EPIDEMIOLOGY OF DELAYS IN CARE OF CHILDREN AND ADOLESCENTS DIAGNOSED WITH CANCER IN CANADA

TAM DANG-TAN

Department of Epidemiology & Biostatistics
McGill University, Montreal

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ABSTRACT

Background: Although rare relative to adult cancers, cancer is still the leading cause of disease-related death in children in developed countries, including Canada. Few studies have specifically examined the epidemiology and public health significance of diagnosis and treatment delays in childhood cancer. This study aimed to investigate the nature of delays in care for children and adolescents with cancer in Canada and to assess the potential impact of such delays on clinical outcomes.

Study Design: I conducted a prospective cohort study to investigate the delays of cancer symptoms reporting, diagnosis, and treatment in children between 0-19 years of age in Canada. This study used a database from Health Canada's Treatment and Outcomes component of the Canadian Childhood Cancer Surveillance and Control Program.

Methodology: Patients were identified from 17 paediatric cancer centres across Canada. Subjects included in this study were residents of Canada, aged less than 20 years, diagnosed with a malignant tumour and had information on date of first symptoms, diagnosis, treatment and outcome available. Descriptive statistics and regression techniques (linear, logistic and Cox regression) were used as appropriate. I measured the individual impact of patient and provider delays on disease severity and prognosis by using judicious control for potential confounding mechanisms and mediating factors.

Study Findings and Significance: By measuring various types of delays in Canada, I found that varying lengths of patient and referral delay, across age groups, types of cancers, and Canadian settings, are the main contributors to diagnosis, HCS and overall

delay. Factors relating to the patients, the parents, healthcare and the cancer may all exert different influences on different segments of cancer care. I also found a negative association between diagnosis delay and disease severity for lymphoma and CNS tumour patients. Furthermore, I found that diagnosis and physician delay had a negative effect, while patient delay had a positive effect, on survival for patients diagnosed with CNS tumours. The information provided from this study may form the basis for new effective policies aimed at eliminating obstacles in cancer the diagnostic and care trajectories for Canadian children with cancer and for improving their prognosis.

RÉSUMÉ

Introduction: Bien qu'il soit rare comparativement au cancer chez les adultes, le cancer demeure la cause principale des décès liés à la maladie chez les enfants dans les pays développés, y compris le Canada. Il existe relativement peu d'études vouées spécifiquement à l'examen de l'épidémiologie et des répercussions sur la santé publique des temps d'attente dans le diagnostic et le traitement du cancer pédiatrique. La présente étude visait à examiner la nature des temps d'attente dans les soins prodigués aux enfants et aux adolescents atteints de cancer au Canada, et d'évaluer les répercussions potentielles de ces délais sur les résultats cliniques.

Modèle d'étude : J'ai réalisé une étude prospective de cohortes pour examiner les temps d'attente dans le signalement des symptômes du cancer, ainsi que dans le diagnostic et le traitement chez les enfants âgés de 0 à 19 ans au Canada. Cette étude utilise une base de données existante du Système de surveillance du traitement et des résultats du Programme canadien de surveillance et de lutte contre le cancer chez les enfants de Santé Canada.

Méthodologie: Les patients étaient sélectionnés dans 17 centres d'oncologie pédiatrique à travers le Canada. Les sujets recutés pour l'étude étaient des résidents canadiens, âgés de moins de 20 ans, qui avaient reçu un diagnostic de tumeur maligne et dont les renseignements sur la date de signalement des premiers symptômes, le diagnostic, les traitements et l'issu de la maladie étaient disponibles. Les techniques de statistiques descriptives et d'analyse de régression (linéaire, logistique et Cox) étaient utilisées comme il convient. J'ai mesuré les répercussions individuelles des temps d'attente

associés au patient et au prestataire des soins de santé sur la gravité de la maladie et le pronostic en utilisant des contrôles judicieux pour tenir compte des facteurs de confusions et des médiateurs potentiels.

Conclusions et retombée: En évaluant les différents types de temps d'attente au Canada, j'ai trouvé que pour tous les groupes d'âge, tous les types de cancer, et tous les milieux canadiens, les temps d'attente associés au patient et à la consultation de spécialistes sont les facteurs principaux entraînant des temps d'attente dans l'établissement du diagnostic et au niveau du système de soins de santé. Les facteurs liés aux patients, aux parents, au système de soins de santé et aux types de cancer exercent tous une influence différente sur les divers secteurs de soins relié au contre le cancer. J'ai également trouvé une association négative entre le retard du diagnostic et la gravité de la maladie chez les patients atteints de lymphome et de tumeur au système nerveux central. De plus, j'ai trouvé que les temps d'attente associés au diagnostic et au médecin avaient un effet négatif tandis que les temps d'attente associés au patient avaient un effet positif sur la survie des patients ayant reçu un diagnostic de tumeur au système nerveux central. L'information fournie par cette étude pourrait servir de base pour l'établissement de politiques efficaces visant à éliminer les obstacles au diagnostic du cancer et aux trajectoires de soins pour les enfants canadiens atteints de cancer afin d'améliorer leur pronostic.

PREFACE

The presentation of this thesis conforms to a traditional format. Included in this thesis is a general introduction stating the objectives and rationale of this study and a comprehensive review of the literature summarizing current knowledge on this topic, followed by a general description of the methodology and statistical analyses. Chapters 7 to 10 are written to address each specific objective and contain a more detailed description of the methodology, a presentation of the results, and finally a summary and discussion of the main findings.

The literature review of diagnosis delays in childhood cancer (in chapter 3) contain an edited version of a manuscript that I wrote, as part of this thesis, entitled: "*Diagnosis delay in childhood cancer: a review*", and published in the journal Cancer (Cancer. 2007 Aug 15; 110(4):703-13). I co-authored this manuscript with Dr. Eduardo Franco, my PhD supervisor (Professor in the Department of Epidemiology and Biostatistics, and Oncology, McGill University). I conceived the objectives of the review, designed and carried out the review and wrote the manuscript. Dr. Franco contributed epidemiological expertise in the interpretation of the findings and contributed to the writing of the manuscript.

As well, the contents of chapter 7 contain a separate manuscript, entitled "*Delays in Diagnosis and Treatment among Children and Adolescents with Cancer in Canada*". This manuscript has been published in Pediatric Blood & Cancer (Pediatr Blood Cancer. 2008 Oct; 51(4): 468-74). I coauthored this manuscript with Dr. Helen Trottier (Department of Social & Preventive Medicine, University of Montreal), Leslie S. Mery (Public Health Agency of Canada), Dr. Howard I. Morrison (Public Health Agency of Canada), Dr. Ronald D. Barr (Department of Paediatrics, McMaster University), Dr.

Mark L. Greenberg (Department of Paediatrics, University of Toronto) and Dr. Eduardo Franco. I planned and designed this study, conceived the objectives, conducted the statistical analyses and wrote the manuscript. Dr. Morrison, Dr. Barr, Dr. Greenberg and Mr. Mery contributed to the planning of this study and provided comments on the manuscript. Dr. Trottier contributed to the statistical analyses and interpretation of the study findings. Dr. Franco participated in the planning of the study and contributed to the statistical analyses, interpretation and writing of the manuscript.

The contents of the published manuscripts have been slightly modified from the original manuscripts to be cohesively integrated in this thesis.

STATEMENT OF ORIGINALITY

The project described in this thesis represents original research. Given the limited information on the epidemiology and public health significance of diagnostic and treatment delays in childhood cancer, useful information for cancer control can be derived from this study. For this study, I had a unique opportunity of working with a national surveillance program that I had a role in coordinating while employed in the Special Population Section at the Public Health Agency of Canada. This allowed me to examine a wide scope of issues concerning delays in the diagnosis of childhood cancer in a detailed study from a national perspective, thus having the weight of evidence that is required for evidence-based decisions.

The data used in this project were obtained from the Treatment and Outcomes component of the Canadian Childhood Cancer Surveillance and Control Program whose primary goal was to evaluate the continuum of cancer care and clinical outcomes. The population-based, longitudinal nature of this program and detailed identification of the pertinent dates for the milestones in the diagnostic and treatment trajectory of each childhood cancer provided a database well-suited for this project. It was while working on this program while employed by the Special Population Section of the Public Health Agency of Canada that I was inspired to pursue a deeper exploration of the present research topic. The specific objectives of this study and the analytical strategies were designed specifically by me for this project and were not part of the Canadian Childhood Cancer Surveillance and Control Program's plan of analysis.

As part of this project, I conducted and published the first comprehensive review of the literature summarizing current knowledge on diagnosis delay in childhood cancer. By measuring various time segments in cancer care, I extended the current findings in the

literature by isolating the main time segments responsible for lengthening the cancer care pathway taken by children and adolescents in Canada. I also advanced current knowledge by examining the influence of several parameters on various types of delays. Furthermore, I examined the relationships between patient and physician delays on disease severity and on prognosis using judicious control for potential confounding factors. To my knowledge, this was the first study to look at the possible mediating effect of disease severity at diagnosis on the relationship between delay and survival.

The information provided from this study may form the basis for effective policies and programs aimed at eliminating obstacles in the cancer care pathway for Canadian children and adolescents with cancer.

STATEMENT OF SUPPORT

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I would like to sincerely thank the granting agencies for the financial support I have received over the course of my doctoral studies. It has been a privilege to be a recipient of an Institute of Cancer Research Doctoral Research Award from the CIHR and a Graduate Fellowship Award from McGill University. I would also like to express my gratitude to the support given to me by the Cancer Research Society Division of Epidemiology at McGill University.

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As this study is brought to a close, I wish to offer a sincere expression of thanks to the countless people who have supported and encouraged me during the length of my doctoral thesis. Particularly, I would like to acknowledge the individuals without whom this project would have been impossible.

Firstly, I would like to express the deepest thanks and appreciation to my supervisor, Dr. Eduardo Franco. His infectious enthusiasm for scientific research, excitement for teaching and constant mentorship and support has been essential at every stage of this project. His influence on my life is immeasurable.

I would like to thank Dr. Robert Platt, Dr. Helen Trottier, Dr. Petr Kavan, Dr. Howard Morrison, Les Mery, Dr. Ronald Barr and Dr. Mark Greenberg for providing me with their expertise, guidance and valuable feedback on my thesis.

To my friends and colleagues whose paths I have crossed during my time at the division of Epidemiology in the Department of Oncology, I thank you for the lively conversations and all the laughter. This experience would not have been the same without you. I also wish to thank Candida Pizzolongo for all her administrative help and her tireless attention to detail.

I would like to take this opportunity to thanks and recognize the help and contributions of the Special Population Section at PHAC and past members of the CCCSCP-TOS

Working group to the planning, past and present members of the CCCSCP Management Committee for overseeing the study, and participating paediatric oncology centres and provincial agencies: Alberta Children's Hospital, Allan Blair Cancer Centre, British Columbia Children's Hospital, CancerCare Manitoba, Le Centre hospitalier de l'Université Laval, Le Centre Hospitalier Universitaire de Sherbrooke, Children's Hospital of Eastern Ontario, Children's Hospital of Western Ontario, Cross Cancer Institute, Hôpital Sainte-Justine, The Hospital for Sick Children, IWK Health Centre, Janeway Children's Health and Rehabilitation Centre, Kingston General Hospital, McMaster Children's Hospital, Montreal Children's Hospital, Paediatric Oncology Group of Ontario, Saskatoon Cancer Centre, Stollery Children's Hospital. I also would like to thank participants who generously gave their time to participate in this study.

And finally to my parents, my brother and Thuy, I wish to express my deepest appreciation for your help, your support and your love. You are my strength. You are my heart. You are my inspiration. You are my everything. To you, I dedicate this thesis with love.

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1. INTRODUCTION

Early diagnosis of cancer is a fundamental goal in oncology because it allows the opportunity for timely treatment, while disease severity is more likely to be in its earliest stages. In consequence, prognosis might be substantially improved and cure can hopefully be attained with minimal side or late effects. This widely held oncological tenet applies to most malignant neoplastic diseases. For cancer in adults, it is generally the patient's ability to recognize his or her symptoms and signs of disease that triggers the latter process. For cancer in children, early recognition requires the watchful eye of parents or guardians for signs that the child is experiencing something different than the usual benign diseases of childhood. Such recognition requires that adolescent patients or parents of affected children connect the perceived signs and symptoms with their knowledge base of what constitutes trivial or ominous indicators of conditions affecting health in general. It is conceivable that the completeness and correctness of this knowledge base are direct correlates of several socio-demographic characteristics, such as age, education, socio-economic status, place of residence, access to information, existing communication barriers, etc. The interplay of these variables will ultimately result in early or delayed action in seeking health care. Furthermore, the overall balance of these factors may also lead to the wrong choice in the port of entry into the health care system. Even if action is taken early enough delays in diagnosis may ensue if patients or parents of an affected child approach the wrong health care professional.

On the other hand, rapid and early cancer diagnosis is not solely a function of the actions taken by the patients or parents. A complex chain of events is triggered once a patient with cancer is seen by a health care professional. Much of the process that is

required to identify the underlying illness requires ruling out diseases with similar symptom patterns, the availability of appropriate diagnostic instrumentation and equipment, and very importantly, the application of a clinical knowledge base that leads to the correct diagnosis. This knowledge base can be that of a single physician (e.g., a family practitioner or a paediatrician) or of a team of clinicians of different specialties sharing their experience in analyzing individual cases. The combination of these various factors related to the health care provider and the factors related to the patient's disease will ultimately lead to a second component in the diagnostic delay; that which is attributable to the health care system.

2. OBJECTIVES OF STUDY

The overall objective of this study is to shed light on to the putative effects of delays on health outcomes among Canadian children and adolescents with cancer in order to obtain an understanding of the critical steps in the diagnostic process that could be amenable to intervention and thus lead to improved treatment results for children with cancer.

Specific study objectives are as follow:

1) To measure and characterize the delay of cancer symptom reporting, diagnosis and treatment in children between 0-19 years of age in Canada.

2) To identify the factors that influence the various delays in care for Canadian children and adolescents with leukemias, lymphomas and CNS tumours.

3) To investigate the impact of delays in the diagnosis of Canadian children and adolescents with leukemias, lymphomas and CNS tumours on disease severity.

4) To investigate the impact of delays in the diagnosis of Canadian children and adolescents with leukemias, lymphomas and CNS tumours on survival.

3. LITERATURE REVIEW

3.1. Epidemiology of Childhood Cancers

Although rare relative to adult cancers, cancer is the leading cause of disease-related death in children in developed countries, including Canada [CCS, 2008]. Between 1999 and 2003, an average of 1,289 children was diagnosed with cancer and 210 died from their disease each year in Canada [NCIC, 2007]. Leukemia is the most common childhood cancer. It accounts for 25% of new cases and 29% of deaths due to cancer in children. The second most common cancers are lymphomas which constitute approximately 17% of new cases and 8% of deaths. This group is followed by brain and spinal cancers, which account for 17% of new cases and 24% of deaths [NCIC, 2007].

Canada is among the countries reporting the highest rates of childhood cancers in the world [Breslow et al., 1983, Huchcroft et al., 1996, IARC, Parkin, 1998]. For the period 1982-1991, the annual age standardized incidence rate for children aged 0-14 in Canada was 14.9 per 100 000 (rates for boys and girls are 16.2 and 13.6 per 100 000, respectively) [IARC, Parkin, 1998]. These rates were higher than the reported equivalent ones in the US and most European countries. From 1999 to 2003, the age standardized incidence rate for children under 20 years of age in Canada was 16.4 per 100 000 per year [NCIC, 2007].

Overall cancer incidence rates for children and adolescents 0-19 years of age have increased from 1985 to 2007 [NCIC, 2007]. This coincides with reports of an increase in childhood cancer incidence rates in North America and Western European countries [NCIC, 2007; Ries et al., 2002; Linet et al., 1999; McNally et al., 2001]. There has been a debate as to whether this increase in incidence is real or artifactual. Reporting practices

and changes in diagnostic definitions have been mentioned as two possible sources of artifactual bias. In their study analyzing incidence data on childhood cancer, diagnosed during the period 1975-1995 from 9 registries in the United States Surveillance, Epidemiology, and End Results (SEER) program, Linet *et al* [1999] found an increase in brain/CNS cancers, leukemia, and neuroblastoma and concluded that the increases were probably due to diagnostic improvements or reporting changes. On the other hand, a similar study done in Northwest England using the Manchester Children's Tumour Registry also found an increase in childhood cancer incidence. However, since it is known that reporting practices have not changed over the study period and that diagnostic re-review of the retained biopsy specimens was done periodically, the increases in childhood cancer were deemed to be real [McNally et al., 2001].

It is reassuring that the increases in incidence of childhood cancers have been more than compensated by concomitant decreases in mortality rates. This has been observed both in Canada [NCIC, 2007] and in the US [Ries et al., 2002], and may be a combined reflection of a continuing trend for early diagnosis and improvements in therapy. In fact, the survival experience of children with cancer has dramatically improved over the last 30 years. Today, three-quarters of childhood cancer patients who survive 5 years after diagnosis are considered cured, whereas the equivalent survival rate in the mid-70's was only 50%.

Cancer remains an important public health concern due to its great physical and psychological impact on the young patients and their families. Many possible risk factors for the development of cancer in children and adolescents have been investigated [Ahlbom et al., 2001; Okcu et al., 2002; Dockerty et al., 2001; Thompson et al., 2001;

Schuz et al., 2001; Stiller, 2002; Sharpe et al., 1995; Sharpe et al., 1999; Stewart et al., 1956]. However, the causes of childhood cancer still remain mostly unknown. A small number of cases can be attributed to genetic conditions, e.g. Down syndrome [Li et al., 1988; Miller et al., 1966; Mulvihill et al., 1977]. Exposure to ionizing radiation is known to increase the risk of cancer [Knox et al., 1988; Boice et al., 1982; NRC, 1980l NRC, 1990; MacMahon et al., 1962; Steward et al., 1956; Savitz et al., 1990]. Hereditary causes have been identified in retinoblastoma [Knudson et al., 1971; Li et al., 1996]. Causes of childhood cancer have been difficult to identify because of the rarity of childhood cancer and the difficulty in identifying past exposure levels in children, particularly during potentially important periods such as pregnancy. Currently, timely treatment has been the most important and successful method of childhood cancer control available. It is also known that early detection of tumours can decrease mortality rates by increasing the likelihood of a timely diagnosis and initiation of treatment [De Camargo et al., 1987].

3.2. Delays in Diagnosis and Treatment in Cancer

The continuum of care for cancer patients begins with the detection of cancer symptoms by the patient or his/her relatives or caretakers, and ends with the patient's remission or death. Along this continuum, delays may occur that can negatively interfere with cancer care. As described above, two broad types of delays can occur: 1) patient delays and 2) health provider delays. Patient delay is defined as the length of time between the onset of signs and symptoms and the patient's first visit to the health care system, whereas the length of delay between the first health care visit and the diagnosis and, eventually, treatment of cancer is called health provider delay.

According to Andersen's model of total patient delay [Andersen et al., 1995; de Nooijer, 2001], the interval between the time a person first becomes aware of an unexplained symptom and the time he or she seeks medical attention can be broken down into 4 stages where delays on the part of the individual may occur. The first two stages are divided into the period between patients' detection of symptoms and their inference of an illness, and the period from illness inference to the decision of seeking medical care (called *appraisal delay* and *illness delay,* respectively). The next step, called *behavioural delay*, is the time between this decision and the act of making an appointment. *Scheduling delay* is the last stage and refers to the time between the making of an appointment and the first medical consultation. Patient delay is difficult to measure since the onset of symptoms may not be clearly identifiable. Moreover, some patients may not admit that they have delayed seeking treatment.

Provider delays can be sub-divided into three different periods [Carvalho et al., 2002]. The time between first health professional visit to the time of referral to a paediatric oncologist is called *referral delay.* This may be followed by *diagnosis delay* which occurs between first consultation with an oncologist and a definitive diagnosis. Lastly, *treatment delay* is the time from diagnosis to cancer treatment. Delays by the patient and the various segments of provider delay should be examined separately, since different corrective actions are required for each.

3.3. Impact of Delays

Previous research has been done on the impact of diagnosis and treatment delays on cancer survival in adults [Facione, 1993; Richards et al., 1999; Koivunen et al., 2001; Allison et al., 1998a; Wurtz et al., 1999; Kowalski et al., 2001; Sainsbury et al., 1999;

Carvalho et al., 2002; Aragoneses et al., 2002; Wallace et al., 2002; Sharp et al., 2002]. Due to the temporal progression of tumour growth, it is generally believed that cancer mortality can be reduced if symptoms are detected, diagnosed and treated at an early cancer stage. However, the relationship between delay of cancer diagnosis and prognosis remains unclear. Most reports support the concept that delays in diagnosis adversely affects prognosis [Richards et al., 1999; Koivunen et al., 2001; Allison et al., 1998a; Kowalski et al., 2001; Carvalho et al., 2002]. A systematic review on the effects of delays on 5-year survival of breast cancer have found that delays of 3-6 months between symptom onset and treatment are associated with lower survival rates for patients [Richards et al., 1999]. In this review, 13 studies investigating the relation between delay and tumour characteristics found that the impact of delay on survival is mediated through the relation between delay and cancer stage. Studies on head and neck cancers have noted that the absence of early symptoms may postpone the decision to seek medical help and thus usually present at advanced stages [Koivunen et al., 2001]. Failure to achieve diagnosis at an early stage is a reason for the poor prognosis of pharyngeal cancer [Vokes et al., 1993; Koivunen et al., 2001]. Studies have found that pharyngeal cancer patients that experienced increased provider delays tended to be more frequently diagnosed with late stage disease [Koivunen et al., 2001; Kowalski et al., 2001; Carvalho et al., 2002]. Koivunen *et al* [2001] found that patient delay of 2 months or more had a 2.5-fold risk for disease-related death. However, no association between the stage of disease and patient delay was found, nor was provider delay associated with a poorer prognosis. This may indicate that the effect of long patient delay on survival is mediated through another mechanism. These results contrast with similar studies of upper aerodigestive tract

cancers, which found that provider delays over 1 month doubled the risk of having late stage disease and consequently, of having poorer prognosis [Allison et al, 1998a; Kowalski et al., 2001, Carvalho, 2001].

Paradoxically, there has also been evidence that shorter patient and provider delays were statistically correlated with adverse survival outcome. Contrary to the findings made by Richards *et al* on delays and breast cancer survival, Sainsbury and colleagues actually found that delays of 3 months or more were not correlated with decreased survival, but rather they seemed to increase it [Sainsbury et al., 1999]. Similarly, the relationship between the delay in head-and-neck cancer diagnosis and prognosis remains unclear. Studies on oral cancer have found that longer diagnostic delays are associated with improved survival [Allison et al., 1998a]. It can be inferred that more aggressive, fast-growing tumours may show rapid progression of symptoms. This would lead patients to present themselves promptly to a medical professional and have their cancer diagnosed and treated quickly. Alternatively, less aggressive, slow growing tumours may lead to longer delays due to the incipient nature of the symptoms and signs of the disease, which may not be promptly recognized by patients. Short delays would thus be associated with the poor prognosis intrinsic to aggressive tumours.

It has been suggested that professional delays are associated with advanced clinical stage, whereas patient delays are not [Allison et al., 1998a; Carvalho et al., 2002]. The null association seen between patient delays and clinical stage may be due to the subjective nature of patient delay measurements, which may lead to a bias towards the null consequent to measurement error. Patients may potentially under-report the delay to a physician to avoid criticism. Under-reporting patients would then be classified in the

non-delay group. This would decrease the chances of finding statistically significant differences in outcome. Caution is needed when comparing the contradictory conclusions of various studies, because the effects of diagnostic delay on survival may vary by anatomical site [Koivunen et al., 2001]. One must also be aware of the data sources for delays. Different biases may occur according to whether data were collected from hospitals, referral letters, or patient interviews. Thus, it may be inappropriate to compare such studies. As well, the differences in tumour growth rate may confound the study findings. In fact, some studies have found no association between delays and prognosis when controlling for cancer stage [Aragoneses et al., 2002], but this finding may merely indicate that the effect of delays on prognosis is mediated via the prognostic effect of disease severity, i.e., delays in diagnosis would not have an effect on prognosis that would extend "downstream" from that of clinical stage (disease severity).

3.4. Factors related to Delays

Development of effective new strategies to shorten delays before presentation of cancer requires an understanding of the determinants of diagnostic delay. Epidemiological research on various cancer sites has consistently shown that age is an important determinant of patient delay [Ramirez et al., 1999; Montella et al., 2001; Allison et al., 1998b]. The evidence suggests that patient delay is significantly greater among older patients [Ramirez et al., 1999]. Conversely, younger age is a risk factor for delay by providers [Ramirez et al., 1999; Montella et al., 2001], which suggests that physicians may be less prone to consider cancer as a likely underlying condition in young patients as compared to old patients. These findings underscore the importance of separately assessing delays by patients and by providers. Patient ethnicity and education

are also associated with delays. In a study in Brazil that spanned nearly 30 years, it was found that black patients with oral cavity cancers tended to have considerably more advanced disease at presentation as compared with white patients, a finding that was attributable to longer patient delays in recognizing oral lesions as important. Interestingly, when the differences in stage distribution and treatment were taken into account in a multivariate analysis of survival, the prognostic disadvantage of black patients disappeared [Franco et al., 1993]. Delays associated with gender, ethnicity, and education may reflect differences in health beliefs [Nelson et al., 2002]. Statistically significant associations between the type of health care professional involved in the first medical visit and provider delay have also been found [Montella et al., 2001]. An increase in diagnostic delay has also been documented for cases that were seen by more than one health care professional [Kowalski et al., 1994]. As well, tumour site, co-morbidities and presentation of symptoms were found to be associated with delays [Ramirez et al., 1999; Allison et al., 1998b]. Lack of clearly definable signs of symptoms have also been found to lead to both patient and provider delays, e.g., absence of lumps in breast cancer [Ramirez et al., 1999] or lack of pain in oral cancer [Kowalski et al., 1994; Carvalho et al., 2002].

3.5. Delays in Childhood Cancer

3.5.1. Introduction

Timely diagnosis immediately followed by effective treatment is an essential approach for control of the public health burden due to childhood cancers. Appropriate early diagnosis and treatment require primary care physicians and parents to be aware of early symptoms of childhood malignancies. Public and professional education can be effective in eliminating disparities in cancer survival [Camargo et al., 1987]. Despite these suggestions, the study of diagnosis delays in children's malignancies has not received as much attention as cancers in adults.

Research on this topic is complicated by methodological difficulties as well as problems inherent to the biological properties and clinical behaviour of childhood cancers. Childhood cancers tend to have short latency periods and often grow rapidly. Tumours in children are very invasive, but are more responsive to treatment than adult tumours. Factors related to perception of the severity of signs and symptoms are also different. Children are usually under the care of their parents, which underscores the importance of parents' knowledge, attitudes, and behaviour in the cancer diagnosis pathway. Conversely, rapid and early cancer diagnosis is not solely a function of the actions taken by the patients or parents. A complex chain of events is triggered once a patient with cancer is seen by a health care professional. The combination of various factors related to the health care provider and the complexity of the patient's disease may also lead to a delay attributable to the health care system.

Few studies have been published on determinants and impacts of diagnosis delays in childhood cancer. Development of effective new strategies to shorten delays in

childhood cancer diagnosis requires an understanding of these delays and their effect on cancer prognosis. To our knowledge, no review has assessed research on this topic. We present, herein, a review of current knowledge on diagnosis delay in childhood cancer and discuss the methodological issues and the challenges faced in this area of research.

3.5.2. Materials and Methods

For this review, we identified epidemiological studies on diagnosis delays in childhood cancer listed in Medline and Pubmed before April 15, 2007. Specifically, we performed a literature search by using the index terms *children, cancer, diagnosis, delay, prognosis, risk factor, epidemiology, cohort, case-control* and alternate synonyms, in various combinations. The reference lists of articles were also examined for any additional publications that were not identified by the bibliographic search. Twenty-three published studies, written in English, were identified and relevant data were abstracted for this review. These studies calculated delays from data extracted retrospectively from patient medical charts, tumour registries and, in some studies, interviews with parents. Delay times were converted to weeks for this review. Table 3.1 summarizes the main characteristics of these 23 investigations.

