cancers, whereas haematological malignancies and tumours of the central nervous system (CNS) account for the majority of childhood cancers [9].

The distribution of cancers varies within age groups. The most common malignancy among infants is neuroblastoma, whereas leukaemias predominate among 1-4-year-old children, and CNS tumours among 5-9-year-old children. After the age of 10, lymphomas, carcinomas, germ-cell tumours and bone tumours become more frequent and embryonic tumours (retinoblastoma, nephroblastoma, hepatoblastoma) become very uncommon [6,11,12,14,15]. Half of all childhood cancers occur in pre-school age after which a decrease in the age-specific incidence is seen until the ages of 8-10 years. Pre-puberty marks the beginning of a new increase, which continues throughout adult life. In all age groups, the incidence is significantly higher in boys than in girls; boys have an overall 20-25% excess risk for cancer due mainly to a greater risk of lymphoma, leukaemia and CNS tumours [12].
Childhood cancers tend to have short latency periods and to grow rapidly. Owing to specific diagnostic procedures and multimodal treatment strategies, the past decades have seen a welcome, marked rise in the probability of cure for all cancer [6,8,16,17]. The overall survival rate for childhood cancer has risen dramatically. In the 1960s, approximate 25% of all children who had had cancer became long-term survivors, whereas today this figure reaches 75%. The past 50 years have seen across-the-board improvements in survival from childhood cancer, mostly so in children diagnosed with acute myeloid leukaemia (14% to 77%), non-hodgkin lymphoma (23% to 83%) and neuroblastoma (13% to 65%). Today’s 5-year survival is highest for children with lymphoma (83-93%), Wilms tumour (92-93%), germ-cell tumours (95-100%), and retinoblastoma (100%) and lowest for children with peripheral nervous system (65%), soft tissue sarcoma (58%) and CNS tumours (73%) [8].

Childhood cancer has extensive consequences and places a heavy physical and psychological burden on the child and its family [18]. Rapid diagnosis helps ensure appropriate and timely therapy and optimizes the chances of cure [13]. Given the severity of childhood cancer and the importance of timely diagnosis [19,20], remarkably little is known about how and when these children enter the
healthcare system. Perhaps, it has always been taken for granted that children are referred and diagnosed quickly whenever necessary?

A fundamental problem in early cancer diagnosis is that mimicking common, transient and harmless conditions [18,21], the presenting symptoms of childhood cancer tend to be unspecific and vague [13,22,23]. The most common presenting symptoms are fever, headache, vomiting, pallor and fatigue, bone pain, limping, weight loss, bleeding or the presence of a mass/lump [24]. Symptoms are by no means pathognomonic for childhood cancer, making the diagnosis in the early course difficult. The positive predictive value (PPV) of, even alert symptoms, is low in general practice, as shown for adult cancer patients [25-28]. Furthermore, a British study recently displayed very low PPVs of the presenting symptoms in childhood cancer [29]. We have only limited knowledge about the symptoms or the symptom combinations that make the GP initiate further investigations. The general purpose of the present research project is to investigate the diagnostic process for childhood cancer. A good diagnostic process presupposes an appropriate healthcare setting and clinical skills.
HEALTHCARE ORGANIZATION AND GENERAL PRACTICE IN DENMARK

The Danish healthcare system is organized into a primary and a secondary healthcare system. All residents in Denmark are entitled to public health care benefits and enjoy free access to primary care, inclusive out-of-hours (OOH) health care services [30]. Almost all citizens are assigned to a certain general practice setting staffed with one or more certified GPs through the regional health authority [30]. An average GP has approximately 1,600 persons (incl. children) on his or her list and delivers primary health care services to these persons during the daytime. OOH primary health care services are supplied by GPs who work rota systems. They are provided from 4.00 pm to 8.00 am, Mondays to Fridays, throughout Saturdays, Sundays and public holidays [31,32]. Almost 41 million consultations (telephone consultation and consultations with practice nurses inclusive) take place in the primary health care system annually [10]. Of these, children under fifteen account for more than 10% [10]. All children in Denmark are offered a total of seven individual preventive health consultations before school age, three of these within the first year of life. The GP plays a central role in preventive health care, diagnosis, treatment; and the GP acts as a gatekeeper between the primary and the secondary healthcare system. Patients need a referral from their GP to receive further medical examination or treatment in hospital or by a specialist, unless in the event of an accident or acute illness.

Children’s encounters are most often caused by cough, fever, earache and skin rash (Grethe Moth, personal communication, 1 March 2012), and by headache and gastrointestinal complaint [3]. The vast majority of presentations in general practice are managed by the GP. The GP must judge the likelihood of critical disease such as cancer on the basis of several factors, such as presenting symptoms, clinical sense and experience, test results, knowledge of predisposing factors, age and gender; and the GP has to deal with diagnostic uncertainty in many situations while still maintaining a high-quality gatekeeper function.

Although the GP is the first stop on the diagnostic pathway, little is known about the nature of presenting symptoms in general practice and when these symptoms appear. Important new knowledge about childhood cancer may be derived from a study of health care seeking patterns and the nature and extent of symptoms predating a childhood cancer diagnosis, which we may call the ‘diagnostic time window’.
PREVIOUS STUDIES ON HEALTH CARE SEEKING PRIOR TO CANCER DIAGNOSIS

Summerton and colleagues studied the consultation pattern in primary care three years before cancer diagnosis in adulthood [33]. They found a pattern of less consultation among breast cancer patients than among their age-matched controls and rising odds of cancer in tandem with increases in the average time between new consultations. In contrast, Thulesius et al. illustrated a higher consultation rate in general practice in the year leading up to diagnosis for children diagnosed with cancer (2.3 times higher for leukaemia, 1.5 higher times for CNS tumour) than among age- and sex-matched controls [34] which indicates a long symptomatic time window. Only very few studies have explored the health-seeking pattern preceding cancer diagnosis in childhood in a controlled set-up. However, Dommett recently showed an increased frequency of consultations among childhood cancer patients in the year before diagnosis, particularly during the last three months before diagnosis [29]; a finding that was consistent among all diagnostic groups. Ansell studied the pre-diagnosis consultation pattern among children diagnosed with brain tumours and reported a higher frequency of disease-relevant symptoms and consultations up to four years before diagnosis [19]. A higher number of consultations among childhood cancer patients than among matched control persons may be due to conditions antedating the cancer and may represent an opportunity for earlier diagnosis. Misinterpretation of symptoms by patients and health providers and organisational problems may protract the time until diagnosis and treatment. The term delay has previously been used to describe the time interval from symptom presentation to treatment initiation. According to current guidelines [35], the term “time interval” is preferred in this thesis.
DEFINING TIME INTERVALS

The time interval from diagnosis to treatment has been characterized by much terminological confusion and little methodological rigor, and a standardized description has only recently been offered [35]. As shown in Figure 1.2, the pathway can be divided into a patient interval, i.e. the time from onset of symptoms related to the malignancy until the first presentation to the GP or another health care provider; a GP interval, i.e. the time from the first symptom presentation to the GP until initiation of an investigation to determine the presence of a potential cancer; a system interval, i.e. the time from the start of the GP-initiated investigation until the start of treatment; and a diagnostic interval, i.e. the time from the first presentation until the date of diagnosis. Further, other time intervals can be described; a primary care interval, i.e. the time from the first presentation until the first referral to the secondary care; a secondary care interval, i.e. the time from referral to treatment start; and a treatment interval, i.e. the time from diagnosis to treatment start. The total time interval covers the entire time span from symptom start to treatment start.

Figure 1.2. The overall milestones and time intervals in the route from first symptom until start of treatment [35].
STUDYING TIME INTERVALS IN THE CANCER PATHWAY

Over the past few years, several studies have explored the time intervals between diagnosis and treatment for adult cancer. In Denmark, interest in this subject was fuelled partly by a higher cancer mortality and a higher tumour stage at treatment start and final staging among Danish cancer patients than in the rest of Western Europe [36-38]. Long time intervals from symptom onset to treatment have been observed among Danish adult cancer patients. A Danish study thus found a median total interval of 98 days for adults [39]. Most of the duration of the total interval was due to long patient and system interval as the median doctor interval was zero days. Moreover, time intervals in the diagnosis of Danish lung cancer patients have been reported to be long [40].

Cancer runs a different course in children than in adults and childhood cancer incidences are both highly age-specific and vary much from one cancer to another. We may therefore safely argue that Danish childhood cancer remains largely un-described and much under-researched.

Previous studies on time intervals in the diagnosis of childhood cancer

International studies have explored the time intervals from the first symptom presentation to treatment in childhood cancer. Most of these studies have focused on time intervals for children with a specific type of cancer [20,21,41-57], and many have focused on time intervals in the diagnosis of retinoblastoma [20,41-43,49,50,55,56].

Other studies have focused on all cancer types [24,34,58-60] or all solid tumours [61-63].

A review from 2007 showed substantial variation in the mean diagnostic interval (from symptom onset to diagnosis) for childhood cancers [64]. An Israeli study reported a mean time interval from symptom onset to diagnosis of 15.8 weeks (0-208 weeks) for all solid childhood cancers [63], and a Canadian study reported a mean time interval of more than seven months for children with brain tumours [45].

Most studies report a shorter pathway for young children than for teenagers [24,52,60,61,63,65]. This age differential may be ascribed to several factors, e.g.
parents tend to pay closer attention to young children [60], visits to the GP are more frequent in young children than in teenagers [63], older children become increasingly autonomous which implies that the detection of symptomatic disease increasingly becomes their own responsibility [63,66], and symptoms are more easily identifiable and their progression more rapid among young children than among teenagers [24]. Finally, the distribution of different cancer types among age groups, and the anatomical site of the tumour may also have an influence [63].

Short intervals were generally seen for children with nephroblastoma (mean 2.5 weeks), whereas the longest intervals were seen for children brain tumours (mean 29.3 weeks) [64]. The shortest patient- and diagnostic interval may be seen in fast growing and aggressive tumours [67]. Moreover, the nature of presenting symptoms and clinical findings may influence the diagnostic strategies, as some may call for watchful waiting (e.g. enlarged lymph glands), whereas others may require immediate intervention (e.g. abdominal mass) [58].

A Mexican study showed a rising risk of longer interval from symptom to diagnosis among children of parents with low education than among children with well-educated parents [59]. Whether such inequalities exist in the diagnosis of childhood cancer in Denmark is unknown. Moreover, the reason why some families hesitate to contact the GP while others do not also remains elusive and largely unexplained [68,69].

Recent research has suggested an association between the time interval from symptom to diagnosis and the type of health professional first consulted [64]. Thus, the time intervals from doctor-seeking to diagnosis was longer for patients who initially consulted the GP than for patients who first consulted the emergency room [21,58] or a paediatrician [63]. Conversely, the risk of prolonged patient intervals was lower if the initial health care contact was with GPs than if it was with paediatricians or other health care professionals [58]. These findings may reflect the complexity of the pathway toward diagnosis in childhood cancer and the difficulties inherent in any study of this aspect of healthcare [35].
CONSEQUENCES OF LONG TIME INTERVAL IN THE CANCER PATHWAY

Long time intervals from symptom onset to diagnosis and treatment may influence the prognosis and the treatment possibilities in children as shown for adult cancer patients [70]. A study from 2011 showed a decreasing trend in mortality with diagnostic intervals of up to five weeks, after which mortality rose [71]. This counterintuitive phenomenon of higher mortality for patients with short diagnostic intervals than for patients with long intervals has been called the ‘waiting time paradox’ [72], and could be explained by the fact that the GPs are quickly expediting the very ill patients. However, it remains indisputable that mortality rises the longer the diagnostic intervals [71]. Knowledge and documentation of this field is sparse for childhood cancers [20]. An American study from 1996 suggested an inversely relation between the duration of symptoms and the ultimately diagnosed stage of medulloblastoma [47], e.g. the most aggressive tumours had the shortest symptomatic window; a situation that much resembles the waiting time paradox seen in adult cancers. Furthermore, children with high risk acute lymphoblastic leukaemia may tend to present more acutely and with a shorter duration of symptoms than children with low risk acute lymphoblastic leukaemia for whom the presentation is often more insidious.

Nevertheless, most authors stress the importance of a timely diagnosis [19,44,64], partly because delay in diagnosis may adversely affect the immune system and heighten the risk of side effects due to the cancer therapy, partly because the patient and his or her relatives carry a significant burden of distress during this period. Even if delay in diagnosis has little genuine influence on outcome, patient and parental anxiety is relieved by rapid diagnosis [18,21]. Undue delay may cause families to lose their thrust in healthcare systems [73,74], and the potential adverse effects of any lost trust on the parents’ and the child’s well-being and physical and mental health will readily translate into substantial healthcare costs [29].
In Denmark and the UK, cancer has now been defined as an ‘acute disease’ on which the secondary care sector should react promptly upon referral of patients with cancer-related symptoms reported by the GPs. The clinical pathway within secondary care should be fast and without bottlenecks or administrative waits. Appropriate, timely and informative referral from primary to secondary care has therefore become a focus area. In accordance with the national initiative that defined ‘cancer as an acute disease’, all patients with suspected or possible suspected cancer symptoms are targeted to be seen in the secondary healthcare within 48 hours after their referral from general practice [75,76]. According to the National Board of Health, the suspicion of leukaemia in childhood should be raised in the presence of pallor, fatigue, irritability, unexplained fever, persistent/recurrent upper respiratory tract infections, generalized lymphadenopathy, persistent/unexplained bone pain and/or unexplained bruising. Further, specific recommendations for children with suspected lymphoma, brain and CNS tumour, neuroblastoma, Wilms’ tumour, soft tissue sarcoma and retinoblastoma has been described [77].

The design of proper strategies to effectively shorten the diagnostic interval requires deep understanding of the symptomatic window, in particular the association between symptom presentation and treatment, the manner in which childhood cancer patients present symptoms and the GPs’ interpretation of rarely encountered symptoms in general practice.
Cancer in childhood is rare (150-160 cases a year in Denmark), and it is a diagnostic challenge for GPs to single out the few patients with cancer among the many patients with transient and less alarming symptoms. Little is known about the time interval before diagnosis although it may constitute an important prognostic factor.

Studying the health care seeking behaviour prior to diagnosis and investigating early symptoms and signs and the time from symptom presentation to diagnosis and treatment may help focus initiatives towards an early diagnosis of childhood cancer in Denmark.

The role of general practice in the diagnosis of childhood cancer remains to be determined and remarkably little is known about the time interval from symptom onset to treatment start, and about the health care seeking behaviour that precedes diagnosis.

Misinterpretation of symptoms may protract the time until diagnosis and treatment for childhood cancer patients. Knowledge of presenting symptoms and clinical signs in primary care is sparse.

The development of new effective strategies that shorten diagnostic intervals requires an understanding of the factors that influence time intervals and knowledge of how childhood cancer patients and their families present themselves to the healthcare system.
CHAPTER 2: AIMS
The overall aims of this thesis are, first, to increase our insight in health care seeking before cancer diagnosis in childhood, second, to shed light on the early symptoms and signs, the time interval from symptom to treatment of childhood cancer and the factors that may influence specific parts of this time interval.

The specific aims of this thesis were as follows:

1. To investigate the use of primary health care during the year preceding childhood cancer diagnosis in a large comparative cross-sectional study, taking age and cancer into account (Paper I).

2. To describe the time intervals from symptom onset to treatment for childhood cancer patients (Paper II).

3. To investigate early symptoms and signs, symptom interpretation and GP involvement in childhood cancer patients, taking cancer type into account (Paper III).

4. To analyse the association between the time interval from the first presentation in general practice to diagnosis (the diagnostic interval) and characteristics for symptoms and referrals (Paper IV).
CHAPTER 3: METHODS
This chapter offers a description of the methods used in the study. Table 3.1 gives an overview of the study population, the data sources and the outcomes of the four papers in the thesis. A further detailed description of methods is given in Chapters 5-8.

Table 3.1. Characteristics of Papers I-IV

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study population</th>
<th>Diagnosis (ICD10)</th>
<th>Data source</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Incident childhood cancer patients (0-15) registered in the DCR¹</td>
<td>C00-D48</td>
<td>Register-based study (DCR¹, CRS², NHSR³)</td>
<td>Use of primary health care services (contacts/diagnostic procedures) in daytime and out-of-hours the year preceding cancer diagnosis</td>
</tr>
<tr>
<td>II</td>
<td>Incident childhood cancer patients (0-14) registered in the DCCR⁴</td>
<td>C00.0 – C96.9 (malignant tumours), D32-33, D35.2-4, D42-43, D44.3-5 (benign CNS tumours)</td>
<td>Questionnaire-based study (parents and GPs)</td>
<td>Time intervals in the pathway from first symptom presentation until start of treatment (patient-, GP-, system-, diagnostic- and total interval)</td>
</tr>
<tr>
<td>III</td>
<td>Like in Paper II</td>
<td>Like in Paper II</td>
<td>Questionnaire-based study (GPs)</td>
<td>GP-involvement, symptoms, clinical findings, symptom interpretation and referral wording</td>
</tr>
<tr>
<td>IV</td>
<td>Like in Paper II</td>
<td>Like in Paper II</td>
<td>Like in Paper II</td>
<td>Associations between the diagnostic interval and presenting symptoms, symptom interpretation and referral wording</td>
</tr>
</tbody>
</table>

¹The Danish Cancer Registry
²The Danish Civil Registration System
³The National Health Services Register
⁴The Danish Childhood Cancer Registry
The register-based part of the study (paper I)

Design
This part of the study was performed as a comparative cross-sectional study using data from three nationwide registries: the Danish Cancer Registry, DCR; the Danish Civil Registration System, CRS; and the Danish National Health Service Register, NHSR. Childhood cancer patients’ utilization of primary health care services was examined during the year preceding their diagnosis and case data were correlated with the similar data for control persons. The children’s utilization of primary health care services was used as a proxy for symptom presentation. For control persons, the term ‘index day’ correlates with the date where the cases were diagnosed. Linkage between individual registries was possible through the use of the civil registration number, CRN a unique 10-digit personal identification number assigned at birth to every Danish citizen [78,79].