Figure 3.1 shows the cancer care pathway milestones that we used to define diagnosis delay and its components. Along this continuum, events may occur that can negatively interfere with cancer care. Studies included in this review have focused on the time between a patient's first symptom recognition to a diagnosis of cancer. This time period, called diagnosis delay in figure 3.1, has also been designated as pre-diagnosis symptomatic interval [Dobrovoljac et al.,2002], symptom duration/interval [Wallach et al., 2006; Goyal et al., 2004; Gjerris et al., 1976; Halperin et al., 1996; Halperin et al.,

2001], time to diagnosis [Fajardo-Gutierrez et al., 2002; Mehta et al., 2002] lag time [Pollock et al., 1991; Rodriguez et al., 2004; Haimi et al., 2004; Saha et al., 1993; Thulesius et al., 2000] or wait time [Klein-Geltink et al., 2005] by different authors. Some studies made a distinction between patient and physician delays. The former was defined as the length of time between the onset of signs and symptoms and the patient's first visit to health care system, whereas the length of delay between the first health care visit and the diagnosis was designated physician delay.

3.5.3. Results

3.5.3.1. Diagnosis delays in Childhood Cancer

Table 3.2 shows the total mean or median diagnosis delay reported in all the studies. Mean delay times varied by cancer type from a low of 2.5 weeks (nephroblastoma) to a high of 29.3 weeks (brain tumour). Haimi et al. [2004] reported a mean diagnosis delay of 15.8 weeks with a range of 0 to 208 weeks for all cancers in Israel. In the case of brain tumours, a Swedish study, by Thulesius et al. [2000], found a median delay of 9 weeks with a range of 1 to 199 weeks, whereas in a study in Eastern Canada, Mehta et al. [2002] found a mean delay of more than 7 months with a 95% confidence interval of 5 to 10 months.

Ten studies separated the total average diagnosis delay into its components, as described above (Table 3.3). Generally, the tendency was for physician delays to be longer than patient delay. Variations were observed in patient delay (range 2 – 12.8 weeks) and physician delay (range 2-15 weeks) for studies that investigated retinoblastoma.

3.5.3.2. Patient factors associated with diagnosis delay

Eleven studies investigated the relation between patient and parental factors and diagnosis delays (Table 3.4). A positive association between the patient's age at diagnosis and diagnosis delay was observed in 7 of 11 studies. Most studies supported the hypothesis that older patients are at higher risk of delayed diagnosis than younger patients. In Mexico, Fajardo-Gutierrez et al. [2002] found that risk of increased diagnosis delay for children between the ages of 10 years and 14 years is 1.8 times that of infants younger than 1 year of age (odds ratio [OR] for 10-14 years of age: 1.8 [95% confidence interval {CI}, 1.4-2.3]). It was also reported that diagnosis delay was shortest for children aged 0-2 years despite no significant differences in histopathology, grade or location of tumours, or parental persistence (number of consultations before diagnosis) across age groups [Chantada et al., 1999]. Dobrovoljac et al. [2002] analyzed patient and physician delays separately and found a positive correlation between age and patient delay, but not physician delay. The negative correlation with age observed by Klein-Geltink et al. [2005] contrasts with the above findings.

Statistically significant difference in diagnosis delay between male and female patients was observed in only 2 of 9 studies. Fajardo-Gutierrez et al. [2002] reported a slight increase in risk of diagnosis delay in male patients (OR=1.1 95% CI: 1-1.3). In an analysis of sex and delay across diagnostic groups, Pollock et al. [1991] found that female patients had significantly longer diagnosis delay only for non-Hodgkin lymphoma. This association remained even after adjusting for age and date of diagnosis. In multivariate regression analyses, they also found that male patients with Ewing sarcoma had a significantly longer delay in diagnosis than female patients with the same disease.

Of the 4 studies that examined the effect of ethnicity on diagnosis delay, 2 studies did not find any significant difference in delay time among patients of different ethnicities [Rodriguez et al., 2004; Halperin et al., 2001]. Pollock et al. [1991] reported a significant association between ethnicity and diagnosis delay only for osteosarcoma, for which white children had longer delay times. Similarly, a study on all cancers examined the differences in lag time of children of different racial origins (based on the father) and found that Arabic children had shorter lag time than Jewish children [Haimi et al., 2004].

Because children are usually under the care of their parents, parental characteristics and behaviour are also important factors in recognizing symptoms and signs of cancer. In Argentina, retinoblastoma patients whose parents had elementary education or lower had a greater risk of longer patient delay (OR=6.34) [Chantada et al., 1999]. This was also observed in Mexico, where children whose parents had the lowest level of education had longer delays in diagnosis than children with parents with highest level of education (OR=1.4 for fathers and 1.5 for mothers) [Fajardo-Gutierrez et al., 2002]. Haimi et al. [2004] looked at various parental factors and found that the parents' age, mothers' profession, fathers' ethnicity and religion were all significantly associated with diagnosis delay. In the case of parental age, children of younger parents had significantly shorter delay times than children of older parents. Although no relationship between father's profession and delay was found, diagnosis delays were shorter for housewives or mothers with academic professions than for mothers with a 'blue collar" profession. However, when parent-related and child-related factors were included in a multivariate analysis, religion and fathers' ethnicity were the only parental factors to remain significantly associated with increased diagnosis delay.

3.5.3.3. Cancer related factors associated with delays

The timely diagnosis of cancer in children is made difficult because of the rarity of the disease and the non-specific presentation of the symptoms. All studies found that cancer type was an important factor related to diagnosis delay (Table 3.5). Statistically significant differences were observed in the risk of a delayed time to diagnosis when different groups of cancers were compared with leukemia. Fajardo-Gutierrez et al. [2002] reported that renal tumours had a 60% increase in risk compared with leukemia, whereas the risk of delay in diagnosis for Hodgkin disease was 7 times that of leukemia. The effect of cancer type on delay remained even after accounting for effects of other covariates, such as age, sex and race. Likewise, Flores et al. [1986] found that patients with brain tumours had significantly longer lag time than patients with either Wilms' tumour or acute leukemia.

Studies have observed that the initial presentation of symptoms is related to diagnosis delay [Dobrovoljac et al., 2002; Haimi et al., 2004; Thulesius et al., 2000]. The rarity and non-specific clinical presentation of symptoms influenced parent delay in seeking medical advice and physician delay in reaching diagnosis [Haimi et al., 2004; Thulesius et al., 2000]. The effect of symptoms on parental delay was inconsistent. A study on all cancers found significantly shorter parent delay when the presenting symptoms were rare compared to common symptoms [Haimi et al., 2004]. However, a study on brain tumours noted that the presentation of symptoms affected provider delay, but not parental delay [Dobrovoljac et al., 2002].

Four out of 5 studies found that the anatomic site of the cancer influences delay in diagnosis. Children with rhabdomyosarcoma located in the pharynx and orbit had a

shorter lag time than children who had it in the face or neck [Pratt et al., 1978]. Flores reported that children with infratentorial brain tumours have shorter lag time than children with supratentorial tumours [Flores et al., 1986]. Similarly, when differentiating cases into brainstem and non-brainstem tumours, Mehta et al. [2002] found a significant difference in lag time for children diagnosed with brain tumours. Only the study by Haimi et al. [2004] did not find a correlation between delay and tumour location. There is also evidence that tumour histology was correlated with delay. One study reported that aggressive fast growing tumours had shorter delays than slowly growing tumours [Dobrovoljac et al., 2002]. However, Mehta et al. [2002] only found an association between histological type and diagnosis delay by comparing medullablastoma versus non-medulloblastoma tumours.

Disease stage at diagnosis is an important factor to consider because it is a possible indicator of chronology of disease progression and a determinant of the constellation of signs and symptoms. Halperin and Friedman [1996] found that medulloblastoma patients with advanced stage exhibited shorter lag times compared with early stage disease. This may suggest that patients with shorter diagnosis delays might ultimately have worst prognoses. However, in a study of 64 children with a solid tumour, the difference in lag time between cancer stages was not significant [Saha et al., 1993]. The effect of white blood cell count on delay was also assessed on 65 children with leukemia and was, again, found not to be significant (OR=1.1; 95% CI 0.6-1.4).

3.5.3.4. Healthcare related factors associated with diagnosis delays

Table 3.6 shows the influence of parameters related to the health care system. Three studies found that timely intervention by the appropriate specialist may reduce

delays. Diagnosis and physician delay was shorter for patients that visited the paediatrician than for patients whose first health contact was a family physician or other specialist [Haimi et al., 2004]. Conversely, the risk of patient delay was lower for patients who first contacted the general practitioner (GP) and the risk of physician delay was lower for patients who first contacted the emergency room (ER) than patients whose first contact was the paediatrician [Klein-Geltink et al., 2005].

The relationship between diagnosis delays and access to health care services showed mixed results. Two studies found that geographical distance was positively associated with diagnosis delays [Fajardo-Gutierrez et al., 2002; Haimi et al., 2004]. Fajardo-Guitierrez et al. [2002] defined distance as "near or far from Mexico City" and found a 1.5 greater risk of delay for people who live farthest from Mexico. However, in a more detailed measure of distance, after adjusting for demographic and disease characteristics, Klein-Geltink et al. [2005] did not find that distance to treating paediatric oncology centre affected diagnosis delay in Canada.

3.5.4. Discussion

Early diagnosis of cancer is a fundamental goal in oncology because it allows an opportunity for timely treatment, while disease severity is still in its earliest stages. Consequently, prognosis may improve and a cure can be attained with minimal side effects or late effects. Previous studies have shown that distributions of diagnosis delay were generally wide and skewed towards low values. Other than brain tumours and retinoblastoma, there was little difference in diagnosis delays between studies across each cancer type. However, given the small number of studies available for the various cancer categories, no conclusion can be made about this observed consistency of delay across

studies or countries. Differences in health care systems may account for the variation in delay observed in brain tumours and retinoblastoma. For example, the long delay observed by Mehta et al [2002], suggests that a single-payer health care system, such as that in Canada, might have an over-reliance on family physicians for triaging health complaints, relative to the situation in the US, where insured patients may access specialists directly. This may conceivably introduce an additional provider layer between the initial patient visit and the final cancer diagnosis, a scenario that could potentially create longer diagnosis delays. A related concern has been expressed for England [Feltbower et al., 2004], a country in which GPs provide the first opportunity for diagnosis.

Most studies in this review have been retrospective cohort studies and are therefore, subject to certain limitations inherent in the design. The use of pre-existing records makes it difficult to ascertain the reliability of the information collected and to obtain information on potential confounding variables. Possible biases may occur if the disease status affected the selection of patients into the study or the collection of exposure information. Parents and patients might have recalled certain events differently if the child was diagnosed with a more severe tumour. However, any diagnosis of cancer would be cause for great worry to all parents and so there would be little reason to believe that the severity of the disease would lead to differential collection of information. It is also doubtful that patients or physicians would know about any study hypothesis on diagnosis delays when data were collected. Therefore, if present then these biases were likely non-differential.

Misinterpretation of ambiguous cancer symptoms by the patients, parents, and

physicians may lead to diagnosis delay. The relationship between symptoms and diagnosis delay is confounded by the association symptoms have with other factors. Symptom patterns vary by diagnostic groups and this may partly account for the differences observed in diagnosis delay among cancer groups (e.g., brain tumours have a slower tumour growth rate than other cancers and therefore would have a slower symptom progression). The effect of symptoms on diagnosis delay may also be mediated by the age of the patient. Younger children may experience cancers with more identifiable signs at onset (such as an abdominal mass in Wilms' tumour) than older children. However, a positive association between age and delay was still present even after studies controlled for the type of cancer [Pollock et al., 1991; Saha et al., 1993; Edgeworth et al., 1996]. This would suggest that the effect of age on delay may be due to more than differences in tumour-specific characteristics. It is possible that the tendency for providers to screen for tumours in children may be different across age groups. Older children may be more self-reliant concerning their health status than younger children; younger patients might have a closer relationship to their parents than older patients. The influence of increased parent knowledge and awareness of the child's disease on timely diagnosis is supported by the finding of a negative association between parental education and diagnosis delay [Fajardo-Gutierrez et al., 2002]. However, this relationship may also be mediated by socio-economic status or access to healthcare.

Once patients enter the health care system, diagnosis delay may be influenced by access to medical care services, knowledge and recognition of the disease by health providers and availability of appropriate diagnostic capability and instrumentation. It is difficult to interpret physicians' ability to diagnose cancer. It has been suggested that

increased vigilance and awareness of cancer on the part of the general practitioner may decrease delay times [Dobrovoljac et al., 2002; Haimi et al., 2004]. However, the severity of the disease and symptoms on presentation at the physicians' office likely influences this relation. Paediatric oncologists and ER physicians will probably see urgent cases in which symptoms are more apparent. Moreover, the added time required for evaluation by the general practitioner, followed by further visits to the paediatric oncologists before making a cancer diagnosis will add another time segment and, thus, may increase diagnosis delay.

The relation between diagnosis delays and disease stage is complex. Although staging of cancer in children is different from that of adults, it is still a general classification of the extent of the disease at presentation, much of which reflects the chronology of disease progression. Because disease stage is determined at diagnosis, studies have only been able to examine this relationship cross-sectionally. A key question remains: Do delays in diagnosis worsen the extent of the disease or does the extent of the disease influence diagnosis delays? Common sense would indicate that longer delays would lead patients to be diagnosed at a more advanced disease stage. However, it can also be concluded that more aggressive, fast-growing tumours may show rapid progression of symptoms even at early stages, which would lead parents to seek medical attention for their child. Alternatively, less aggressive, slow growing tumours may lead to longer delays due to the incipient nature of the disease symptoms, which parents may not notice as quickly. Therefore, the aggressiveness of disease with the attendant severity of the symptoms likely plays a role in the relationship between diagnosis delay and cancer stage. The actual period of disease development is a concern in studies on cancer

prognosis. For example, a child might be developing a tumour for some time before seeking a diagnosis. A more advanced disease would lead to a rapid diagnosis, but this short diagnosis delay may not lead to a better cancer prognosis.

The impact of diagnosis delays on the prognosis of children with cancer is still unknown. It has generally been believed that long delays would lead to worse prognosis. In the context of childhood cancer, however, few studies have been specifically designed to investigate this assumption, or they have not conducted thorough analyses. Seven studies explored this relationship and found conflicting results. Four studies reported negative associations between delays and survival [Pratt CB et al., 1978; DerKinderren et al., 1989; Rodriguez et al., 2004; Haimi et al., 2004], whereas the remaining studies did not [Butros et al., 2002; Goyal et al., 2004; Saha et al., 1993]. DerKinderen et al. [1989] found that retinoblastoma patients with a physician delay ≥1 week had a significantly higher death rate (OR=5.1) than patients with a shorter delay. Rodrigues et al. [2004] also found that retinoblastoma patients with a delay of <6 months had a statistically significantly higher 5-year survival rate than patients with longer delay. Conversely, Goyal et al. [2004] did not find any significant differences in event-free survival between patients with <3 months, 3 months to 6 months, and > 6 months diagnosis delay. Similarly, Saha et al. [1993] did not find that delay times were predictive of event-free survival even after adjusting for possible confounding variable. None of the studies examined the possible mediating effect of disease severity at diagnosis on the relation between delay and survival. Research on adult cancers supports the hypothesis that delays in diagnosis adversely affects prognosis [Richards et al., 1999; Koivunen et al., 2001; Kowalski et al., 2001]. Conversely, some studies found that longer delays were

associated with increased survival [Sainsbury et al., 1999; Allison et al., 1998a]. It has been reported that the impact of delay on survival is likely mediated through the relation between delay and cancer stage [Richards et al., 1999]. It can be concluded that more aggressive, fast-growing tumours may show rapid progression of symptoms. This would lead patients to present themselves promptly to a medical professional and have their cancer diagnosed and treated quickly. Alternatively, less aggressive, slow growing tumours may lead to longer delays due to the early nature of the disease symptoms. Short delays would thus be associated with the poor prognosis intrinsic to aggressive tumours.

Research on diagnosis delays in childhood cancer is still in its early stages. More studies are needed to investigate the potential impact of delays on prognosis outcomes. Information on factors that influence delays independently of each other and the individual impact of patient and provider delays on disease severity and prognosis would be useful to form effective policies and programs aimed at eliminating obstacles in the cancer care pathway for children with cancer.

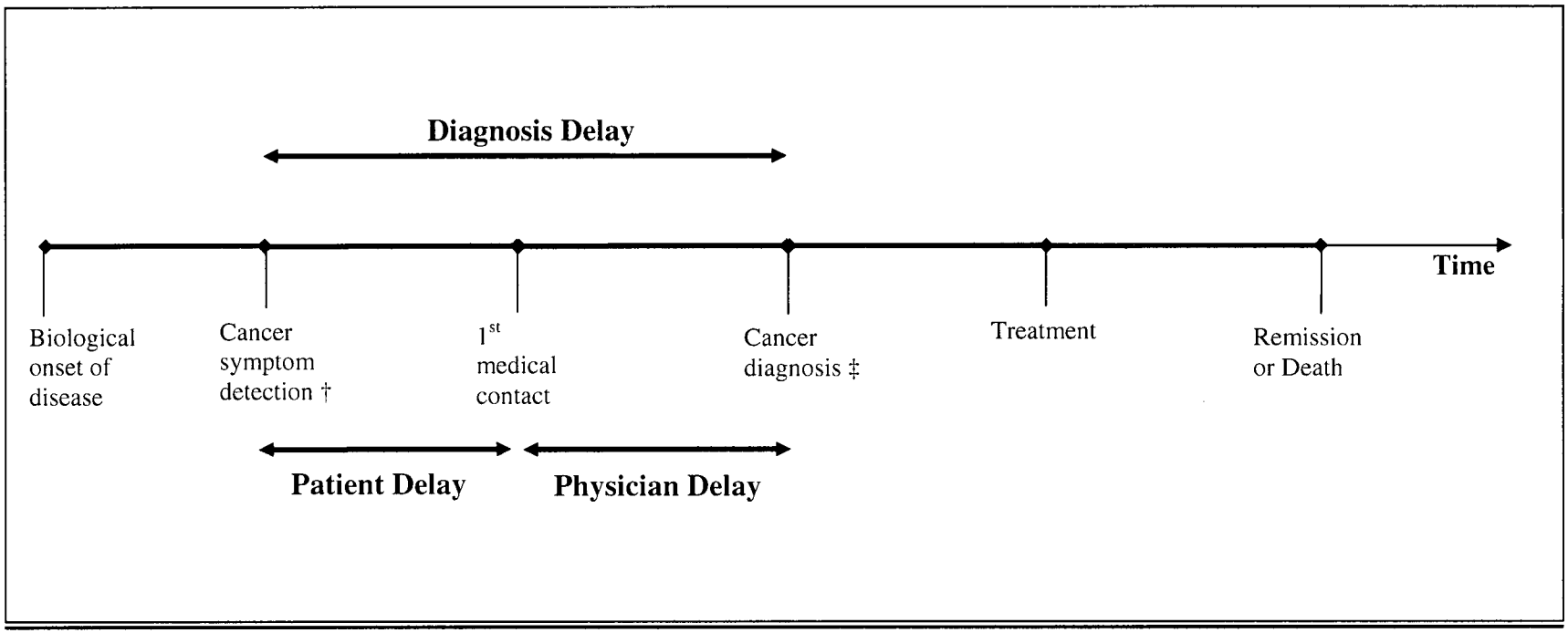


Figure 3.1: Diagnosis delay in the cancer care pathway

†: Cancer symptom detection defined by date of 1st reported symptom that lead to a diagnosis of cancer, symptoms reported by parents.

‡: Cancer diagnosis defined by date of imaging technique, biopsy or surgery that obtained diagnostic material.

Table 3.1: Characteristics of studies investigating delays in diagnosis of childhood tumours

Study (first author)	Year	Country	Patient Population	Sample size	Age (years)	Study type	Cancer type	Data source
Gjerris	1976	Denmark	Hospital-based	299	0-14	retrospective cohort	Brain tumour	Medical chart
Pratt	1978	USA	Hospital-based	46	4 months-20	descriptive	Head and neck rhabdomyosarcoma	Medical charts
Haik	1985	USA	Hospital-based	254	1 month-3.5	descriptive	Retinoblastoma	Medical charts
Flores	1986	USA	Hospital-based	79	0-19	retrospective cohort	Brain tumours vs Wilms' and acute leukemia	Medical charts
DerKinderen*	1989	Netherlands	Population	130	0-20	retrospective cohort	Retinoblastoma	Medical charts / Parent interview
Pollock	1991	USA	POG Protocol	2665	0-29	cross-sectional	Lymphoma and solid tumours	POG Protocol Database
Saha	1993	England	Hospital-based	236	0-15	retrospective cohort	All cancers	Medical charts
Edgeworth	1995	England	Hospital-based	74	0-16	descriptive	Brain Tumour	Medical charts / Parent interview
Halperin*	1996	USA	Hospital-based	72	0-20	cross-sectional	Medulloblastoma	Medical charts
Goddard	1999	England	Hospital-based	100	0-8	retrospective cohort	Retinoblastoma	Parent interview
Chantada	1999	Argentina	Population	95	0-9	prospective cohort	Retinoblastoma	Medical charts / Parent interview
Thulesius	2000	Sweden	Population	68	0-16	descriptive	All cancers	Medical charts
Wirix	2000	Belgium	Hospital-based	33	0-7	descriptive	Retinoblastoma	Medical charts
Halperin	2001	USA	Hospital-based	122	0-20	retrospective cohort	Medulloblastoma	Medical charts
Butros	2002	USA	Hospital-based	57	1.5 months-9.69	retrospective cohort	Retinoblastoma	Medical charts
Mehta	2002	Canada	Population	104	0-17	retrospective cohort	Brain tumours	Brain tumour database
Dobrovoljac	2002	Switzerland	Hospital-based	252	0-17	retrospective cohort	Brain Tumour	Medical charts

Study (first author)	Year	Country	Patient Population	Sample size	Age (years)	Study type	Cancer type	Data source
Fajardo-Gutierrez	2002	Mexico	Hospital-based	4940	0-14	retrospective cohort	All cancers	Medical charts
Haimi	2004	Israel	Hospital-based	315	0-20	retrospective cohort	All cancers (excluding Leukemia)	Medical charts / Questionnaire
Goyal	2004	England	Hospital-based	103	4-22	retrospective cohort	Bone Cancer	Medical charts
Rodrigues	2004	Brazil	Hospital-based	327	2 months-12	retrospective cohort	Retinoblastoma	Medical charts
Klein-geltink	2005	Canada	Population	2316	0-14	prospective cohort	All cancers	CCCSCP database
Wallach*	2006	Switzerland	Population	139	0-20	retrospective cohort	Retinoblastoma	Medical charts

* Age not specified

POG=Paediatric Oncology Group; CCCSCP=Canadian Childhood Cancer Surveillance and Control Program

Table 3.2: Diagnosis delay (in weeks) for childhood cancers as measured in published studies

Cancer type	Mehta‡ (Canada)	Pollock *‡ (USA)	Halperin (USA)	Pratt *‡ (USA)	Flores (USA)	Butros *‡ (USA)	Saha * (England)	Edgeworth (England)	Goyal *‡ (England)	Goddard* (England)
All cancers	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Acute leukemia	NA	NA	NA	NA	4.5	NA	5.4	NA	NA	NA
Brain tumour	29.3	9.4	14.3	NA	26	NA	13	20	NA	NA
Bone tumour	NA	11.5-20.8	NA	NA	NA	NA	8.4	NA	15.2	NA
Lymphoma	NA	7.1-14	NA	NA	NA	NA	8.4	NA	NA	NA
Neuroblastoma	NA	5.4	NA	NA	NA	NA	5.3	NA	NA	NA
Renal tumour	NA	NA	NA	NA	2.8	NA	2.5	NA	NA	NA
Retinoblastoma	NA	NA	NA	NA	NA	6-9	NA	NA	NA	8
Head and neck Rhabdomyosarcoma	NA	NA	NA	8	NA	NA	NA	NA	NA	NA

NA = not applicable (disease category not included in study)

* = Median

**=result for 59 patients diagnosed between 1994-2004

‡ Delay times were converted to weeks

Table 3.2: (continued)

Cancer type	Dobrovoljac*‡ (Switzerland)	Wallach**‡ (Switzerland)	Gjerris *‡ (Denmark)	Thulesius * (Sweden)	Haimi (Israel)	Fajardo-Gutierrez *‡ (Mexico)	Rodrigues ‡ (Brazil)
All cancers	NA	NA	NA	NA	15.8	NA	NA
Acute leukemia	NA	NA	NA	3	NA	4	NA
Brain tumour	8.6	NA	24	9	21.4	NA	NA
Bone tumour	NA	NA	NA	NA	17.7	NA	NA
Lymphoma	NA	NA	NA	NA	10.1	20	NA
Neuroblastoma	NA	NA	NA	NA	16	NA	NA
Renal tumour	NA	NA	NA	NA	6.7	NA	NA
Retinoblastoma	NA	9	NA	NA	12.6	20	23.2
Head and neck Rhabdomyosarcoma	NA	NA	NA	NA	NA	NA	NA

NA = not applicable (disease category not included in study)

* = Median

**=result for 59 patients diagnosed between 1994-2004

‡ Delay times were converted to weeks

Table 3.3: Patient and physician delays (weeks) in childhood cancer measured in different studies

Cancer Diagnosis	Klein-Geltink*		Haimi		Dobrovoljac *		Edgeworth		Wirix	
	patient delay	physician delay †	patient delay	physician delay	patient delay	physician delay	patient delay	physician delay	patient delay	physician delay
All cancers	NA	NA	4.4	11.2	NA	NA	NA	NA	NA	NA
Acute leukemia	1	0.1	NA	NA	NA	NA	NA	NA	NA	NA
Brain tumour	2	1.1	NA	NA	3	16	2	4.3	NA	NA
Bone tumour	3.9	1.4	NA	NA	NA	NA	NA	NA	NA	NA
Lymphoma	1.4	1	NA	NA	NA	NA	NA	NA	NA	NA
Neuroblastoma	0.6	0.6	NA	NA	NA	NA	NA	NA	NA	NA
Renal tumour	0.4	0.3	NA	NA	NA	NA	NA	NA	NA	NA
Soft tissue tumour	1.7	1	NA	NA	NA	NA	NA	NA	NA	NA
Germ cell tumour	0.6	1	NA	NA	NA	NA	NA	NA	NA	NA
Retinoblastoma	NA	NA	NA	NA	NA	NA	NA	NA	12.8	NA

NA = not applicable (disease category not included in study)

* Median

**Results given for patients with a family history of retinoblastoma. Patients without a family history of retinoblastoma have a mean patient delay of 5 weeks and a physician delay of 9 weeks.

† Time from first healthcare contact to assessment by an oncologist

‡ Median time was 15 weeks for patients taken to a paediatrician and 15 weeks for patients taken to an ophthalmologist. .

Table 3.3: (continued)

Cancer Diagnosis	DerKinderen *		Haik **		Chantada *		Goddard *		Butros *	
	patient delay	physician delay	patient delay	physician delay †	patient delay‡	physician delay	patient delay	physician delay †	patient delay	physician delay †
All cancers	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Acute leukemia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brain tumour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bone tumour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lymphoma	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Neuroblastoma	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Renal tumour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Soft tissue tumour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Germ cell tumour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Retinoblastoma	4	10	2	5	15	NA	2.5	2	6	15

NA = not applicable (disease category not included in study)

* Median

**Results given for patients with a family history of retinoblastoma. Patients without a family history of retinoblastoma have a mean patient delay of 5 weeks and a physician delay of 9 weeks.

† Time from first healthcare contact to assessment by an oncologist

‡ Median time was 15 weeks for patients taken to a paediatrician and 15 weeks for patients taken to an ophthalmologist. .