Study population
Children with cancer were sampled from the DCR [80], which holds information on cancer diagnosis in Denmark coded according to the Danish version of the International Classification of Diseases ICD-10 (ICD-10) (Chapter II, C00-D48) [81]. Information was collected on all children aged 0-15 years recorded with an incident cancer from 1 January 2002 to 31 December 2008. The study population was divided into five diagnostic subgroups according to the ICD-10 codes (A-E) (Table 3.2).

Table 3.2. Cancer subgroups

<table>
<thead>
<tr>
<th>Cancer subgroup</th>
<th>ICD10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Leukaemia</td>
<td>C91-C95</td>
</tr>
<tr>
<td>B Lymphoma*</td>
<td>C81-85, C96</td>
</tr>
<tr>
<td>C CNS tumour</td>
<td>C70-72, C75.1-3, D32-33, D35.2-4, D42-43, D44.3-5</td>
</tr>
<tr>
<td>D Bone tumour</td>
<td>C40-41</td>
</tr>
<tr>
<td>E Other solid tumour</td>
<td>Remaining ICD10 codes, chapter II</td>
</tr>
</tbody>
</table>

* Inclusive Morbus Letterer-Siwe.
Ten children for each childhood cancer patient were randomly selected to serve as control persons. The principle of incidence density sampling [82] was used to ensure inclusion of control persons who had the same gender and the same age (born on the same date) as the cases and no history of cancer on index day. Study participants were included only if resident in Denmark at the date of diagnosis/index day and throughout the full year preceding the cancer diagnosis (full lifetime if diagnosis sooner than one year of age). Figure 3.1 depicts the sampling of childhood cancer patients.

The study population consisted of 1,278 children with a cancer diagnosis and 12,780 control persons (Table 3.3).

Data
All primary health care services provided to citizens in Denmark are registered in the NHSR with specific codes and the unique GP setting identification number assigned for the general practice where the patient is listed. The NHSR provided data on consultations in daytime and OOH and diagnostic procedures performed during the daytime the year before diagnosis/index day for all study participants. Telephone-calls triaged to consultations and home visits were excluded. The CRS provided information on residence and vital status (alive or dead). See Paper I for details.
Methods

Table 3.3. Descriptive data on the study population in the register-based part of the study

<table>
<thead>
<tr>
<th></th>
<th>Childhood cancer patients</th>
<th>Control persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>All</td>
<td>1278</td>
<td>(100)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>667</td>
<td>(52.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>611</td>
<td>(47.8)</td>
</tr>
<tr>
<td>Age at diagnosis/index day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 years</td>
<td>114</td>
<td>(8.9)</td>
</tr>
<tr>
<td>1-4 years</td>
<td>403</td>
<td>(31.5)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>299</td>
<td>(23.4)</td>
</tr>
<tr>
<td>10-15 years</td>
<td>462</td>
<td>(36.2)</td>
</tr>
<tr>
<td>Mean age at diagnosis/index day</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Cancer subgroups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td>354</td>
<td>(27.7)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>105</td>
<td>(8.2)</td>
</tr>
<tr>
<td>CNS tumour</td>
<td>298</td>
<td>(23.3)</td>
</tr>
<tr>
<td>Bone tumour</td>
<td>65</td>
<td>(5.1)</td>
</tr>
<tr>
<td>Other solid tumour</td>
<td>456</td>
<td>(35.7)</td>
</tr>
<tr>
<td>Deaths (% of total cases)</td>
<td>189</td>
<td>(15.6)</td>
</tr>
</tbody>
</table>

*At the date of retrieval

Statistically analyses

For children with cancer and for the control persons, the monthly and quarterly rates and the rate ratios between the two groups’ daytime contacts, daytime diagnostic tests and OOH contacts during the study period were calculated. 95%-confidence intervals (95% CIs) were assessed from a negative binomial regression model applying cluster robust variance estimation to account for heterogeneity between subjects. The models were adjusted for age and gender. Subgroup analysis was made for each of the five cancer subgroups (A-E) and for their corresponding control persons. Curves for date of latest GP visits before diagnosis and associated confidence bands were drawn applying a standard Kaplan-Maier procedure and normal approximation on a reversed time scale. Data were analysed using the statistical software Stata 12.0 (StataCorp LP, TX, USA).
THE QUESTIONNAIRE-BASED PART OF THE STUDY (PAPERS II-IV)

Design
This part of the study was conducted as a population-based cohort study. All children in Denmark with an incident malignant cancer or a benign tumour of the CNS diagnosed during a four-year period (2007-2010) were attempted included. Patients were sampled from the Danish Childhood Cancer Registry (DCCR). Data were obtained via registries and questionnaires. The CRN was used to link registers on an individual level.

Questionnaires for parents and for GPs
Three questionnaires were developed: one for parents, one for bereaved parents and one for GPs (Appendix I-III). The contents of the questionnaire for bereaved parents and the contents of the ordinary parent questionnaire were equivalent. Grammatically, the two questionnaires differed slightly as verbs were in past tense. (“Was” replaced the word “is” when concerning the child). In the thesis, these two questionnaires are collectively referred to as the questionnaire for parents (Q (Parent)). The questionnaire for GPs is referred to as the Q (GP).

Development of questionnaires
A thorough literature search was performed using the search terms; child, malignancies, childhood cancer, diagnosis, delay, time intervals, questionnaires questionnaire study, general practice, family practice, and primary care in different combinations. The reference lists of keys paper were studied. The literature search revealed no appropriate questionnaires for the present study, and the questionnaires were therefore designed by the research group. The themes of the Q (Parent) and the Q (GP) were identified on the basis of literature studies, preceding interviews, clinical experience and from studies on time intervals in the diagnosis of adult cancers that had been performed at the Research Unit for General Practice, Aarhus University. The themes in the Q (Parent) included: family characteristics; a detailed description of the dates of the symptom start, the first presentation to the GP and other milestones in the diagnostic pathway; the symptom presentation (at onset and at first presentation), the child’s
comorbidity, the GP’s involvement in the diagnostic process and questions evaluating the diagnostic process and the course after diagnosis.

The themes in the Q (GP) included: the GP’s involvement in the diagnosis; a detailed description of the dates, e.g. the first presentation, the referral, and other milestones in the diagnostic process; the symptom presentation and clinical findings, the symptom interpretation, and the wording of the referral letter.

Whenever possible, questions from earlier surveys were used [40,83,84] where they had proved effective in describing a Danish population (its socioeconomic status, dates in the diagnostic pathway and symptom interpretation); otherwise, ad hoc questions were constructed. The themes and questions (“the item bank”) were carefully discussed within the research group. Specific hypotheses were constructed concerning each topic. Much benefit was derived from contacts with GPs, paediatricians, experts within relevant issues and from interviewing parents at the Department of Paediatrics (unit A4), Aarhus University Hospital in order to ensure the content validity of the questionnaires [85-87].

Pilot testing
Following a face validity test of the Q (Parent) among parents, the questionnaire were pilot-tested and commented by eight pairs of parents at the Department of Paediatrics (unit A4), Aarhus University Hospital. The test revealed a logical pattern of answers. Afterward, the parents were telephone interviewed by the author to test if the questions were understood and to test their reliability [88]. The Q (GP) was reviewed by GP colleagues and the scientific staff at the Research Unit for General Practice, Aarhus University. Based on their comments, the Q (GP) was adjusted and a regular pilot-test was performed. The Q (GP) was completed and commented by ten GPs. Only minor changes to the phrasing of the questions were made and no questions or themes were dropped or added before producing a final version with a high content validity in relation to the research question [87]. The questionnaires were processed in the computer programme Teleform Enterprise version 8.0 (Cardiff software Inc., San Marcos, CS, USA) for data capture by optical scanning.
Sampling of childhood cancer patients

The DCCR covers data on children diagnosed with cancer inclusive low-grade CNS tumours based on several existing Danish clinical databases. The Registry is annually validated against the DCR and its completeness is high [89].

From December 2009 to February 2011, the DCCR provided data (CRN, name, diagnosis, date of diagnosis and date of treatment start) on all children registered with an incident cancer diagnosis from 1 January 2007 to 31 December 2010 according to the Danish version of the ICD-10 [81]. Children diagnosed with the following ICD-10 codes: C00.0 – C96.9 (malignant) and D32, D33, D35.2-4, D42, D43, D44.3-5 (benign tumours in the CNS) were included. Records of updated information were provided by the research nurse, when necessary.

For each child, apart for those with a temporary CRN (N=6), the company CSC Scandihealth provided the following data: name, vital status, residence, biological parent’s vital status and residence, and the GP at time being. It also provided the name and address on the child’s GP at the date of diagnosis using data from ‘patient list registries’.

Data collection

Data from parents and GP were obtained through questionnaires. Data collection from GPs was conditional on parent’s approval, as described on page 41. GPs were initially informed about the study to minimise the risk of offending either parents or GPs by collecting data (Appendix I). We believed that the GP would contact us, if he/she found the study inappropriate. The information letter was sent to the GP with whom the child was listed at present time. If the child was no longer alive, the information letter was sent to the GP with whom the child was listed at the date of diagnosis. In one particular situation, the GP advised against contacting the family.

Data were collected in the following order: First, the Q (Parent)s were sent (Appendix I). The Q (Parent) was addressed to the mother unless the child had the same residence as the father and yet not the same as the mother. Updated information on the child’s vital status was collected the day before sending the questionnaire. Questionnaire data on children diagnosed in 2007 and 2008 were collected in December 2009. The remaining data were collected onwards, although a minimum three months after the child had been diagnosed. A
specific cover letter and the questionnaire for bereaved parents were used, if necessary (Appendix II). In such situations, the questionnaire was sent a minimum six months after parental bereavement (Appendix II).

Second, the Q (GP) was sent if parents consented (96%; 363/377) (Appendix II). The Q (GP) was sent to the person who was the child’s GP at the date of diagnosis. In practices with more than one GP, the GP most familiar with the child was asked to fill in the Q (GP).

The data collection ended in September 2011. Non-responding parents and GPs received a reminder after three weeks [90-92]. The GPs received a £28 (240 DKR) fee for their participation. The flowchart of the questionnaire-based part of the study is presented in Figure 3.2.
Data entry

When receiving the questionnaires, handwritten data were coded by JMA. Presenting symptoms were coded according to the International Classification of Primary Care 2nd Edition (ICPC-2) [93]. An assistant scanned all returned questionnaires; and whenever the Teleform-programme was in doubt of an answer, the questionnaire was thoroughly examined by the assistant and JMA. A previous study has documented the accuracy of this processing [94]. Data were transferred to the statistical software program STATA (Stata software, version 11.2, StataCorp, Tx, USA) and checked for errors. If errors were encountered, the original questionnaire was inspected and the study database entry corrected.

Variables

Table 3.4 presents the variables used in this part of the study.
### Table 3.4. Variables used for analyses in the questionnaire-based part of the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description of variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of first symptom(^1)</td>
<td>The date when the first symptom was noticed by the child/parents. In some situations, the dates were given as approximate dates. For example, if the record said “June”, 15 June was chosen as the date. If it said “in the beginning of June”, 1 June was chosen and if “late in June”, 30 June was chosen.</td>
</tr>
<tr>
<td>Date of first presentation(^2,3)</td>
<td>The date when the patient was first seen in general practice with symptoms related to the suspected cancer.</td>
</tr>
<tr>
<td>Date of first work-up in general practice(^2)</td>
<td>The date when the GP started the first diagnostic work-up (blood test, etc.)</td>
</tr>
<tr>
<td>Date of referral(^2)</td>
<td>The date when the GP referred the child to another health care provider/hospital for further clinical diagnostic.</td>
</tr>
<tr>
<td>Date of diagnosis(^3)</td>
<td>The date for diagnostic procedure: bone marrow aspirate (leukaemia), imaging (solid tumour).</td>
</tr>
<tr>
<td>Date of treatment start(^4)</td>
<td>The date of treatment initiation (chemotherapy, radiotherapy or operation). If expectant management: the date of diagnosis was defined as the date of treatment start. If palliative treatment: the date of treatment start was defined as the date of first treatment in aim of palliative care.</td>
</tr>
<tr>
<td>Patient interval(^4)</td>
<td>The time from onset of symptom(s) related to the malignancy to first presentation in general practice.</td>
</tr>
<tr>
<td>GP interval(^5)</td>
<td>The time from first presentation to first work-up in general practice.</td>
</tr>
<tr>
<td>System interval(^6)</td>
<td>The time from the start of first work-up to start of treatment.</td>
</tr>
<tr>
<td>Diagnostic interval (DI)(^6)</td>
<td>The time from first presentation to the GP to the date of diagnosis.</td>
</tr>
<tr>
<td>Total interval(^7)</td>
<td>The time from first symptom until start of treatment.</td>
</tr>
<tr>
<td>Parental educational(^7)</td>
<td>The mother’s highest education. The educational level was graduated into a low (no vocational education/few or more vocational courses), middle (vocational education of maximum three years/higher education of maximum three years) and high (higher education of minimum three years) educational level.</td>
</tr>
<tr>
<td>GP involvement(^2)</td>
<td>The GP was asked if he/she/the general practice was involved (fully or partly) in the diagnostic process toward the child’s cancer diagnosis (yes/no)</td>
</tr>
<tr>
<td>Symptoms and clinical findings(^2)</td>
<td>The GPs were asked about symptoms and clinical findings at the date at first presentation (check-box questions). Open questions enabled the GPs to add symptoms or clinical findings not mentioned in the check-box.</td>
</tr>
<tr>
<td>Symptom interpretation(^2)</td>
<td>The GPs were asked whether the symptoms in their clinical judgement were interpreted as either “alarm (red flag signs), indicating cancer disease”; as “serious, indicating severe disease” or as “vague, not indicating severe disease”.</td>
</tr>
<tr>
<td>Referral wording(^2)</td>
<td>Based on the GPS electronic medical record, we asked the GPs to categorise the contents of the referral letter in one of these categories: “cancer suspicion”, “serious illness, not specific cancer” or “something wrong”.</td>
</tr>
</tbody>
</table>

\(^1\) Reported in the Q (Parent)

\(^2\) Reported in the Q (GP)

\(^3\) Recorded in the DCCR

\(^4\) Measured by the Q (Parent)s

\(^5\) Measured by the Q (GP)s

\(^6\) Measured by the Q (GP)s/DCCR

\(^7\) Measured by the Q (Parent)s/DCCR.
Statistical analyses
Analyses in Paper II-IV were restricted to pathways involving a GP in the diagnosis (see Table 3.4).

**Paper II**
Time intervals were presented in days (medians, interquartile intervals (IQI)s). Long intervals were defined as the 4th quartile of each interval. Differences between groups were tested using the Kruskal-Wallis test. Due to multiple testing, we used a p-value of 0.0025 or less as significance level (Bonferroni correction: (0.05/20)). In the multivariate analyses, we used the logistic regression to calculate the association between long intervals and variables. Results were presented as prevalence ratios (PR)s with 95%-confidence intervals (95% CI). We used generalised linear models with log link for the Bernoulli family, i.e., modelling the PR. The models were adjusted for the clustering of patients within GPs by using robust variance estimates [95].

**Paper III**
The GP-reported symptoms were categorized into chapters according to the ICPC-2 [93] and analyses on symptom frequency, symptom interpretation and combinations of ICPC-2 chapters were performed. Categorical associations were tested by χ²-tests. A p-value of 0.05 or less was defined as statistically significant.

**Paper IV**
Like in Paper II, the diagnostic intervals were presented in days (median, IQIs), and a long diagnostic interval was defined as the 4th quartile of each interval. Differences between groups were tested using the Kruskal-Wallis test. Categorical associations were tested by χ² tests. A p-value of 0.05 or less was defined as statistically significant. We used regression analyses to calculate the association between long diagnostic intervals (≥75 percentile) and the independent variables. We adjusted for gender, age and diagnostic cancer group. The models were adjusted for the clustering of patients with GPs like in Paper II. Results were presented in PRs with 95% CIs.
Data in Paper II-IV, inclusive analyses on non-responders (page 128), were analysed using Stata 11.2 (StataCorp LP, TX, USA). See Papers II-IV for further details.

Approval and ethics
The study was approved by the Danish Data Protection Agency (J.no. 2008-41-2956) and by the Multipractice Study Committee under the Danish College of General Practitioners and the Organisation of General Practitioners in Denmark, who recommended GPs to participate in the study. According to the Scientific Committee for the Region of Central Jutland, the Biomedical Research Ethics Committee System Act did not apply to this project. The data collection from the GPs was approved by the National Board of Health conditional on the parents’ approval (discussed on page 127).
CHAPTER 4: RESULTS IN SUMMARY

This chapter offers a brief summary of each paper in the thesis. A more detailed description of the results is presented in Chapters 5 to 8.

Table 4.1. Study results presented in Papers I-IV

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study results presented</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Childhood cancer and the health care seeking preceding diagnosis</td>
</tr>
<tr>
<td>II</td>
<td>Time intervals from symptom onset to treatment for childhood cancer patients</td>
</tr>
<tr>
<td>III</td>
<td>Presenting symptoms, symptom interpretation and GP involvement among childhood cancer patients</td>
</tr>
<tr>
<td>IV</td>
<td>Associations between the diagnostic interval and symptom and referral characteristics</td>
</tr>
</tbody>
</table>
THE REGISTER-BASED PART OF THE STUDY

Paper I

The use of daytime contacts, daytime diagnostic tests and OOH contacts in primary care was calculated for 1,278 children with cancer and 12,780 control persons for the year preceding the patients’ diagnosis and the controls’ index day. In this period, childhood cancer patients had a higher monthly daytime consultation rate in primary care than controls. A statistically significant, progressive increase in their contacts was seen in the six-month period before their diagnosis, especially during the last three months (IRR= 3.19, 95%CI: 2.99-3.39) (p<0.0001). Children with lymphoma, bone tumours and other solid tumours had higher consultation rates than the background population during the last five months before diagnosis, whereas children with CNS tumours had higher consultation rates than all other childhood cancer patients during the entire year before diagnosis. Children with leukaemia had higher consultation rates than other children in the three months before diagnosis (IRR=3.34, 95%CI: 3.00-3.71) (p<0.0001). An overall increase in OOH contacts (from four months prior diagnosis) and diagnostic tests (from three months prior diagnosis) in general practice was also seen for children with cancer. Within the preceding year, 93.3% of the cases and 79.7% of the controls had consulted their GP; during the three months before diagnosis, 81.8% of the cases and 44.8% of the controls had consulted their GP (see Paper I for further details).
THE QUESTIONNAIRE-BASED PART OF THE STUDY

A total of 550 childhood cancer patients were eligible for inclusion and questionnaires were sent to their parents. The parents’ response rate was 69% (n=377/550). Permission to send a Q (GP) was given by 96% (363/377) of the parents. The GPs’ response rate was 87%, which allowed 315 children to be included in the analyses. Thus, 315 out of a total number of 550 eligible childhood cancer patients (57%) participated in the study. The GPs were involved in the diagnostic process in 80% (253/315) of the cases. Analysis of the parents’ responses revealed a lower mean age (p=0.036) among non-responders (N=173) than among responders (N=377). Apart from this, no statistically significant difference was observed (Table 9.1). Analysis of the GPs’ responses revealed a higher percentage of child deaths (p=0.026) among non-responders (N=48) than among responders (N=315) (Table 1 in Paper II).

Paper II

Girls experienced longer patient intervals (median: 9 days, IQI: 1-33 vs. median: 5 days, IQI: 0-18) (p=0.015) and total intervals (median: 55 days, IQI: 27-123 vs. median: 36 days, IQI: 14-87) (p=0.012) than boys. The likelihood of long patient intervals among girls than among boys was confirmed in the multivariate analyses (adjusted PR: 1.8, 95%CI: 1.1-2.8). Gender was not significantly associated with the length of any of the other intervals.

The child’s age at diagnosis was associated with the length of all time intervals, except the GP interval. The median system interval varied statistically significantly (p<0.0025) between the age groups (0-4; 5-9; 10-14 years) as the oldest children had longer system intervals (median: 34 days, IQI: 14-57) than the younger children (median: 8 days, IQI: 4-31). The patient interval was shortest for children aged 10-14, although not statistically significantly so. Adjusted analyses revealed that children aged 5-9 had a higher likelihood of a long patient interval (adjusted PR: 1.8, 95%CI: 1.1-3.1), a long diagnostic interval (adjusted PR: 1.7, 95%CI: 1.0-2.9) and a long total interval (adjusted PR: 1.8, 95%CI: 1.0-3.3) than children aged 0-4. The oldest age group had a higher likelihood of experiencing a long system interval (adjusted PR: 1.6, 95%CI: 1.0-2.7) and a long total interval (adjusted PR: 1.9, 95%CI: 1.1-3.3) than the youngest age group.
Cancer type was associated with all time intervals, except the GP interval. Patients with bone tumours had a longer median total interval (median: 88 days, IQI: 57-132) than other patients, e.g. patients with leukaemia (median: 25 days, IQI: 11-48). However, children with CNS tumours experienced the longest upper quartile interval which reached 191 days or more.

Overall, GP intervals were shorter (median: 0 days, IQI: 0-7) than the other time intervals. However, 25% of the children of mothers with the lowest educational level experienced a minimum 18 days of GP interval compared with three or seven days for children of mothers with middle or high education. The adjusted analyses showed that parents with a low educational level were facing the highest likelihood of a longer patient interval (adjusted PR: 1.6, 95%CI: 0.9-2.9) and a longer GP interval (adjusted PR: 1.7, 95%CI:0.8-3.4), but the difference did not reach a level of statistical insignificance.

For 62 (20%) children, the pathway toward diagnosis did not involve the GP, e.g. they were referred OOH to hospital. These children could have had a more aggressive tumour growth and a shorter interval from symptom to treatment. This was confirmed by the significantly shorter patient (median: 2 days, IQI: 0-12) (p=0.027) and total intervals (median: 21 days, IQI: 9-63) (p=0.010) for children whose GP was not involved than for children whose GP was involved with (patient interval: median: 6 days, IQI: 0-27) and (total interval: median: 43 days, IQI: 19-104) (see also Paper II for details).

Paper III

On average 2.4 symptoms were reported per child at presentation. Symptoms categorised as general and unspecified according to the ICPC2 classification were most often reported (71.9%), except for patients with CNS tumours among whom headache and other neurological ICPC2 symptoms predominated. The most commonly reported symptoms were pain (26.9%), swelling/lump (26.1%) and fatigue (20.6%) (see Appendix IV for details).

Overall, GPs interpreted symptoms as alarm symptom in 20.2% of cases; as serious but not alarm symptoms in 52.9%; and as vague symptoms in 26.9%. Symptom interpretation varied significantly by diagnosis (p<0.001), but not by age group (see Paper III for details).
Results in summary

Paper IV

Alarm symptoms were more common among lymphoma patients (43.2%) than among bone tumour patients (5.3%) for whom vague symptoms were more commonly reported. Cancer suspicion was stated in the referral letter for 44 (36.7%) of the patients with haematological cancer, for 8 (15.7%) of the patients with a CNS tumour and for none of the patients with a bone tumour.

The median diagnostic interval was 18 days (IQR 5-50 days) and varied between age groups and between cancer groups. The highest likelihood for a prolonged interval was observed for children aged 5-9 years (adjusted PR: 1.7, 95%CI: 1.0-2.9) and for children with bone (adjusted PR: 2.8, 95%CI: 1.1-6.8) and CNS tumours (adjusted PR: 3.4, 95%CI: 1.7-7.0). Gender and socio-economic status did not seem to affect the length of the diagnostic interval. A statistically insignificant decrease in the diagnostic interval was observed from 2007/8 to 2009/10, especially regarding the 75 percentile which went from 60 to 42 days.

The diagnostic interval was statistically significantly shorter when fatigue was reported than when it was not reported (p=0.003). Children with pain had a statistically insignificantly longer diagnostic interval. No single symptom was statistically significantly associated with a long interval across cancer types.

Symptom interpretation and the wording of the referral letter were highly associated with the diagnostic interval. Thus, the likelihood of a long interval was 3.0 times higher when GPs interpreted symptoms as “vague” than when interpreted them as “alarm”, and the median diagnostic interval was nearly a month when the wording was “something wrong” compared with a week when “cancer suspicion” was put into words.

For children with leukaemia, the presence of fatigue, anaemia or bruising was associated with a shorter diagnostic interval than when no such symptoms or clinical findings were reported. The mentioning of pain was associated with a statistically significantly higher likelihood of a long interval than any mentioning of pain (adjusted PR: 5.6, 95%CI: 1.6-19.9). For children with lymphomas, however, the presence of pain, as opposed to no pain, was associated with a statistically significantly shorter diagnostic interval (p=0.048). For children with CNS tumours, the presence of vomiting was statistically significantly associated with a shorter diagnostic interval than when no such presence was reported (p=0.020) (see Paper IV for details).
This chapter discusses the methodological issues of the studies in relation to design, sampling, data quality, outcome measures and analyses. Special emphasis is devoted to the definitions of time intervals and milestones used. The validity of the studies is discussed in terms of both internal validity (information bias, selection bias and confounding) and external validity.
DATA VALIDITY

Design

In Paper I, cases were identified on the basis of a cancer diagnosis, and age- and gender-matched children without cancer were identified as control persons. The design hereby resembled the design of a case-control study. The utilization of primary health care services was studied in the year prior diagnosis of childhood cancer for a group of children with cancer and compared with the similar for a group of children without a cancer diagnosis. Such services, consultations and diagnostic tests were considered a proxy for symptom presentation in primary care in the year prior diagnosis. The strength of this design lies in the size and the comprehensiveness of its sample and the inclusion of a large number of population controls, which ensures an adequate robustness of its estimates.

The incidence density sampling of the reference group allowed us to estimate the risk of having contact with general practice in a background population of children. The inclusion of ten age- and gender-matched control persons per case minimised any potential confounding, notably because, contrary to adults, children’s health care use is only little influenced by life-style factors and chronic diseases.

The registries from which data were drawn held no accessible information on the reason for the patient’s or the control’s encounter. One weakness in this part of the study was therefore that we could not describe why patients consulted the GP. However, analysis of the use of clinical investigations (tests) afforded us with reasonable insight into whether the GPs made any further clinical examinations and hence information, even if indirect, on the reason for the encounter. The nature of the study was explorative.

Papers II, III and IV were designed as cross-sectional studies where children with cancer were sampled from a clinical database and data were collected retrospectively via postal questionnaires filled in by doctors and parents. This design made it possible to collect data retrospectively on the milestones in each child’s cancer pathway. These data were then analysed as longitudinal data in a cohort of retrospectively sampled children. This design allowed data to be obtained on the time intervals from the first symptom to initiation of treatment for childhood cancer patients (Paper II) as well as data on presenting symptoms.
and clinical findings (Paper III). The design also made it possible to establish associations between the diagnostic interval and a range of variables (Paper IV) in a large population of childhood cancer patients.

A four-year cohort was chosen to balance the wish for a large sample of study participants and a high level of statistical precision against the risk of impaired recall. For practical reasons, a larger group of children with cancer was included by the start of the study. They partly represented a group of children whose pathways had begun more than a year before the data collection. For the remaining and consecutively sampled study participants, the data collection was performed 3-6 months after diagnosis (further discussed in section on information bias).

The choice of a questionnaire survey involves certain limitations in the precise identification of multiple time points [35,72,96] and the collection of clinical information on issues that have not been written down, e.g. information on the GP’s ‘gut-feeling’. An interview study might have shed more light on the use of important diagnostic tools and granted a deeper insight into diagnostic processing in general practice. Audits and thorough scrutiny of the children’s medical records could also have been useful. However, such study designs demand high amounts of resources and any costs incurred should be balanced against the aims of the study. Prospective collection of information on daily symptoms and diagnostic processes in a large follow-up study is needed to solve problems related to recall. However, it would be a major challenge to obtain a sufficient sample size and a sufficiently long follow-up time in any study of rare diseases like childhood cancers.

A study design that gathers data from parents’ reports, GPs’ data from their electronic medical records and data from the DCCR and which combines these data for analysis is therefore here regarded as an efficient and appropriate method for answering the specific aims of the present thesis.
QUALITY OF DATA

The register data

The classification of cancer diagnoses in the DCR is based on the WHO classification [81] and cancers are coded by the physicians in charge of the discharge. The data were registered prospectively and registration was hence independent of the GPs’ or the study participants’ memories. Comprehensive evaluation has shown that the DCR is 95-98% complete and valid [80].

As from 1 January 2004, the exact date of diagnosis has been recorded in the DCR based on the international hierarchy [97] that uses the dates of histological confirmation, admission to hospital and date of death. Until 2004, the first day in the month of hospital admission was used as the date of diagnosis if no histological diagnosis was available. The primary health service utilization during the month before the diagnosis may therefore have been underestimated for children diagnosed in 2002 and 2003 and for their respective control persons (Paper I). These potential misclassifications were equally distributed among cases and control persons (same index day as the date of diagnosis for cases) and the effect, if any, is therefore likely to be small.

The NHSR collects data for reasons of reimbursement of the GPs. The health personnel are strongly motivated for securing high register completeness and validity as 75% of the GP’s salary is based on fee-for-services [30]. Only information on fee-for-services (consultation and diagnostic procedures) was extracted from the NHSR, and any underreporting is likely to be minimal. From April 2008, data from the NHSR were date-specific. Formerly, many services were registered on the third Friday of the current month, a common day for GPs to report to the NHSR. As we categorized time by calendar months and as the custom of registration among GPs is patient-independent, this procedure may have introduced only small inaccuracies in the analyses.

In Papers II-IV, the sampling of childhood cancer patient from the DCCR had several advantages. This clinical database is updated several times annually, it holds records as from the start of treatment, it holds the child’s CRN, and it offers a quick and patient-related interchange of data [89]. Using the Danish Cancer registry as the golden standard, we estimated the completeness of the DCCR to be 96.6%. The DCCR registered 1,101 children with cancer under 15 from 1 January 2002 to 31 December 2008 (ICD10: C0-D48) whereas the Danish
Cancer Registry registered 1,140 children with cancer in this period. In the DCCR, the date of diagnosis is defined as the date of bone marrow aspirate (leukaemia) or diagnostic imaging (solid tumour). As mentioned on page 122 diagnosis is defined differently in the DCR. This difference may give rise to discrepancies in a comparison of DCCR and DCR coverage.

The study population in the questionnaire-based part of the study was restricted to children aged 14 or less because the DCCR’s completeness is known to decline for children above this age. Older children may be treated by other departments than a paediatric department. Records on patients with cancer in the eye (ICD10, C69) may not be complete either because these patients are treated at departments of ophthalmology and often bypass the childhood oncological centres. Previous studies have described long time intervals for children with retinoblastoma [20,41,42,50,55,56]. However, retinoblastomas are rare (five cases per year in Denmark), and a potential under-representation is of minimal effect. Specific data on children treated entirely at departments of neurosurgery without follow-up at departments of paediatric oncology do not exist, but if such pathways do exist, CNS tumour patients would potentially be under-represented in the DCCR (and in the present study).

Questionnaire data
No pre-designed questionnaires were available and the questionnaires therefore had to be developed by the research group after a thorough literature search. Whenever possible, questions, scales and definitions from earlier surveys were used to enhance the validity of the questionnaires. Previously used items about socioeconomic status, dates in the diagnostic pathway and symptom interpretation have previously proved effective in describing a Danish population [39,40] and they were therefore used again. The questions on symptoms and clinical findings were carefully discussed with parents, GPs and paediatricians. This approach served to optimise the content validity of the questionnaires [87]. The content validity of the Q (Parent) was primarily ensured during the first, smaller pilot study where the respondents were interviewed after having answered the items. Both questionnaires were pilot-tested and adjusted based on the comments obtained. Parents were telephone-interviewed by the author to test if the questions were understood and to test the reliability of the questions and their sufficiency and appropriateness for different subgroups of childhood cancer patients (construct validity) [87].
For most items, a test against a golden standard (criterion validity) made no sense, as no such true values could be found. The far majority of the items used in these studies were factual and single items [87]. The usage of latent variables, e.g. tools for assessing the patient’s evaluation would have required psychometric tests, such as item-response analyses and factor analyses to ensure the construct validity [87,98,99].

The parent’s educational level was used as a proxy for socio-economic status, as education remains relatively stable beyond early adulthood and is less affected by changes in health status than income and occupational status [100]. Definitions of time intervals were in line with the current guidelines (Papers II and IV) [35]. However, the diagnostic pathway may sometimes appear complex and non-linear, and in such situations, it is often difficult to define and to recall accurate dates [35] (further discussed in the section on information bias).

Where data could be obtained from multiple sources, it was decided to obtain the data from the source a priory considered or hypothesized to enjoy the highest level of validity. For milestones or time intervals important to the child’s initial pathway, the principle of proximity suggested that the parents were the experts, and the Q (Parent) was therefore the main source for obtaining data on the patient interval. Acknowledging the parent’s position in this regard is tantamount to acknowledging that a symptom is not necessarily a medically well-defined entity in the parents’ eyes [101] and that the date they report may, indeed, mark the date of the first symptom presentation, but may equally well mark the beginning of parental worry over health-related issues other than cancer symptoms. Likewise, the GPs were considered experts on the GP interval and presenting symptoms, and information on the GP interval was obtained in the Q (GP). We learned that for the majority of children with cancer, the date of the first investigation and the date of the first referral were the same meaning that the GP interval differed only slightly from the primary care interval (Figure 1.2).