Table 3.4: Parental or patient-related factors analyzed as possible correlates of delays in different studies

Patient factor	Study (first author)	Statistical Analysis	Summary of findings	Conclusion
Age	Mehta	Chi-square	p=0.8	No statistically significant difference
	Klein-geltink	Logistic regression	Multiple results	Negative correlation. Older patients have a reduced risk of patient and physician delay.
	Pollock	Pearson Correlation	P < 0.001	Positive correlation. Diagnosis delay is longer for older children.
	Halperin	Kruskal-Wallis test	p = 0.11	No statistically significant difference
	Saha	F-test	p < 0.001	Statistically significant difference. Diagnosis delay longer for older children.
	Dobrovoljac	Pearson Correlation	r=0.32, p<0.0001	Positive correlation. Diagnosis delay longer for older children.
	Haimi	ANOVA	p < 0.01	Positive correlation. Diagnosis delay longer for older children.
	Goyal	Mann-Whitney U-test	P = 0.05	Statistically significant difference. Diagnosis delay longer for older children. Patient delay longer only for Ewing's sarcoma patients.
	Goddard	Kruskal-Wallis test	result not shown	No statistically significant difference in patient delay. Statistically significant difference in physician delay. Physician delay inversely related to patient age.
	Fajardo-Gutierrez	Logistic regression	OR for age <1 vs 10-14=1.8 (95% CI 1.4-2.3)	Positive correlation. Older children had a higher risk of diagnosis delay.
	Rodrigues	Mann-Whitney U-test	P=0.001	Positive correlation. Diagnosis delay longer for children >24 months of age than children under 24 months.
Sex	Mehta	Chi-square	p=0.131	No statistically significant difference
	Pollock	Pooled t-test	p = 0.18	No statistically significant difference overall. Girls had longer delay than boys for non-Hodgkin lymphoma only; boys had longer delays than girls for Ewing sarcoma
	Halperin	Kruskal-Wallis test	p = 0.08	No statistically significant difference
	Saha	2 x 2 table	1.2 (0.9-1.6)	No association
	Dobrovoljac	Wilcoxon rank sum test	result not shown	No statistically significant difference

Patient factor	Study (first author)	Statistical Analysis	Summary of findings	Conclusion
	Haimi	t-test	result not shown	No statistically significant difference
	Rodrigues	Mann-Whitney U-test	P=0.949	No statistically significant difference
	Fajardo-Gutierrez	Logistic regression	OR=1.1 (95% CI 1-1.3)	Small increased risk of delays for boys
	Gjerris	Chi-square	result not shown	No statistically significant difference
Race	Pollock	Pooled t-test	p = 0.23	No statistically significant difference. White children had longer delay than non-white children for osteosarcoma only.
	Halperin	Kruskal-Wallis test	p = 0.89	No statistically significant difference
	Rodrigues	Mann-Whitney U-test	P=0.5333	No statistically significant difference
	Haimi	Wilcoxon rank sum test	p < 0.05	Children of Isreali, Ashkenazi or Arabic origin had shorter delays than children of Sephardic fathers.
Parental age	Haimi	F-test	p < 0.01	Children of younger parents had shorter delays than children of older parents.
Parental Education	Fajardo-Gutierrez	Logistic regression	OR (fathers) = 1.4 (95% CI 1.1-1.8); OR (mothers) = 1.5 (95% CI 1.2-2.1)	Higher risk of long delays for children of parents with 0 to 5 years of education had a higher risk of long delays than parents with over 12 years of education.
	Chantada	Logistic regression	OR=6.34 (95% CI 3.7-29.3)	Children whose parents had with elementary education or lower had a greater risk of longer patient delay.

Table 3.5: Disease-related factors analyzed as possible correlates of delays in different studies

Cancer factor	Study (first author)	Statistical Analysis	Results	Conclusion
Cancer Type	Klein-geltink	Logistic regression	Multiple results	Cancer type influenced the risk of diagnosis patient and physician delay. Compared to children diagnosed with leukemia, children with bone tumours had the highest risk of increased patient delay; while children with CNS tumours had the highest risk of increased physician delay.
	Pollock	ANOVA	$p = 0.0001$	Statistically significant difference in diagnosis delay among tumour types. Difference remained after adjustment for age, sex and race.
	Flores	Chi-Square, test not specified	$p < 0.0001$ at 4 weeks	Brain tumours had statistically significant delay compared to leukemia and Wilms' tumour.
	Saha	F-test	$p<0.001$	Statistically significant difference in diagnosis delay among cancer type when compared to leukemia.
	Thulesius	Chi-Square test	$p = 0.002$	Diagnosis delay, patient delay and physician delay was statistically significantly shorter for leukemia patients than for brain tumour patients.
	Haimi	F-test	Result not shown	Statistically significant difference. Shortest delay: Wilms' Tumour (Median=2.5 weeks); Longest delay: Epithelial Tumours (Median=13 weeks)
	Fajardo-Gutierrez	Logistic regression	Multiple results	Compared to leukemia, other cancer types have a higher risk of longer delay. (e.g. lowest OR Renal Tumour=1.6 (95% CI 1.2-2.1); Highest OR Hodgkin disease=7 (95% CI 5.3-9.3))
Symptoms	Pollock	t-test	Multiple results	Depending on cancer types, children with shorter lag times had statistically significantly more likely to present certain symptoms (e.g. For neuroblastoma, abdominal masses were more common in patients with shorter diagnosis delay).
	Dobrovoljac	Wilcoxon rank sum test	$p = 0.007$	Patients with symptoms of increased intracranial pressure had a shorter diagnosis delay and physician delay than other patients.
	Goddard	Kruskal-Wallis test	Result not shown	No statistically significant difference in patient delay. Statistically significant difference in physician delay.
	Haimi	Kruskal-Wallis test	Result not shown	Statistically significant longer overall delay and physician delay when presenting symptom is pain. Shorter parent delay when symptom is rare.
	Rodrigues	Mann-Whitney U-test	$P=0.014$	Patients with strabismus had a statistically significantly longer diagnosis delay than patients with other symptoms (Leukocoria or tumour).
Tumour histology	Mehta	chi-square	$p=0.006$	Statistically significant difference in diagnosis delay between medulloblastoma vs non-medulloblastoma.

Cancer factor	Study (first author)	Statistical Analysis	Results	Conclusion
	Dobrovoljac	Wilcoxon rank sum test	Result not shown	Negative correlation. Fast growing tumours have shorter delays than slow growing tumours.
Tumour location	Mehta	Chi-square	$p = 0.014$	Statistically significant difference in delay between tumours located in the brainstem vs. non-brainstem.
	Dobrovoljac	Kruskal-Wallis test	Result not shown	No statistically significant difference
	Haimi	Kruskal-Wallis test	$p < 0.01$	Statistically significant difference in delay according to site of primary tumour.
	Goyal	Linear regression	P=0.002	Physician delay was longer for patients with axial site tumours than limb tumours.
	Gjerris	Chi-square	$p < 0.01$	Statistically significant difference in delay between supratentorial and infratentorial tumours.
WBC count	Saha	2 x 2 table	OR = 1.1 (95% CI 0.6-1.4)	No association
Cancer Stage	Halperin	t-test	$p = 0.01$	Patients with early cancer stage had statistically significantly longer diagnosis delays than patients with advanced cancer stage.
	Saha	F-test	$p = 0.23$	No statistically significant difference
	Chantada	Logistic regression	Result not shown	Patients with disease stage II, III and IV had a statistically significantly longer patient delay than patients with disease stage I.
	Gjerris	Chi-square	$p < 0.05$	Patients with a grade 1 malignancy had statistically significantly longer delay than patients with grade 4 malignancy.
	Wallach	Logistic regression	OR=8.09 (95% CI 1.86-35.23)	Patients with >6 months diagnosis delay had a higher risk of being diagnosed with a higher stage.
	Rodrigues	Mann-Whitney U-test	P<0.001	Patients with localized disease had a statistically significantly shorter diagnosis delay than patients with advanced or metastatic disease.

Table 3.6: Healthcare system-related factors analyzed as possible correlates of delays in different studies

Health care factor	Study (first author)	Statistical Analysis	Results	Conclusion
Distance	Klein-geltink	Logistic regression	Multiple results	No association for patient or physician delay
	Fajardo-Gutierrez	Logistic regression	OR = 1.5 (95% CI 1.4-1.8)	Children who lived near Mexico City had a lower risk of lag time than children who lived far from Mexico City.
	Chantada	Logistic regression	Result not shown	No statistically significant difference in patient delay between patients living in urban and rural or between those living in Buenos Aires and the rest of the country.
Number of visits	Haimi	Pearson Correlation	Result not shown	Positive correlation between the number of times a child visits a physician and lag time
First health professional contacted	Klein-geltink	Logistic regression	Patient delay: OR for GP = 0.63 (95% CI 0.42-0.95); Physician delay*: OR for ER = 0.31 (95% CI 0.20-0.48)	Compared to a first paediatrician contact: Patients who first visited the GP had a lower risk of patient delay. Patients who first visited the ER had a lower risk of physician delay.
	Chantada	Logistic regression	Result not shown	No statistically significant difference in patient delay.
	Goddard	Kruskal-Wallis test	Result not shown	No statistically significant difference in patient delay. Statistically significant difference in physician delay.
	Goyal	Linear regression	P=0.02	Diagnosis delay and patient delay was longer for patients that initially contacted the GP than for patient that contacted the ER.
	Haimi	Kruskal-Wallis test	Result not shown	Diagnosis and physician delay shorter for patients examined by paediatricians compared to family physicians or other specialist

*= time from first healthcare contact to assessment by an oncologist

4. RATIONALE AND SIGNIFICANCE

Few health studies have specifically examined the epidemiology and public health significance of diagnostic and treatment delays in childhood cancer. In the absence of established screening strategies for pre-invasive cancers or precursors in childhood cancers, useful information for cancer control can be derived from this study. This population-based study measured and characterized various types of delays in Canada and obtained important information on the factors that influence patient and provider delays. This study also shed light on the relationships between the individual patient and provider delays on disease severity and prognosis using judicious control for potential confounding mechanisms and factors. The information obtained from this study may form the basis for new effective policies and programs aimed at eliminating bottlenecks and obstacles in the diagnostic and care trajectories for Canadian children with cancer and for improving their short- and long-term prognosis.

5. METHODOLOGY

A prospective cohort study was conducted to investigate the waiting time of cancer symptoms reporting, diagnosis, and treatment in children between 0-19 years of age in Canada. This study took advantage of a database from the Treatments and Outcomes Surveillance (TOS) component of the Canadian Childhood Cancer Surveillance and Control Program (CCCSCP) that I had a role in coordinating while I was employed in the Special Population Section at Health Canada from 2001-2002. Detailed information related to the patients, their diagnoses, and their cancer therapies was obtained prospectively from all paediatric oncology centres and provincial cancer registries across Canada from 1995 to 2000.

5.1. Source Population

5.1.1. Canadian Childhood Cancer Surveillance and Control Program

The CCCSCP began as part of the federal government's Brighter Futures Initiative in 1992 and is a partnership of Health Canada, paediatric oncology centres, provincial cancer registries, and universities [Gibbons et al., 1994]. The Special Populations Section of the Centre for Chronic Disease Prevention and Control Division is currently coordinating this nationwide information system at the Population and Public Health Branch of Health Canada.

The goal of the CCCSCP is to help reduce the severity and mortality of childhood cancer. The CCCSCP seeks to accomplish this goal by: 1) producing accurate descriptive

data on childhood cancer and identifying its risk factors; 2) evaluating the continuum of cancer care and clinical outcomes; 4) identifying the psychosocial and physical long-term effects of cancer on survivors; 5) estimating the severity of financial effects of childhood cancer on the Canadian health care system; and 6) disseminating findings to stakeholders and the general public.

The CCCSCP includes 3 active components: Etiology Investigation, Late Effects Investigation and the TOS system. For this study, I used data available in the TOS component of the CCCSCP. This nationwide population-based surveillance program is based in paediatric oncology centres and provincial cancer registries across Canada. Extensive information on diagnosis, treatment and outcome was collected prospectively from childhood cancer patients (0-19 years of age) at diagnosis and at 6-monthly follow-up intervals for five years.

A total of 17 paediatric oncology centres representing all regions and health jurisdictions across Canada contribute data to the CCCSCP-TOS (Appendix 1). All provinces, except Ontario, have participated in this component since 1995. Ontario patients were also entered into TOS, however only partial data were provided by the Paediatric Oncology Group of Ontario (POGO). Patients from Ontario were excluded because of differences in data collection that preclude direct comparison of delays with other provinces. Data collection is complete up to the end of 2000. Unfortunately, the CCCSCP was discontinued and data collection and data entry was stopped. Although efforts are being made by the Special Population Section division to re-activate data collection for the program, data past the year 2000 were unavailable to me for inclusion in this thesis.

5.1.2. Data Collection

Seventeen paediatric cancer centres across Canada have participated in TOS-CCCSCP. In the western provinces (Manitoba, Saskatchewan, Alberta and British Columbia), the provincial cancer registries have coordinated the program activities. For most regions, case accrual is 95% population-based. Baseline information for each patient was collected through a questionnaire within 4 weeks of treatment initiation. Follow-up information, such as treatment, outcomes and complications, was collected every 6 months for a maximum of 5 years after diagnosis or until death. The two CCCSCP-TOS questionnaires are shown in Appendix 2.

5.2. Study Population

Subjects included in this study satisfied the following inclusion criteria: (i) are residents of Canada, (ii) are aged less than 20 years, (iii) were diagnosed with a malignant tumour between the years 1995 to 2000 inclusive (as listed in the International Classification of Childhood Cancer (ICCC) [Kramarova and Stiller, 1996]), and (iv) information on date of first symptoms, diagnosis, treatment and outcome are available. Of the 3865 eligible patients in the TOS program, I excluded 83 patients diagnosed with Langerhans cell histiocytosis or myelodyplastic syndrome (not ICCC-related diagnoses). Consent was obtained from 2978 (78.7%) of the remaining 3782 patients. While the male-to-female ratio was the same between respondents and non-respondents ($p=0.81$), the non-consenting patients tended to be older than the consenting patients ($p<0.00$). Among

consenting patients, 82 were excluded because of inconsistencies in the reported data, yielding a final sample of 2896 patients.

For the purpose of objectives 2, 3 and 4, the analyses were conducted separately by cancer type and limited to leukemia, lymphoma and CNS tumour patients. Due to the differences in diagnosis procedures and patient/parent behaviour for each type of cancer, it was more meaningful to examine these associations separately by individual type of cancer, specifically on patients with leukemia, lymphoma and CNS tumours. Of the eligible consenting patients, there were 963 leukemia patients, 397 lymphoma patients and 543 CNS tumour patients.

5.3. Data Quality Control

A detailed quality control evaluation of the data was conducted by the CCCSCP at each centre. All data managers took part in a training session to ensure a uniform method of data entry. In case of transfers, regional hospital representatives were asked to send a patient's TOS information to the new treating institution. Follow-up for patients transferred to another paediatric oncology centre became the new centre's responsibility. If a patient had not visited a centre or regional hospital in the last follow-up period, then no other information was collected. Quality of the data was evaluated at data collection, data entry and merging of the databases. Data were checked for duplicates and completeness. Blinded random selection of cases, with respect to the TOS and hospital data managers, was conducted annually to verify the original information. I conducted a final assessment of data quality prior to conducting the statistical analysis to identify potential errors in data entry. Details on TOS-CCCSCP and data completeness have been

previously reported [Gibbons et al., 1994; CCCSCP, 2003; Klein-Geltink et al., 2005]. In brief, the CCCSCP reported a 90% to 100% agreement in the number of new cases in TOS-CCCSCP compared to the Canadian Cancer Registry (CCR) for most cancers [CCCSCP, 2003].

5.4. Ethical Approval

Conducting this study entailed obtaining permission from all 17 paediatric oncology centres that participate in the CCCSCP. All centres responded in writing approving the release of the data to the investigators at McGill. A key requirement in the agreement with the centres was that the McGill investigators guaranteed the anonymity and confidentiality of all patients' records. This was done by an anonymization procedure performed by CCCSCP data managers at Health Canada whereby all personal identifiers (including Medicare numbers) were stripped from the records after the baseline and follow-up information was entirely merged into a single file. A randomly chosen and unique numeric ID was then added to each record and the dataset was transferred to me in Montreal. The research protocol was approved by the McGill Institutional Review Board (Appendix 3).

5.5. Study Variables

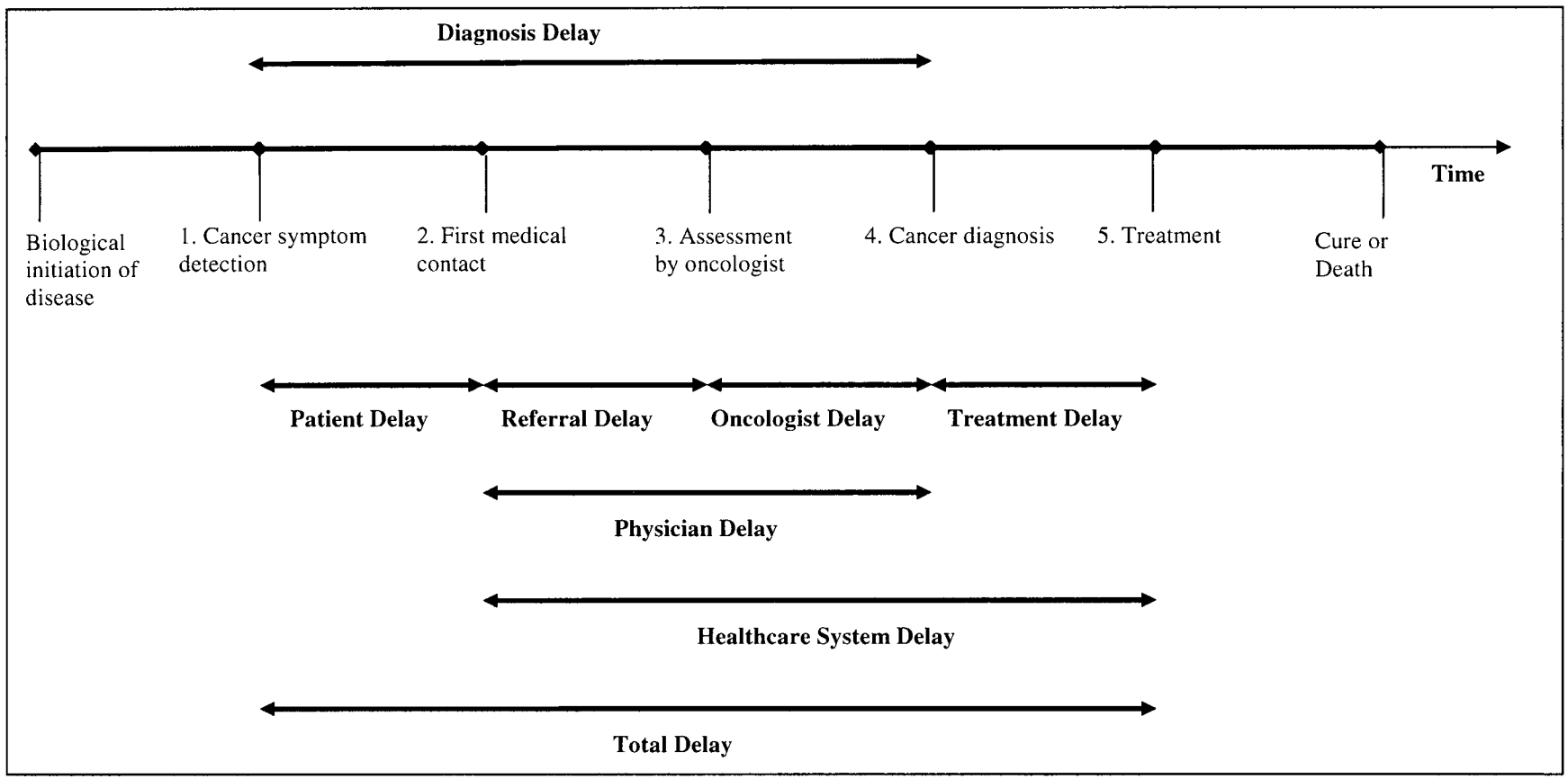
The information needed for this study was extracted from data entered in the TOS-CCCSCP database and, in the case of some socio-economic variables, from the 2001 Census data provided by Statistics Canada. The study variables fell into two main classifications: socio-demographic and clinical factors. Survival was analyzed in relation

to the time to diagnosis and other socio-demographic and clinical parameters in the care pathway of childhood cancer patients.

5.5.1. Delay variables

For simplicity of terminology, I studied delays as relevant component intervals in the trajectory of care of childhood cancer patients without implying any value judgment in terms of clinical acceptability. The TOS baseline questionnaire (Appendix 2) contains dates for the following milestones in the diagnostic and treatment trajectory of each childhood cancer: 1) date of onset of initial complaint, 2) date of first health care contact for complaint, 3) date of first assessment by treating oncologist/surgeon, 4) date of definitive diagnostic procedure, 5) date of first therapeutic intervention. As displayed in Figure 5.1, attribution of delay variables will be defined as the intervals (in days) between pairs of dates as follows: patient delay=dates #1 and #2; referral delay=dates #2 and #3; Oncologist delay=dates #3 and #4; treatment delay=dates #4 and #5. Composite delays were also investigated in this study and defined as: diagnosis delay= dates #1 and #4; physician delay= dates #2 and #4; health care system delay (HCS delay) =dates #2 and #5; and total delay=#1 and #5.

Figure 5.1: Definition of delay variables along the cancer care continuum (relative distances between time points are not representative of actual time intervals)



5.5.2. Study Outcomes

For the analysis of determinants of delays (Objective 2), patient delay, physician delay and HCS delay were considered outcomes. After consultations with two clinical experts in childhood cancer who served as co-investigators in the grant that funded this study (Drs. Ronald Barr and Mark Greenberg), it was determined that there is no acceptable clinical threshold of delay. Since there is no *a priori* known acceptable delay, I conducted three different univariate regression analyses using different thresholds of delay to get a broad picture of the relationship between delay and its potential determinants. Delay variables were treated as a continuous outcome variable in univariate linear regressions. Due to the skewness in the distribution of individual delay variables, a logarithmic transformation was used with 1 added to all delays (to avoid indeterminate results for zero values). For the logistic regression analyses, delay variables were treated as dichotomous outcomes in the analyses by using the median of each delay and a 'long' delay as the thresholds of dichotomization. The 'long' delay was defined by the 75^{th} percentile, rounded to the closest meaningful bi-weekly calendar length of time (e.g. 58 days rounded to 60 days or 42 days to 45 days).

Delay measures served as explanatory variables for the analysis of disease severity (Objective 3). Disease severity information was obtained from the TOS database using the extended information available in the questionnaires (Appendix 2). Disease-specific staging and classification was duly coded in the TOS database on the basis of tumour type specific characteristics. For each case, disease severity was defined as 'low' or 'high' at diagnosis using different fields in the database that indicate the extent of neoplastic spread. This was defined after extensive deliberations with the clinical experts and included the actual stage for a given tumour type supplemented with additional

information on disease severity. A description of the disease severity classification is described further in Appendix 4.

For the survival analysis (Objective 4), survival time was the outcome of interest and was also obtained from the TOS database. Survival time was defined as the interval from date of diagnosis to date of death or last confirmation of a follow-up status as alive, as received by the TOS. The censorship variable was defined binarily as per the occurrence of death from all causes; cases who were alive contributed survival time until the date of last documented information in the database.

5.5.3. Explanatory and control variables

Pertinent baseline data on socio-demographic, health care system and disease characteristics were obtained from the TOS baseline questionnaire (Appendix 2). Information for the socio-economic variables was taken from the 2001 Statistics Canada Census data.

5.5.3.1. Variables related to the patient

Age: Age at diagnosis was classified into four categories. For the descriptive analyses (Objective 1), age was defined based on conventional groupings in childhood cancer epidemiology and categorized into 5 age-groups: <1, 1–4, 5–9, 10–14 and 15–19. This categorization was made to take into consideration the distribution of cancer types across age groups and the different phases of child growth that would affect their care and behaviour. For the analyses on the determinants of delays (Objective 2), disease severity (Objective 3) and patient survival (Objective 4), age was categorized into four groups

according to the quartile values for age, separately for patients with leukemia, lymphoma and CNS tumours.

Patient Sex: Patients were dichotomized into two groups. Males were used as the reference group.

Body Mass Index (BMI): BMI was calculated for the patients and categorized as low, mid and high based on the tertiles of BMI. The mid-level BMI was used as the reference category in analyses.

5.5.3.2. Variables related to the healthcare system

Type of health professional first contacted: Three groups of healthcare professional first contacted by the patients were examined. Patients who first visited the hospital emergency (ER) or other health providers (includes opthalmologists, neonatalogists, neurologists, oncologists, paediatricians, optometrists, chiropractors) were compared to patients who first contacted the general practitioners (GP) to assess the effect of the type of first healthcare professional contacted by the patients on delay.

Province and regions: Provinces and territories included are: Newfoundland (NL), Prince Edward Island (PE), Nova Scotia (NS), New Brunswick (NB), Quebec (QC), Manitoba (MB), Saskatchewan (SK), Alberta (AB), British Columbia (BC), the Yukon (YT) and the Northwest Territories (NT). In the interest of statistical precision, regions were grouped as: Atlantic (NL, PE, NS and NB), Quebec, Prairies (MB, SK and AB) and BC.

5.5.3.3. Variables related to cancer

Cancer type: Cancer diagnoses were classified according to the ICCC [Kramarova and Stiller, 1996]. This classification has 12 diagnostic groups: 1. Leukemia; 2. Lymphoma and reticuloendothelial neoplasm; 3. CNS and miscellaneous intracranial and intraspinal neoplasms; 4. Sympathetic nervous system tumours; 5. Retinoblastoma; 6. Renal tumours; 7. Hepatic tumours; 8. Malignant bone tumours; 9. Soft tissue sarcomas; 10. Germ cell, trophoblastic and other gonadal neoplasms; 11. Carcinomas and other malignant epithelial neoplasms; 12. Other and unspecified malignant neoplasms.

Subtype: For the analyses on the determinants of delays (objective 2), disease severity (objective 3) and patient survival (objective 4), leukemia, lymphoma and CNS tumours were dichotomized by cancer subtype. The subtype groups were divided as follows: Leukemia into Acute lymphoblastic leukemia (ALL) and Non-ALL; Lymphoma into Hodgkin Lymphoma and Non-Hodgkin Lymphoma; and CNS tumours into Medulloblastoma and Other.

5.5.3.4. Variables related to socioeconomic status

Income and Population size: Contextual information of SES was obtained by linkage with Statistics Canada Census 2001 information on median income and population size for residential clusters represented by the first 3 characters of the postal codes, known as Forward Sortation Area (FSA). Such information on SES has been proposed as a reliable indicator of availability of health promotion information and quality of health care when

compared to actual patient-specific SES data [Gorey et al., 1997].

Information on median family income and population size for a FSA was obtained from Census data and was linked to each individual in the CCCSCP database. Four categories of income and population size were formed based on the quartiles of each variable for the study population (Objective 1) and for leukemia, lymphoma and CNS tumour patient (Objective 2-4).

Community Type: Patients were defined as either living in rural or urban areas based on a classification determined by Statistics Canada and Canada post [Statistics Canada, 1999]. This variable was derived by looking at the second position in the FSA. Any patients with a FSA with a "0" in the second position are defined as living in a "rural" area; while an FSA with any other number at that position is defined as "urban".

5.6. Methodological Issues

The following section describes the general limitations and strengths of the present study. Methodological issues pertaining to specific study objectives and analyses are also discussed in the respective chapters.

5.6.1. Selection bias

Given the nature of this study, selection bias may be introduced if different criteria relating to the outcome were used in the recruitment of exposed and non-exposed groups (with "exposure" used to denote the independent variable of interest in a given analysis). However, this is not a concern since all subjects diagnosed with cancer in

Canada were recruited into the TOS-CCCSCP cohort before any knowledge of the outcomes was known. As well, the study hypotheses were unknown to both patients and physicians at the time of data collection; therefore any selection biases are unlikely. The potential for selection bias due to differences in participation of the eligible patients is possible. However, this is unlikely since the outcomes and delay status were unknown at the time of study recruitment.

It is conceivable that biases would have occurred if patients with distinct delay times were more or less likely to seek medical care outside of Canada, which would have prevented the complete ascertainment of the survival experience of some patients in specific delay categories. Although record linkage with external death registration databases was not attempted in this study, the proportions of losses to follow-up were low and non-differential by delay types and categories. Furthermore, the existence of a high-quality, free and universal health care system in Canada lessens considerably the likelihood that parents would have sought care for their affected children in the US or other countries.

5.6.2. Information bias

Information biases may occur if the exposure status affects the ascertainment of the disease status. Misclassification of delay times might be a concern since the date information (primarily date of disease onset) was obtained from medical records and from patients or parents, which may have resulted in inaccurate recall. However, there is no reason to think that the recall of the date of symptom onset by either medical charts or from the patients/parents would lead to differential, systematic error. All the patients in this study have cancer and should experience the same sense of urgency towards the

reporting of their disease. Thus, such errors in recall are likely to have been mostly random with respect to the selected socio-demographic indicators that were considered for analysis.

5.6.3. External Validity

The TOS-CCCSCP was a national surveillance program that sought to encompass all the Canadian children diagnosed with cancer between 1995 to the end of 2000. Comparisons between the number of incident cancer cases in the TOS program and the Canadian Cancer Registry have previously been reported [Canadian Childhood Cancer Surveillance Control Program, 2003] and were shown to be generally similar.

Cancer patients from Ontario and patients who did not access paediatric oncology centres were not captured in this study. For the province of Ontario, only partial patient information was provided by The Paediatric Oncology Group of Ontario (POGO). These data did not contain the dates required to create the delay variables. Only the time from diagnosis to treatment was available from Ontario data. Therefore, the inclusion of Ontario was not possible. Thus, these findings can not be generalized to all children with cancer in Canada.

That being said, this study is the first that treats the subject of delays from a national perspective, thus having the weight of evidence that is required for evidence-based decisions. This investigation went beyond those that restricted case accrual to local jurisdictions or individual hospitals and therefore avoids the limitations of studies based on a single institution's experience.

6. STATISTICAL ANALYSIS

This section describes the main statistical methods used to analyze the data for this study. Supplemental details on the application of these methods for the purposes of the specific objectives are described in subsequent chapters. All analyses were conducted using Stata software (Stata Corporation, Version 9, College Station, TX, USA, 2005).

6.1. Linear Regression

Simple linear regression was used to model the relationship between independent variables and various delay variables (objective 2). This statistical method is used to describe the relationship between a single continuous dependent variable *y* and a single independent variable x. The relationship is expressed as:

$$\mathbf{Y = \beta 0 + \beta\ 1X + \varepsilon,}$$

where β_0 and β_1 are referred to as the model parameters and are determined using the least squares criterion; ε represents random error with mean 0 [Kleinbaum et al, 1998]. The value of the β estimates represent the slope of the best fit line for the relationship between the dependent variable y and the independent variable x. When the independent variable is categorical with k categories (as is the case in this study), the variable is grouped into a set of k-1 dummy variables. The remaining category acts as the reference group against which all other dummy variables are compared. Therefore, for a given dummy variable, the β estimate is the mean difference in y between that category and the baseline.

6.2. Logistic Regression

Logistic regression was used to model the associations between baseline risk factors and delays (Objective 2), as well as the association between delay and disease severity (Objective 3). Logistic regression is a model, appropriate for analyzing data with naturally dichotomous outcomes or when the outcome can be defined as a binary variable (i.e. long or short delay). Multivariate regression includes more than one independent variable and takes into account many variables simultaneously and adjusts for these potential confounding (variable that is related to both the variable under investigation and outcome of interest, and is not a mediating variable) or mediating variables (variable that occurs in the causal pathway from an independent to dependent variable and is related to both variables).

In this model, if Y is the probability of the outcome, then the 'odds' of developing the outcome is represented by Y/(1-Y). The log odds of disease or 'logit Y' can be represented as a linear function of the independent variables X, as shown below:

$$\mathbf{Ln\ [Y/(1-Y)] = \beta 0 + \beta 1X1 + \beta 1X1 + \ldots + \beta nXn}$$

For a given variable X, the regression coefficients (β) can be exponentiated and converted into odds ratios (OR), which estimates the risk of a level of X relative to the baseline, while adjusting for the other variables in the model. For variables with multiple categories the use of "dummy" regressors, described above also applies, but in a multiplicative scale.

6.3. Kaplan Meier

The Kaplan-Meier method (also known as product limit method) is a non-parametric approach for analysis of survival data [Kaplan & Meier, 1958]. The estimated probability of remaining event-free until time (t) ($\hat{S}(t)$) is equal to the cumulative product of the probabilities of surviving through each successive interval. In my analyses, these intervals are defined by consecutive times at which a patient is alive or deceased from any causes. Patients who are censored prior to a given event are not considered beyond their censored time.

Statistical comparisons in the survival distributions between delay groups were determined using the log-rank test [Kleinbaum et al, 1998]. The log-rank test is a non-parametric test that is used to test the null hypothesis that there is no difference between the populations in the probability of death at any time point.

6.4. Cox Proportional Hazards Regression

The Cox proportional-hazards (PH) regression [Cox, 1972] was used to estimate the effect of various delays on time to death (Objective 4), while controlling for potential confounders and disease severity. The Cox PH regression is a semi-parametric model used to conduct multivariate analyses on censored survival data. This method is based on the hazard function which denotes the instantaneous risk for the event to occur immediately after certain time, given that the individual has survived up that time [Kleinbaum et al, 1998]. The Cox PH model is usually written in terms of the hazard function and gives an expression for the hazard at time t for an individual with a given specification of a set of explanatory variables. The hazard function is expressed as:

$$\mathbf{H(t,X) = H0(t) \times \exp(\beta 0 + \beta 1X1 + \beta 1X1 + \ldots + \beta nXn),}$$

where X1 ... X_n are a set of variables and $H_0(t)$ is the baseline hazard at time t (representing the hazard for a person with all variables X=0). The hazard ratio (HR) for an individual relative to the baseline, $H(t) / H_0(t)$, can therefore be obtained by dividing both sides of the equation by $H_0(t)$ and taking logarithms.

For categorical variables, the estimated HR is interpreted as the instantaneous relative rate of death, at any time, for an individual with the risk factor present compared with an individual with the risk factor absent; given both individuals are the same on all other covariates. As described above, variables with k categories are considered in the model through a set of k-1 dummy variables.

6.5. Model Selection Strategy

6.5.1. Akaike Information Criteria

In the analyses to determine factors related to delays (objective 2), there is no primary exposure variable of interest; rather the focus is largely exploratory. Therefore, the change in parameter estimate criterion [Rothman & Greenland, 1998] was not used for the selection of variables in the multivariate analyses, since the latter implies that there is clearly an independent variable that must be assessed in light of empirical confounders. Instead, the model selection strategy used an all-subset regression approach and looked at the Akaike Information Criterion (AIC) to build the multivariate models. The Akaike model selection procedure requires the calculation of AIC for each model for all combinations of independent variables under consideration and designates the model with the minimum value of AIC as the "best" model [Kleinbaum et al, 1998], which

provides the best balance between joint explanatory value among all predictors and parsimony. Terms with a p-value over 0.15 were removed from the models and those with a p-value under 0.10 were eligible for addition into the models.

6.5.2. Change-in-estimate Criteria for the Selection of Confounders Variables

To model the association between delay and disease severity (objective 3) and survival (objective 4), potential empirical confounders were examined from factors related to the patient, the cancer and health care in regression models. The assessment of confounding consisted of comparing a crude estimate of the main relationship of interest with an estimate of the same relationship after accounting for the potential confounder [Rothman & Greenland, 1998]. In this study, a variable was deemed to be an empirical confounder if the estimate of the main independent variable changed by 5% or more, in either direction, when the potential confounder is removed from the model.

6.5.3. Interactions

For all multivariate models described above, the presence of statistically significant interactions between independent variables was verified, from all possible interactions, using the likelihood ratio test. This test can be used to assess the difference between a given model and any nested model that is a subset of the given model. The likelihood ratio test is a test of the significance of the difference in likelihood ratios between the full model (with interaction term) and the reduced model (without the interaction term) [Kleinbaum et al, 1998]. A resulting statistically significant model chi-square means that the interaction effect is contributing statistically significantly to the empirical value of the full model and should be retained.

7. DELAYS IN DIAGNOSIS AND TREATMENT AMONG CHILDREN AND ADOLESCENTS WITH CANCER IN CANADA

7.1. Introduction

Few studies have investigated wait times in children with cancer. Previous studies have shown that time to diagnosis varies by cancer type, ranging from the shortest mean time to diagnosis of 2.5 weeks for renal tumours [Saha et al., 1993] to the longest time, that is, 29.3 weeks for brain tumours [Mehta et al., 2002]. It has been reported that the time for patients to report to a health professional is longer than the time needed for referral to a specialist [Klein-Geltink et al., 2005]. In the absence of screening for pre-invasive cancers or precursors, useful information for cancer control can be derived by measuring the delays as a surveillance exercise. Appropriate benchmarks for timely cancer care require a detailed understanding of the delays that may occur along the continuum of care.

7.2. Objectives

The objective of this study was to characterize the different components of delay in Canadian cancer patients aged 0-19 years that were enrolled in the TOS component of the CCCSCP from 1995 to 2000.

7.3. Methods

We conducted an observational study of the trajectory of care for Canadian patients aged 0-19 years with a malignant tumour as listed in the ICCC [Kramarova et al., 1996] and enrolled in the TOS component of the CCCSCP from 1995 to 2000 inclusive.

TOS is a nationwide population-based surveillance program and covers all children admitted to paediatric oncology centres and registered in selected provincial cancer registries across Canada. Patient information was collected prospectively and abstracted from medical charts. The CCCSCP data collection and extraction team for all 17 cancer paediatric centres were trained to use a standard approach to collect all the information for the CCCSCP. Random audits were conducted yearly to ensure the accuracy and standardization of data collection and to allow for corrective actions if necessary. Further details on TOS-CCCSCP and data completeness have been reported in previous studies [Klein-Geltink et al., 2005; Gibbons et al., 1994; CCCSCP, 2003].

Of the 3865 eligible patients in the TOS program, we excluded 83 patients diagnosed with Langerhans cell histiocytosis or myelodyplastic syndrome (not ICCC-related diagnoses). Consent was obtained from 79% of the remaining 3782 patients. While the male-to-female ratio was the same between consenting and non-consenting patients, the non-consenting patients tended to be older than the consenting patients. Among consenting patients, 82 were excluded because of inconsistencies in the reported data, yielding a final sample of 2896 patients. The numbers of patients analyzed for each type of delay differ due to each delay variable being evaluated separately for missing dates and errors in data entry.

The study included the time from the onset of patients' symptoms to the start of treatment for cancer. Different components of delay were derived from the date of onset of symptoms, initial health care contact for health complaint, first assessment by treating oncologist/surgeon, cancer diagnosis and first treatment (Figure 5.1).

Medians, 25^{th} and 75^{th} percentiles were calculated for the delays across categories

of variables. Temporal variations were assessed by grouping patients by year of diagnosis from 1995 to 2000. We tested the equality of individual delays within subgroups of selected variables (sex, age group, type of tumour, year of disease onset) by the Wilcoxon rank sum test and the Kruskal-Wallis test. Age at diagnosis was categorized into 5 groups: <1, 1–4, 5–9, 10–14 and 15–19. Tumour type was classified according to the ICCC. Provinces and territories included are: Newfoundland (NL), Prince Edward Island (PE), Nova Scotia (NS), New Brunswick (NB), Quebec (QC), Manitoba (MB), Saskatchewan (SK), Alberta (AB), British Columbia (BC), the Yukon (YT) and the Northwest Territories (NT). For statistical precision, regions were grouped as: Atlantic (NL, PE, NS and NB), Quebec, Prairies (MB, SK and AB) and BC.

Comparisons of the combined delay times related to the health care system among provinces or regions and over time were based on geometric means standardized by tumour type; the combined Canadian data for all years was taken to be the standard for the distribution of types. This was done by multiplying the type-specific mean delay for each province or region by weights represented by the average proportion of the respective tumour types in the combined provincial data. Due to the skewness in the distribution of individual delay data, we used logarithmic transformation with 1 added to all delays (to avoid indeterminate results for zero values). The antilog of the weighted means minus 1 for the individual provinces or regions is equivalent to a geometric mean delay that controls for the confounding effect of tumour type on delays. This statistical approach permitted a more complete assessment of the regional data with standardization for variations in disease distribution. Since there are no clinical criteria for delays, we used arbitrary categories with 'long' heath care system delays exceeding 1 and 2 months

as possible benchmarks for the time-varying frequencies of delays that may be perceived as excessive for policy decisions.

7.4. Results

The mean age at disease onset was 7.7 years (standard deviation=5.5) with approximately 30% of the patients in the 1-4 age group and 21% in both the 5-9 and 10-14 age groups. The male:female ratio was 1.22. Leukemia was the most common diagnosis comprising almost a third of the patients, followed by CNS tumours and lymphomas.

Table 7.1 shows the distribution of delay times expressed as median values and respective inter-quartile ranges according to the main sociodemographic variables. Median diagnosis delay was 1 month (Table 7.1). Patient and diagnosis delay increased with age (P=0.0001). Diagnosis delay in infants (<1-year) was 18 days (7–36) and increased to 50 days among patients 15-19 years old. HCS delay in patients 15-19 years of age was over twice that in patients in age groups under the age of 9. Total delay in infants was 22 days (10–41) compared to a delay of almost 2 months for patients 15-19 years of age.

Regarding tumour type (Table 7.1), the shortest total delay of 14 days (8–32) was observed for renal tumours, followed by hepatic tumours (16 days [10–45]). Carcinomas and bone tumours had the longest total delay of 87 days (35–229) and 66 days (41–121), respectively. A substantial variation in diagnosis delays across cancer type was also observed (P=0.0001). Hepatic tumour and renal tumour patients had the shortest median diagnosis delay at 13 days and 14 days, respectively, followed by leukemia patients (18 days). Diagnosis delay of approximately 2 months was observed for patients diagnosed

with retinoblastoma (58 days), carcinomas (59 days), bone tumours (61 days) and other neoplasms (62 days). Patient delay ranged from 3 days for renal tumours and hepatic tumours to 30 days for bone tumours. Median physician delay was 8 days (2–28). Leukemia had the shortest median physician delay at 3 days (1–14).

There was considerable variation in patient (P=0.0001), referral (P=0.0001), physician (P=0.0001), and HCS delay (P=0.0001) times among Canadian provinces. The longest diagnosis delay was experienced by patients in MB (37 [18–78]) and SK (39 [16–102]; P=0031). Newfoundland had a median physician delay that was at least twice as long as for other Canadian provinces and territories (other than YT). Atlantic region and the Yukon had shorter patient delays but longer referral delays (aside from NS) than the rest of Canada. The median oncologist delay across provinces never exceeded 3 days. To control for the potentially confounding influence of inter-provincial variations in cancer type distribution, we compared cancer-type standardized geometric means for HCS delay for all provinces. Excluding YT, whose estimate lacked precision due to small numbers (only 3 patients), the longest mean HCS delays were seen for NL (25.9 days) and PE (21.8 days). The lowest mean HCS delay was seen for Quebec (15.3 days). The other provinces had mean HCS delays in the range of 15.6-18.6 days. Apart from precision issues, the rankings of provinces according to HCS delay are not substantially different whether we used the above standardized geometric means or the equivalent unadjusted median times shown in Table 7.1. Figure 7.1 for the main categories of delays, intervals were heavily skewed towards low values but differed among cancer types. CNS tumours had a broader range of delay times than leukemia and lymphoma. The distribution of treatment delay centred greatly around low values as patients generally obtained their

first cancer treatment quickly after diagnosis (Figure 7.1). Treatment delay was 1 week or longer for patients diagnosed with lymphomas, bone tumours and soft tissue sarcomas.

Figure 7.2 shows time trends in all categories of delays. Statistically significant downward trends were observed for diagnosis delay ($P<0.002$) and total delay ($P<0.017$) from 1995 to 2000. Diagnosis delay was 34 days (14–83) in 1995 and decreased to 26 days (10–61) in 2000. Similarly, total delay decreased from 39 days (18–91) in 1995 to 31 days (14–61) in 2000. We also examined the time trends in HCS delays times among Canadian regions (Figure 7.3). Except for the Atlantic region, which exhibited a peak of unusual delays in 1997 the cancer-type standardized mean HCS delays remained steady over time across Canadian regions or, as in the case in BC, declined ($P=0.046$). The proportion of patients exceeding 30 days (Figure 7.3, middle graph) and 60 days (Figure 7.3, bottom graph) generally declined from 1995-2000. Consistent with the peak in mean delays in 1997, there were noticeable increases in the proportions of patients who experienced HCS delays exceeding these thresholds in the Atlantic region at the same time. However, these increases were compensated in subsequent years to levels that were among the lowest for Canadian regions, particularly in 2000. A direct comparison of Canadian provinces (territories excluded) indicated that despite some fluctuation there were improvements in mean HCS delays for most provinces in 1999-2000 (data not shown). In 2000, the mean HCS delays ranged from 7.3 days in PEI to 15.6 days in Saskatchewan. The numbers of provinces with mean HCS delays exceeding 20 days were 3 in 1995, 2 in 1996, 3 in 1997, 2 in 1998, 0 in 1999, and 0 in 2000.

7.5. Discussion

For simplicity of terminology, we studied delays as relevant component intervals in the trajectory of care of childhood cancer patients without implying any value judgment in terms of clinical acceptability. We also examined time trends for the overall combination of delay times that can be considered as part of the surveillance oversight by the Canadian provincial health care system, that is, the time elapsed from first medical contact by the patient until the onset of treatment. Diagnosis delay and total delay for all cancers was approximately 1 month. Oncologist delay and treatment delay were short. Patient delay and referral delay were the longest time segments and thus were responsible for driving the overall length of the delays. Compared to a previous study conducted in Israel, our study found a shorter diagnosis delay than the median of 49 days reported by Haimi et al. [2004] for all cancers. Although patient delay was similar in both studies (9 days vs. 7 days), physician delay was shorter in the present analysis (8 days vs. 30 days). The diagnosis delays for the different types of cancer were comparable to those found in previous studies.

As in previous studies, this study found that young children tended to have shorter patient delay times than older ones [Saha et al., 1993; Haimi et al., 2004; Pollock et al., 1991; Dobrovoljac et al., 2002; Fajardo-Gutierrez et al., 2002]. Saha et al [1993] suggested that organ size in young children may lead to faster progression of symptoms and therefore alert the caregivers earlier. Another explanation may be in the reporting differences between younger and older patients. Among young children, one expects that close parental observation of the child might help the recognition of symptoms and signs; whereas among older children and adolescents the recognition of signs and symptoms may be more often initiated by the patients themselves. It is also possible that adolescents

may undervalue the symptoms that they may experience and are more likely to delay calling attention to their illness, the end result being increased delays. Physician delay was also longer for older patients than younger patients. The relatively short oncologist delay suggests that longer physician delays in older patients are mainly attributed to the difference in referral delay. In an earlier study undertaken by the CCCSCP, the delay in referral of adolescents to adult-oriented centres was twice as long as that for paediatric cancer centres [Klein-Geltink et al., 2005b].

The difference in the various types of delay among cancer types was in agreement with previous studies [Saha et al., 1993; Klein-Geltink et al., 2005; Haimi et al., 2004; Pollock et al., 1991; Dobrovoljac et al., 2002; Fajardo-Gutierrez et al., 2002; Flores et al., 1986]. Interaction between cancer type and age may possibly account for this observation, as the types with the shortest delays (hepatic and renal) would typically be cancers of younger patients while bone tumours, carcinomas and other malignancies would probably have an older age distribution. The longest diagnosis delay was found for carcinomas, bone tumours and retinoblastoma. Intermediate lengths of patient and referral delay for carcinoma indicate that both time intervals contribute to the delay in diagnosis. For retinoblastoma, the longer patient and shorter referral delay suggests that diagnosis delay is mainly attributed to the patients' caregiver, in view of the age distribution of these patients. Similarly, delay to the diagnosis of bone cancers is likely influenced by the patients as evidenced by the longer patient delay and shorter referral delay. Lymphomas, bone tumours and soft tissue sarcomas typically require molecular and other diagnostic tests before administering first treatment and that may account for the observed longer treatment delay.

As expected, the various delays differed slightly among Canadian provinces. Median diagnosis delay never exceeded one and a half months. In the Atlantic region and the Yukon, patient delay was shorter than in the other provinces; however referral delay was found to be longer (except in NS). Patient referral to a paediatric oncologist accounts for the majority of the diagnosis delay in these regions, which suggests that access to healthcare may be hampered by specific conditions. Conversely, shorter referral delays and longer patient delays were observed in the other provinces.

Total delay and diagnosis delay decreased from 1995-2000. It is possible that increased access to information resources have made patients more vigilant for signs of cancer. As well, one would also presume that progress in diagnostic methods would lead to more accurate and rapid diagnoses, thus lowering delay times. Despite sporadic fluctuations in HCS delay, there has been a general trend for improvements in the most recent years covered by our study.

There are some limitations to this study. Firstly, it was difficult to ascertain the reliability and accuracy of the information collected. This may be particularly so for the reported initial onset of symptoms. However, this concern is alleviated by the random audits that were conducted by the CCCSCP at each cancer centre. Secondly, non-consenting patients and patients enrolled in Ontario were not included in this study. Therefore, the results from this study should not be generalized to all Canadian children with cancer. The use of private insurance may be a concern in this area of research; however, this is less of a concern in countries with universal health care coverage, such as Canada. In Canada, the health system is designed to ensure that access to medical services is provided to all residents and paid for by public tax revenues without direct

charges to the patient. In this study, the use of private insurance for cancer care is negligible and unlikely to have materially influenced our findings. Lastly, misclassification might be a concern since the date information (primarily date of disease onset) was obtained from medical records and from patients or parents, which may have resulted in inaccurate recall. However, such errors are likely to have been mostly random with respect to the selected sociodemographic indicators that we considered for analysis. Likewise, any interpretation of the regional variation in HCS delays, either collectively or over time, is confounded by the composition of cancer types found in each region. We resorted to a standardized approach to make such comparisons so as to control for the confounding effect of the underlying disease on delays.

Detailed descriptions of the various delay components across Canada offer an opportunity to isolate the main time segment responsible for lengthening the cancer care pathway taken by children and adolescents within each subgroup. Varying lengths of patient delay and referral delay, across age groups, types of cancers, and Canadian settings, are the main contributors to diagnosis, HCS and overall delay. We believe that the sources of variation seen in our study may be indicative of similar patterns in other jurisdictions. Furthermore, this study examines various delays that may occur along the cancer care continuum from a national perspective, thus having the weight of evidence that is required for evidence-based decisions. The information provided by this study may be used to assist the implementation of intervention programs aimed at reducing delay where these can be most effective.

Table 7.1: Median** delays (25% - 75% percentiles) in days by type according to sociodemographic variables and cancer type

	N*	Patient delay	N	Referral delay	N	Oncologist delay	N	Physician delay	N	Diagnosis delay	N	Treatment delay	N	HCS delay	N	Total delay
Overall	2801	9 (1 - 31)	2792	4 (0 - 24)	2678	1 (0 - 5)	2787	8 (2- 28)	2812	30 (13 - 69)	2656	1 (0 - 6)	2737	12 (4 - 35)	2761	34 (16 - 76)
Sex																
Female	1264	9 (1 - 31)	1259	5 (0 - 25)	1202	2 (1 - 5)	1261	8 (3 - 30)	1265	31 (13 - 71)	1199	1 (0 - 6)	1240	12 (5 - 37)	1246	35 (16 - 79)
Male	1537	9 (1 - 30)	1533	4 (0 - 23)	1476	1 (0 - 5)	1526	7 (2 - 27)	1547	29 (13 - 68)	1457	1 (0 - 6)	1497	12 (4 - 34)	1515	33 (15 - 73)
Age group																
< 1	241	2 (0 - 14)	239	2 (0 - 13)	231	3 (1 - 7)	239	7 (3 - 20)	241	18 (7 - 36)	214	1 (0 - 6)	229	10 (5 - 26)	234	22 (10 - 41)
1-4	920	7 (1 - 23)	918	3 (0 - 16)	898	1 (1 - 4)	920	6 (2 - 20)	926	22 (10 - 54)	873	1 (0 - 3)	900	9 (4 - 25)	908	24 (12 - 58)
5-9	633	10 (1 - 31)	629	4 (0 - 24)	608	1 (0 - 5)	627	7 (2 - 29)	363	31 (14 - 66)	590	1 (0 - 5)	613	11 (4 - 33)	621	34 (16 - 71)
10-14	603	14 (2 - 40)	604	7 (1 - 30)	574	2 (0 - 5)	602	9 (3 - 37)	606	37 (18 - 91)	579	2 (0 - 9)	599	18 (6 - 46)	600	44 (22 - 97)
15-19	404	14 (0 - 53)	402	12 (1 - 44)	367	1 (0 - 5)	399	14 (3 - 44)	403	50 (22 - 128)	400	2 (0 - 13)	396	23 (7 - 54)	398	58 (28 - 136)
Cancer Type																
Leukemia	944	8 (1 - 21)	941	2 (0 - 12)	939	1 (0 - 2)	943	3 (1 - 14)	946	19 (9 - 36)	917	1 (0 - 3)	931	6 (3 - 16)	935	21 (11 - 39)
Lymphoma	394	11 (2 - 39)	388	11 (1 - 39)	326	1 (0 - 4)	384	11 (4 - 41)	392	39 (18 - 90)	374	9 (3 - 20)	382	27 (11 - 54)	386	52 (27 - 98)
CNS tumour	511	14 (0 - 42)	511	7 (1 - 46)	502	4 (1 - 8)	507	16 (4 - 56)	514	48 (23 - 119)	457	0 (0 - 0)	486	19 (5 - 61)	496	49 (24 - 121)
Neuroblastoma	197	7 (0 - 26)	194	5 (0 - 23)	192	4 (2 - 8)	195	10 (5 - 32)	197	29 (12- 68)	183	2 (0 - 7)	193	16 (8 - 33)	194	31 (17 - 71)
Retinoblastoma	54	12 (0 - 61)	53	5 (1 - 28)	56	2 (0 - 7)	54	12 (3 - 45)	56	58 (18 - 117)	52	0 (0 - 2)	53	15 (4 - 48)	55	61 (19 - 157)
Renal tumour	172	3 (0 - 14)	170	2 (0 - 7)	166	3 (1 - 6)	170	6 (3 - 12)	171	14 (7 - 34)	153	0 (0 - 4)	166	7 (4 - 13)	167	14 (8 - 32)
Hepatic tumour	41	3 (0 - 18)	40	2 (0 - 8)	41	3 (1 - 5)	40	5 (3 - 11)	41	13 (6 - 35)	37	4 (2 - 6)	38	10 (5 - 18)	40	16 (10 - 45)
Bone Tumour	142	30 (4 - 62)	143	12 (2 - 35)	129	4 (1 - 6)	145	15 (6 - 37)	143	61 (32 - 114)	141	7 (4 - 12)	143	24 (13 - 48)	142	66 (41 - 121)
Sarcoma	152	11 (1 - 45)	155	9 (2 - 31)	137	1 (0 - 7)	155	11 (3 - 35)	154	36 (18 - 108)	142	8 (0 - 15)	153	23 (11- 57)	151	44 (26 - 129)
Germ cell neoplasm	118	7 (0 - 46)	119	7 (1 - 37)	107	2 (0 - 6)	117	9 (4 - 42)	120	41 (12 - 94)	114	0 (0 - 3)	116	14 (5 - 47)	118	45 (14 - 98)
Carcinoma	66	17 (0 - 73)	68	18 (0 - 58)	76	0 (0 - 6)	68	22 (1 - 58)	68	59 (33 - 193)	78	0 (0 - 0)	67	35 (8 - 87)	67	87 (35 - 229)
Other neoplasm	10	15 (3 - 123)	10	3 (0 - 12)	8	7 (1 - 21)	9	14 (9 - 29)	10	62 (22 - 146)	8	1 (0 - 8)	9	14 (9 - 27)	10	65 (21 - 146)

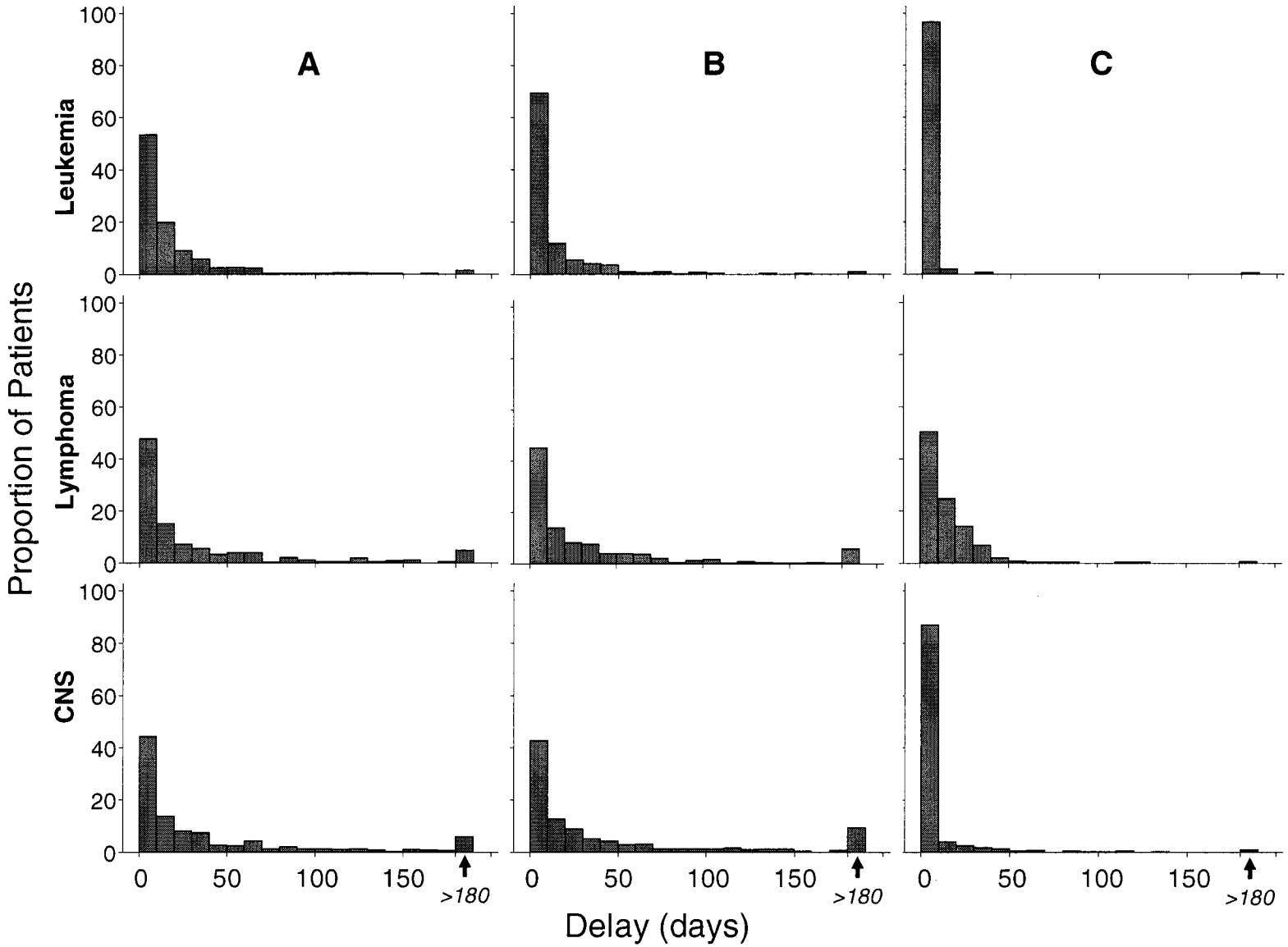
* The numbers of patients for each type of delay differ due to each delay variable being evaluated separately for missing dates and errors in data entry; **The medians are not additive between the different time segments