GPs’ assessments were based on their patients’ files and on their clinical judgment. System and diagnostic intervals were calculated from the Q (GP) and from the dates of diagnosis and treatment start recorded in the DCCR. The total interval was calculated from the Q (Parent) and the DCCR; and whenever possible, prospectively registered dates were used for the measurement of time intervals to minimise information bias. The use of validated questionnaires or scales for determining especially the milestones would have strengthened the
discipline of the validity of the results. However, no such instrument yet exists [35], and the use of established items on which there is international consensus makes the measurement of the milestones, the time intervals and the symptoms as reliable as is currently possible.

To minimise intra-observer variation, all coding was done by JMA and discussed with one or two members of the research group if any doubts arose. The scanning was done by only two persons who were very familiar with the process. These procedures maximised the completeness and the accuracy of the questionnaire data.
OUTCOME MEASURES AND STATISTICAL ANALYSES

In Paper I, the monthly and quarterly rates of daytime consultations, daytime diagnostic procedures and OOH services were calculated for the children with cancer and for control persons. Some patients are frequent attenders in general practice, and the 10% most attending patients seem to account for 30-50% of all contacts [102]. Previous studies have shown that social, economic and psychological factors influence consulting behaviour [103-106]. 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 [107]. By using the negative binomial regression model [107,108], we sought to account for the heterogeneity between subjects [109,110].

Time intervals were far from normally distributed and some intervals were very long. The mean allows the extremes to affect the results. All the time intervals (Papers II and IV) were therefore presented as median rather than mean to prevent any overestimation. The study population was heterogenous with respect to age and cancer types. A clinically ‘appropriate’ cut-point (dichotomisation into short vs. long time intervals) for one type of cancer may have been inappropriate for another. The cut-points were therefore defined as the upper quartiles for each group studied. A logistic regression model was used to estimate the association between long intervals and the independent variables investigated [108]. Prevalence ratios were preferred to odd ratios that would tend to overestimate the associations as the prevalence of the outcome measure was above 20% [111].

Patients listed within the same practice are likely to share features and 21% (67/315) of the general practices completed more than one questionnaire. It was therefore decided to adjust for clustering of patients with the same GP [95].

Although the study was nationwide and one of the largest so far in the literature describing time intervals for a cohort of all types of childhood cancers, the statistical precision was small in some subgroup analyses.
Selection bias

Descriptive studies are vulnerable to selection bias, which stems from the procedures used to select subjects and from factors that influence study participation [112].

In Paper I, except for six children registered with an incorrect CRN, complete information was available on the primary health care use of all children diagnosed with a primary cancer in Denmark during eight years and a random sample of control persons with the same age and gender. No loss to follow-up occurred in the register-based part of the study, and selection biases are unlikely explanations for our findings.

In Papers II-IV, the response rate among parents was moderate (69%) and the GP response rate was high (87%). In Denmark, parents must approve collection of data on their children from general practice. In our study, the vast majority (363/377; 96%) of the responding parents approved the data collection from general practice; the parents of 14 children did not (4%). No meaningful discrepancies were observed among those who did and those who did not give their approval to the Q (GP).

The parents’ mandatory approval of data collection in general practice meant that if they were non-responders (N=173) (Figure 3.2), the Q (GP) could not be sent. In case of selection bias, the prevalence of symptoms, the time interval from symptom to diagnosis or the association between exposure and outcome will not be the same among study participants (study population) as among those eligible for the study (target population). For instance, if children of non-participating parents had relatively longer time intervals before diagnosis, the analyses may have underestimated the proportion of those with long intervals and therefore underestimated the time intervals.

Analysis showed no statistically significant discrepancies between the responders and the non-responders of the Q (Parent), apart from the mothers’ mean age (Table 9.1). A Mexican study has suggested a shorter time interval from symptom presentation to diagnosis in children of younger parents than in children of older parents [59]. If this observation applies in general, the patient interval reported in the present studies could have been overestimated. This is,
however, not necessarily so as health care conditions in Denmark may not be comparable with those in Mexico.

Language difficulties could in some situations have contributed to a delayed diagnosis and perhaps such difficulties could also have affected the ability to participate in the questionnaire based study. The Q (Parent) did, however, not include the parent’s mother tongue.

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<th>Table 9.1. Analysis of parental response to the Q (Parent)</th>
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<td>Bone tumours</td>
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<td>Other solid tumours</td>
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1When questionnaire to parents was sent.

*Statistically significant difference between responders and non-responders of the Q (Parent) (p=0.036).

Information bias

Information bias in a study may arise when the information collected is erroneous. Misclassification of the exposure, the outcome or of confounding factors can cause such errors [112].
Concerns about information bias were minimal in the register-based part of the study (Paper I). Registration errors do occur, yet most likely non-differentially. Misclassifications would tend to pull the relative risk towards one and hence to weaken the strength of a possible association.

The retrospective nature of the questionnaire-based studies (Paper II-IV) makes them prone to recall bias. Recall bias will affect both the accuracy of the data (e.g. dates) and the interpretation of the experiences depending on the outcome of the cancer trajectory. Accuracy aspects may be particularly relevant for the reported date of symptom onset, the date of first presentation and the symptom interpretation. Previous studies have found that irrespective of the time since diagnosis, most parents gave very detailed accounts of the events leading up to their child’s cancer diagnosis [113]. Furthermore, so-called ‘calendar landmarks’ may help parents recall dates [114].

As also mentioned in the discussion about the design of the questionnaire part, incident childhood cancer patients diagnosed over a four-year period (2007-2010) were sampled to ensure a sufficient number of study participants. Data collection began in December 2009 and was completed in September 2011. Thus, 45% of the parents received the Q (parent) a year or less after their child’s diagnosis. The remaining 55% parents received the Q (Parent) more than a year after the diagnosis (range 12-34 months). This procedure may have introduced a higher risk of recall bias for the latter group of participating parents than for the former group. This is considered no particular problem as recall may not necessarily decline in tandem with time since events, especially not for events of such impact.

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 files [115]. A comparison of the answers to items on GP involvement, date of diagnosis and presenting symptom in parent and GP questionnaires showed a high degree of agreement, although GPs reported fewer symptoms per child than the parents (mean (parent) = 3.2; mean (GP) = 2.4, p<0.05). For instance, a child may have presented with a main complaint which was recorded by the GP and perhaps less indicative symptoms such as fatigue may not have been recorded in the patient’s file. On this basis, potential “alarm” symptom like weight loss, swelling/lump were perhaps more likely to be recorded and reported than vague symptoms. On the other hand, GPs may remember the clinical trajectory well and upon reflection could have
added symptoms that were not recorded in the clinical notes as it is very seldom that a GP has a child with a cancer in the practice and may therefore remember the case very well.

The dates on diagnosis and treatment start were obtained from the DCCR, where they were registered prospectively, which minimises the information bias.

The dates of the start of work-up in general practice were obtained from the GPs’ electronic patient files, which minimises information bias. The child/parents were the only source of information on the date of symptom onset. The Q (GP) and the Q (Parent) asked for the date of first presentation, which ended the patient interval (assessed by parents) and started the GP interval (assessed by GPs). The questionnaires were scrutinized in case of discrepancies between the date of first presentation as assessed by the parents and the GPs. Writing errors or misunderstanding sometimes explained these discrepancies. However, the parents and the GP apparently did not always agree on the date when the child first presented in general practice within the course toward diagnosis. Some parents elaborated ‘...my kid has always been ill’ and reported a very early date as their first GP contact, while other parents recognized and reported the very last consultation in general practice prior to final diagnosis, although the Q (GP) stated a much earlier presentation. The dates of first presentation reported in the Q (GP) and in the Q (Parent) were plotted against each other (Figure 9.1) and agreement appeared to be acceptable (linear pattern). However, we could have underestimated the GP intervals as we learned that parents tended to report the presentation in general practice earlier than the GPs (rank test: p=0.005). Inversely, the date given by the parents may sometimes have been the best ‘guesstimate’ (‘...after four weeks, we contacted the GP’) and not always an exact date, while GPs were able to provide the precise date on the basis of their electronic files and calendars.
Confounding

A confounder is a factor related to both possible cause and possible effect and an effect of the exposure and an intermediate step in the causal pathway from exposure to effect [112].

In Paper I, the effect of confounding by age and gender was eliminated by a random selection of control persons with the same gender and day of birth as the cases. However, the possibility of residual confounding by factors not accounted for, e.g. pre-existing co-morbidity, cannot be excluded in the register-based part of the study. One should, however, be careful not to adjust for intermediate variables such as infectious diseases when studying health care utilization prior to a diagnosis of leukaemia. Genetic disorders and syndromes

Figure 9.1. Scatter plot of date of first presentation reported by parents and GPs. The red line indicates their complete agreement on time from first presentation to diagnosis.
can predispose to malignancies in childhood [11,12,116] and in such cases, the child may already have a different and perhaps a more frequent health care utilization pattern than other children, which would tend to overestimate the association between childhood cancer and the consultation frequency. These conditions are very rare and therefore have very little influence in a large population-based study.

In Papers II-IV, patients in whose diagnostic pathway the GPs were not involved were excluded to ensure a more homogeneous study group. Children with severe comorbidity were excluded on the basis of items A and 27 in the Q (Parent) (Appendix I-II) because the DCCR holds no information on these items. In general, parents gave very detailed information on previous and co-existing disease.

In Paper II, we identified gender, age, diagnostic group and socioeconomic position as potential confounders. The analyses were stratified for age, gender, diagnostic groups and maternal educational level (as a proxy for socioeconomic position). We accounted for the same co-variables in the multivariate analyses and for clustering within general practices to take confounders into consideration.

In Paper III, we described the symptom frequency for all cancers and for each of the five main diagnostic groups without any further stratification. A larger study would allow symptom presentation to be stratified by age, which could have added some valuable clinical information. However, stratification on gender would have only minimal clinical value as we do not believe that the GPs take gender into account in their interpretation of, at least younger children’s symptoms and clinical signs. Gender-specific childhood cancers are rare.

In Paper IV, we identified the same variables in the multivariate model as in Paper II, except for socioeconomic position. Socioeconomics have been shown to influence the consultation rates [117] and the participation in preventive child health examination in general practice [117,118]. No precise hypothesis of an association between parental education and the length of diagnostic interval was defined by the research group. We are unable to exclude a potential effect on the results owing to residual confounding by factors not accounted for, such as geographical and logistic factors.
EXTERNAL VALIDITY

Generalizability

In the present study, the distribution of gender, age groups and diagnostic groups in the study population of patients was overall in concordance with the incidence rates for childhood cancers [12]. The population-based approach with complete inclusion of patients with a diagnostic route that involved general practice affords the present study with potential of being generalizable to other healthcare systems in highly developed western countries where general practice serves at the front line of medical advice and healthcare.

However, general practice was not involved in the diagnostic pathway of 62 children. Their tumours could have been more aggressive and their time intervals shorter, e.g. because they were emergency cases. This was confirmed by the significantly shorter patient and total intervals for children in whose diagnostic pathway the GP was not involved (page 46).
ETHICS

The research group thoroughly discussed the ethical aspects of conducting a study partly based on questionnaires from parents who without doubt found themselves in a difficult situation; this concern was, of course, particularly pertinent in cases where bereaved parents were contacted.

Obtaining their participation was, however, deemed important because even if the benefit of their participation would not fall to themselves, they could help other parents by providing valuable information that would inform future clinical practice, e.g. by providing information on a diagnostic pathway that was characterized by vague symptomatology, by identifying inexpediencies in the diagnostic strategy and by pointing to bottlenecks causing delay.

The questionnaire study gave rise to no negatively loaded comments from either parents or GPs. On the contrary, we received many positively comments, especially from parents.
CHAPTER 10: DISCUSSION OF RESULTS

This chapter discusses and considers the results (Papers I-IV) of the present studies in relation to other studies of health care utilization, time intervals toward diagnosis and treatment, presenting symptoms and factors affecting the diagnostic interval.
RESULTS AND COMPARISONS WITH OTHER STUDIES IN GENERAL

The description of how children attend the GP with symptoms leading to a specific diagnosis of childhood cancer covered, among others, their health care seeking pattern, the time intervals towards diagnosis, the presenting symptoms and factors affecting the diagnostic interval. Most studies [20,21,41-57], but not all [24,34,58-63] have described the pathway for a single cancer type and have typically been based on data obtained retrospectively from hospital medical records. Research on time intervals toward diagnosis in childhood cancer is still in its early stages, and some papers stem from developing countries [55,59]. Discrepancies in the findings of these studies may be attributed to differences in the culture, organization and capacity of the healthcare systems.

In the literature, the terminology on the time interval toward childhood diagnosis is inconsistent and the methods used for its description are not always clear, which complicates comparison across the studies [35,96,101]. Most existing literature describes a diagnosis interval, e.g. the time interval from symptom onset to diagnosis [64]. Various authors have referred to this interval as the symptom interval [119], the prediagnosis symptomatic interval, the lag time, the wait time, the symptom duration and the time to diagnosis [64]. The present thesis follows current guidelines [35] and splits this interval into a patient interval, a GP interval and a system interval. On the one hand, this allows a deeper look into each particular interval, whereas, on the other hand, it hampers comparison with other studies that make no such distinction. In the present study, the total interval is the best comparator with what other studies designate the diagnosis interval, even if it covers the entire interval between diagnosis and treatment. In case of no treatment (e.g. an inoperable CNS tumour), the date of first treatment was defined as the date of diagnosis (Table 3.4).
HEALTH CARE SEEKING BEFORE DIAGNOSIS (AIM 1)

The register-based study documented the rising consultation rates for childhood cancer patients in the year before their diagnosis (Paper I). The daytime consultation rates rose consistently from six months before diagnosis until the day of diagnosis, especially during the last three months. The utilization of OOH services and diagnostic procedures in daytime also rose in the months before diagnosis. General practice was involved in pre-diagnosis in 80% of the childhood cancer patients (Paper II). The growing use of health care services just before diagnosis is hardly unexpected as it reflects the growing activity in primary care leading up to the diagnosis. Surprisingly, health care seeking patterns began to change many months before the diagnosis. Children with lymphoma, bone tumours and other solid tumours had more frequent contacts to general practice five months before their diagnosis, while children with CNS tumours had more frequent contacts to the GP during the entire year before their diagnosis. These findings may indicate the existence of a ‘diagnostic time window’ which represents an opportunity to narrow the time interval if alarm symptoms can be identified as early as possible.

It should, however, be emphasised that these results represent averages for a population of children with cancer, and that some children may therefore consult much more, others much less. A similar increase in the consultation rates in primary care was recently revealed in a British study with approximately the same number of study participants as in our study. The authors reported a higher consultation rate for childhood cancer patients than for control persons in the year prior to diagnosis, particularly in the last three months before diagnosis [29].

Our findings of excess consultation rates more than one year before diagnosis were in keeping with those of Ansell, who studied the pre-diagnosis consultation patterns of children (N=195) with brain tumours (children more than one year old) and controls matched on age and gender (N=285). The authors found an excess of disease-relevant symptoms and consultation up to four years before diagnosis, escalating in the two years before diagnosis [19]. A smaller study showed that children with brain tumours on average had 4.6 (range 1-12) consultations with professionals before they had a diagnosis [53].
In the present study a minor excess of consultations was described for children with cancer already 10-12 months prior diagnosis. Further studies are needed to explore possible reasons for this *bimodal* pattern of consultation rates.

Our results underpin that the majority of children with subsequent cancer are seen in primary care before their diagnosis and they indicate that symptoms predating a childhood cancer may appear long before diagnosis. Health care seeking behaviour varies, and estimates in the present study were given as averages for a large group of children with cancer. Some families have a high threshold for health care seeking, while others have a low threshold. Previous studies have shown that social, economic and psychological factors influence consulting behaviour [103-106]. Other factors such as the child’s age, gender and parental education may also influence consulting behaviour [1,2,120].
The literature offers no good answer as to whether the time intervals for diagnosing childhood cancer are more or less comparable with those found for adults. In a Danish study on adult cancer patients, 25% waited 168 days or more from their first symptom until treatment [121]. Our study is thus the first to analyse the time intervals from symptom onset to treatment of childhood cancer patients in a consecutive nationwide cohort (Paper II). For 25% of the children with cancer, this pathway from first symptom onset to treatment was short (≤19 days). However, 25% of the children experienced time intervals of more than three months from symptom onset to treatment. The longest total intervals in the study were observed for children with tumours in the CNS and in bone. Symptom patterns vary by diagnostic groups, and this may, of course, account for differences in the total intervals observed among cancer groups. Some CNS tumours may, for instance, have a slow tumour growth and a slow symptom progression. Our findings were consistent with those of a large review on delay in the diagnosis of childhood cancer in which the author showed the longest mean intervals for children with brain tumours (mean 29.3 weeks) [64]. For reason discussed on page 126, the median provides the best comparator. A recent paper revealed a median time interval between symptom onset and diagnosis of 3.3 months for 81 children with brain tumours [122], and a review on CNS tumours by the same author showed a time interval from first symptom to diagnosis ranging from 1 to 27 months [119]. We found a median total interval of 76 days for children with a CNS tumour. In line with our findings, bone tumours have also previously been found to be characterised by long intervals from symptom onset to diagnosis [61]. The majority of studies have measured time intervals on the basis of medical charts in which registration of symptom onset may not have been as careful as in the present study.