Table 7.1. Median** delays (25% - 75% percentiles) in days by type according to sociodemographic variables and cancer type (continued)

	N*	Patient delay	N	Referral delay	N	Oncologist delay	N	Physician delay	N	Diagnosis delay	N	Treatment delay	N	HCS delay	N	Total delay
Province																
Newfoundland	116	2 (1 - 8)	117	16 (5 - 55)	112	3 (1 - 7)	117	22 (7 - 61)	118	33 (15 - 80)	115	1 (0 - 5)	115	26 (10 - 64)	116	33 (16 - 80)
Prince Edward Island	24	1 (0 - 16)	23	11 (3 - 34)	25	1 (1 - 2)	23	11 (5 - 34)	25	26 (15 - 61)	25	0 (0 - 1)	23	23 (5 - 44)	25	34 (19 - 62)
Nova Scotia	197	3 (0 - 24)	188	5 (1 - 27)	190	1 (0 - 4)	187	9 (3 - 37)	193	29 (9 - 70)	188	1 (0 - 7)	185	14 (4 - 43)	190	32 (11 - 86)
New Brunswick	137	4 (0 - 26)	136	10 (2 - 30)	125	1 (0 - 5)	137	10 (4 - 29)	137	29 (11 - 61)	132	0 (0 - 4)	134	15 (5 - 34)	135	32 (15 - 91)
Quebec	972	12 (2 - 31)	971	3 (0 - 21)	932	2 (1 - 6)	971	8 (3 - 27)	980	30 (14 - 64)	884	2 (0 - 6)	957	11 (5 - 32)	969	32 (16 - 69)
Manitoba	141	14 (2 - 37)	139	7 (1 - 37)	132	1 (1 - 4)	140	9 (2 - 38)	140	37 (18 - 78)	139	1 (0 - 5)	138	16 (4 - 47)	138	45 (22 - 79)
Saskatchewan	214	15 (1 - 50)	217	6 (1 - 25)	198	1 (0 - 5)	217	8 (3 - 32)	215	39 (16 - 102)	197	2 (0 - 7)	206	15 (6 - 42)	204	46 (22 - 124)
Alberta	497	7 (0 - 31)	500	3 (0 - 20)	491	1 (0 - 4)	499	6 (2 - 23)	498	30 (9 - 69)	495	1 (0 - 8)	491	11 (4 - 33)	490	34 (13 - 77)
British Columbia	493	9 (2 - 29)	491	4 (1 - 21)	463	1 (1 - 3)	486	6 (2 - 25)	496	26 (12 - 66)	471	1 (0 - 5)	478	10 (3 - 32)	484	31 (15 - 68)
North West Territories	7	18 (0 - 72)	7	1 (0 - 22)	7	1 (1 - 2)	7	1 (1 - 24)	7	20 (6 - 84)	7	0 (0 - 1)	7	5 (2 - 24)	7	23 (6 - 85)
Yukon	3	0 (0 - 2)	3	28 (11 - 103)	3	0 (0 - 1)	3	29 (11 - 103)	3	31 (11 - 103)	3	9 (0 - 18)	3	38 (11 - 121)	3	40 (11 - 121)

* The numbers of patients for each type of delay differ due to each delay variable being evaluated separately for missing dates and errors in data entry; **The medians are not additive between the different time segments

Figure 7.1: Distribution of patient delay, physician delay and treatment delay for leukemia, lymphoma and CNS cancer patients



Legend for Figure 2: A: Patient delay; B: Physician delay; C: Treatment delay

Figure 7.2: Time trend of median delays from 1995 to 2000

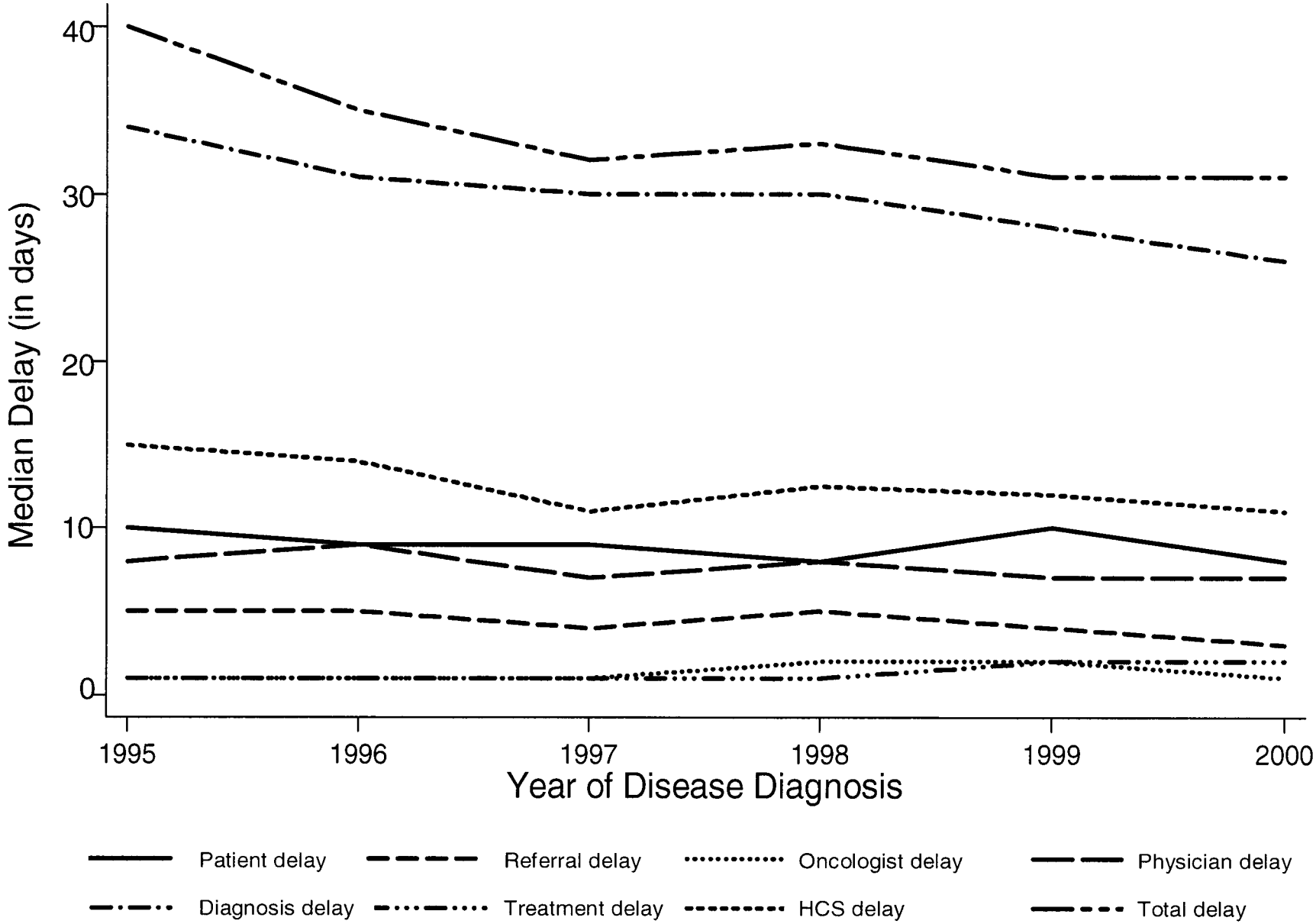
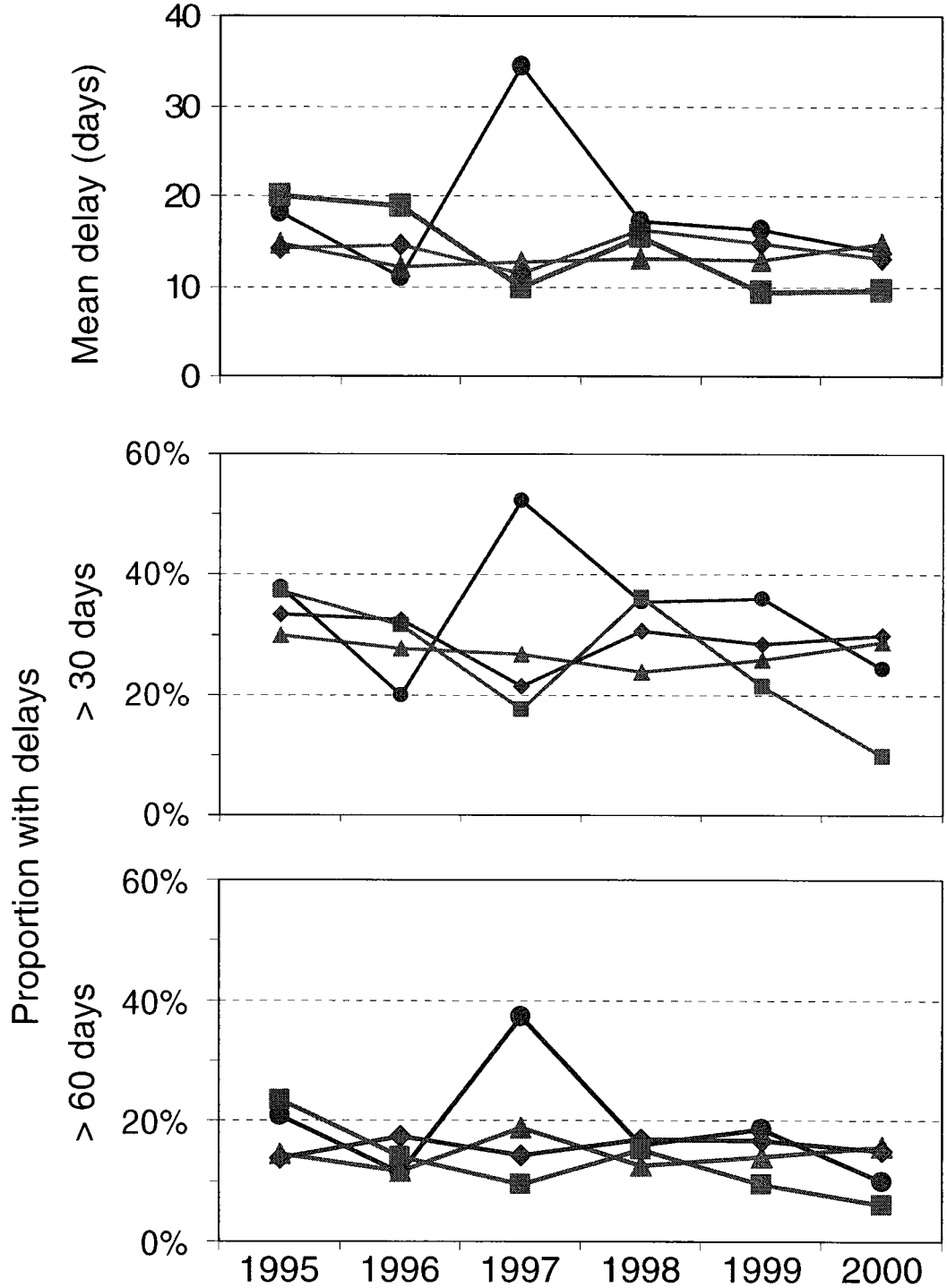


Figure 7.3: Time trends for geometric mean healthcare system delays and for proportion of patients over 30 days and 60 days of healthcare system delay for the 4 geographical regions.



Legend for Figure 4:
Blue line with circle points: Atlantic Provinces; Red line with triangle points: Quebec; Purple line with diamond points: Prairie Provinces; Green line with square points: British Columbia

8. DETERMINANTS OF DELAYS IN CARE FOR CHILDREN AND ADOLESCENTS WITH CANCER

8.1. Introduction

The development of effective new strategies to minimize delays that may occur along the cancer care pathway requires an understanding of their determinants. For cancer in adults, the diagnostic process is triggered by factors that center primarily on the patients and the patient's ability to recognize his or her disease. For cancer in children, early recognition also requires the attention of parents for signs that the child is experiencing something different than the usual benign diseases of childhood. The often ambiguous nature of cancer symptoms and the relative rarity of malignant diseases in childhood, make it difficult to immediately consider a diagnosis of cancer. As a consequence, most children with cancer are symptomatic or have clinical evidence of disease for a period of time before the illness is recognized and a diagnosis is made. Misinterpretation of these symptoms and signs by the patients, parents and health providers may lead to delays in diagnosis. Few studies have been published on the determinants of diagnosis and treatment delays in childhood cancer. As reported in chapter 3, the findings are still inconsistent and the determinants of delays remain largely unknown. In this chapter, the investigation on the possible correlates of delays will focus on patients with leukemia, lymphoma and CNS tumours, for these constitute the commonest cancers in this age group (childhood 0-14 and adolescence 15-19 years), which permits a statistical analysis with adequate precision.

8.2. Objective

The objective of this investigation was to assess the relationship between patient delay, physician delay and HCS delay and factors related to the patients, their disease and the health care system for children and adolescents with leukemias, lymphomas and CNS tumour in Canada.

8.3. Methods

A prospective cohort study was conducted on subjects enrolled in TOS-CCCSCP. The patients were less than 20 years old when they were diagnosed with a malignant disease between the years 1995 and 2000 inclusive. Also, study inclusion required that information on date of first symptoms, diagnosis, and treatment were available. Due to the differences in diagnostic procedures and patient/parent behaviour for each type of cancer, it was more meaningful to examine these associations separately for each cancer, specifically in patients with leukemias, lymphomas and CNS tumours. Of the eligible consenting patients, there were 963 with leukemias, 397 with lymphomas and 543 with CNS tumours.

In this chapter, the investigation focused on three time intervals from the onset of patient symptoms to the start of treatment: patient delay, physician delay and HCS delay. The association between these delays and exploratory variables, previously discussed in Chapter 5, were examined using regression methods. In brief, the following parameters were investigated as potential predictors/correlates of delays: patient age, sex, BMI, geographic region of residence, family income, population size, community type, type of health professional first contacted and cancer subtype. Patient age at disease diagnosis was categorized according to the quartile values of age for leukemias, lymphomas and

CNS tumours. BMI was categorized as low, medium and high based on the tertiles for each of the 3 cancer types. The mid level BMI was used as the reference category in analyses. Family income and population size were estimated from information for residential clusters represented by the 3 first characters of the postal codes (FSA) provided by Statistics Canada 2001 census. Four categories of income and population size were formed based on the quartiles of the study population's family income for each cancer type. Community type (rural or urban) was determined from the 2nd character of the FSA (a zero refers to a rural area, while a non-zero is an urban area).

Three groups of healthcare professional first contacted by the patients were examined. Patients who first visited the ER or other health providers were compared to patients who first contacted a GP to assess the effect of the type of first healthcare professional contacted by the patients on delay. Canadian regions were classified as Atlantic (Newfoundland Prince Edward Island, Nova Scotia and New Brunswick), Quebec, Prairies (Manitoba, Saskatchewan and Alberta) and British Columbia (BC). Twenty cases in the Yukon and the Northwest Territories were not included in the analyses for region. Patient delay was also used as an exploratory variable and was categorized according to its quartile limits to assess their effect on later delays.

8.4. Statistical Analysis

The crude association between delays and the exploratory variables were investigated using two methods of univariate regression: linear regression and logistic regression. The delay variables were treated as a continuous outcome variable in linear regression analyses of the potential predictive value of all exploratory factors. Due to the skewed distribution of individual delay variables, a logarithmic transformation was used

with 1 day added to all delays (to avoid indeterminate results for zero values). The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day. Since all the independent variables in this study were either categorical or categorized into groups, the results provided information on the average difference in delay between a category level of an independent variable and the reference level of that variable.

Delays were also defined as dichotomous outcome variables in logistic regression models. Unlike the linear models in which delays were treated in continuous form, the logistic regression models provide a more practical public health meaning because they identified predictors or correlates of delay according to pre-determined definitions of what constitutes each form of delay. Since there is no *a priori* known threshold for acceptable delay, delay variables were treated as dichotomous outcomes in the univariate logistic regression by using the median of each delay and, in a second set of analyses, a 'long' delay as the thresholds of dichotomization for the logistic regression analyses. The 'long' delay was defined by the 75^{th} percentile, rounded to the closest meaningful length of calendar time (e.g. 58 days was rounded to 60 days or 42 days to 45 days). In the interest of simplicity and precision, only the delay dichotomized according to the median was used in multivariate logistic regression. Also, for simplicity I used the designation "risk" of delays when discussing the various associations with candidate predictors merely to denote the differences in times for specific delay segments between patient categories.

Unconditional univariate and multivariate logistic regression were used to measure the association (OR) and the 95% CI between delays and the potential predictive

factors for leukemia, lymphoma and CNS tumour patients. The results obtained provide an estimate of the relative risk of delay that patients in one category level, for a given independent variable, have compared to patients in the baseline, while adjusting for confounding. Since there is no primary exposure variable of interest, the change in parameter estimate criterion [Rothman & Greenland, 1998] was not used for the selection of variables in the multivariate analyses. Instead, the model selection strategy used an all-subset regression approach and used the Akaike Information Criterion (AIC) to build the multivariate models. Statistically significant interactions between all combinations of independent variables were tested by the likelihood ratio test comparing the initial models with only main covariate effects with the same model after addition of the relevant cross-product terms. Interactions were considered to be present if p-value for the interaction term was statistically significant ($P<0.05$).

8.5. Results

Characteristics of the study population are shown in Table 8.1. The mean ages of patients diagnosed with leukemias, lymphomas and CNS tumours reflect the differences in age-specific incidence of these diseases between childhood and adolescence. Over half of the patients were males. The majority of the patients consulted a GP as a first health care provider, particularly for lymphoma. Patient delay and physician delay was longest for CNS tumours, while HCS delay was longest for patients with lymphomas. All 3 delays were shortest for patients with leukemia. The distribution of delay variables are presented in Table 8.2- 8.4. The results were generally consistent across the 3 univariate regression analyses.

8.5.1. Determinants of delays in cancer care in children and adolescents diagnosed with leukemias

8.5.1.1. Determinants of patient delays

The time between patient symptom recognition and presentation to a health provider is an essential time segment to consider when researching delays. Compared to the reference group, patients in the other age groups had an increased risk of patient delay; the highest being for patients in the oldest age group (OR = 1.80; 95% CI 1.2-2.6) (Table 8.5). Family income also influenced patient delay, and there was a risk of delay in the two higher income groups compared to the lowest income group (Q3: OR=1.75; 95% CI 1.2-2.6, Q4: OR=1.64; 95% CI 1.1-2.4). The Atlantic region had almost half the risk of delay as the province of Quebec (OR=0.41; 95% CI 0.3-0.6), while the other regions did not show any difference in risk with Quebec. The risk of patient delays differed for patients diagnosed with ALL compared to patients diagnosed with other types of leukemia. Patients with other types of leukemia had a decreased risk of patient delay compared to patients with ALL (OR=0.67; 95% CI 0.5-0.9).

In multivariate analyses, patient age, family income, region and cancer subtype remained associated with patient delay (Table 8.6). Older patients had greater patient delay than children in the reference group. Although family income was still a statistically significant predictor of patient delay, patient delay for the highest income group was no longer statistically significantly different from the lowest income group. The Atlantic and Prairies regions had a lower risk of patient delay when compared to Quebec in the final model. Compared to patients with ALL, patients with other forms of

leukemia maintained the same decrease in risk of delay in the multivariate model (OR=0.63; 95% CI 0.4-0.9).

8.5.1.2. Determinants of physician delays

Once under the care of health providers, the time required for patients to be referred and diagnosed by an oncologist is a key time interval to consider. As shown in Table 8.7, children in the low-BMI group had a greater risk of physician delay (OR=1.49; 95% CI 1.1-2.1) than children in the mid-BMI group. Families in the highest income group had a lower risk of physician delay (OR=0.62; 95% CI 0.4-0.9). With respect to first health professional contacted, patients who first contacted a GP were more likely to have longer physician delay than patients who first visited the ER (OR=0.45; 95% CI 0.3-0.6) and other health professionals (OR=0.6; 95% CI 0.4-0.9). The Atlantic region had more than twice the risk of physician delay than Quebec (OR=2.31; 95% CI 1.5-3.5), while the other regions did not show any difference in physician delay relative to Quebec. The risk of physician delay was generally lower for patients living in more populated areas compared to those living in less populated ones. Patient delay was associated with physician delay; the latter decreased when patient delay was over a day.

In multivariate analyses, patient BMI, region, first health professional contacted, population size and patient delay remained important factors associated with physician delay (Table 8.8). Low-BMI patients had a greater risk of physician delay compared to mid-BMI patients. In this model, the Atlantic region no longer had a statistically significantly greater risk of physician delay than Quebec. Conversely, the Prairies region and BC had a lower risk of delay. Patients whose first visit was to a GP were at greater risk of physician delay than patients who went to an ER or other health professionals.

Compared to patients with a patient delay less than 1 day, children with longer patient delay had a lower risk of physician delay.

8.5.1.3. Determinants of health care systems delays

In univariate analyses using the median as the dichotomization criterion, only the type of healthcare professional first contacted and patient delay were associated with HCS delay (Table 8.9). Patients who visited an ER experienced less delay than those who first visited a GP (OR=0.42; 95% CI 0.3-0.6). Patients with a patient delay of more than 1 day had a reduced risk of HCS delay. Patients with a patient delay over 3 weeks had the lowest risk of HCS delay (OR=0.25; 95% CI 0.2-0.4). In these univariate analyses, HCS delay did not differ across geographical regions. However, using the 'long' criterion for dichotomization, the Atlantic region showed a 2.5 times increase in risk of HCS delay compared to Quebec.

In multivariate analyses, first healthcare professional consulted and patient delay remained associated with HCS delay (Table 8.10). As in univariate analyses, the risk of delay was lower for patients who first visited an ER rather than a GP and for patients with longer patient delays. Although HCS delay did not differ across regions in univariate analyses, when accounting for the type of health care professional and patient delay, patients living in BC and the Prairie regions had a lower risk of HCS delay than those in Quebec.

8.5.2. Determinants of delays in cancer care in children and adolescents diagnosed with lymphomas

8.5.2.1. Determinants of patient delays

Compared to the reference group, patients in the other age groups generally had an increased risk of patient delay, with patients between the ages of 13-15 years showing a statistically significant increase in risk (OR = 2.01; 95% CI 1.1-3.6) (Table 8.11). A statistically significant increase in risk was not observed in 'long delay' univariate analysis. The type of health professional first contacted also influenced patient delay, and there was an increased risk of delay in the 'other' group compared to the patients who visited a GP (OR=2.11; 95% CI 1.2-3.8). The risk of patient delays differed between patients with Hodgkin and non-Hodgkin lymphoma. Non-Hodgkin lymphoma patients had a reduced risk of patient delay compared to patients with Hodgkin lymphoma (OR=0.59; 95% CI 0.4-0.9).

However, in multivariate analyses, the type of lymphoma was no longer a statistically significant predictor in the final model (Table 8.12). The age of the patient was still statistically significantly associated with delay. Unlike the univariate model, all age groups had a statistically significantly greater risk of patient delay when compared to the youngest age group in the final model.

8.5.2.2. Determinants of physician delays

Patient age was positively associated with physician delay. Compared to the youngest patient group, the oldest patient group had 2.21 times the risk of physician delay (Table 8.13). However, this was not observed in 'long delay' univariate analysis. With respect to first health professional contacted, patients who first visited an ER were less likely to have longer physician delay than patients who first contacted a GP (OR=0.3; 95% CI 0.2-0.5). The risk of physician delay was lower for non-Hodgkin lymphoma

patients than for patients with Hodgkin lymphoma (OR=0.48; 95% CI 0.3-0.7). Patient delay influenced physician delay and the risk of delay decreased when patient delay was over 2 days.

In multivariate analyses, physician delay was influenced by health professional first contacted, population size, cancer subtype and patient delay, but not patient age (Table 8.14). Although not related to physician delay in univariate analyses, population size was associated with physician delay in the final model. Patients living in more populated areas had a statistically significantly greater risk of physician delay than those living in the least populated areas. Patients whose first visit was to a GP were at greater risk of physician delay than patients who went to an ER or other health professionals. Compared to the reference groups, children with longer patient delays had a lower risk of physician delay.

8.5.2.3. Determinants of health care systems delays

In univariate analyses, the risk of HCS delay increased with increasing age. The oldest patients group had almost 3 times the risk of long HCS delay than patients in the reference group (OR=2.95; 95% CI 1.6-5.3) (Table 8.15). However, there was no statistically significant difference in HCS delay between age groups compared to the youngest age group in 'long delay' univariate analysis. Children in the low-BMI group had a lower risk of HCS delay than patients in the mid-BMI group (OR=0.46; 95% CI 0.3-0.8). Family income was positively associated with HCS delay. The risk of HCS delay was 2 times greater for patients in the second quartile income group than for those in the lowest income category. However, when looking at the 'long delay' univariate analysis, the risk of HCS delay between patients in the higher income groups compared

to those in the lowest income groups appears to be reduced (though not statistically significantly). The type of healthcare professional first contacted was associated with HCS delay. Patients who first visited an ER experienced less delay than those that first visited a GP (OR=0.39; 95% CI 0.2-0.6). Compared to Hodgkin lymphoma patients, the risk of HCS delay for patients with other types of lymphoma was lower (OR=0.28; 95% CI 0.2-0.4). The results show that patients with a patient delay of more than 2 days had a reduced risk of HCS delay.

In multivariate analyses, family income, first healthcare professional consulted, cancer subtype and patient delay were the only variables that remained associated with HCS delay (Table 8.16). Unlike in univariate analyses, patient age and BMI did not remain statistically significant predictors of HCS delay in the final multivariate model. The risk of delay differed by cancer subtype. Family income and patient delay also influenced HCS delay; higher family income increased the risk of HCS delay, while longer patient delay reduced the risk.

8.5.3. Determinants of delays in cancer care in children and adolescents diagnosed with a CNS tumours

8.5.3.1. Determinants of patient delays

The results show evidence of a relationship between patient age and patient delay for patients with CNS tumours (Table 8.17). Compared to the youngest age group, older patients had an increased risk of patient delay. Generally, patients who visited an ER or other health professionals had a greater risk of delay than patients who visited a GP. Patients who visited 'other' health professionals had almost twice the risk of delay than

patients that visited a GP (OR=1.94; 95% CI 1.3-3.0). Compared to the province of Quebec, the Atlantic region had half the risk of delay (OR=0.50; 95% CI 0.3-0.8), while the other regions did not show any difference in risk to Quebec.

In multivariate analyses, patient age, region and health professional first contacted remained statistically significant predictors in the final model (Table 8.18). The risk of patient delay was greater in older age groups that in the youngest age group. The Atlantic region still had a lower risk of patient delay when compared to Quebec. Contrary to the results in the univariate analysis, urban residence was associated with patient delay in the multivariate model. Patients living in urban areas had a lower risk of delay than patients living in rural areas (OR=0.6; 95% CI 0.4-0.9).

8.5.3.2. Determinants of physician delays

Three variables were associated with physician delay for patients with CNS tumours: Family income, type of health professional first contacted and patient delay (Table 8.19). Families in the highest income group had a lower risk of physician delay (OR=0.55; 95% CI 0.3-0.9). This association was not observed in the 'long delay' univariate analysis. With respect to first health professional contacted, patients who first contacted a GP were more likely to have longer physician delay than patients who first visited an ER (OR=0.29; 95% CI 0.2-0.5). Patient delay seemed to influence physician delay; the risk of the latter was lower in the longer patient delay groups compared to the reference group.

In multivariate analyses, family income was no longer associated with physician delay. Four parameters were statistically significant predictors of physician delay in the final model: patient age, region, health professional first contacted and patient delay

(Table 8.20). The oldest patient group had over twice the risk of physician delay than the children in the youngest age group. In these models, the Prairies and BC had over half the risk of delay than Quebec. Patients whose first visit was to a GP were at greater risk of physician delay than patients who went to an ER or other health professionals. Compared to the reference groups, children with longer patient delays had a lower risk of physician delay.

8.5.3.3. Determinants of health care systems delays

In univariate analyses, family income was associated with HCS delay. Patients in the highest income group had a statistically significantly lower risk of HCS delay than patients in the lowest income group (OR: 0.54; 95% CI 0.3-0.9) (Table 8.21). Patients whose first visit was to an ER showed a 70% reduction in risk of HCS delay relative to patients who first visited a GP (OR=0.26; 95% CI 0.2-0.4). Compared to patients who reported no patient delay, patients with longer patient delay showed a much lower risk of HCS delay.

However, in the 'long delay' univariate analyses, patient age, BMI and cancer subtype were statistically significant predictors of delay, while family income was not. When compared to the youngest age group, patients in the oldest age group had a greater risk of delay (OR=2.75; 95% CI 1.5-5.1). Children in the high-BMI group had a greater risk of HCS delay than patients in the mid-BMI group (OR=2.17; 95% CI 1.1-4.4). Regarding cancer subtype, the risk of HCS delay was 3 times greater (OR=3.09; 95% CI 1.7-5.8) for non-medulloblastoma patient compared to medulloblastoma patients. This association between HCS delay and health professional first contacted, as well as patient delay remained statistically significant when looking at the univariate results from the

'long delay' analyses.

In multivariate analyses, patient age, first healthcare professional consulted and patient delay were the only variables associated with HCS delay (Table 8.22). Patients in the oldest age group had a greater risk of delay than the patients in the youngest age group. As in univariate analyses, the risk of delay increased in older patients and was lower for patients who first visited an ER rather than a GP. Again, the risk of HCS delay was lower for patients in longer patient delay groups relative to patients who experienced no patient delay. However, family income was not related to HCS delay in multivariate analyses.

8.6. Discussion

In order to narrow down the associations of parameters in the cancer care pathway, I dissected the pathway into varying segments and found that the factors evaluated in this study influenced each type of delay differently. Although the sex of the patient was not associated with any delay, the age of the patient was an important risk factor for patient delays. Previous studies [Saha et al., 1993; Flores et al., 1986] have reported that the risk of longer diagnosis delays generally increased for children in older age groups. This study found that the effect of age may act primarily on the time segment attributable to the patient. For all three cancer types, the risk of longer patient delay increased for children in the older age groups. The relationship between age and patient delay remained in multivariate models even after accounting for cancer type and other statistically significant variables. This may be due, at least in part, to parents' tendency to pay more attention to their children when they are younger, whereas teens

tend to rely more on themselves and may be more reluctant to disclose symptoms to their parents.

If one assumes that patients' help-seeking behaviour is the sole reason for this observed effect of age on delay, then the effect of age should not extend to delays that occur once patients have entered into the health care system. It stands to reason that once into the health care system, events such as referral, diagnosis and treatment are likely out of the patient's control (assuming that compliance to recommended follow-up health care visits is not age-dependent), and so patient age should not influence these events. In fact, this study found that patient age does not affect physician delay or HCS delay in patients with leukemias and CNS tumours. However, age did have an effect on these delays in lymphoma patients. Interestingly, in multivariate models that account for the type of health professional first contacted, cancer subtype and patient delay, age was no longer a statistically significant predictor of these delays in lymphoma patients. Conversely, in models controlling for the same variables, age became a statistically significant predictor of physician delay and a marginally statistically significant predictor of HCS delay in patients with CNS tumours. This may be due to differences in the biology of diseases exhibited by the different age groups, e.g. younger patients may have more aggressive tumours that require more immediate care or lead to a less complicated diagnosis. It has been shown that the embryonal tumour medulloblastoma is more common in children than in adolescents [Bendel et al., 2006].

Patient BMI did not have an effect on patient delay for all three cancers, but patients with leukemias in the low-BMI group had a greater risk of longer physician delay compared to the mid-BMI group. It may be that leukemia in patients with a lower

BMI is a more indolent disease and therefore might have a longer time to referral or diagnosis. Lymphoma patients in the low-BMI group had a lower risk of long HCS delay. However, BMI did not influence physician delay. This suggests that the effect of BMI on HCS delay occurs from the time between diagnosis and treatment. However, this effect does not remain in the multivariate model.

This study found that patients with leukemias living in the highest income areas were more likely to experience longer patient delays and less likely to have physician delays than people living in areas with the lowest income. In Canada, one would not expect that financial concerns would have any effect on delays. Universal health coverage favours a scenario in which parents would not encounter economic barriers to deter them from seeking immediate medical attention when they perceive that their child is experiencing a seemingly serious health condition. However, family income may reflect parental level of education or the relative affluence of a given community in terms of availability of diagnostic services and access to cancer care. It has been found that patients whose parents have a higher education have a reduced risk of diagnosis delay [Fajardo-Gutierrez et al., 2002]. Population size and the type of community in which the patient lives may also reflect the availability of health services, but neither of these factors were associated with patient delay in any of the three cancers. However, population size, like family income, was related to physician delay in leukemia patients, which suggests that greater and equitable access to health care resources plays a role in reducing the time differential required to obtain a diagnosis. Family income was inversely related to physician delay and HCS delay in CNS tumour patients, but not population size or type of community. It is possible that greater family income may

allow for faster access to cancer care than is permitted via the normal universal access channels in the health care system.

The type of health professional first contacted by the patient to inquire about their symptoms had an effect on physician delay and HCS delay for all 3 cancers. Patients who were first seen in an ER had a lower risk of delay than patients whose first visit was to a GP. It stands to reason that visiting the ER would lead to a faster referral to an oncologist and a faster diagnosis, thereby diminishing the referral period. However, it is also likely that patients who feel the need to visit an ER have more severe symptoms and are more easily diagnosed.

The influence of cancer subtype on delay varies according to the type of cancer and the form of delay. While there was no association between cancer subtype and delay in patients with CNS tumours, in the case of leukemia, patients with ALL had a higher risk of patient delay than non-ALL patients. This may be related to the type of identifiable symptoms that are exhibited by the two groups. Conversely, in lymphoma, cancer subtype was related to physician delay and HCS delay, but not patient delay. Non-Hodgkin lymphoma patients had a lower risk of physician and HCS delay than patients with Hodgkin lymphoma. This may be attributed to the presentation of the cancer symptoms experienced by Hodgkin and non-Hodgkin lymphoma patients. In contrast to those with non-Hodgkin lymphomas, patients with Hodgkin lymphomas typically have an indolent onset of disease, and the involved lymph nodes, particularly those in the neck may wax and wane, a pattern also seen in inflammatory lymph node disease. This could explain the difference in delays between the lymphoma subtypes.

There was no difference in the risk of any delay between regions for lymphoma

patients. However, patients with leukemias and CNS tumours living in the Atlantic region had a lower risk of patient delay than patients in Quebec. Conversely, leukemia patients in the Atlantic region had a greater risk of physician delay than Quebec patients. Differences in cancer awareness, health practices and health resources in each region may account for these observations. Again, disease severity may play a role in this relationship. For example, it is possible that if leukemia patients in Quebec have a longer patient delay than patient in the Atlantic region, the disease would have had more time to progress and be more evident on presentation to a healthcare professional. This would require immediate action and would therefore have a shorter physician delay time. However, in multivariate models, the increase in risk of physician delay in the Atlantic region no longer remained statistically significant, but the Prairies and BC showed a lower risk of physician delay than Quebec.

An interesting finding in this study that has not been investigated previously is the effect of patient delay on the risk of "downstream" delays. Once patients enter the healthcare system, the times to diagnosis and treatment were shorter for patients who experienced longer patient delays. Since times of treatment delay and oncologist delay are relatively short (as shown in chapter 7), the observed effect of patient delay is likely influenced by the relationship between patient delay and referral delay. It is possible that patients with longer patient delays have more severe disease or more overtly recognizable signs and symptoms that will alert physicians to a possible diagnosis of cancer and lead to faster referrals to an oncologist.

In conclusion, the present study adds to current findings in the literature by examining the influence of several variables on various types of delays in the care of

children and adolescents with cancer. Factors relating to the patients, the parents, the health care system and the cancer itself may all exert different influences on the various segments of the cancer care pathway. Further investigation on this topic would clarify the mechanisms behind these relationships.

Table 8.1: Description of leukemia, lymphoma and CNS tumour patients

Study Population Characteristics	Leukemias N=963	Lymphomas N=397	CNS Tumours N=543
Patient age (years) [Mean (SD)]	6.7 (4.8)	11.8 (4.8)	8.3 (4.9)
Sex [n(%)]			
Female	422 (43.8)	148 (37.3)	257 (47.3)
Male	541 (56.2)	249 (62.7)	286 (52.7)
Body Mass Index [Mean (SD)]	18.21 (9.9)	20.71 (16.9)	18.50 (9.0)
Median income ($) [Mean (SD)]	53749 (12799)	53925 (13322)	52986 (14086)
Population size [Mean (SD)]	30 766 (20 767)	30 446 (21 688)	29 996 (19 363)
First health contact [n (%)]			
GP	474 (49.2)	244 (61.5)	184 (33.9)
ER	154 (16.0)	60 (15.1)	176 (32.4)
Other	323 (33.5)	88 (22.2)	166 (30.6)
Region [n (%)]			
Quebec	337 (35.0)	143 (36.0)	194 (35.7)
Atlantic	160 (16.6)	57 (14.4)	121 (22.3)
Prairies	268 (27.8)	132 (33.3)	148 (27.3)
British Columbia	195 (20.3)	62 (15.6)	79 (14.6)
Cancer suptype [n (%)]			
ALL	791 (82.1)	--	--
Non-ALL	170 (17.7)	--	--
Hodgkin lymphoma	--	200 (50.4)	--
Non-Hodgkin lymphoma	--	177 (44.6)	--
Medulloblastoma	--	--	113 (20.8)
Other CNS tumour	--	--	414 (76.2)
Community Type [n (%)]			
Rural	249 (25.9)	101 (25.4)	145 (26.7)
Urban	658 (68.3)	268 (67.5)	348 (64.1)
Patient delay (days) [Median (IQR)]	8 (1-21)	11 (2-39)	14 (0-42)
Physician delay (days) [Median (IQR)]	3 (1-14)	11 (4-41)	16 (4-56)
HCS delay (days) [Median (IQR)]	6 (3-16)	27 (11-54)	19 (5-61)

Note: Totals are not equal across categories due to missing values.

Table 8.2: Distribution of delays (in days) across socio-demographic variables for leukemia patients

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Age												
under 2.88	55	80	51	48	13	87	78	59	49	63	56	64
2.89 - 4.86	47	72	67	55	13	82	80	64	63	46	65	62
4.87 - 10.32	44	68	60	63	11	94	76	52	44	70	59	56
10.33 and up	43	58	58	75	19	79	68	68	51	64	52	67
Sex												
M	80	127	101	105	22	145	135	110	90	103	100	114
F	109	151	135	136	34	197	167	133	117	140	132	135
BMI												
Low (under 15.58)	49	74	84	63	14	112	84	59	61	82	59	64
Mid (15.59 - 17.71)	52	79	53	77	13	84	90	74	57	63	62	76
High (17.72 and up)	47	89	74	62	16	105	87	67	59	75	73	67
Family income												
Under $ 45 052	41	80	55	42	8	71	69	68	38	57	49	68
$ 45 053 - $ 51 907	52	80	45	47	8	84	73	57	44	54	62	59
$ 51 908 - $ 60 675	35	55	59	67	21	77	65	52	53	61	44	54
$ 60 676 and up	42	51	61	61	14	91	61	51	63	54	49	50
Community type												
Rural	44	90	55	55	11	81	78	71	48	55	63	72
Urban	133	178	167	169	40	248	200	160	153	178	146	163

Note: Totals are not equal across categories because of missing values.

Table 8.2: Distribution of delays (in days) across socio-demographic variables for leukemia patients (cont.)

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Population size												
under 16 072	54	56	54	54	12	72	78	57	45	62	52	58
16 073 - 26 146	41	66	64	49	12	100	49	58	60	60	39	59
26 147 - 39 809	43	67	49	59	12	77	72	56	36	60	60	57
39 810 and up	32	77	53	55	15	74	69	57	57	44	53	57
Region												
Quebec	47	96	96	94	20	129	111	73	74	81	100	74
Atlantic	51	50	31	24	4	36	55	59	20	42	28	62
Prairies	62	70	53	77	24	95	80	64	54	71	64	69
British Columbia	28	62	55	45	8	80	55	47	57	49	39	44
First health contact												
GP	109	135	111	113	18	139	160	150	74	110	123	152
Other	38	30	33	48	12	57	39	43	24	42	37	46
ER	41	111	92	76	25	144	101	49	107	88	71	50
Cancer subtype												
ALL	137	232	200	207	42	287	257	191	179	203	199	193
Non-ALL	50	46	36	34	14	55	45	50	28	40	33	54

Note: Totals are not equal across categories because of missing values.

Table 8.3: Distribution of delays (in days) across socio-demographic variables for lymphoma patients

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Age												
under 8.24	27	34	21	18	31	27	16	25	35	22	19	19
8.25 - 13.09	26	20	27	26	23	19	29	25	27	23	22	26
13.1 - 15.64	20	22	28	27	23	23	23	25	17	33	21	23
15.65 and up	26	20	25	28	16	22	35	23	12	20	35	28
Sex												
M	41	36	38	33	29	37	40	39	27	38	37	42
F	58	60	63	66	64	54	63	59	64	60	60	54
BMI												
Low (under 16.94)	24	25	34	26	21	26	28	32	20	27	23	36
Mid (16.95 - 20.74)	31	30	28	21	33	29	24	23	38	30	22	17
High (20.75 and up)	29	25	27	33	23	19	38	30	14	28	38	29
Family income												
Under $ 45 003	22	21	27	19	17	24	20	22	22	27	15	21
$ 45 004 - $ 51 696	19	26	24	23	17	21	27	26	18	19	32	23
$ 51 697 - $ 61 135	25	23	24	17	23	18	21	25	23	22	18	21
$ 61 136 and up	25	20	21	24	25	21	24	19	24	16	23	24
Community type												
Rural	25	23	29	23	24	23	27	22	27	24	24	21
Urban	69	68	68	62	59	62	69	71	61	62	67	69

Note: Totals are not equal across categories because of missing values.

Table 8.3: Distribution of delays (in days) across socio-demographic variables for lymphoma patients (cont.)

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Population size												
under 15 734	29	21	22	18	20	26	18	24	19	25	20	22
15 735 - 25 171	21	24	26	20	21	17	25	25	23	18	28	21
25 172 - 39 811	19	27	22	22	17	16	27	26	19	17	23	26
39 812 and up	22	18	26	23	24	25	22	17	26	24	17	20
Region												
Quebec	23	42	43	34	30	41	36	33	37	35	36	31
Atlantic	23	10	16	8	9	9	15	20	15	9	14	16
Prairies	39	20	26	46	33	31	34	31	22	37	31	37
British Columbia	13	23	15	11	19	10	18	13	15	17	16	11
First health contact												
GP	63	65	59	56	40	53	74	69	41	60	64	71
Other	12	9	18	20	21	7	12	18	12	15	14	15
ER	24	22	22	20	29	30	17	10	35	21	19	10
Cancer Subtype												
Hodgkin lymphoma	49	46	46	58	28	47	55	65	27	40	59	67
Non-Hodgkin lymphoma	44	46	51	35	58	39	43	31	57	56	34	25

Note: Totals are not equal across categories because of missing values.

Table 8.4: Distribution of delays (in days) across socio-demographic variables for CNS tumour patients

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Age												
under 4.42	36	42	29	24	24	43	42	21	27	36	39	20
4.43 - 7.74	26	30	30	42	39	38	20	29	36	36	23	27
7.75 - 11.83	29	28	37	35	31	30	33	36	25	32	34	34
11.84 and up	42	19	33	29	17	31	32	41	19	29	28	41
Sex												
M	61	64	61	60	57	63	68	56	50	67	63	54
F	72	55	68	70	54	79	59	71	57	66	61	68
BMI												
Low (under 15.68)	25	26	14	18	14	28	26	18	16	31	18	17
Mid (15.69 - 18.42)	19	22	22	20	16	27	25	18	15	22	29	18
High (18.43 and up)	26	14	18	28	12	21	18	32	12	23	16	29
Family income												
Under $ 43 688	36	27	25	26	19	31	37	27	21	28	36	24
$ 43 689 - $ 49 993	28	22	30	30	27	34	23	25	31	25	23	29
$ 49 994 - $ 59 562	30	27	25	29	19	25	32	33	15	29	31	32
$ 59 563 and up	24	29	32	28	32	33	26	20	27	36	24	18
Community type												
Rural	29	32	36	37	28	34	33	43	31	27	35	40
Urban	93	77	82	78	73	91	90	67	67	95	82	68

Note: Totals are not equal across categories because of missing values.

Table 8.4: Distribution of delays (in days) across socio-demographic variables for CNS tumour patients (cont.)

Study Variables	Patient Delay				Physician Delay				HCS delay			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Population size												
under 16 567	29	30	26	27	33	25	33	20	34	22	31	19
16 568 - 26 503	32	20	34	26	30	26	32	24	23	34	26	25
26 504 - 38 822	31	30	21	31	14	39	30	29	22	29	26	31
38 823 and up	26	25	31	29	20	33	23	32	15	33	31	28
Region												
Quebec	37	43	56	45	31	52	55	39	40	46	48	39
Atlantic	46	25	24	21	24	24	36	30	21	28	29	32
Prairies	39	26	34	41	36	45	24	39	33	38	28	36
British Columbia	10	25	15	23	20	21	12	18	13	21	19	14
First health contact												
GP	52	52	41	34	23	42	59	53	24	38	62	50
Other	45	25	48	50	35	40	36	51	23	43	34	48
ER	35	41	39	45	51	58	32	23	58	51	27	24
Cancer subtype												
Medulloblastoma	20	30	33	26	27	35	34	14	33	27	37	13
Other CNS tumour	106	86	93	101	80	102	89	110	72	101	83	106

Note: Totals are not equal across categories because of missing values.

Table 8.5: Crude association between patient delay and socio-demographic variables for leukemia patients

	Patient Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 2.88	ref (---)	ref (---)	ref (---)
2.89 - 4.86	1.53 (-0.2-4.6)	1.40 (1.0-2.0)	1.15 (0.7-1.8)
4.87 - 10.32	1.93 (0.0-5.2)	1.50 (1.0-2.2)	1.42 (0.9-2.2)
10.33 and up	3.25 (0.9-7.3)	1.80 (1.2-2.6)	1.83 (1.2-2.8)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-0.19 (-1.3-1.6)	1.05 (0.8-1.4)	1.01 (0.8-1.4)
BMI			
Low (under 15.58)	0.11 (-1.4-2.8)	0.83 (0.6-1.2)	1.38 (0.9-2.0)
Mid (15.59 - 17.71)	ref (---)	ref (---)	ref (---)
High (17.72 and up)	-0.53 (-1.8-1.8)	0.84 (0.6-1.2)	0.97 (0.7-1.4)
Family income			
Under $ 45 052	ref (---)	ref (---)	ref (---)
$ 45 053 - $ 51 907	-0.47 (-1.6-1.7)	0.87 (0.6-1.3)	1.11 (0.7-1.8)
$ 51 908 - $ 60 675	3.62 (1.0-8.2)	1.75 (1.2-2.6)	1.88 (1.2-2.9)
$ 60 676 and up	2.39 (0.2-6.2)	1.64 (1.1-2.4)	1.66 (1.1-2.6)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	1.58 (-0.4-4.8)	1.30 (0.9-1.9)	1.49 (1.0-2.2)
ER	1.50 (-0.1-3.9)	1.20 (0.9-1.6)	0.98 (0.7-1.4)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	-5.13 (-5.3--4.4)	0.41 (0.3-0.6)	0.46 (0.3-0.8)
Prairies	-1.72 (-2.9-0.4)	0.74 (0.5-1.0)	1.06 (0.7-1.5)
British Columbia	-0.97 (-2.5-1.8)	0.84 (0.6-1.2)	0.79 (0.5-1.2)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	0.77 (-0.6-3.2)	1.32 (1.0-1.8)	1.21 (0.9-1.7)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.5: Crude association between patient delay and socio-demographic variables for leukemia patients (cont.)

	Patient Delay		
	Linear* Δ Y‡ (95% CI)	Median** OR (95% CI)	Long*** OR (95% CI)
Population size			
under 16 072	ref (---)	ref (---)	ref (---)
16 073 - 26 146	0.22 (-1.3-3.2)	1.08 (0.7-1.6)	0.87 (0.6-1.4)
26 147 - 39 809	0.47 (-1.2-3.6)	1.00 (0.7-1.5)	1.13 (0.7-1.7)
39 810 and up	0.69 (-1.0-3.9)	1.01 (0.7-1.5)	1.03 (0.7-1.6)
Cancer subtype			
ALL	ref (---)	ref (---)	ref (---)
Non-ALL	-2.92 (-3.7--1.6)	0.67 (0.5-0.9)	0.71 (0.5-1.1)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.
**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.
*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.
‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.6: Multivariate analyses of patient delay for leukemia patients

	OR (95% CI)
Age	
under 2.88	ref (---)
2.89 - 4.86	1.20 (0.8-1.7)
4.87 - 10.32	1.48 (1.0-2.2)
10.33 and up	2.02 (1.4-3.0)
Family income	
Under $ 45 052	ref (---)
$ 45 053 - $ 51 907	0.78 (0.5-1.2)
$ 51 908 - $ 60 675	1.63 (1.1-2.5)
$ 60 676 and up	1.49 (1.0-2.2)
Region	
Quebec	ref (---)
Atlantic	0.40 (0.3-0.6)
Prairies	0.65 (0.5-0.9)
British Columbia	0.78 (0.5-1.1)
Cancer subtype	
ALL	ref (---)
Non-ALL	0.63 (0.4-0.9)

Table 8.7: Crude association between physician delay and socio-demographic variables for leukemia patients

	Physician Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 2.88	ref (---)	ref (---)	ref (---)
2.89 - 4.86	0.24 (-0.9-2.2)	1.11 (0.8-1.6)	1.10 (0.7-1.7)
4.87 - 10.32	-0.41 (-1.3-1.2)	0.89 (0.6-1.3)	0.87 (0.6-1.3)
10.33 and up	0.27 (-0.9-2.2)	1.01 (0.7-1.5)	1.24 (0.8-1.9)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-0.31 (-1.1-0.8)	0.89 (0.7-1.1)	0.92 (0.7-1.2)
BMI			
Low (under 15.58)	1.13 (-0.1-3.1)	1.49 (1.1-2.1)	1.41 (0.9-2.1)
Mid (15.59 - 17.71)	ref (---)	ref (---)	ref (---)
High (17.72 and up)	0.56 (-0.5-2.2)	1.12 (0.8-1.6)	1.15 (0.8-1.7)
Family income			
Under $ 45 052	ref (---)	ref (---)	ref (---)
$ 45 053 - $ 51 907	-0.48 (-1.6-1.5)	0.81 (0.6-1.2)	0.75 (0.5-1.1)
$ 51 908 - $ 60 675	-1.37 (-2.2-0.2)	0.69 (0.5-1.0)	0.69 (0.5-1.1)
$ 60 676 and up	-1.64 (-2.3--0.3)	0.62 (0.4-0.9)	0.67 (0.4-1.0)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-1.36 (-2.4-0.3)	0.60 (0.4-0.9)	0.84 (0.6-1.3)
ER	-3.44 (-3.7--2.9)	0.45 (0.3-0.6)	0.38 (0.3-0.6)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	3.84 (1.6-7.3)	2.31 (1.5-3.5)	2.21 (1.5-3.4)
Prairies	0.12 (-0.8-1.6)	0.98 (0.7-1.4)	1.15 (0.8-1.7)
British Columbia	0.26 (-0.8-2.0)	0.94 (0.7-1.3)	1.17 (0.8-1.8)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.7: Crude association between physician delay and socio-demographic variables for leukemia patients (cont.)

	Physician Delay		
	Linear* Δ Y‡ (95% CI)	Median** OR (95% CI)	Long*** OR (95% CI)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-1.31 (-2.0--0.1)	0.77 (0.6-1.0)	0.79 (0.6-1.1)
Population size			
under 16 072	ref (---)	ref (---)	ref (---)
16 073 - 26 146	-0.97 (-1.8-0.6)	0.59 (0.4-0.9)	1.02 (0.7-1.6)
26 147 - 39 809	-0.08 (-1.2-1.9)	0.89 (0.6-1.3)	0.99 (0.6-1.5)
39 810 and up	-0.41 (-1.4-1.4)	0.88 (0.6-1.3)	1.03 (0.7-1.6)
Cancer Subtype			
ALL	ref (---)	ref (---)	ref (---)
Non-ALL	1.05 (-0.3-2.9)	1.05 (0.8-1.5)	1.34 (0.9-1.9)
Patient Delay Category			
under 1	ref (---)	ref (---)	ref (---)
1 - 7	-8.78 (-8.4--8.8)	0.28 (0.2-0.4)	0.30 (0.2-0.5)
8 - 20	-9.73 (-9.0--10.1)	0.26 (0.2-0.4)	0.18 (0.1-0.3)
21 and up	-10.21 (-9.4--10.8)	0.19 (0.1-0.3)	0.16 (0.1-0.3)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.
**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.
*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.
‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.8: Multivariate analyses of physician delay for leukemia patients

	OR (95% CI)
BMI	
Low (under 15.58)	1.70 (1.2-2.5)
Mid (15.59 - 17.71)	ref (---)
High (17.72 and up)	1.17 (0.8-1.7)
Region	
Quebec	ref (---)
Atlantic	1.30 (0.8-2.1)
Prairies	0.51 (0.3-0.8)
British Columbia	0.61 (0.4-0.9)
First health contact	
GP	ref (---)
Other	0.48 (0.3-0.7)
ER	0.41 (0.3-0.6)
Population size	
under 16 072	ref (---)
16 073 - 26 146	0.62 (0.4-0.9)
26 147 - 39 809	1.05 (0.7-1.6)
39 810 and up	1.00 (0.7-1.5)
Patient Delay Category	
under 1	ref (---)
1 - 7	0.30 (0.2-0.5)
8 - 20	0.29 (0.2-0.5)
21 and up	0.19 (0.1-0.3)

Table 8.9: Crude association between HCS delay and socio-demographic variables for leukemia patients

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 2.88	ref (---)	ref (---)	ref (---)
2.89 - 4.86	-0.37 (-1.7-1.8)	1.09 (0.8-1.6)	0.96 (0.6-1.4)
4.87 - 10.32	-0.56 (-1.8-1.6)	0.94 (0.7-1.4)	0.79 (0.5-1.2)
10.33 and up	-0.05 (-1.5-2.3)	0.97 (0.7-1.4)	1.05 (0.7-1.6)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-0.34 (-1.3-1.1)	0.94 (0.7-1.2)	0.90 (0.7-1.2)
BMI			
Low (under 15.58)	0.97 (-0.5-3.3)	1.34 (0.9-1.9)	1.38 (0.9-2.0)
Mid (15.59 - 17.71)	ref (---)	ref (---)	ref (---)
High (17.72 and up)	0.31 (-1.0-2.3)	1.21 (0.9-1.7)	1.10 (0.7-1.6)
Family income			
Under $ 45 052	ref (---)	ref (---)	ref (---)
$ 45 053 - $ 51 907	-0.39 (-1.9-2.1)	1.00 (0.7-1.5)	0.77 (0.5-1.2)
$ 51 908 - $ 60 675	-1.47 (-2.6-0.6)	0.70 (0.5-1.0)	0.72 (0.5-1.1)
$ 60 676 and up	-2.12 (-3.1--0.4)	0.69 (0.5-1.0)	0.67 (0.4-1.0)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-0.25 (-1.9-2.3)	0.84 (0.6-1.2)	0.78 (0.5-1.2)
ER	-4.38 (-4.8--3.7)	0.42 (0.3-0.6)	0.37 (0.3-0.5)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	4.07 (1.5-7.9)	1.29 (0.9-1.9)	2.50 (1.7-3.8)
Prairies	0.70 (-0.7-2.8)	0.95 (0.7-1.3)	1.21 (0.8-1.7)
British Columbia	-0.29 (-1.5-1.6)	0.70 (0.5-1.0)	1.05 (0.7-1.6)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-1.34 (-2.3-0.2)	0.71 (0.5-1.0)	0.83 (0.6-1.1)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.9: Crude association between HCS delay and socio-demographic variables for leukemia patients (cont.)