Older children were more likely than younger children to experience long total intervals. Similar findings have been reported by other studies [24,52,61,63-65], and delayed doctor seeking among teenagers has been claimed as a reason for this discrepancy [24,66]. However, our findings may contradict this hypothesis as we illustrated a shorter patient interval for children aged 10-14 than for young children. A longer time interval among the oldest children would therefore seem to be related more to the healthcare system than to the cancer patient’s health care seeking behavior.
Surprisingly, girls were almost twice as likely as boys to experience long patient intervals. These findings are not readily explainable and may be due to measurement errors because girls tend to report less severe symptoms earlier than boys or it may reflect real differences, e.g. in culture or parents’ way of coping with the child’s symptoms, but any explanation remains speculative.

However, differences in the time interval from symptom onset to diagnosis between boys and girls have been described in only a few other studies [59,61]. An American study revealed that girls with non-Hodgkin lymphoma had a significantly longer time interval than boys [61]. In contrast, the same study found significantly longer intervals for boys than for girls with Ewing sarcoma [61]. Our study did not have sufficient statistical power to calculate the time intervals for single diagnoses stratified for gender. The majority of the studies report no association between time intervals and gender [64].

This present study revealed no statistically significant association between socio-economics and time intervals, and the literature on this subject is sparse. Multivariate analyses show the highest likelihood of a longer patient interval and a longer GP interval for parents with low education than for parents with high education, albeit the difference is statistically insignificant. Similar findings have been presented by Fajardo-Gutierrez [59] in a study from Mexico City, where the healthcare system and social conditions are likely to differ from those in Denmark. In contrast, a Canadian study showed that leukaemia patients living in the highest income areas were more likely to experience long patients delays, but less likely to have extended delays in the healthcare system [123]. We were unable to go deeper into such issues as the data included no information on parental income.

The GPs were involved in the diagnosis of four of five children diagnosed with cancer in Denmark. The remaining children were typically referred to the department of paediatrics by other GPs (e.g. OOH), other departments or the emergency room. We calculated the patient and the total intervals for these children and learned that they were significantly shorter in such situations. Few papers have studied the association between time intervals and the first health care professional encountered. The finding of a longer total interval for children who bypass general practice is in line with previous suggestions [21,63]. Such children could have a more prompt debut of symptoms due to more aggressive tumour growth. In the secondary healthcare system, the threshold for suspicion of severe disease such as cancer and for diagnostic tests like blood tests and x-
rays differ markedly from the thresholds in general practice. If children who reached secondary care directly had a more pronounced symptomatology, their diagnostic intervals would, all things equal be shorter. However, the question may also be raised whether the continuity of care and the GP’s gatekeeper role may have an adverse effect [124] and potentially result in self-restricting care-seeking [125].
SYMPTOMS, SYMPTOM INTERPRETATION & GP INVOLVEMENT (AIM 3)

GP's reported their involvement in 80% of the initial diagnostic pathways for children subsequently diagnosed with a malignant cancer or a benign CNS tumour (Paper III). Differences in the GP's involvement in the various subgroups of childhood cancer patients were small and insignificant. In a Danish study, GP's were seen to play a role in the diagnosis of cancer among adults and to be involved in 86% of their diagnoses [121], which is consistent with our findings in children. A Swedish study of 68 childhood cancer patients showed that the GP's were involved in the diagnostic pathway in two-thirds of the cases; less for children with brain tumours (50%) than for children with leukaemia (80%) [34]. The Swedish healthcare system is organised with no strict gatekeeper, and a lower GP involvement in Sweden than in Denmark is therefore to be expected.

Presenting symptoms were few. Almost three in four symptoms and signs were general and unspecified. Overall, symptoms like pain, swelling/lump or fatigue were reported for every fourth child. The present study explored the presenting symptoms for the five cancer subgroups and found, among others, that patients with CNS tumours presented with headache and vomiting as their main complaints, followed by other neurological symptoms such as disturbances in gait. These results were overall in line with those of a large review on the presentation of childhood CNS tumours [119].

It should be noticed that most studies report the number and nature of symptoms that were present at diagnosis. The number of symptoms at the first presentation could thus be lower than at diagnosis because symptoms may progress, as recently shown by Wilne et al [122]. Regarding the complaints of children with CNS tumours, the present study reports a slightly higher symptom frequency of headache and vomiting than Wilne’s review [119]. However, as discussed in on page 126, the statistical precision of the present study was small in some subgroup analyses. Most children under the age of three/four are unable to clearly describe symptoms like headache, nausea and visual disturbances, and the reporting of such symptoms may therefore be inadequate. However, the symptoms reported in Paper III were consistent with those reported in the literature [13,23,24].
The GPs interpreted the majority of the children’s symptoms as serious. In one fourth of the cases, the symptoms were interpreted as vague and non-specific, while in one fifth they were interpreted as alarming. For children subsequently diagnosed with a bone tumour, only one in twenty had alarm symptoms. Among adult cancer patients, half of the patients had alarm symptom when first presenting to their GP [83]. Our data suggest that presenting symptoms among children with cancer are less likely to be interpreted as alarm symptoms than similar symptoms among adult cancer patients.
Minimising the time intervals toward diagnosis requires an understanding of the determinants of these time intervals. Children with vague symptoms are likely to be exposed to prolonged diagnostic intervals (Paper IV). The median diagnostic interval was 18 days (IQR 5-50 days). Few studies have focused on the time from the first presentation of a symptom to a health care professional until diagnosis. In countries with no gatekeeper system, this interval is most often called the ‘physician delay’, which corresponds to the diagnostic interval in our study. Importantly, however, our study included only those with a pathway involving general practice (page 140).

The symptom interpretation and the wording of the referral letter were closely associated with the duration of the diagnostic interval (Paper IV). Similarly, the odds for experiencing a long diagnostic interval were four times higher for adult cancer patients presenting with vague and uncharacteristic symptoms than for patients presenting with alarm symptoms or any serious symptoms, as also illustrated in British Journal of Cancer [71].

To our knowledge, only few studies have explored the association between presenting symptoms and the time intervals in the diagnosis of childhood cancer. In the present thesis, vomiting seems to be associated with shorter diagnostic intervals for children with CNS tumours, as recently also described in an interview study of symptoms and the time to diagnosis in children with brain tumours [46]. A German study on brain tumours revealed that early morning vomiting significantly shortened the time interval from symptom onset to diagnosis [57]. The study also showed that primary symptoms such as disturbed motor function, other focal disorders, disturbed vigilance, disturbed eye motility and changes in growth/weight were positively correlated with a shorter interval between symptom onset and diagnosis. A British study showed that longer time intervals from symptom onset to diagnosis were associated with head tilt, cranial nerve palsies, endocrine and growth abnormalities and reduced visual acuity; and shorter intervals with nausea and/or vomiting, abnormal gait, coordination difficulties, focal motor weakness and apnoea [122].

Pain could act as a symptom that prolonged the diagnostic interval as reported, among others, by Haimi and colleagues [126]. They suggested that when the
child complained of pain, time intervals were longer than when the child presented with other symptoms and when patients did not have this symptom [126].

The present study indicates that some symptoms may be associated with longer diagnostic intervals perhaps because the GPs are misled, and it stresses the challenging aspect in singling out the very few children with severe disease among the many in general practice.
DISCUSSION OF THE RESULTS OF ALL THE FOUR STUDIES

In Paper II, both parents and GPs reported relatively short intervals. As discussed in section on information bias, such intervals will always be estimated, not precise intervals. A smaller study on children with brain tumours showed a median time interval from the first evaluation by a GP to referral of nine days; i.e. this interval was longer than we found [67]. It seems reasonable to compare this interval with the median GP interval of 0 days, which we found. Especially as we learned that the primary care interval did only differ slightly from the GP intervals, as the date of first investigation and the date of first referral were merely the same date (page 124). The median primary care interval in the present study was 1 day (IQI 0-13 days). Further, it seems as if either parents or GPs link the rise in health care utilization (Paper I) to the start of the course toward the diagnosis. The present study stresses the importance of recognition of symptoms or signs that make children attend more frequently. It is demonstrated that the GPs acted upon symptoms by using practice-based diagnostic tests. This suggests that a closer examination of such diagnostic test routines may identify those who should be suspected of having cancer. The present study also makes clear that the very short time interval from the first presentation to diagnosis reported by GPs may not reflect optimal clinical knowledge about symptom presentation. Fortunately, parents may continue to return to their GP even if the GP is unable to identify a specific problem [18], and if symptoms persist or progress the diagnosis should be re-assessed.
CHAPTER 11:
CONCLUSIONS AND IMPLICATIONS
CONCLUSIONS

The diagnosis of childhood cancer is not always straightforward. The index of cancer suspicion tends to be low because of the rarity of cancer in children and their non-specific presenting symptoms [127]. In the register-based part of this thesis, a marked increase in primary health care services (in daytime and OOH) was reported for children subsequently diagnosed with cancer, and findings indicate that symptoms of childhood cancer occur months before the diagnosis is established (Paper I). More importantly, the use of primary health care services began and rose progressively already six months before diagnosis, and children with CNS tumours used general practice more than controls in the entire year leading up to diagnosis.

General practice played an initial role in the early diagnosis in four of five children with cancer. A certain degree of delay in diagnosis appears unavoidable as alternative diagnoses will be investigated at the outset [126]. Many children were diagnosed quickly and without delays, and a median of 43 days passed from questionnaire-reported symptom onset to treatment start (total interval) (Paper II). However, every fourth child experienced a time interval of minimum three months. Children with tumours in the CNS and in bone were facing particularly long intervals. Time intervals were shortest for the children aged 0-4 years and for children with leukaemia and lymphomas. In general, girls seemed to hesitate longer than boys before seeking doctor. Presenting symptoms were mostly nonspecific and unlikely to immediately suggest a cancer diagnosis. Alarm symptoms were seen among 20% at presentation in general practice (Paper III). Symptom interpretation and the wording of the referral letter seemed to have a strong influence on the diagnostic interval (Paper IV).
Conclusions and implications

IMPLICATIONS

The present study indicates that the symptom presentation of some cancers is associated with the diagnostic interval and that some symptoms may contribute to a long diagnostic pathway, even if the GPs tend to use diagnostic tests several months before the diagnosis is made. The use of available diagnostic tests in primary care is perhaps only of limited value in assisting in the diagnosis of most cases of childhood cancer. Our study supports the idea that the care seeking pattern may serve as a possible tool for raising clinical awareness in the decision-making and the diagnosis of serious disease with a low prevalence in general practice. The findings also support the recommendation of urgent referral of a child who presents several times with the same problem, but who has no clear diagnosis [76,77].

The GP’s symptom interpretation and the wording of the referral letter were highly indicative for the length of the diagnostic interval in childhood cancer, which demonstrates that the GP plays a crucial role in the timely diagnosis of childhood cancer. But this finding also raises the very important question if the long waits following non-acute referrals for vague, non-alarm symptoms testify to either a lack of attention among healthcare providers or a lack of resources in today’s healthcare system. The present findings provide ample grounds for a stronger focus on the diagnostic work-up process after referrals in the healthcare system in general and for children with non-specific symptoms in particular. The present study also stresses that GPs should be aware of their role as coordinators and of their impact on processes that can accelerate the diagnostic pathway.

The observed tendency towards a more rapid diagnostic interval over the study period could be ascribed to the national implementation of fast-track pathways for children suspected of having cancer. Our findings emphasize that for a considerable proportion of the children subsequently diagnosed with cancer, the suspicion of cancer was not raised at their first presentations in general practice and this prolonged the diagnostic interval. Our study emphasizes the need for a very detailed medical history in children presenting with vague or persistent symptoms to ensure timely diagnosis of this very rare condition in general practice.
CHAPTER 12:
PERSPECTIVES AND FUTURE RESEARCH
We have seen that general practice is an important player in the diagnosis of childhood cancer. This general finding calls for more clinical and health service research on the role of general practice in diagnosing rare diseases. This thesis has illustrated an increased health care seeking predating childhood cancer diagnosis. The use of diagnostic procedures also rose in the time before diagnosis. Such findings call for further fine granular clinical studies including deeper case studies on incident cancer patients and controls to try to find more cancer-predictive early clinical symptoms and signs. This research should both address symptoms and signs predictive of childhood cancer in general, and it should simultaneously seek to identify symptoms and signs that are unique to particular, frequent childhood cancer types. As part of this research, we need deeper investigations on the feasibility of the different diagnostic tests, and the development of new diagnostic biomarkers and tools should be stimulated.

The study may suggest possible social inequalities in doctor seeking and management in general practice. Such findings call for further investigations of awareness of child symptoms and barriers for doctor seeking, and they raise the question whether the GP threshold for referral of vulnerable patient groups for further diagnostic work-up is appropriate. We also need further studies and explanations of the tendency towards gender differences observed in our study.

The needed future research should have a clinical focus as argued above, but it should also address evidence-based ways of organizing the health care in the most appropriate way where the clinician strikes the balance between the needed and timely diagnosis of those with severe disease and at the same time still maintains a high-quality gatekeeper and gate-advisor function with acceptable referral rates to the secondary healthcare system. An important part of this is to perform research that gives a balanced answer to the question whether further improvement mainly should be geared to increase parents’ and doctors’ clinical knowledge of childhood cancer and their symptoms and signs or if we should improve the available diagnostic tools available for GPs or, finally, if we should focus on a better organization of and access to diagnostic tests and diagnostic help from hospitals when the GP asks for help on behalf of his or her patient [74]. It is obvious that another important future topic is to investigate the prognostic impact of delay in diagnosis. Delay will always put psychological stress on families and doctors and we therefore also need research on the impact of delay on the GP-patient-family relationship and on ways to ensure the restoration of potentially distorted relations.
CHAPTER 13:
ENGLISH SUMMARY
This PhD thesis is based on the project “Childhood malignancies. From symptom to treatment” conducted from 2009 to 2012 in Denmark. The thesis is based on four papers and focuses on the diagnosis of childhood cancer in primary care.

Introduction

Cancer in childhood is rare, and children with cancer in early stages often present with non-specific symptoms or symptoms that do not suggest serious disease. Although the GP provides frontline medical advice and is the first stop on the diagnostic pathway, remarkably little is known about presenting symptoms and health care seeking in primary care predating a childhood cancer diagnosis. In the face of the severity of childhood cancer and the challenges in timely diagnostic work-up stands remarkably little knowledge of the time interval from first symptom until diagnosis and treatment of childhood cancer patients. The development of new effective strategies to shorten diagnostic intervals requires an understanding of the factors that influence time intervals, as well as knowledge of how childhood cancer patients and their families present themselves to the healthcare system.

Aims

The overall aim of this thesis was to increase our insight in health care seeking before cancer diagnosis in childhood and to investigate the early symptoms and signs and the time interval from symptom onset to treatment of childhood cancer. The specific aims of this thesis were the following:

1. To investigate the use of primary health care during the year preceding childhood cancer diagnosis (Paper I).
2. To describe the time intervals from symptom onset to treatment for childhood cancer patients (Paper II).
3. To investigate early symptoms and signs, symptom interpretation and GP involvement in childhood cancer patients (Paper III).
4. To analyse the association between the time interval from the first presentation in general practice to diagnosis (the diagnostic interval) and characteristics for symptoms and referrals (Paper IV).
Methods
Two different study designs were employed: a nationwide population-based matched comparative study provided a comprehensive overview of childhood cancer patients’ overall healthcare utilization in primary care. A comparative study design was applied to describe the pathway from symptom onset to treatment, presenting symptoms and signs, and to identify predictive factors for a long diagnostic interval, using data obtained via questionnaires sent to parents and GPs.

Results
During the six months before diagnosis, children with cancer used primary care more than controls. During the last three months prior to diagnosis, the children had a 3-fold higher use of primary health care compared to their controls. This was consistent across all cancer types. However, children with brain tumours consulted the GP more than controls the entire year until diagnosis, whereas the consultations rate for children with bone tumours, lymphoma and other solid tumours were similar to those of the control children until five months before the diagnosis. For children with leukaemia the use of general practice increased three month before diagnosis. Childhood cancer patient also had a marked use of out-of-hours services during the last five months prior to diagnosis. The utilization of practice-based diagnostic procedures increased three months prior to diagnosis.

Every fourth child experiences a time interval of minimum three months from first symptom to start of treatment. Children with tumours in the CNS and in bone were facing particularly long intervals. Time intervals were shortest for the children aged 0-4 years and for children with leukaemia and lymphomas. In general, girls seemed to hesitate longer than boys before doctor seeking. Presenting symptoms were mostly nonspecific and unlikely to immediately suggest a diagnosis of cancer and alarm symptoms were seen only among 20% at presentation in general practice. The most frequently reported symptoms were pain, swelling/lump and fatigue/weakness. Symptoms varied significantly with cancer type and the GP’s symptom interpretation varied according to cancer type. Symptom interpretation and the wording of the referral letter had strong influence on the length of the diagnostic interval. Pain could act as a symptom prolonging the diagnostic interval.
Conclusions and perspectives

General practice was an important player in the diagnosis of childhood cancer. This thesis shows that excess health care use, a proxy for symptoms of childhood cancer, occurs months before the diagnosis is established. Further clinical studies should further elucidate cancer-predictive early clinical symptoms and signs. The diagnostic work-up seemed to be longer in older children, which leaves room for diagnostic improvement. Further, the study suggests possible social inequalities in the pattern of doctor-seeking and management in primary care. Investigations of awareness of child symptoms and barriers for doctor seeking in vulnerable patient groups are needed. The results emphasizes the need for a very detailed medical history in children presenting with vague or persistent symptoms and stress the importance of the awareness of non-alarm symptoms and a timely access to diagnostic tests when general practice is involved in the diagnostic of childhood cancer.
CHAPTER 14:
DANISH SUMMARY

Introduktion
Kræft hos børn er sjælden. De tidlige symptomer på kræft er ofte vague og uspecifikke, og de giver derfor ikke misタンke om alvorlig sygdom. Den diagnostiske udredning starter ofte i almen praksis, der udgør sundhedsektorens frontlinje. Der mangler imidlertid viden om, hvilke symptomer børn med kræft præsenterer i den primære sundhedssektor, hvordan de anvender den praktiserende læge i tiden forud for, at en diagnose stilles, samt hvordan den praktiserende læge vurderer de tidlige symptomer og tegn på kræft hos børn

Der er behov for at få detaljeret indsigt i omfanget af og årsagerne til unødvendig ventetid for at kunne tilrettelægge en indsats, der sikrer tidlig diagnostik og hurtig behandling af børn med kræft.