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Population size			
under 16 072	ref (---)	ref (---)	ref (---)
16 073 - 26 146	-0.77 (-2.0-1.3)	0.79 (0.5-1.2)	0.95 (0.6-1.4)
26 147 - 39 809	0.50 (-1.1-3.2)	1.19 (0.8-1.7)	1.00 (0.7-1.5)
39 810 and up	-0.56 (-1.8-1.6)	1.06 (0.7-1.5)	0.97 (0.6-1.5)
Cancer Subtype			
ALL	ref (---)	ref (---)	ref (---)
Non-ALL	2.36 (0.4-5.0)	1.31 (0.9-1.8)	1.54 (1.1-2.2)
Patient Delay Category			
under 1	ref (---)	ref (---)	ref (---)
1 - 7	-9.99 (-9.8--9.6)	0.41 (0.3-0.6)	0.29 (0.2-0.4)
8 - 20	-11.18 (-10.7--11.2)	0.28 (0.2-0.4)	0.16 (0.1-0.3)
21 and up	-11.93 (-11.2--12.3)	0.25 (0.2-0.4)	0.14 (0.1-0.2)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.
**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.
*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.
‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.10: Multivariate analyses of HCS delay for leukemia patients

	OR (95% CI)
Region	
Quebec	ref (---)
Atlantic	0.72 (0.5-1.1)
Prairies	0.61 (0.4-0.9)
British Columbia	0.47 (0.3-0.7)
First health contact	
GP	ref (---)
Other	0.65 (0.4-1.0)
ER	0.36 (0.3-0.5)
Patient Delay Category	
under 1	ref (---)
1 - 7	0.45 (0.3-0.7)
8 - 20	0.30 (0.2-0.5)
21 and up	0.26 (0.2-0.4)

Table 8.11: Crude association of patient delay and socio-demographic variables for lymphoma patients

	Patient Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 8.24	ref (---)	ref (---)	ref (---)
8.25 - 13.09	2.62 (-1.0-12.5)	1.77 (1.0-3.1)	1.60 (0.8-3.0)
13.1 - 15.64	6.58 (0.8-21.5)	2.01 (1.1-3.6)	1.80 (1.0-3.4)
15.65 and up	4.10 (-0.3-15.8)	1.77 (1.0-3.1)	1.75 (0.9-3.3)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	1.41 (-1.5-8.2)	1.20 (0.8-1.8)	1.04 (0.7-1.6)
BMI			
Low (under 16.94)	-3.83 (-5.0-1.3)	0.67 (0.4-1.1)	0.74 (0.4-1.3)
Mid (16.95 - 20.74)	ref (---)	ref (---)	ref (---)
High (20.75 and up)	-0.36 (-3.4-8.7)	0.91 (0.5-1.5)	0.83 (0.5-1.5)
Family income			
Under $ 45 003	ref (---)	ref (---)	ref (---)
$ 45 004 - $ 51 696	0.85 (-2.7-12.0)	0.98 (0.5-1.7)	1.47 (0.8-2.8)
$ 51 697 - $ 61 135	-2.16 (-4.0-5.1)	0.82 (0.5-1.5)	0.84 (0.4-1.7)
$ 61 136 and up	0.13 (-3.0-10.4)	0.93 (0.5-1.7)	1.68 (0.9-3.2)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	6.73 (0.3-21.1)	2.11 (1.2-3.8)	1.62 (0.9-2.9)
ER	0.45 (-2.5-7.1)	1.02 (0.6-1.7)	0.87 (0.5-1.5)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	-6.68 (-7.0--3.2)	0.63 (0.3-1.2)	0.48 (0.2-1.0)
Prairies	-0.36 (-3.4-7.7)	1.03 (0.6-1.7)	1.37 (0.8-2.3)
British Columbia	-2.69 (-5.1-5.3)	0.61 (0.3-1.1)	0.71 (0.4-1.4)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-0.83 (-3.0-5.8)	0.88 (0.6-1.4)	1.05 (0.6-1.7)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.11: Crude association of patient delay and socio-demographic variables for lymphoma patients (cont.)

	Patient Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Population size			
under 15 734	ref (---)	ref (---)	ref (---)
15 735 - 25 171	2.70 (-1.3-14.4)	1.31 (0.7-2.3)	1.12 (0.6-2.2)
25 172 - 39 811	1.80 (-1.6-12.2)	1.20 (0.7-2.1)	1.18 (0.6-2.3)
39 812 and up	3.86 (-0.8-17.1)	1.53 (0.8-2.8)	1.41 (0.7-2.7)
Cancer subtype			
Hodgkin lymphoma	ref (---)	ref (---)	ref (---)
Non-Hodgkin lymphoma	-2.54 (-4.2-1.8)	0.86 (0.6-1.3)	0.59 (0.4-0.9)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.
**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.
*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.
‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.12: Multivariate analyses of patient delay for lymphoma patients

	OR (95% CI)
Age	
under 8.24	ref (---)
8.25 - 13.09	1.90 (1.1-3.4)
13.1 - 15.64	2.22 (1.2-4.0)
15.65 and up	2.00 (1.1-3.6)
First health contact	
GP	ref (---)
Other	2.33 (1.3-4.3)
ER	1.09 (0.7-1.8)

Table 8.13: Crude association of physician delay and socio-demographic variables for lymphoma patients

	Physician Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 8.24	ref (---)	ref (---)	ref (---)
8.25 - 13.09	5.11 (-0.5-18.7)	1.86 (1.1-3.3)	1.29 (0.7-2.5)
13.1 - 15.64	1.00 (-2.5-10.3)	1.51 (0.9-2.7)	1.05 (0.5-2.1)
15.65 and up	4.47 (-0.8-17.4)	2.21 (1.2-3.9)	0.96 (0.5-1.9)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-1.81 (-4.2-3.9)	0.86 (0.6-1.3)	0.87 (0.5-1.4)
BMI			
Low (under 16.94)	-5.34 (-6.9-0.3)	0.58 (0.3-1.0)	0.67 (0.4-1.3)
Mid (16.95 - 20.74)	ref (---)	ref (---)	ref (---)
High (20.75 and up)	-0.45 (-4.4-10.0)	1.27 (0.7-2.2)	1.01 (0.5-1.9)
Family income			
Under $ 45 003	ref (---)	ref (---)	ref (---)
$ 45 004 - $ 51 696	-0.59 (-4.5-11.3)	1.36 (0.7-2.5)	0.78 (0.4-1.6)
$ 51 697 - $ 61 135	-1.92 (-5.1-8.5)	1.07 (0.6-2.0)	0.95 (0.5-1.9)
$ 61 136 and up	-3.09 (-5.6-5.9)	0.91 (0.5-1.7)	0.70 (0.3-1.4)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-5.71 (-8.4-1.2)	0.67 (0.4-1.2)	0.98 (0.5-1.9)
ER	-11.00 (-11.1--9.3)	0.30 (0.2-0.5)	0.28 (0.1-0.6)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	7.41 (-0.5-25.9)	1.94 (1.0-3.8)	2.12 (1.0-4.3)
Prairies	-0.63 (-3.6-6.5)	1.05 (0.6-1.7)	1.11 (0.6-2.0)
British Columbia	-1.25 (-4.6-7.6)	1.10 (0.6-2.0)	1.00 (0.5-2.1)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.13: Crude association of physician delay and socio-demographic variables for lymphoma patients (cont.)

	Physician Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	2.17 (-1.8-11.6)	1.10 (0.7-1.8)	1.03 (0.6-1.8)
Population size			
under 15 734	ref (---)	ref (---)	ref (---)
15 735 - 25 171	1.60 (-3.1-14.7)	1.41 (0.8-2.6)	0.90 (0.4-1.8)
25 172 - 39 811	2.12 (-2.9-15.8)	1.76 (1.0-3.2)	1.10 (0.6-2.2)
39 812 and up	-3.16 (-5.3-4.5)	0.87 (0.5-1.6)	0.72 (0.4-1.5)
Cancer subtype			
Hodgkin lymphoma	ref (---)	ref (---)	ref (---)
Non-Hodgkin lymphoma	-10.62 (-10.8--8.8)	0.48 (0.3-0.7)	0.47 (0.3-0.8)
Patient Delay Category			
under 2	ref (---)	ref (---)	ref (---)
2 – 10	-14.66 (-13.9--11.7)	0.42 (0.2-0.8)	0.26 (0.1-0.5)
11 – 38	-13.97 (-13.5--10.5)	0.48 (0.3-0.9)	0.20 (0.1-0.4)
39 and up	-15.41 (-14.2--13.3)	0.36 (0.2-0.7)	0.29 (0.2-0.6)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.14: Multivariate analyses of physician delay for lymphoma patients

	OR (95% CI)
Health Professional	
GP	ref (---)
Other	0.81 (0.4-1.5)
ER	0.30 (0.2-0.5)
Population size	
under 15 734	ref (---)
15 735 - 25 171	1.54 (0.8-2.9)
25 172 - 39 811	2.17 (1.1-4.2)
39 812 and up	0.94 (0.5-1.8)
Cancer Subtype	
Hodgkin disease	ref (---)
Other	0.49 (0.3-0.8)
Patient Delay Category	
under 2	ref (---)
2 - 10	0.34 (0.2-0.7)
11 - 38	0.42 (0.2-0.8)
39 and up	0.29 (0.2-0.6)

Table 8.15: Crude association of HCS delay and socio-demographic variables for lymphoma patients

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 8.24	ref (---)	ref (---)	ref (---)
8.25 - 13.09	5.82 (-1.4-21.7)	1.44 (0.8-2.5)	1.73 (0.8-3.5)
13.1 - 15.64	6.07 (-1.3-22.4)	1.32 (0.7-2.3)	1.44 (0.7-3.0)
15.65 and up	14.81 (3.4-38.7)	2.95 (1.6-5.3)	2.12 (1.0-4.3)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-6.37 (-9.5-0.9)	0.76 (0.5-1.1)	0.62 (0.4-1.0)
BMI			
Low (under 16.94)	-10.83 (-12.6—4.5)	0.46 (0.3-0.8)	0.40 (0.2-0.8)
Mid (16.95 - 20.74)	ref (---)	ref (---)	ref (---)
High (20.75 and up)	4.80 (-3.8-23.3)	1.27 (0.7-2.2)	0.96 (0.5-1.8)
Family income			
Under $ 45 003	ref (---)	ref (---)	ref (---)
$ 45 004 - $ 51 696	0.67 (-5.8-17.3)	2.02 (1.1-3.7)	0.79 (0.4-1.6)
$ 51 697 - $ 61 135	-1.70 (-7.1-13.1)	1.18 (0.6-2.2)	0.83 (0.4-1.7)
$ 61 136 and up	0.79 (-5.8-17.8)	1.60 (0.9-2.9)	0.97 (0.5-1.9)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-6.35 (-12.3-6.1)	0.80 (0.4-1.4)	0.90 (0.5-1.7)
ER	-20.09 (-20.0—18.2)	0.39 (0.2-0.6)	0.28 (0.1-0.6)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	3.54 (-4.2-20.6)	1.34 (0.7-2.5)	1.52 (0.7-3.1)
Prairies	7.39 (-0.5-22.7)	1.24 (0.8-2.0)	1.34 (0.8-2.4)
British Columbia	0.90 (-5.4-15.1)	0.91 (0.5-1.7)	0.81 (0.4-1.8)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.15: Crude association of HCS delay and socio-demographic variables for lymphoma patients (cont.)

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	2.46 (-3.4-15.5)	1.25 (0.8-2.0)	1.25 (0.7-2.2)
Population size			
under 15 734	ref (---)	ref (---)	ref (---)
15 735 - 25 171	0.53 (-6.0-17.4)	1.25 (0.7-2.3)	1.01 (0.5-2.1)
25 172 - 39 811	1.90 (-5.4-20.3)	1.43 (0.8-2.6)	1.23 (0.6-2.5)
39 812 and up	-3.41 (-8.0-9.7)	0.78 (0.4-1.4)	0.92 (0.4-1.9)
Cancer subtype			
Hodgkin lymphoma	ref (---)	ref (---)	ref (---)
Non-Hodgkin lymphoma	-21.38 (-21.1--19.8)	0.28 (0.2-0.4)	0.32 (0.2-0.5)
Patient Delay Category			
under 2	ref (---)	ref (---)	ref (---)
2 – 10	-22.22 (-21.7--18.1)	0.33 (0.2-0.6)	0.23 (0.1-0.5)
11 – 38	-18.81 (-19.7--12.1)	0.36 (0.2-0.6)	0.23 (0.1-0.5)
39 and up	-18.37 (-19.6--10.9)	0.42 (0.2-0.8)	0.37 (0.2-0.7)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.16: Multivariate analyses of HCS delay for lymphoma patients

	OR (95% CI)
Family income	
Under $ 45 003	ref (---)
$ 45 004 - $ 51 696	2.51 (1.3-4.9)
$ 51 697 - $ 61 135	1.00 (0.5-2.0)
$ 61 136 and up	1.75 (0.9-3.5)
First health contact	
GP	ref (---)
Other	1.19 (0.6-2.3)
ER	0.45 (0.3-0.8)
Cancer Subtype	
Hodgkin disease	ref (---)
Other	0.22 (0.1-0.4)
Patient Delay Category	
under 2	ref (---)
2 - 10	0.26 (0.1-0.5)
11 - 38	0.32 (0.2-0.6)
39 and up	0.31 (0.2-0.6)

Table 8.17: Crude association of patient delay and socio-demographic variables for CNS tumour patients

	Patient Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 4.42	ref (---)	ref (---)	ref (---)
4.43 - 7.74	6.03 (0.6-19.6)	1.89 (1.2-3.1)	1.42 (0.8-2.4)
7.75 - 11.83	5.17 (0.2-17.7)	1.86 (1.1-3.0)	1.22 (0.7-2.1)
11.84 and up	1.73 (-1.5-10.5)	1.50 (0.9-2.5)	1.27 (0.7-2.1)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	-0.38 (-2.8-4.9)	1.12 (0.8-1.6)	0.99 (0.7-1.4)
BMI			
Low (under 15.68)	3.85 (-1.0-20.4)	1.63 (0.9-3.0)	1.42 (0.7-2.8)
Mid (15.69 - 18.42)	ref (---)	ref (---)	ref (---)
High (18.43 and up)	4.56 (-0.7-22.2)	1.83 (1.0-3.4)	1.84 (1.0-3.6)
Family income			
Under $ 43 688	ref (---)	ref (---)	ref (---)
$ 43 689 - $ 49 993	3.98 (-0.7-16.8)	1.48 (0.9-2.5)	1.52 (0.9-2.6)
$ 49 994 - $ 59 562	3.06 (-1.1-14.7)	1.17 (0.7-2.0)	1.28 (0.7-2.2)
$ 59 563 and up	2.72 (-1.2-13.9)	1.40 (0.8-2.4)	1.45 (0.8-2.5)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	4.63 (0.1-14.7)	1.94 (1.3-3.0)	1.76 (1.1-2.8)
ER	3.09 (-0.7-11.8)	1.53 (1.0-2.4)	1.47 (0.9-2.3)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	-7.21 (-7.3--4.9)	0.50 (0.3-0.8)	0.59 (0.4-1.0)
Prairies	-1.09 (-4.0-6.7)	0.91 (0.6-1.4)	1.12 (0.7-1.8)
British Columbia	2.33 (-3.0-16.5)	0.86 (0.5-1.5)	0.99 (0.6-1.7)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-2.83 (-4.4-2.5)	0.79 (0.5-1.2)	0.90 (0.6-1.4)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.17: Crude association of patient delay and socio-demographic variables for CNS tumour patients (cont.)

	Patient Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Population size			
under 16 567	ref (---)	ref (---)	ref (---)
16 568 - 26 503	0.81 (-2.4-10.7)	1.28 (0.8-2.2)	1.12 (0.7-1.9)
26 504 - 38 822	1.21 (-2.2-11.6)	0.95 (0.6-1.6)	0.88 (0.5-1.5)
38 823 and up	2.41 (-1.7-14.5)	1.31 (0.8-2.2)	0.97 (0.6-1.7)
Cancer subtype			
Medulloblastoma	ref (---)	ref (---)	ref (---)
Other CNS tumour	-1.48 (-3.7-5.7)	0.86 (0.6-1.3)	1.08 (0.7-1.7)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.
**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.
*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.
‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.18: Multivariate analyses of patient delay for CNS tumour patients

	OR (95% CI)
Age	
under 4.42	ref (---)
4.43 - 7.74	1.91 (1.1-3.2)
7.75 - 11.83	1.86 (1.1-3.1)
11.84 and up	1.55 (0.9-2.6)
Region	
Quebec	ref (---)
Atlantic	0.51 (0.3-0.8)
Prairies	0.95 (0.6-1.6)
British Columbia	1.05 (0.6-1.9)
First health contact	
GP	ref (---)
Other	1.92 (1.2-3.0)
ER	1.46 (0.9-2.3)
Urbanization	
Rural	ref (---)
Urban	0.60 (0.4-0.9)

Table 8.19: Crude association of physician delay and socio-demographic variables for CNS tumour patients

	Physician Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 4.42	ref (---)	ref (---)	ref (---)
4.43 - 7.74	-2.97 (-5.3-4.1)	0.68 (0.4-1.1)	1.30 (0.7-2.3)
7.75 - 11.83	2.58 (-2.5-14.9)	1.20 (0.7-2.0)	2.09 (1.2-3.6)
11.84 and up	11.60 (2.0-33.0)	1.62 (1.0-2.7)	2.10 (1.2-3.7)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	2.33 (-1.9-10.4)	0.95 (0.7-1.3)	1.18 (0.8-1.7)
BMI			
Low (under 15.68)	1.27 (-3.8-16.5)	0.95 (0.5-1.7)	1.00 (0.5-2.0)
Mid (15.69 - 18.42)	ref (---)	ref (---)	ref (---)
High (18.43 and up)	13.26 (1.5-43.7)	1.45 (0.8-2.7)	1.81 (0.9-3.5)
Family income			
Under $ 43 688	ref (---)	ref (---)	ref (---)
$ 43 689 - $ 49 993	-3.23 (-6.3-6.5)	0.61 (0.4-1.0)	1.02 (0.6-1.8)
$ 49 994 - $ 59 562	5.90 (-1.9-25.2)	1.15 (0.7-2.0)	1.55 (0.9-2.7)
$ 59 563 and up	-6.52 (-7.9--0.4)	0.55 (0.3-0.9)	0.66 (0.4-1.2)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-4.59 (-8.3-4.8)	0.67 (0.4-1.0)	0.82 (0.5-1.3)
ER	-14.79 (-14.0--13.5)	0.29 (0.2-0.5)	0.32 (0.2-0.5)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	1.21 (-3.7-12.8)	1.21 (0.8-2.0)	1.17 (0.7-2.0)
Prairies	-0.30 (-4.3-9.2)	0.69 (0.4-1.1)	1.05 (0.6-1.7)
British Columbia	-1.86 (-5.9-9.0)	0.65 (0.4-1.1)	0.93 (0.5-1.7)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.19: Crude association of physician delay and socio-demographic variables for CNS tumour patients (cont.)

	Physician Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-3.53 (-6.0-3.3)	0.78 (0.5-1.2)	0.66 (0.4-1.0)
Population size			
under 16 567	ref (---)	ref (---)	ref (---)
16 568 - 26 503	2.60 (-2.1-14.8)	1.09 (0.6-1.9)	1.09 (0.6-2.0)
26 504 - 38 822	8.25 (0.6-26.5)	1.22 (0.7-2.1)	1.24 (0.7-2.3)
38 823 and up	5.52 (-0.7-21.0)	1.14 (0.7-1.9)	1.49 (0.8-2.7)
Cancer subtype			
Medulloblastoma	ref (---)	ref (---)	ref (---)
Other CNS tumour	6.77 (0.8-20.1)	1.41 (0.9-2.2)	1.56 (1.0-2.6)
Patient Delay Category			
0	ref (---)	ref (---)	ref (---)
0.1 - 13	-18.49 (-18.4--13.3)	0.39 (0.2-0.7)	0.42 (0.2-0.7)
14 - 41	-24.21 (-21.3--24.6)	0.21 (0.1-0.4)	0.32 (0.2-0.6)
42 and up	-25.58 (-22.0--27.2)	0.18 (0.1-0.3)	0.29 (0.2-0.5)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.20: Multivariate analyses of physician delay for CNS tumour patients

	OR (95% CI)
Age	
under 4.42	ref (---)
4.43 - 7.74	0.90 (0.5-1.6)
7.75 - 11.83	1.56 (0.9-2.7)
11.84 and up	2.22 (1.3-3.9)
Region	
Quebec	ref (---)
Atlantic	0.68 (0.4-1.2)
Prairies	0.48 (0.3-0.8)
British Columbia	0.46 (0.2-0.9)
First health contact	
GP	ref (---)
Other	0.66 (0.4-1.1)
ER	0.24 (0.1-0.4)
Patient Delay Category	
0	ref (---)
0.1 - 13	0.41 (0.2-0.7)
14 - 41	0.18 (0.1-0.3)
42 and up	0.19 (0.1-0.3)

Table 8.21: Crude association of HCS delay and socio-demographic variables for CNS tumour patients

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Age			
under 4.42	ref (---)	ref (---)	ref (---)
4.43 - 7.74	-2.63 (-5.7-6.2)	0.74 (0.4-1.2)	1.45 (0.8-2.8)
7.75 - 11.83	3.93 (-2.3-19.0)	1.27 (0.8-2.1)	1.91 (1.0-3.5)
11.84 and up	11.33 (1.3-33.9)	1.53 (0.9-2.6)	2.75 (1.5-5.1)
Sex			
Male	ref (---)	ref (---)	ref (---)
Female	1.85 (-2.7-10.7)	1.05 (0.7-1.5)	1.23 (0.8-1.9)
BMI			
Low (under 15.68)	3.94 (-2.7-22.6)	1.71 (0.9-3.2)	1.04 (0.5-2.2)
Mid (15.69 - 18.42)	ref (---)	ref (---)	ref (---)
High (18.43 and up)	14.73 (2.1-47.1)	1.73 (0.9-3.2)	2.17 (1.1-4.4)
Family income			
Under $ 43 688	ref (---)	ref (---)	ref (---)
$ 43 689 - $ 49 993	-0.74 (-5.4-12.2)	0.76 (0.4-1.3)	1.30 (0.7-2.4)
$ 49 994 - $ 59 562	9.00 (-0.6-32.0)	1.17 (0.7-2.0)	1.51 (0.8-2.8)
$ 59 563 and up	-6.63 (-8.4-0.4)	0.54 (0.3-0.9)	0.73 (0.4-1.4)
First health contact			
GP	ref (---)	ref (---)	ref (---)
Other	-1.76 (-7.5-11.2)	0.69 (0.4-1.1)	1.19 (0.7-1.9)
ER	-17.67 (-16.5--16.9)	0.26 (0.2-0.4)	0.44 (0.3-0.8)
Region			
Quebec	ref (---)	ref (---)	ref (---)
Atlantic	4.88 (-2.1-20.2)	1.23 (0.8-2.0)	1.41 (0.8-2.4)
Prairies	0.32 (-4.3-10.9)	0.89 (0.6-1.4)	1.25 (0.7-2.1)
British Columbia	1.20 (-4.8-15.9)	0.96 (0.5-1.7)	0.91 (0.5-1.8)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75^{th} percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.21: Crude association of HCS delay and socio-demographic variables for CNS tumour patients (cont.)

	HCS Delay		
	Linear*	Median**	Long***
	Δ Y‡ (95% CI)	OR (95% CI)	OR (95% CI)
Community type			
Rural	ref (---)	ref (---)	ref (---)
Urban	-4.38 (-7.2-3.3)	0.72 (0.5-1.1)	0.65 (0.4-1.0)
Population size			
under 16 567	ref (---)	ref (---)	ref (---)
16 568 - 26 503	2.73 (-2.5-16.3)	1.00 (0.6-1.7)	1.38 (0.7-2.7)
26 504 - 38 822	7.34 (-0.3-25.8)	1.25 (0.7-2.1)	1.84 (1.0-3.5)
38 823 and up	9.37 (0.7-30.0)	1.38 (0.8-2.4)	1.62 (0.8-3.1)
Cancer subtype			
Medulloblastoma	ref (---)	ref (---)	ref (---)
Other CNS tumour	9.03 (1.9-24.4)	1.31 (0.9-2.0)	3.09 (1.7-5.8)
Patient Delay Category			
0	ref (---)	ref (---)	ref (---)
1 - 13	-20.55 (-20.7--14.5)	0.42 (0.2-0.7)	0.30 (0.2-0.5)
14 - 41	-27.95 (-24.5--28.8)	0.24 (0.1-0.4)	0.26 (0.1-0.5)
42 and up	-27.77 (-24.4--28.4)	0.22 (0.1-0.4)	0.30 (0.2-0.6)

*Delay variable was treated as a continuous outcome variable in linear regression analyses.

**Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the median of the delay variable as the threshold of dichotomization.

*** Delay variable was treated as a dichotomous outcome in the univariate logistic regression by using the 75th percentile, rounded to the closest meaningful length of calendar time, as the threshold of dichotomization.

‡The estimates obtained from the linear regression were used to calculate the antilog of the predicted log delay followed by a subtraction of 1 day.

Table 8.22: Multivariate analyses of HCS delay for CNS tumour patients

	OR (95% CI)
Age	
under 4.42	ref (---)
4.43 - 7.74	0.93 (0.5-1.6)
7.75 - 11.83	1.49 (0.9-2.6)
11.84 and up	1.79 (1.0-3.2)
First health contact	
GP	ref (---)
Other	0.72 (0.4-1.2)
ER	0.24 (0.2-0.4)
Patient Delay Category	
0	ref (---)
0.1 - 13	0.47 (0.3-0.8)
14 - 41	0.23 (0.1-0.4)
42 and up	0.23 (0.1-0.4)

9. RELATIONSHIP BETWEEN DELAYS IN CARE FOR CHILDREN AND ADOLESCENTS WITH CANCER AND DISEASE SEVERITY

9.1. Introduction

The interest in the study and reduction of wait times in cancer care is generally based on the belief that early diagnosis of cancer may substantially improves prognosis by allowing for the opportunity for timely treatment while the disease is more likely to be in its earliest stages. Previous studies on delays of care in childhood cancer have focused on measuring delays that occur along the cancer care pathway and identifying their determinants. However, few studies have explored the impact of these delays on patient's disease severity and prognosis. The study of the relationship between disease severity and delays will shed light on the underlying role that delays may play on the prognostic pathway model.

9.2. Objective

The objective of this analysis is to assess the association between various types of delays (diagnosis, patient and physician) and the disease severity in Canadian children and adolescents with leukemias, lymphomas and CNS tumours.

9.3. Methods

A prospective cohort study was conducted on subjects enrolled in TOS-CCCSCP. The patients were aged less than 20 years and were diagnosed with cancer between the years 1995 and 2000 inclusive. Study inclusion required that information on the dates of first symptoms, diagnosis and treatment were available. Also, information on disease

stage or risk classification was a requisite for study inclusion. The relationship between disease severity and delay was examined separately for patients with leukemias, lymphomas and CNS tumours. Of the eligible consenting patients, there were 846 with leukemias, 324 with lymphomas and 284 with CNS tumours.

In this chapter, the analyses focused on the relationship between patient disease severity and diagnosis delay, as well as patient delay and physician delay. The associations between these delays and disease severity were examined using logistic regression methods with and without adjustment for demographic factors and empirical confounders.

Although staging of cancer in children and adolescents is different from that in adults, as it incorporates additional prognostic variables that are not mere indicators of disease severity, it still serves as a general classification of the extent of disease at presentation, much of which reflects the chronology of disease progression. However staging systems for childhood cancers are highly specific for each type of cancer and some cancers are not usually staged. To test the hypothesis that longer delays in the diagnosis of childhood cancer are associated with more advanced disease severity, the tumour severity was dichotomized (as low or high), separately for each cancer type, based on the available information of the disease, clinical stage, metastatic spread and organ involvement. These thresholds were established *a priori* based on those agreed upon extensive consultation with the clinical experts who are members of our research team. Further details on the classification methods are presented in Appendix 4.