Formål
Det overordnede formål med denne afhandling er at bidrage med ny viden om kræfttramte børns symptomer og lægesøgningsmønstre i almen praksis i perioden, før deres diagnose stilles, samt at undersøge tidsintervallet fra første barnets første symptom til behandlingsstart. De specifikke formål var at:

1. at undersøge børns brug af almen praksis i året op til en kræftdiagnose (Artikel I)
2. at beskrive tidsintervaller for perioden fra symptomudvikling til behandling hos børn med kræft (Artikel II)
3. at undersøge tidlige symptomer og kliniske fund, symptomtolkning og lægeinvolvering hos børn med kræft (Artikel III)
4. at analysere sammenhængen i det diagnostiske forløb fra første lægesøgning til diagnose samt symptom- og henvisningskarakteristika. (Artikel IV)

Metode
Der blev anvendt to forskellige studiedesign. Et nationalt populationsbaseret, matchet sammenlignende studie gav et detaljeret overblik over
børnekæftpatienters brug af ydelser i almen praksis. Studiet blev gennemført for at beskrive tidsforløbet fra første symptom til behandling, symptomer og kliniske fund, og for at identificere hvilke faktorer, der havde betydning for et langt forløb frem mod behandling. Data hertil blev indhentet via spørgeskemaer til forældre og praktiserende læger.

Resultater

Seks måneder før diagnosen havde børn med kræft et større forbrug af ydelser i almen praksis, og i løbet af de sidste tre måneder havde børnene med kræft et tre gange så højt forbrug af ydelser i almen praksis som kontrolpersonerne. Denne stigning i lægesøgningen og sundhedsydelserne i almen praksis sås for børn med alle kræfttyper. Børn med hjernetumorer havde flere konsultationer hos den praktiserende læge i hele året inden diagnosen end kontrollerne, mens konsultationsraten for børn med lymfom, knogletumor og andre solide tumorer var den samme som for kontrollerne indtil fem måneder før diagnosen. For børn med leukæmi begyndte brugen af almen praksis at stige tre måneder, før diagnosen blev stillet. Børnekæftpatienter havde derudover et markant øget brug af vagtlæge i de sidste fem måneder, før diagnosen blev stillet, ligesom deres brug af praksisbaserede diagnostiske tests steg i de sidste tre måneder, før diagnosen blev stillet.

Konklusion og perspektiver


40. Bjerager M. Delay in diagnosis and treatment of lung cancer [thesis]. Aarhus: Research Unit and Department of General Practice, Faculty of Health Sciences, University of Aarhus, 2006.


47. Halperin EC, Friedman HS. Is there a correlation between duration of presenting symptoms and stage of medulloblastoma at the time of diagnosis? Cancer 1996;78:874-80.


APPENDIX I

QUESTIONNAIRE TO THE PARENTS
Indbydelse til at deltage i en spørgeskemaundersøgelse

Kære forældre til [Barnets navn]

Vi sender dette brev til dig, fordi vi fra sygehusenes eDb-registre har fået oplyst, at dit barn inden for de seneste år har været indlagt på grund af en kraftsygdom eller en godartet svulst. Der er desværre altid en lille risiko for fejlregistrering, og skulle vores oplysninger ikke være korrekte, beder vi dig kontakte os, så vi kan afklare, hvordan fejlen er opstået.

For tiden samarbejder vi på børnekraftafdelingerne i Danmark, Forskningsenheden for Almen Praksis og Aarhus Universitet om at undersøge, hvordan kæft og andre former for svulster opdages hos børn. Vi ser på børnernes tidlige sygdomstegn og på tiden, fra de første sygdomstegn opstår, til diagnosen stilles, og behandlingen starter. Undersøgelsen afhænger i høj grad af forældres erfaringer, og derfor beder vi om din hjælp. Vi har stor forståelse for, at det er en svær tid for dig og din familie. Vi håber ikke, at det virker stødende, at vi kontakter dig. Vores håb er, at du vil deltage i undersøgelsen og dermed bidrage til, at kæftframed familier i fremtiden tilbydes den bedst mulige indsats i sundhedsvæsnet.

Hvad beder vi dig om?


Fortrolighed


Mange tak for din hjælp!

Jette Ahrensberg, speciallæge i almen medicin, projektansvarig læge, Forskningsenheden for Almen Praksis, Aarhus Universitet; tlf.: 8942 6073; mail: jette.ahrensberg@alm.au.dk
Overlæge Henrik Schröder, Børneafdeling A, Aarhus Universitetshospital
Læge Rikke Pilegaard Hansen, professor Peter Vedsted og professor Frede Olesen, Forskningsenheden for Almen Praksis, Aarhus Universitet
Først beder vi dig hjælpe os med at sikre, at vore oplysninger er korrekte. Dernæst spørger vi om lor til at måtte sende et lægeopgælsemekskema og om ev. at måtte hente opgælsemekskema fra dit barns sygehushjem. Det er væsentligt, at du udnytter denne side, selv om du måske ikke udnytter resten af skemaet.

A) Er vore oplysninger korrekte?
Vi har via sygehusets adh-system fået oplyst, at dit barn inden for de seneste år har fået konstateret en kraftsygdom?

Ja, og diagnoisen var: ____________________________
Gå herved videre til spørgsmål B nedenfor (vedr. informeret samtykke).

Nej

Du skal ikke udnytte mere af skemaet, men returnere det til den medfølgende koord. Vi beklager venlig hensyn dertil. Du er velkommen til at kontakte Jette Ahrensberg (projektkoordinator) vedhæftet vedhæftet yderligere afklarings.

B) Informeret samtykke
For at få en komplet beskrivelse af dit barns sygdomsforløb vil vi bede om lov til at spørge barnets praksisrende læge om fortaltet ved hjælp af et lægeopgælsemekskema. Du kan godt undvære at bevare resten af skemaet her og almindelig viderefølge denne formular.

Vær sikr på at fortælle på næste side
Den tidligste sygdomstid

6. Hvornår opstod alvorligste sygdomstegnsymptomer(i), der gjav mistanke om, at der var "et eller andet galt" med dit barns helse?
   (Sev in så nøjagtig dato som muligt)
   
   dag
   måned
   år

7. Hvilkjek sygdomstegnsymptomer(i) havde dit barn allerede?
   (Lyst nedenfor viser mere af de sygdomstegn, barnet kan have haft. Vi bejde dig således krydse ud for det(i) sygdomstegn, der først blev observeret hos barnet. (Sev in. flere krydser)
   
   Sygdomstegnsymptomer
   
   Fætter
   Tænding til benandes/infeksion
   Arleg
   Sjovmened
   Tænding til blæ mælter
   Uddsat
   Træthed/mindre energi
   Hævet laad
   Vredføle
   Hovedpine
   Nedsat appetit
   Knælem
   Ophæld
   Knæpærnfald
   Problemer med synet, skolen
   Smert
   Voksevækst
   Hovde
   Bakken (næse, mundhule, øjnene og lgh.)
   Vejen/kræf/skælvede/under
   Fjertsanludning
   Synlig trøndehævelse
   Ikke synlig, men følelig trøndehævelse
   Sigt i uren
   Håde
   Pyovitsforandrinni
   "Noget galt" (uden nærmere at kunne sætte ord på)
   Ingen sygdomstegn

8. Hvis dit barn havde andre sygdomstegnsymptomer, der ikke er nævnt i skemaet, må du meget skrive det her:
   
   

9. Hvad tænkte du, at barnet fejlede, da du først gang observerede, "at noget var galt"?
   (Sev in. flere krydser)
   
   

10. Havia du først erfaringer med det danske sundhedsystem, før barnet fik kraft?
   (Sev in. flere krydser)
   
   Ja, gennem min/vores uddannelse (bc. gyge/plejekår, læge, SSKU-assistent, mv)
   Ja, gennem tidligere sygdom (egne eller nærmeste påræknings)
   
   

11. Hvornår fik du første gang mistanke om, at der kunne være noget såvolds fort med dit barn?
   (Sev in. så nøjagtig dato som muligt)
   
   dag
   måned
   år
12. Hvilket/sygdomstegn eller symptomer(e) havde dit barn i anledning til, at du fik det ærlige i dag?  
(Sælger gerne flere kryds)

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fieber</td>
</tr>
<tr>
<td>Tendens til børstelandinfektion</td>
</tr>
<tr>
<td>Skønhed</td>
</tr>
<tr>
<td>Svanemodad</td>
</tr>
<tr>
<td>Tendens til blå mærker</td>
</tr>
<tr>
<td>Udsættet</td>
</tr>
<tr>
<td>Træthed/mindre energi</td>
</tr>
<tr>
<td>Hævle lidt</td>
</tr>
<tr>
<td>Vægttab</td>
</tr>
<tr>
<td>Hovedpine</td>
</tr>
<tr>
<td>Nedsat appetit</td>
</tr>
<tr>
<td>Kvalme</td>
</tr>
<tr>
<td>Opkast</td>
</tr>
<tr>
<td>Krampofald</td>
</tr>
<tr>
<td>Produseret med svigt br. skolen</td>
</tr>
<tr>
<td>Smørter</td>
</tr>
<tr>
<td>Voksenværk</td>
</tr>
<tr>
<td>Hoste</td>
</tr>
<tr>
<td>Blødning (hæse, mundhule, øreråd og f.t.)</td>
</tr>
<tr>
<td>Vejrtrækningsværnelændad</td>
</tr>
<tr>
<td>Tilfældetalbækning</td>
</tr>
<tr>
<td>Smykning knude/hævete</td>
</tr>
<tr>
<td>Ikke synlig, men fast knude/hævete</td>
</tr>
<tr>
<td>Blox i urinen</td>
</tr>
<tr>
<td>Ilalten</td>
</tr>
<tr>
<td>Psykisk forandring</td>
</tr>
<tr>
<td>&quot;Noget palt&quot; (uden nærmere at kunne sætte ord på)</td>
</tr>
<tr>
<td>Ingen sygdomstegn</td>
</tr>
</tbody>
</table>

13. Hvis dit barn havde andre sygdomstegns/symptomer, der gav anledning til, at du fik det ærlige i dag, og som ikke er nævnt i skemaet, må du meget gerne skrive det her:  


14. Hvilken dato blev barnet første gang undersøgt af en læge i sygdomsforløbet?  
(Skriv en så nøjagtig dato som muligt)  

dag:  
måned:  
år:  

15. Hvor blev barnet første gang undersøgt af en læge?  
(Sælger af kryds)

- hos barnets praktiserende læge  
- hos en anden praktiserende læge  
- adskiltstagen  
- hos ungdoms  
- hos sygehuset  

Barnet blev undersøgt i alt i sygehus/hos speciallæge  

Forud, angiv her:  


16. Hvilken dato blev barnet første gang i kontakt med barnets praktiserende læge i sygdomsforløbet?  
(Sælger af kryds)

- hvis du nævnte barnets praktiserende læge i "eller" inden praktiserende læge" overfor, skal du angive samme dato som i spørgsmål 14.  

(Skriv en så nøjagtig dato som muligt)  

dag:  
måned:  
år:  

17. Hvor mange dage gik det, fra I besluttede hos lægen, til barnet blev set af lægen?  
(Sælger af kryds)

- 0 dage (barnet blev undersøgt samme dag)  
- 1 - 3 dage  
- 4 - 7 dage  
- 8 - 14 dage  
- 15 - 21 dage  
- 22 dage eller mere  
- Husker ikke
18. Da du først åbnede øjen, hvad tanke du, det sandsynligvis drejede sig om?

- [ ] Ikke
- [ ] Jeg havde ikke overvejelser, hvad det kunne være

19. Følgte du på daglige tidspunkter, at det kunne være en alvorlig sygdom?

- [ ] Ja, i høj grad
- [ ] Ja, i mindre grad
- [ ] Nej, egentlig ikke
- [ ] Nej, slet ikke
- [ ] Ved ikke

20. Overvejede du på daglige tidspunkter, at det kunne være kræft?

- [ ] Ja, i høj grad
- [ ] Ja, i mindre grad
- [ ] Nej, egentlig ikke
- [ ] Nej, slet ikke
- [ ] Ved ikke

21. Hvor mange gange var i alt hos din spædbarnlæge, inden det første gang blev henvist til yderligere undersøgelse?

- [ ] 1-3 gange
- [ ] 4-6 gange
- [ ] 7 gange eller mere
- [ ] Husker ikke

22. Hvilken dato blev barnet henvist til yderligere undersøgelse?

- [ ] Dag
- [ ] Måned
- [ ] År

23. Hvilken dato blev barnet indlagt på en barneskikkeafdeling (Aalborg, Aarhus, Odense eller Rigshospitalet)?

- [ ] Dag
- [ ] Måned
- [ ] År

24. Hvilken dato var du til stede, at barnet havde kræft?

- [ ] Dag
- [ ] Måned
- [ ] År

25. Hvilken dato startede selve behandlingen for kræft (kemoterapie, strålebehandling eller operation)?

- [ ] Dag
- [ ] Måned
- [ ] År
26. Hvilke personer i sundhedsvæsenet var involveret i dit barns sygdomsforløb, inden barnet blev indlagt på en børnekraftstofhøj (~Sæt evt. flere krydsker~)
   - Praksisende læge/vikar for praktiserende læge
   - Vaglæge
   - Sundhedsplejefore
   - Sygeplejerske
   - Psykiater
   - Privat praktiserende læge (f.eks. barnslæge, ortopediker, hudlæge mv.)
   - Læge(r) på anden sygehusafdeling end børnekraftstofhøj (f.eks. på lokalt sygehus)
   - Knæknævende
   - Andre, selv hvem:

   Det er ofte svært at få øje på barns tidlige tegn på sygdom og et vide, hvordan man skal reagere. Nogle foreldre behøver også at lære sig selv for, at det er vigtigt at have  selv tilgængelighed til en læge til at tage stilling til følgende udsagn:

27. Har dit barn nu eller tidligere haft andre længereværende sygdomme?
   - Nej
   - Ja, selv gerne diagnoser:

28. Hvordan synes du alt i alt dit barns helbred var, før barnet først gang fik symptomer på kraftsygdommen? (~Sæt et kryds~)
   - Fremragende
   - Værligt godt
   - Godt
   - Mindre godt
   - Dårligt

29. Jeg ville ønskede ikke at kontakte lægen for tidligt, da vi var bange for at virke "pulverede". (~Sæt et kryds~)
   - Helt enig
   - Enig
   - Hverken enig eller uenig
   - Uenig
   - Helt uenig

30. Jeg tænker indirekte på, at jeg vil kunne have kontaktet en læge tidligere i forholdet for at få barnet underlagt. (~Sæt et kryds~)
   - Helt enig
   - Enig
   - Hverken enig eller uenig
   - Uenig
   - Helt uenig

31. Jeg mener, min/vores måde at håndtere barnets sygdomsmøde på var helt korrekt. (~Sæt et kryds~)
   - Helt enig
   - Enig
   - Hverken enig eller uenig
   - Uenig
   - Helt uenig

32. Skulle barnets praktiserende læge en rolle i barnets tidligste sygdomsforløb? (~Sæt et kryds~)
   - Ja, i høj grad
   - Ja, i nogen grad
   - Ja, i mindre grad
   - Nej, barnets praktiserende læge var på ingen måde involveret i forholdet før diagnosen

33. Mit barns kraftsygdomsforløb blev taget alvorligt af barnets praktiserende læge. (~Sæt et kryds~)
   - Helt enig
   - Enig
   - Hverken enig eller uenig
   - Uenig
   - Helt uenig
<table>
<thead>
<tr>
<th>Nr.</th>
<th>Spørgsmål</th>
<th>Alternativer</th>
<th>kode</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.</td>
<td>Den praktiserende læge informerede tilstrækkeligt om, at barnet kunne føles noget alvorligt. (Sæt et kryds)</td>
<td>Helt enig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hvis enig eller uenig</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Uenig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Helt uenig</td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Jeg synes, barnets praktiserende læge var for søt at inddele udordning/ henvise barnet til indlæggelse. (Sæt et kryds)</td>
<td>Ja, det mener jeg i høj grad</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ja, det mener jeg i nogen grad</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nej, det mener jeg ikke</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nej, det mener jeg bestemt ikke</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ved ikke</td>
<td></td>
</tr>
<tr>
<td>36.</td>
<td>Alt i alt er jeg fuldt tilfreds med den praktiserende lægernes indsats i tiden frem mod diagnosen. (Sæt et kryds)</td>
<td>Helt enig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hvis enig eller uenig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uenig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Helt uenig</td>
<td></td>
</tr>
<tr>
<td>37.</td>
<td>Har du overvejet at lade dit barn skifte læge efter dit barns sygdomsforløb? (sæt et kryds)</td>
<td>Ja, men barnet har ikke skiftet læge</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ja, og barnet har skiftet læge til en anden læge i samme lægehus som den tidligere læge</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ja, og barnet har skiftet læge til en anden læge i en anden lægepraksis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nej, altid</td>
<td></td>
</tr>
</tbody>
</table>

**Hvordan gør du til med det?**

Vær varsom og forudseende på næste side.
APPENDIX II

QUESTIONNAIRE TO THE BEREAVED PARENTS
Kræft hos børn
- tidlige symptomer og sygdomsforløb

Forskningsenheden for Almen Praksis
Aarhus Universitet
Indbydelse til at deltage i undersøgelse af børnekølforløb

Kære [Forælders navn],

I et samarbejde mellem Århus Universitetshospital, Forskningsenheden for Almen Praksis og Aarhus Universitet undersøger vi, hvordan mistanken om kæft hos børn opstår. Vi undersøger, hvordan tiden fra de første sygdomstegn til behandlingsstart forløber. Undersøgelsen bygger på forældres oplysninger om deres børns sygdomsforløb, og vi henvender os til forældre til børn, der siden 1. januar 2007 har fået stillet en kæftdiagnose. Vi har fra sygehusets edb-registre fået oplyst, at dit barn, [Barnets navn], har været alvorligt sygt som følge af en kæftsygdom, og at du siden har mistet dit barn.

I edb-registre er der desværre altid en lille risiko for fejregistrering, og skulle vores oplysninger ikke være korrekte, beder vi dig kontakte os, så vi kan opklare årsagen til fejregistreringen.

Vi har stor forståelse for, at det er en meget sær situation for dig og din familie. Vi håber ikke, at det virker stødende, at vi kontakter dig, men vi vil i sundhedsvæsenet gerne lære af dine erfaringer. Vores håb er derfor, at du vil deltage i undersøgelsen, og dermed bidrage til uddannelsen af læger og til, at kæftfamblener fremover tilbydes den bedst mulige hjælp i sundhedsvæsenet.

Hvad beder vi dig om?


Fortrolighed

Mange tak for din hjælp!

Jette Ahrensberg, speciallæge i almen medicin, projektansvarlig læge, Forskningsenheden for Almen Praksis, Aarhus Universitet, tlf. 89-42 60 73
Overlæge Henrik Schröder, Børnepædagog A, Århus Universitetshospital
Læge Rikke Pilegaard Hansen, professor Peter Vedsted og professor Frede Olesen, Forskningsenheden for Almen Praksis, Aarhus Universitet
Først beder vi dig hjælpe os med at sikre, at vore oplysninger er korrekte. Dernæst spørger vi om tv for at modtage en afgørelse til jeres følgeskema. Det er vigtigt, at du udfylder denne side, selv om du måske ikke har mulighed for at udfylde resten af skemaet.

A) Er vore oplysninger korrekte?

Vi har valgt at spørge om tv for at sikre, at vore oplysninger er korrekte. Dernæst spørger vi om tv for at modtage en afgørelse til jeres følgeskema. Det er vigtigt, at du udfylder denne side, selv om du måske ikke har mulighed for at udfylde resten af skemaet.

Fik barnet konstateret en kraftsforstyrrelse eller anden form for sygdom?

- Ja, og diagnosen var ____________
  - Gå herved vedligeholdelse til spånskem til næsthed (vedt: informeret samtykke).
  - Nej

Du skal ikke udfylde mere af skemaet, men notere det i den medfølgende kvadet. Vi beklager vores henvendelse. Du er meget velkommen til at kontakte Jette Andersen, (projektansvarlig læge) ved behov for yderligere atførsel.

B) Informeret samtykke

For at få en komplet beskrivelse af dit barns sygdomsforløb vil vi bede om tv for at spørge barnets praktiserende læge om forløbet ved hjælp af et spånskema. Du kan godt undvære at tænke på resten af skemaet her og altid vedligehold samtidig give denne tilfældige.

Må vi indhente oplysninger vedr. dit barns sygdomsforløb hos den læge, der var barnets praktiserende læge, da kraftsforstyrrelsen blev konstateret?

- Ja
  
  **Dato:** ____________ **(vedkommende)**
  
  **Lægens navn og ad.:** ____________

- Nej

I tilfælde tilfælde vil du være en stor hjælp, at vi må indhente oplysninger fra dit barns sygdomsforløb.

Må i tilfælde tilfælde indhente oplysninger fra dit barns sygdomsforløb?

- Ja
  
  **Dato:** ____________ **(underkrift)**

- Nej

---

Vær varig at fortsætte på næste side
8. Hvis dit barn havde andre sygdomstegn/symptomer, der ikke er nævnt i skemaet, må du meget gernære sikre det her.

9. Hvad tænkte du, at barnet fejlede, da du først gang observerede, "at noget var galt"?

10. Hoved erfaringer med det danske sundhedsstatistisk, før barnet fik kraft?

11. Hvornår fik du første gang misfandt, at der kunne være noget uvanligt galt med dit barn?

Viser venligst at forudsætte på næste side
12. Hvilket sygdomme steg eller symptom er du blevet anbefalet til at døde?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Anbefalt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fåer</td>
<td>☐</td>
</tr>
<tr>
<td>Tendens til betændelse ss.</td>
<td>☐</td>
</tr>
<tr>
<td>Blodhævning</td>
<td>☐</td>
</tr>
<tr>
<td>Sm melhed</td>
<td>☐</td>
</tr>
<tr>
<td>Tendens til blød mærker</td>
<td>☐</td>
</tr>
<tr>
<td>Udstødning</td>
<td>☐</td>
</tr>
<tr>
<td>Sved</td>
<td>☐</td>
</tr>
<tr>
<td>Tætt medstyrke energi</td>
<td>☐</td>
</tr>
<tr>
<td>Hævet øje</td>
<td>☐</td>
</tr>
<tr>
<td>Vægttab</td>
<td>☐</td>
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<tr>
<td>Hovedpine</td>
<td>☐</td>
</tr>
<tr>
<td>Nedsat appetit</td>
<td>☐</td>
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<tr>
<td>Kvinde</td>
<td>☐</td>
</tr>
<tr>
<td>Opfind</td>
<td>☐</td>
</tr>
<tr>
<td>Krisenafhold</td>
<td>☐</td>
</tr>
<tr>
<td>Problemer med symet fr. skallen</td>
<td>☐</td>
</tr>
</tbody>
</table>

13. Hvis du har hørt andre sygdomme/symtomer der gav anledning til at døde lægehjælp, og som ikke er nævnt i skemaet, må du meget gerne skrive det her.

14. Hvornår blev børnet første gang undersøgt af en læge i sygdommeforløbet?

(Skriv en så nøjagtig dato som muligt)

<table>
<thead>
<tr>
<th>Dag</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

15. Hvornår blev børnet første gang undersøgt af en læge? (Se efter krydset)

- ☐ Hos børnets praktiserende læge
- ☐ Hos en anden praktiserende læge, der er ansat i en forebyggende læge
- ☐ Pår stædtet
- ☐ Hos vælgemig
- ☐ Vælgemig
- ☐ Børnet var alene i et forløb på sygehus/hos speciallæge
- ☐ Andet, angiv her

16. Hvornår blev børnet første gang i kontakt med børnets praktiserende læge i sygdommeforløbet? (Hvis du nøjagtig speaker "børnets praktiserende læge" eller "en pratisererende læge" ovenfor, skal du angive samme dato som i spørgsmål 14.)

(Skriv en så nøjagtig dato som muligt)

<table>
<thead>
<tr>
<th>Dag</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

17. Hvor mange dage gik der, fra det første tid hos lægen, til børnet blev set af lægen? (Se efter krydset)

- ☐ 0 dage (børnet blev undersøgt samme dag)
- ☐ 1 - 3 dage
- ☐ 4 - 7 dage
- ☐ 8 - 14 dage
- ☐ 15 - 21 dage
- ☐ 22 dage eller mere
- ☐ Husker ikke
### Kraft hos børn - tidlige symptomer og sygdomsforløb

**Dinejeres overvejelser om sygdomstegn**

Kraft er en spædes sygdom hos børn og symptomerne kan i begyndelsen være ukarakteristiske og ligne tegn på helt almindelige stunder (f.eks. forhåbelige, voldsomt etc.). De næstte spørgsmål handler om, hvilke overvejelser eller tenkning du gjorde dig om barnets sygdomstegn tidligst i forlægget.

**18. Da du først først gang søgte læge, hvad tænkte du, det sandsynligvis drejede sig om?**

Skriv her:

- Jeg havde ikke overvejelser, hvad det kunne være

**19. Følgende duft på daværende tidspunkt, at det kunne være en alvorlig sygdom?**

(Sæt et kryds)

- Ja, i høj grad
- Ja, i mindre grad
- Nej, egentlig ikke
- Nej, det ikke
- Værd ikke

**20. Overvejede duft på daværende tidspunkt, at det kunne være kraft?** (Sæt et kryds)

- Ja, i høj grad
- Ja, i mindre grad
- Nej, egentlig ikke
- Nej, det ikke
- Værd ikke

---

**Tiden fra første lægesagning til diagnosen blev stillet**

De næstte spørgsmål handler om tiden, før barnet blev undersøgt af en læge, og frem til at diagnosen blev stillet.

**21. Hvor mange gange var barnet i alt hos sin praktiserende læge, inden det første gang blev henvist til yderligere undersøgelser? (hos speciallæge, i ambulatorium eller indlag på sygehus)**

- 0 gange
- 1 - 3 gange
- 4 - 6 gange
- 7 eller flere gange
- Husker ikke

**22. Hvilkene dato blev barnet henvist til yderligere undersøgelser (hos speciallæge, i ambulatorium eller indlag på sygehus)?**

(Skriv en så rettaget dato som muligt)

<table>
<thead>
<tr>
<th>Dag</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

**23. Hvilkene dato blev barnet indlagt på en børnekraftskjærling? (Aalborg, Aarhus, Odense eller Rigshospitalet)?**

(Skriv en så rettaget dato som muligt)

<table>
<thead>
<tr>
<th>Dag</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

**24. Hvilkene dato fik du at vide, at barnet havde kraft eller anden form for svelst?**

(Skriv en så rettaget dato som muligt)

<table>
<thead>
<tr>
<th>Dag</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

**25. Hvilkene dato startede selve behandlingen for kraft? (kæmterapi, strålebehandling eller operation)**

(Skriv en så rettaget dato som muligt)

| Dag | Måned | År |
Appendix II

26. Hvilke personer i sundhedsvæsenet var involveret i dit barns sygdomsforløb, inden barnet blev indlagt på en børnekræftforsyning? (Sæt ev. flere kryds:)

☐ Praktiserende lægehvilekør for praktiserende læge
☐ Vagtlæge
☐ Sundhedsplejende
☐ Sygeplejende
☐ Fysioterapeut
☐ Privat praktiserende specielllæge (f.eks. børnelæge, ortopedikør, hudlæge mv.)
☐ Læge(r) på anden sygehusforsyning end børnekræftforsyning (f.eks. til lokalt sygehus)
☐ Kiropraktør
☐ Andre, skriv hvem:

Det er ofte svært at få øje på barnes tidlige tegn på sygdom og at vide, hvordan man skal reagere. Nogle foreslår helebalken begejstre sig selv for at f.eks. at have sige læge tidligere. Nu stiller vi dig et par spørgsmål om barnets helbred før kraftsygdommen og forbedrer dig om at tage stilling til følgende udsagn:

27. Hvalde dit barn tidligere haft andre længerevarende sygdomme?

☐ Nej
☐ Ja, skriv gerne diagnose(r):

Kryd:

28. Hvordan synes du alt i alt dit barns helbred var, før barnet først gengik symptomer på kraftsygdommen? (Sæt alt kryds)

☐ Fraværende
☐ Verrig godt
☐ Gudt
☐ Mindre godt
☐ Dyrkligt

29. Jeg vil ønske at kontakte lægen for tidligt, da vi var bange for at vekre "spyvede". (Sæt alt kryds)

☐ Helt eng
☐ Eng
☐ Hverken eng eller ueng
☐ Ueng
☐ Helt ueng

Vær vigtigt at fremsendte på næste side

30. Jeg tænker indlæggelse på, at jeg endnu ikke har kontaktet en læge tidligere i forbindelse med at få barnet undersøgt. (Sæt alt kryds:

☐ Helt eng
☐ Eng
☐ Hverken eng eller ueng
☐ Ueng
☐ Helt ueng

31. Jeg mener, min/vores måde at håndtere barnets sygdomstegn på var helt korrekt. (Sæt alt kryds)

☐ Helt eng
☐ Eng
☐ Hverken eng eller ueng
☐ Ueng
☐ Helt ueng

De sidste spørgsmål handler om, hvordan du oplevede kontakten med barnets praktiserende læge, og hvordan du vurderer lægnes indstal i dit barns sygdomsforløb. Vi understreger, at sagen ikke får kendskab til dine svar.

32. Spillede barnets praktiserende læge en rolle i barnets tidligste sygdomsforløb? (Sæt alt kryds)

☐ Ja, i høj grad
☐ Ja, i nogen grad
☐ Ja, i mindre grad
☐ Nej, barnets praktiserende læge var på ingen måde involveret i forbindelse med diagnoseførelse blev stillet (på 1 spørgsmål 37)

33. Mil barns blodsprøve/sygdomstegn blev taget alvorligt af barnets praktiserende læge. (Sæt alt kryds)

☐ Helt eng
☐ Eng
☐ Hverken eng eller ueng
☐ Ueng
☐ Helt ueng

Vær vigtigt at fremsendte på næste side
Kraft hos børn - tidlige symptomer og sygdomsforløb

14. Den praktiserende læge informerede tilstrækkeligt om, at barnet kunne føje noget alvorligt. (Sæt et kryds)
   ☐ Istelt
   ☐ Erigt
   ☐ Hverken erigt eller uerigt
   ☐ Uerigt
   ☐ Helt uerigt

35. Jeg synes, barnets praktiserende læge var for sent til at indlede uddedning/ henvising barnet til indlæggelse. (Sæt et kryds)
   ☐ Ja, det mener jeg i høj grad
   ☐ Ja, det mener jeg i nogen grad
   ☐ Nej, det mener jeg ikke
   ☐ Nej, det mener jeg bestemt ikke
   ☐ Ved ikke

Lydhygger dit svare her:__________________________________________________________

36. Alt i alt er jeg fuldt tilfreds med den praktiserende læges indsats i tiden frem mod diagnosen. (Sæt et kryds)
   ☐ Istelt
   ☐ Erigt
   ☐ Hverken erigt eller uerigt
   ☐ Uerigt
   ☐ Helt uerigt

37. Overvejede du at lade dit barn skifte læge, efter barnet fik konstateret kræft eller anden børn for svulst?
   ☐ Ja, men barnet skiftede ikke læge
   ☐ Ja, og barnet skiftede læge til en anden læge i samme lægehus som den tidligere læge
   ☐ Ja, og barnet skiftede læge til en anden læge i en anden lægepraksis
   ☐ Nej, aldrig

39. Hvordan havde barnets praktiserende læge i forhold til barnet og familien i øvrigt, efter at barnet fik konstateret kræft eller anden form for svulst? (Sæt et kryds)
   ☐ En stor rolle
   ☐ En mindre rolle
   ☐ Ingen rolle
   ☐ Ved ikke

40. Var barnets praktiserende læge tilstrækkeligt involveret i dit barns sygdomsforløb, efter at diagnosen blev stillet? (Sæt et kryds)
   ☐ Ja, det har været helt tilstrækkeligt
   ☐ Ja, i nogen grad, men jeg kunne godt have ønsket, at lægen var mere involveret
   ☐ Nej, det har været utilstrækkeligt, jeg har havt at løge var mere involveret
   ☐ Ved ikke

41. Hvis du har yderligere kommentarer til dit barns sygdomsforløb, er du meget velkommen til at skrive dem her:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Vær virkelig at brænde på næste side
APPENDIX III

QUESTIONNAIRE TO THE GPs
Kræft hos børn
-tidlige symptomer og sygdomsforløb
Lægespørgeskema

Projektansvarlig læge Jette Ahrnsberg
Forskningsenheden for Almen Praksis
Aarhus Universitet
Bankegade Allé 2
8000 Århus C
Tlf. 89 42 60 73
e-mail: jette.ahrensberg@alm.au.dk

Forskningsenheden for Almen Praksis
Aarhus Universitet
Til orientering:

Dette brev blot til orientering om, at vi i forbindelse med undersøgelsen, "Børncancer. Tidlige symptomer og forløb tid fra symptome debut til behandlingsstart" i den kommende tid planlægger at udsende et spørgeskema til forældrene til

[Barnets navn, barnets CPRnr]


Vi har valgt at orientere dig, idet der er erfaring for at sådanne henvendelser til forældre i enkelte tilfælde vil medføre kontakt til barnets praktiserende læge med henblik på afklaring af spørgsmålet vedr. barnets forløb. Vi beder dig i så fald have forståelse for undersøgelsens formål.

Såfremt forældrene giver os tilladelse dertil, vil vi senere bede den læge, der var barnets praktiserende læge på diagnosetidspunktet om at udfylde et spørgeskema.

Med venlig hilsen

Jette Ahrensberg, speciallæge i almen medicin, projektansvarlig læge, Forskningsenheden for Almen Praksis, Aarhus Universitet, tlf.: 8942 6073, mail: jette.ahrensberg@alm.au.dk

Overlæge Henrik Schroder, Børneafdeling A, Århus Universitetshospital

Læge Rikke Pilegaard Hansen, professor Peter Vedsted og professor Frede Olesen,
Forskningsenheden for Almen Praksis, Aarhus Universitet
Kære kollegra

Vedr. [Barnets navn, barnets CPRnr]

Almen praksis spiller en helt afgørende rolle i tidlig diagnosisk af kæft hos børn. Symptomer på kæft hos børn er ofte vage og ukarakteristiske, og det kan være en klinisk udfordring at finde netop disse børn. Vi vil skabe ny viden om, hvilke symptomer, vi som praktiserende læger skal være ekstra opmerksomme på.

Med dette brev beder vi dig deltage i en undersøgelse af det præhosptale diagnostikste forløb hos et konkret barn, der fik konstateret kæft (inkl. godartet hjernesvulst). Formålet er at kortlægge forløbet for at optimere vores lægefaglige tilgang til børn med kæft.


Spørgeskemaerne indeholder spørgsmål om tidlige symptomer, dine objektive fund, det konkrete udredningsforløb, karakteristika vedrørende barnet/familien og om læge-patient-forhold.


Du er velkommen til at ringe eller maille til mig, hvis du har spørgsmål eller kommentarer.

På forhånd tak for hjælp!

Med venlig hilse – på projektgruppens vegne

Jette Ahrensberg, speciallæge i almen medicin, Forskningsenheden for Almen Praksis i Århus, Tlf. 89 42 60 73,
mailadr. jette.ahrensberg@alm.au.dk
Henrik Schröder, overlæge, dr.med., Børneafdeling A, Århus Universitetshospital
Peter Veistsed, professor, ph.d., Forskningsenheden for Almen Praksis i Århus
Frede Olsen, professor, dr.med., Forskningsenheden for Almen Praksis i Århus
Rikke Plejgaard Hansen, læge, ph.d., Forskningsenheden for Almen Praksis i Århus

Dato/lnr
## Kraft hos børn - tidlige symptomer og sygdomsforløb

### Generelle oplysninger

- Er du:
  - Fast læge i praksis med patientnummer (inkl. del-patientnummer)
  - Uddannelseslæge
  - Vikar for praktiserende læge/afstødningspamvanvæsen
  - Andet: ____________________________

### Den første del af spørgeskemaet omhandler udredningen af børnet fra første henvendelse. Tidligere behandlingsprotokoll, eller behandlingsprotokoll fra andre tidligere behandlinger, kan tilsættes her.

1. **Var du/din praksis på et tidspunkt involveret i børnets udredningsforløb?**

   - Ja, praksis var involveret (helt eller delvist) i det forløb, der førte frem mod børnets cancerdiagnose. (Gå videre til spørgsmål 2 på næste side)
   - Nej, praksis var ikke involveret. Udfyld venligst:

     - Børnet blev indlagt i anden læge uden forudgående kontakt til mig/min praksis
     - Andet: ____________________________

   **Hvis du svarede "Nej", gå nu til spørgsmål til børn 20 (side 9).**

### Tidslinje fra symptomdebølte til diagnose

<table>
<thead>
<tr>
<th>Dato for første</th>
<th>Dato for start på lægens uderudning</th>
<th>Dato for indlæggelse på børnets udredningforløb</th>
<th>Dato for start på behandling</th>
</tr>
</thead>
<tbody>
<tr>
<td>lægebesøg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juni</td>
<td>Juli</td>
<td>August</td>
<td>September</td>
</tr>
</tbody>
</table>

I nogle tilfælde er der flere datoer sammensatstilende. Vi beder dig besvare spørgsmalet så nøjagtigt som muligt ud fra dine journalnotater og dine hukommelse.

**Hvis du ikke kan angive de nøjagtige datoer, giver du det samme et skriftligt dokument.**

Vi vil efterfølgende spørge dig, hvilke symptomer eller ægtes børnet henvendte sig på de ovenfor navneførte tidspunkter i forhold til, og hvilke objektive fund der var til stede. Med "symptomer" mener vi de sygdomsbeskeder og kager, børnet eller familien fremførte i konsultationen.

2. **Hvilkøen dato blev børnet set FØRSTE gang af dig/din praksis på grund af symptomer?**, der, efter dit sken i dag, skyldes den aktuelle cancerdiagnose?

   **(Går til en så nøjagtig dato som muligt)**

<table>
<thead>
<tr>
<th>Dato</th>
<th>Måned</th>
<th>År</th>
</tr>
</thead>
</table>

3. **Omtrent hvor længe havde børnet haft disse symptomer, inden du/din praksis blev involveret?** (ved kun at fylde)

   - Under 1 uge
   - Mellem 1 og 2 uger
   - Mellem 2 og 4 uger
   - Mellem 4 og 8 uger
   - Over 8 uger
   - Vidt ikke
### Kraftighed hos børn - tidlige symptomer og sygdomsforløb

**Lægeopgavevæsen**

4. Hvilken dato påbegyndte dædlin praksis videre udredning (ud over anamnese og objektiv undersøgelse) for at be- eller afkærte ulovlig sygdom, herunder cancer (f.eks. biotraf, henvisning til røntgenundersøgelse osv.)?

(Skriv en så nøjagtig dato som muligt)

<table>
<thead>
<tr>
<th>dag</th>
<th>måned</th>
<th>år</th>
</tr>
</thead>
</table>

Ikke relevante

5. Hvor mange gange så dædlin praksis barnet fra første henvendelse, til dædlin praksis færdigførte den egentlige udredning for at be- eller afkærte ulovlig sygdom, herunder cancer?

(Skriv værdigt antal)

6. Hvilken dato henviste dædlin praksis første gang barnet til varerings- eller undersøgelse (ved privatpraksisrende speciallæge, i ambulatorium eller indlagt?)?

(Skriv en så nøjagtig dato som muligt)

<table>
<thead>
<tr>
<th>dag</th>
<th>måned</th>
<th>år</th>
</tr>
</thead>
</table>

Barnet blev ikke henviset til eg. min praksis

7. Hvilken dato overgav dædlin praksis ansvaret for den endelige udredning af barnet til specialisatortudredning (ved privatpraksisrende speciallæge, i ambulatorium eller indlagt?)?

(Skriv en så nøjagtig dato som muligt)

| dag | måned | år |

8. Hvilken dato blev den endelige diagnose stillfæld (se evt. afslutning)

(Skriv en så nøjagtig dato som muligt)

| dag | måned | år |

Ikke relevante/husker ikke

---

### Kraftighed hos børn - tidlige symptomer og sygdomsforløb

**Lægeopgavevæsen**

5. Hvilke symptomer havde børnet? A: ved første kontakt, B: ved start af udredning

<table>
<thead>
<tr>
<th>symptomer</th>
<th>A: først kontakt</th>
<th>B: start af udredning</th>
</tr>
</thead>
</table>

Almindelige symptomer

6. Hvilke symptomer, hvis dædlin praksis påbegyndte videre udredning for at be- eller afkærte ulovlig sygdom. (dato angivet i spm. 2)

<table>
<thead>
<tr>
<th>symptomer</th>
<th>dato angivet</th>
</tr>
</thead>
</table>

---

**Symptom/sygdomstechnik**

(Sæt gerne flere krydsede)

<table>
<thead>
<tr>
<th>Udefraart</th>
<th>følelseslignende</th>
<th>Tidligere til hjerntilstand</th>
<th>Hjemme hjerneskadet</th>
<th>Vækstvækst</th>
</tr>
</thead>
</table>

---

**Vær werklig at fortsætte på næste side**
10. Hvis barnet havde andre symptomer end dem, der er anført i skemaet, beder vi dig skrive dem her:
   a) Andre symptomer på tidspunktet før første kontakt til digtøn praksis:
      Kode:  
   b) Andre symptomer, da diudin praksis påbegyndte videre udredning:
      Kode:  

11. Hvilket) symptom(er) eller symptommonster lagde du mest vægt på?
   ved første kontakt (se 9a):
      Kode:  
   da videre udredning påbegyndtes (se 9b):
      Kode:  

12. Hvordan opfattede du de otte symptomer, der fik dig til at udelade barnet? (sæt et kryds)

   □ som et klassisk alarmsymptom på cancer
   □ som et alment symptom, der gav misstank om alvorlig sygdom
   □ som et karakteristisk symptom, der ikke udvideligt gav misstank om alvorlig sygdom

   På næste side spørges vi til de objektive og tilnærmende funder, dauddin praksis konstaterede hos barnet i forbindelse med den kliniske vurdering af barnet. Vi spørges dig, hvilke objektive tegn på sygdom der sås hos barnet ved:

   a) første kontakt til digtøn praksis og
   b) på det tidspunkt, hvor diudin praksis påbegyndte videre udredning.

   De to tidspunkter og de objektive fund kan være sammenfaldende.

| Kvalitativ| Objektivt
|-----------|----------
| Objektivt| Klinisk fund | (Sæt gørre flere kryds) | (Sæt gørre flere kryds) |
| Intensitet | Førhøjet temperatur | | |
|           | Infektion med eller uden fokus | | |
|           | Begyndelsesmærk | | |
|           | Blå marker | | |
|           | Udslutning | | |
|           | Dærlig trækk | | |
|           | Smertefuld | | |
|           | Høvlede glandler | | |
|           | Perikolur | | |
|           | Høvlede led | | |
|           | Knappenfand | | |
|           | Synsprøvning | | |
|           | Smertekværl | | |
|           | Patrose | | |
|           | Stivskopiske fund | | |
|           | Dæmpning over linjefæld | | |
|           | Irregularitet | | |
|           | Tæskar | | |
|           | Sygdom utydnings/tumor | | |
|           | Ikke sygdom, men påviset utydnings/tumor | | |
|           | Pålægningse gang | | |
|           | Psykisk forandring | | |
|           | "Noget galt" (klinisk intuition, der uvist dominerer) | | |
|           | Blod larmen (sygdom eller ved stik) | | |
|           | Blodkonsentr杵 | | |
|           | Ingen objektive fund | | |

Vær venlig at fortælle på næste side
Kraft hos børn - tidlige symptomer og sygdomsforløb
Lægeopsøgelsesformular

14. Hvis der var andre objektive fund end dem, der er anført i skemaet, bedes du anføre dem her:
   a) Andre objektive fund ved første kontakt
   b) Andre objektive fund, da du din praksis påbegyndte videre udredning

Udredning og henvisning
Nu spørgér vi mere specifikt om, hvilke diagnosiskt tilspig du din praksis havde(set under hensyndesforløb, og hvad der lå til grund for dit valg om at henvise barnet til videre udredning.

15. Hvilke diagnosiskt tilspig du din praksis inden den primære indlæggelse af barnet? (Se alle fra krydset)
   - Laboratoriodiagnostik i egen praksis
   - Laboratoriodiagnostik i andet laboratorium
   - Henvisning til billeddiagnostik
   - Henvisning til vurdering hos praktiserende speciaallege
   - Henvisning til vurdering på sygehus (ambulatorium, akut eller aktivt indlæggelse)
   - Andet

16. Hvilke faktorer var medbestemmende for dit valg om at henvise barnet til speciaallege (praktiserende eller på sygehus)? (Se alle fra krydset)
   - Kliniske fund
   - Andre diagnosiskt fund (blodprøve, urind, billeddiagnostik, andet)
   - Klinisk intuition - "noget alvorligt går"
   - Ørne fra foreldre/familie
   - Andet

Henvisning og information
De følgende spørgsmål omhandler henvisningsprocedure og informationer givet på henvisningstidspunktet.

17. Hvilket fra nedenstående udsagn beskriver bedst indholdet af din henvisning eller din evn. telefoniske kontakt til speciallæge (praktiserende eller på sygehus)? (Se alle fra krydset)
   - Misforståede om, at "noget var galt", og jeg ønskede barnet vurdert
   - Misforståede om alvorlig sygdom, man ikke specifik cancer
   - Misforståede om cancer fremgik kort, da den kliniske beskrivelse af alvorlige fund
   - Husker ikke
   - Barnet blev ikke henvist af mormor praksis (på vejret til spørgsmål 20)

18. Gjorde du brug af pakkeforløbet for kraft hos børn, da du henviste barnet til indlæggelse/ambulatorium? (Se alle fra krydset)
   - Ja
   - Nej

19. Informerede du i forløbet foreslåede om, at barnet kunne vise sig at fejla noget alvorligt såsom kraft?(Se alle fra krydset)
   - Ja, jeg nævnte, at jeg havde en misforstående praksis om kraft
   - Ja, jeg nævnte, at jeg mistænkte alvorlig sygdom (ikke specifik praksis)
   - Nej
   - Husker ikke
   - Ikke relevante

Vær venlig at fortsætte på næste side

7 / 12
Kraftig hos børn - tidlig symptomer og sygdomsforløb
Længeregnskabens

Nu nogle mere generelle spørgsmål vedrørende barnet og barnets familie.

20. Hvordan vurderede du barnets helbredstilstand før den aktuelle sygdom? (sæt et kryr)
- Fremragende
- Vældig god
- God
- Mindre god
- Ødelig
- Jeg tror på praksis kendte ikke barnet før det aktuelle sygdomsforløb

21. Hvordan var forældres/barnets brug af almen praksis, efter dit skøn, før den aktuelle sygdom? (sæt et kryr)
- Brugte sjældent læge
- Havs et gennemgribt forbrug af lægeaafleveringer
- Uhyppige brugere - altid med relevante problemstillinger
- Uhyppige brugere - tidliger med mindre relevante problemstillinger
- Jeg tror ikke på forældres/barnets tidligere brug af almen praksis

22. Hvordan reagerede familien sædvanligvis på symptomer før den aktuelle sygdom? (sæt et kryr)
- Forældrene/barnet sagde tidligere end gennemsnitligt råd ved symptomer hos barnet
- Forældrene/barnet reagerede som gennemsnitligt ved symptomer hos barnet
- Forældrene/barnet forsøgte oftest selv at klare symptomer hos barnet
- Forældrene/barnet foreslog oftest symptomer hos barnet
- Ved ikke

23. Overordnet set finder jeg det diagnosestforslag (sæt et kryr)
- Helt tilfredsstillende
- Tilsyneladende
- Uuforklarlig
- Helt uuforklarlig
- Ved ikke

24. Var venteridderne for længe? (sæt et kryr)
- Nej
- Ja

Det gik alt for (sæt evt. flere steder)
- Familien afvreden inden første lægevagning
- Venterød på tilknyttelse/laboratoriediagnostik (ordineret i praksis)
- Venterød på tilknyttelse/laboratoriediagnostik (ordineret i praksis)
- Venterød på vurdering eller undersøgelser ved praktiserende speciallæge
- Venterød på vurdering eller undersøgelser på sygehus
- Venterød, induction i behandling påbegyndt (efter at diagnosen var stillet)
- Andre

25. Set i bakspeklet synes jeg, at jeg var for længe om at få mistanke om alvorlig sygdom i dette tilfælde (sæt et kryr)
- Helt eng
- Eng
- Hvorlangt eng eller ueng
- Ueng
- Helt ueng

Vær varigt at fortælle på næste side
APPENDIX IV

TABLE 1
<table>
<thead>
<tr>
<th>Table 1, Frequency of GP-reported ICPC and selected symptoms at first presentation in general practice for all and according to gender and diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of children</strong></td>
</tr>
<tr>
<td><strong>ICPC</strong></td>
</tr>
<tr>
<td>A) General and unspecified</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Weakness</td>
</tr>
<tr>
<td>Swelling/lump</td>
</tr>
<tr>
<td>B) Blood, Blood Forming Organs and Immune Mechanism</td>
</tr>
<tr>
<td>Paleness</td>
</tr>
<tr>
<td>D) Digestive</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>F) Eye</td>
</tr>
<tr>
<td>L) Musculoskeletal</td>
</tr>
<tr>
<td>Limping</td>
</tr>
<tr>
<td>N) Neurological</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>R) Respiratory</td>
</tr>
<tr>
<td>S) Skin</td>
</tr>
<tr>
<td>T) Endocrine/Metabolic and Nutritional</td>
</tr>
<tr>
<td>Other ICPCs</td>
</tr>
</tbody>
</table>

1=significant difference between genders (p<0.05); 2=significant difference between diagnostic groups.

*ICPC: A (General and unspecified), B (Blood, Blood Forming Organs and Immune Mechanism), C (Digestive), D (Eye), E (Musculoskeletal), N (Neurological), R (Respiratory), S (Skin), T (Endocrine/Metabolic and Nutritional). Other ICPCs: (Ear, Cardiovascular, Psychological, Urological and Female Genital).

Notice that children most often had several symptoms, and that the sum of the symptom frequency therefore exceeds 100 per cent.