For these analyses, patient, physician and diagnosis delay were treated as categorical explanatory variables. Four categories of each delay were created based on

the quartiles values of each delay for each cancer type.

9.4. Statistical Analysis

For this study objective, the influence of the patient, physician and diagnosis delays on disease severity was analyzed in logistic regression models for leukemia, lymphoma and CNS tumour patients. Odds ratios (OR) and their respective 95% CI were used to report the magnitude and precision of the associations, respectively. The results obtained provide an estimate of the relative risk of a high disease severity for patients in one level of delay compared to patients in the referent category, while controlling for confounding or mediation by other variables. In model 1, analyses were done with an adjustment for patient age and sex. In Model 2, analyses were adjusted for empirical confounders. Potential empirical confounders were examined from factors related to the patient, the cancer and health care. In brief, the following parameters were investigated as potential confounders: patient age, sex, BMI, geographic region, family income, population size, community type, type of health professional first contacted and cancer subtype. These variables are described in Chapter 5. The selection criterion for confounding was based on changes in ORs of 5% or greater from the crude model mutually adjusting for disease severity and the delay variable. Statistically significant interactions between all combinations of independent variables were tested with the likelihood ratio test for the difference between a given model with the interaction term and the nested model, without the interaction term, which is a subset of the given model. Interactions were considered to be present if p-value for the interaction term was statistically significant ($P<0.05$).

9.5. Results

Patient characteristics of the 846 leukemia, 324 lymphoma and 284 CNS tumour patients are given in Table 9.1. In all, 349 (42%) of those with leukemias, 141 (44%) of those with lymphomas and 56 (20%) of those with CNS tumours had a high disease severity at diagnosis (based on the criteria defined in the Appendix 4). The distribution of the study population characteristics was similar to that presented in Chapter 8.

9.5.1. Relationship between delays of cancer care and disease severity in children and adolescents diagnosed with leukemias

Results from the crude model shows that there was a general increase in risk of high disease severity for patients with longer diagnosis delay compared to patients with less than 9 days of diagnosis delay (Table 9.2). Patients in the 19-35 days diagnosis delay group had 36 % greater odds of high disease severity than those in the baseline delay category. However, these results did not reach statistical significance. When controlling for patient age and sex (model 1), there was no longer an increase in risk for patients with over 19 days of diagnosis delay. Similarly, the effect of longer diagnosis delay on disease severity was no longer present when empirical confounders were taken into account in model 2.

While patient delay had no apparent effect on the risk of higher disease severity, Physician delay showed a 26% to 38% reduction in ORs for patients experiencing more than 1 day of physician delay in the crude model. However, these results were not statistically significant and the effect of delay on disease severity was mostly removed in

models 1 and 2 when confounding or mediating variables were taken into account.

9.5.2. Relationship between delays of cancer care and disease severity in children and adolescents diagnosed with lymphomas

There was a statistically significant association between diagnosis delay and high disease severity. Patient with a diagnosis delay over 3 months had a 60% reduction in risk of high severity compared to patients with less than 18 days of delay (Table 9.3). This association remained the same even after adjusting for patient age and sex (model 1). When controlling for empirical confounders, the results still showed that patients with longer diagnosis delays had lower ORs than patients in the reference group, however these results were no longer statistically significant.

The results from the crude model show a statistically significant positive association between patient delay and high disease severity. Patients with more than 2 days of patients delay had almost 2 to 3 times the likelihood of having a higher disease severity; the highest being for patients with patient delays between 11-38 days. Model 1 showed no change in the association between patient delay and disease severity. In model 2, the association between patient delay and disease severity remained similar and statistically significant even adjusting for empirical confounders. When all confounding variables were controlled for in the analysis, patients with patient delays of 11-38 days had almost 3 times the risk of having high disease severity (OR=2.98; 95% CI 1.4-6.2), and patients with delays of over 39 days had 2.5 times the risk of high disease severity (OR=2.49; 95% CI 1.2-5.3) than the reference group.

Conversely, physician delay shows an inverse association with disease severity. In the crude model, patients with longer physician delay had a statistically significant lower risk of high disease severity than patients with less than 4 days of physician delay. Patients with physician delays over 40 days had a 75% reduction in the risk of having high disease severity compared to the reference group (OR=0.24; 95% CI 0.1-0.5). As seen in model 1, the association between physician delay and disease severity remained unchanged when controlling for patient age and sex. The magnitude of association was slightly reduced after accounting for the empirical confounders (model 1), however the longest delay group still had a statistically significantly lower risk of high disease severity than the shortest delay group (OR=0.39; 95% CI 0.2-0.9) (model 2).

9.5.3. Relationship between delays of cancer care and disease severity in children and adolescents diagnosed with a CNS tumours

In the crude model, there was a statistically significant association between diagnosis delay and disease severity. Generally, patients in the groups with a diagnosis delay over 23 days had a lower risk of high disease severity than the reference group (Table 9.4). Patients with a diagnosis delay over 119 days showed a statistically significant reduction in risk and were almost a third less likely to have high disease severity than patients with less than 23 days of delay (OR=0.32, 95% CI 0.1-0.8). This statistically significant association did not change even after controlling for patient age and sex (model 1) or for empirical confounders (model 2).

Patient delay was also inversely associated with disease severity. Patient with a delay of over 42 days had a 70% lower odds of having high disease severity than patients

with no patient delay (OR=0.29; 95% CI 0.1-0.9). This reduction in risk did not change after accounting for patient age and sex (model 1). However, after accounting for empirical confounders (model 2), patients in the longest delay group were even less likely to have high disease severity compared to the shortest delay group (OR=0.12; 95% CI 0.0-0.5). Patients in delay quartiles 2 and 3 appeared to have an increase in risk of high disease severity compared to the reference group, but the results were not statistically significant. As seen in model 2, these 2 groups showed an inverse relationship to disease severity with the inclusion of the empirical confounders.

Conversely, there was a general increase in odds of high disease severity in patients with a physician delay over 4 days compared to patients with less physician delay. Although these results are not statistically significant, the positive association between physician delay and disease severity remained consistent from the crude model to the model accounting for patient age and sex and the model controlling for the empirical confounders. In model 2, patients with 56 days of delay showed a 77% increase in the odds of higher disease severity over the baseline group (OR=1.77; 95% 0.5-5.8).

9.6. Discussion

The relationship between delays in cancer care and disease severity is complex and dependent on the underlying disease. Although it may be logical to think that longer delays would lead patients to be diagnosed at a more advanced stage of disease, studies on childhood cancer have found conflicting results [Halperin et al. 1996, Saha et al.1993]. In this study, I have shown that the association between delays and disease severity

differs by type of delay and type of cancer (leukemias, lymphomas and CNS tumours). For patients with leukemias, diagnosis delay was not associated with disease severity. These findings corroborate and extend those of Saha et al. [1993], who reported no statistically significant difference in delay time between cancer stages for patients with solid tumours or between different levels of white blood cell count for leukemia patients. This study also shows that disease severity was not related to patient delay or to physician delay.

For patients diagnosed with lymphomas, longer diagnosis delay was associated with a lower risk of having a high disease severity. Both patient delay and physician delay were associated with disease severity. Longer patient delay was associated with a higher disease severity. Rapid and early diagnosis of lymphoma is a function of the patients' or parents' ability to recognize the disease signs and symptoms and seek timely care. While it may appear as though the onus of reducing patient delay rest solely on the patients, it is also possible that GPs may have misinterpreted vague symptoms, such as fatigue, and prolonged the process of diagnosing the disease. This finding suggests that increased awareness of lymphoma symptoms on the part of the patients and their caregivers may help in reducing patient delay and, in turn, disease severity. Conversely, it was found that longer physician delay was associated with a lower disease severity. This favours the scenario in which patients with aggressive, fast-growing tumours may show rapid progression of symptoms, which would lead to a faster diagnosis of the child's illness. Alternatively, less aggressive, slow growing tumours may lead to longer delays due to the indolent nature of the symptoms. Therefore, the biology of the disease with the attendant severity of the symptoms likely plays a role in the relationship between

diagnosis delay and cancer severity.

In the analyses of patients with CNS tumours, I found that diagnosis delay and patient delay were associated with disease severity, but physician delay was not. A longer diagnosis delay was associated with a decrease in risk of high disease severity. These findings are similar to those reported by Halperin et al. [1996], who found that patients with advanced stage medulloblastoma exhibited shorter diagnosis delay compared with those who had early stage disease. A similar association was observed for patients with a long patient delay. Since disease severity was associated with patient delay but not physician delay, it can be deduced that the correlation between diagnosis delay and disease severity is likely to be attributed primarily to patient delay. Again, the aggressiveness of the tumour and the nature of its symptoms likely influence the length of diagnosis and patient delay.

Aside from the positive association between patient delay and disease severity found for patients with lymphomas, the findings of this study are contrary to the general belief that delays lead to a statistically significantly greater disease severity. The negative association between diagnosis delay and disease severity for patients with lymphomas and CNS tumours suggests that tumour biology and the extent of the disease severity may actually be the main determinants of the length of delay times (and the associated complexity of diagnostic workup) and not vice versa. This may lead to the conclusion that the study of delays to diagnosis of cancer in children and adolescents should no longer be of public health concern. However, the measurement of diagnosis delay and patient delay is restricted by the date of disease symptom detection. Since a cancer may be present for some time before being symptomatic and detected, the date

being recorded does not necessarily capture the actual time of disease development. Therefore, it is difficult to determine the true effect of delays on disease severity and prognosis.

In addition to the study limitations discussed previously, other limitations should be considered when interpreting the present findings. Since staging of cancer in children and adolescents is not performed uniformly across different cancer types and regions in Canada, a broad definition of disease severity was created. It is possible that misclassification of patients according to disease severity may have occurred. Differential misclassification would occur if the sorting of disease severity was related to the delay status of the patients. However, classification of disease severity was made using general clinical guidelines established with the help of paediatric experts in the field of childhood cancer without prior knowledge of the patient's delay status. Thus, any misclassification bias would likely be non-differential.

My results support the need for educational programs, for the general population and for health care professionals, aimed at the identification of early signs and symptoms of cancer in children and adolescents to permit timely diagnosis and care. Moreover, it has been reported in a study of adults with cancers that delays were positively associated with patient survival, while having no association with disease stage [Koivunen et al., 2001] and suggested that the effect of long delay on survival may be mediated through another mechanism. Regardless, the aim of cancer care should always be timely diagnosis and treatment before the cancer reaches an advanced stage.

Table 9.1: Description of leukemia, lymphoma and CNS tumour patients

Study Population Characteristics	Leukemias N=846	Lymphomas N=324	CNS Tumours N=284
Patient age (years) [Mean (SD)]	6.62 (4.8)	12.49 (4.5)	8.28 (4.8)
Sex [n(%)]			
Female	368 (43.5)	123 (38.0)	138 (48.6)
Male	478 (56.5)	201 (62.0)	146 (51.4)
Body Mass Index [Mean (SD)]	18.27 (10.3)	20.89 (18.1)	18.13 (4.9)
Median income [Mean (SD)]	53 666 (12 500)	53 562 (13 529)	54 021 (14 564)
Population size [Mean (SD)]	31 224 (21 091)	29 860 (20 455)	30 070 (18 104)
First Health Contact [n (%)]			
GP	421 (49.8)	205 (63.3)	101 (35.6)
ER	130 (15.4)	44 (13.6)	80 (28.2)
Other	286 (33.8)	70 (21.6)	96 (33.8)
Region [n (%)]			
Quebec	307 (36.3)	131 (40.4)	82 (28.9)
Atlantic	133 (15.7)	45 (13.9)	60 (21.1)
Prairies	224 (26.5)	104 (32.1)	76 (26.8)
British Columbia	179 (21.2)	41 (12.7)	66 (23.2)
Community Type [n (%)]			
Rural	227 (26.8)	82 (25.3)	145 (26.7)
Urban	581 (68.7)	222 (68.5)	348 (64.1)
Cancer subtype [n (%)]			
ALL	736 (87.0)	--	--
Non-ALL	110 (13.0)	--	--
Hodgkin lymphoma	--	198 (61.1)	--
Non-Hodgkin lymphoma	--	126 (38.9)	--
Medulloblastoma	--	--	73 (25.7)
Other	--	--	211 (74.3)
Patient Delay Category (days) [Median (IQR)]	8 (1-21)	11 (2-39)	14 (0-42)
Physician Delay (days) [Median (IQR)]	3 (1-14)	11 (4-41)	16 (4-56)
Diagnosis Delay (days) [Median (IQR)]	19 (9-36)	39 (18-90)	48 (23-119)

Table 9.2: Association between delays and high disease severity for patients with leukemias

Type of Delay	Crude OR (95%CI)	Model 1* OR (95%CI)	Model 2** OR (95%CI)
Diagnosis Delay Category [a]			
under 9	ref (---)	ref (---)	ref (---)
9 - 18	1.18 (0.8-1.8)	1.21 (0.8-1.9)	1.17 (0.7-1.8)
19 - 35	1.36 (0.9-2.0)	0.99 (0.6-1.6)	0.98 (0.6-1.6)
36 and up	1.21 (0.8-1.8)	0.89 (0.6-1.4)	0.90 (0.6-1.4)
Patient Delay Category [b]			
under 1	ref (---)	ref (---)	ref (---)
1 - 7	0.97 (0.6-1.5)	1.08 (0.7-1.7)	1.14 (0.7-1.9)
8 - 20	0.92 (0.6-1.4)	0.99 (0.6-1.6)	1.00 (0.6-1.7)
21 and up	1.14 (0.8-1.7)	0.97 (0.6-1.6)	1.06 (0.6-1.8)
Physician Delay Category [c]			
under 1	ref (---)	ref (---)	ref (---)
1 - 2	0.74 (0.4-1.4)	1.14 (0.5-2.4)	1.11 (0.5-2.4)
3 - 13	0.62 (0.3-1.2)	0.94 (0.4-2.0)	0.89 (0.4-1.9)
14 and up	0.74 (0.4-1.4)	1.00 (0.5-2.2)	0.90 (0.4-2.0)

* Model adjusted for age and sex

* * Model adjusted for empirical confounders as identified in exploratory analyses: a) age and BMI; b) age, BMI and cancer subtype; c) age, region and cancer subtype.

Table 9.3: Association between delays and disease severity for patients with lymphomas

Type of Delay	Crude OR (95%CI)	Model 1* OR (95%CI)	Model 2** OR (95%CI)
Diagnosis Delay Category [a]			
under 18 days	ref (---)	ref (---)	ref (---)
18 – 38 days	0.58 (0.3-1.1)	0.67 (0.3-1.3)	0.73 (0.3-1.6)
39 – 89 days	0.51 (0.3-1.0)	0.56 (0.3-1.1)	0.81 (0.4-1.8)
90 and up days	0.40 (0.2-0.8)	0.44 (0.2-0.9)	0.59 (0.3-1.3)
Patient Delay Category [b]			
under 2 days	ref (---)	ref (---)	ref (---)
2 – 10 days	2.12 (1.1-4.1)	2.02 (1.0-4.0)	1.92 (0.9-4.2)
11 – 38 days	3.08 (1.6-5.9)	3.30 (1.7-6.5)	2.98 (1.4-6.2)
39 and up days	2.15 (1.1-4.1)	2.20 (1.1-4.3)	2.49 (1.2-5.3)
Physician Delay Category [c]			
under 4 days	ref (---)	ref (---)	ref (---)
4 – 10 days	0.99 (0.5-1.9)	1.11 (0.6-2.2)	1.28 (0.6-2.8)
11 – 40 days	0.34 (0.2-0.6)	0.39 (0.2-0.8)	0.48 (0.2-1.0)
41 and up days	0.24 (0.1-0.5)	0.25 (0.1-0.5)	0.39 (0.2-0.9)

* Crude model adjusted for age and sex

* * Crude model adjusted for empirical confounders: a) age, sex, BMI, income, region, health professional, population size and cancer subtype; b) a) age, BMI, income, region, population size and cancer subtype; c) age, BMI, region, health professional, population size, urban and cancer subtype.

Table 9.4: Association between delays and disease severity for patients with CNS tumours

Type of Delay	Crude OR (95%CI)	Model 1* OR (95%CI)	Model 2** OR (95%CI)
Diagnosis Delay Category [a]			
under 23 days	ref (---)	ref (---)	ref (---)
23 – 47 days	0.59 (0.3-1.3)	0.60 (0.3-1.4)	0.62 (0.2-1.7)
48 – 118 days	0.62 (0.3-1.3)	0.67 (0.3-1.5)	0.64 (0.2-1.7)
119 and up days	0.32 (0.1-0.8)	0.38 (0.1-1.0)	0.27 (0.1-0.9)
Patient Delay Category [b]			
0 day	ref (---)	ref (---)	ref (---)
0.1 – 13 days	1.39 (0.6-3.3)	1.22 (0.5-2.9)	0.76 (0.3-2.1)
14 – 41 days	1.51 (0.7-3.4)	1.36 (0.6-3.1)	0.98 (0.4-2.6)
42 and up days	0.29 (0.1-0.9)	0.26 (0.1-0.8)	0.12 (0.0-0.5)
Physician Delay Category [c]			
under 4 days	ref (---)	ref (---)	ref (---)
4 – 15 days	1.40 (0.6-3.2)	1.48 (0.6-3.5)	1.23 (0.4-3.4)
16 – 55 days	1.32 (0.5-3.2)	1.39 (0.6-3.5)	1.20 (0.4-3.7)
56 and up days	1.38 (0.6-3.4)	1.62 (0.6-4.1)	1.77 (0.5-5.8)

* Crude model adjusted for age and sex

* * Crude model adjusted for empirical confounders: a) age, BMI, income, region, health professional, population size, urban and cancer subtype; b) age, income, region, health professional, population size, urban and cancer subtype; c)age, BMI, income, region, health professional, population size, urban and cancer subtype.

10. IMPACT OF DELAYS IN CARE ON CANCER SURVIVAL

10.1. Introduction

In previous chapters, I examined the distribution of delays in Canada, factors related to delays and the association between delays and disease severity. However, the impact of diagnosis delays on the prognosis of children with cancer is still unknown. It is generally believed that long delays would lead to worse prognosis. However, few studies have been specifically designed or have conducted thorough analyses to investigate this assumption in the context of childhood cancer. Several studies explored this relationship and found conflicting results [Pratt CB et al., 1978; DerKinderren et al., 1989; Rodriguez et al., 2004; Haimi et al., 2004; Butros et al., 2002; Goyal et al., 2004; Saha et al., 1993]. A few studies on adult cancers found that longer delays were associated with increased survival [Sainsbury et al., 1999; Allison et al., 1998a]. Conversely, some studies support the hypothesis that delays in diagnosis adversely affect prognosis [Richards et al., 1999; Koivunen et al., 2001; Kowalski et al., 2001]. It has been reported that the impact of delay on survival is likely mediated through the relation between delay and cancer stage [Richards et al., 1999]; delays in treatment would allow the disease to progress and reach high levels of tumour severity, which would adversely affect prognosis. None of these studies on children and adolescents has looked at the possible mediating effect of disease severity at diagnosis on the relationship between delay and survival.

10.2. Objective

The objective of these analyses was to investigate the impact of delays in the diagnosis of Canadian children and adolescents with leukemias, lymphomas and CNS

tumours on survival.

10.3. Methods

A survival analysis was conducted on subjects enrolled in TOS-CCCSCP. The patients were aged less than 20 years and were diagnosed with a malignant disease, as listed in the ICCC, between the years 1995 and 2000 inclusive. Study inclusion required that information on the dates of symptom onset, of first health consultation and of diagnosis are available. The survival analyses were restricted to patients with leukemias, lymphomas and CNS tumours and the impact of delays on disease prognosis were examined separately for each type of cancer. Patients who entered the CCCSCP at the end of the data collection period did not have any follow-up visits and did not contribute any follow-up time; therefore they were excluded from the survival analyses. Of the eligible consenting patients, 874 leukemia, 360 lymphoma, and 503 CNS tumour cases contributed person-time in the survival analysis.

In this chapter, the analyses focused on the impact of diagnosis delay, as well as patient delay and physician delay on disease prognosis. The associations between these delays and disease prognosis were examined using survival analysis with and without adjustment for empirical confounders and disease severity. Survival time was defined as the interval from the date of diagnosis to the date of death or last confirmation of a follow-up status as alive, as received by the TOS. To test the hypothesis that longer delays in the diagnosis of cancer in children and adolescents are associated with worse cancer prognosis, the censorship variable was defined in a binary manner, as per the occurrence of death (alive or dead). Cases who are alive contributed survival time until

the date of last documented information in the database. Losses to follow-up were defined as lack of information for 2 scheduled visits (period of 12 months) after the last follow-up entry. Losses to follow-up were verified and such cases were flagged and communicated to the TOS-CCCSCP managers so that they could contact the originating paediatric oncology centre to request updated information. Responses to these update requests were entered in the database.

For these analyses, patient, physician and diagnosis delay were treated as categorical explanatory variables for the survival. Four categories of each delay were created based on the quartile values of each delay for each cancer type.

10.4. Statistical Analysis

I used the Kaplan-Meier technique to plot the cumulative probability of survival (i.e., proportion remaining alive) against follow-up time. Statistical comparisons in the survival distributions between delay groups were determined using the log-rank test [Kalbfleisch & Prentice, 1980]. The Cox PH regression model [Cox, 1972] was used to estimate the effect of the various delays on patient survival, while controlling for potential confounders and disease severity. Hazard ratios (HR) of death and their respective 95% CIs were computed for categories of each delay variable. The results obtained provide an estimate of the average instantaneous relative risk of death, at any time, for patients in one level of delay compared to patients in the referent delay category (lowest delay, taken as baseline), while controlling for confounding and mediation. In model 1, analyses were done with an adjustment for empirical confounders. Potential empirical confounders were examined from factors related to the patient, the cancer and

health care. In brief, the following parameters were investigated as potential confounders: patient age, sex, BMI, geographic region, family income, population size, community type, type of health professional first contacted and cancer subtype. These variables are described in Chapter 5. The selection criterion for confounding was based on changes in HRs of 5% or greater from the crude model containing the delay variable while adjusting for disease survival (previously described in chapter 5 & 9). In Model 2, analyses were adjusted for empirical confounders and disease severity. As a preliminary step, I verified that all models satisfied the proportional hazards assumption graphically by plotting the –log[-log S(t)] for the delay variables. Statistically significant interactions between all combinations of independent variables were tested with the likelihood ratio test for the difference between a given model with the interaction term and the nested model, without the interaction term, which is a subset of the given model. Interactions were considered to be present if p-value for the interaction term was statistically significant ($P<0.05$).

10.5. Results

Patient characteristics of the 874 leukemia, 360 lymphoma and 503 CNS tumour patients are given in Table 10.1. The distribution of delay variables was similar to the ones presented for the entire study population as presented in chapter 8. For all three cancer types under investigation, the majority of the patients diagnosed between 1995 and 2000 survived to the end of the study period. There were 7 (0.8%) leukemia patients, 18 (5%) lymphoma patients and 45 (9%) CNS tumour patients lost to follow-up, based on the above criterion. In all, 95 (11%) leukemia patients, 23 (6%) lymphoma patients and

89 (18%) CNS tumour patients died by the study closing date. Death rates for leukemia, lymphoma and CNS tumour patients are presented in Tables 10.2-10.4.

Among leukemia patients, there were no survival differences between diagnosis delay groups (p=0.5643) (Figure 10.1). Similarly, no statistically significant differences were observed between patient delay groups (p=0.6617) or physician delay groups (p=0.5430). Similar comparisons for lymphoma patients also showed no survival differences between diagnosis delay groups (Figure 10.2). On the other hand, statistically significant differences in survival were observed for CNS tumour patients between the four diagnosis delay groups (p=0.0000) (Figure 10.3). Patients in the shortest diagnosis delay group had statistically significantly worse survival than those in the other groups. Survival differences were also observed between patient delay groups (p=0.0158). Comparisons of physician delay groups also showed statistically significant differences in survival (p=0.0152). CNS tumour patients in the shortest diagnosis delay and physician delay groups had statistically significantly worse survival than the other groups. In contrast, patients in the shortest patient delay group had better survival than the other delay groups.

10.5.1. Impact of delays of cancer care on survival for children and adolescents diagnosed with leukemia

Results from the crude model showed that there was a general decreasing trend in HRs for patients with longer diagnosis delay compared to patients with less than 9 days of diagnosis delay (Table 10.5). Patients in the longest delay group had 35% lower risk of death than baseline patients. However, these results were not statistically significant.

When controlling for empirical confounders, there was no material change in the estimates (model 1). Similarly, no changes in the estimates were observed when disease severity was taken into account in model 2.

Though not statistically significant, patient delay exhibited a similar decreasing trend for the risk of death with longer patient delay in the crude analysis. However, the effect of patient delay on survival was removed when confounding variables and disease severity were taken into account. Regarding physician delay, patients with a delay between 1-13 days had an increase of almost 50% in hazard estimates compared to patients with a delay of less than 1 day after adjusting the model for empirical confounders (model 1). Again, this observed effect was not statistically significant and was lessened when disease severity was included in the model (model 2).

10.5.2. Impact of delays of cancer care on survival for children and adolescents diagnosed with lymphoma

There was no statistically significant association between diagnosis delay and survival (Table 10.6). After controlling for empirical confounders and disease severity, patients with a delay between 18-38 days and over 90 days had a 30% greater risk of death than patients in the reference group. A similar pattern of association was observed between patient delay and patient survival. Patients with a delay between 18-38 days and over 90 days had over 2 times the risk of death than patients with less than 18 days of delay even after accounting for empirical confounders and disease severity (HR=2.35; 95% CI 0.4-13.2 and HR=2.17; 95% CI 0.4-11.5 respectively). Conversely, patients with

a delay between 11 and 38 days had half the risk of death than the comparison delay group (HR=0.51; 95% CI 0.1-4.1).

Although not statistically significant, the results showed an increase in the HRs for the 2 groups between 4 to 40 days physician delay compared to the reference group, but a decrease in the HR for the group with a physician delay over 40 days. As seen in model 2, the association between physician delay and survival remained unchanged when adjusted for empirical confounders and disease severity. Patients with physician delays over 40 days had a 60% reduction in risk of death compared to the reference group (OR=0.41; 95% CI 0.0-4.1), while the other 2 groups showed an increase in risk of death.

10.5.3. Impact of delays of cancer care on survival for children and adolescents diagnosed with a CNS tumours

In the crude model, there was a statistically significant association between diagnosis delay and survival (Table 10.7). Generally, there was a protective effect of diagnosis delay on survival. Patients in the groups with a diagnosis delay over 23 days had a 50%-75% lower risk of death relative to those in the reference group. Patients with a diagnosis delay over 119 days showed a statistically significant reduction in risk and had almost a quarter of the risk of death than patients with less than 23 days of delay by the censor date (HR=0.24, 95% CI 0.1-0.5). This statistically significant association did not change even after controlling for empirical confounders (model 1). When disease severity was taken into account (model 2), the risk of death for patients with longer diagnosis delay was no longer statistically significant or, in the case of the longest delay group, decreased by 6%.

Similar protective effects were observed between physician delay and survival. Patients with a physician delay over 4 days had a 33% to 59% reduction in HR compared to the reference group. Patients with a physician delay over 59 days had the lowest risk of death (OR=0.41; 95% CI 0.2-0.8). These results remained the same even after controlling for empirical confounders (model 1). When disease severity was taken into account, the apparent protective effect of physician delay on survival became even more pronounced. Patients with a physician delay over 4 days were 57% to 67% less likely to have died than the reference group by the study closing date.

Conversely, there was a general increase in risk of dying in patients with any patient delay compared to patients with no patient delay. Patients in the second quartile group had over 2.4 times the risk of death than patients with no patient delay (HR=2.41; 95% CI 1.2-4.7). Accounting for empirical confounders, the results showed that the patients with a delay between 14-41 days were also 2.4 times more likely to die than patients with no delay (HR=2.45; 95% CI 1.2-4.9). However, the effect of patient delay on survival was lessened and was no longer statistically significant when disease severity was taken into account (model 2).

10.6. Discussion

Despite the attention placed on reducing wait times for cancer care, the impact of diagnosis delays on the prognosis of children and adolescents with cancer is still unknown. It is generally believed that early diagnosis of cancer would lead to improved prognosis by allowing for the opportunity for timely treatment, while disease severity is still in its earliest stages. However, few studies have been specifically designed or have conducted thorough analyses to investigate this assumption in the context of childhood

cancer. Seven studies explored this relationship and found conflicting results. Four studies reported negative associations between delays and survival [Pratt CB et al., 1978; DerKinderren et al., 1989; Rodriguez et al., 2004; Haimi et al., 2004], while the remaining studies did not [Butros et al., 2002; Goyal et al., 2004; Saha et al., 1993]. DerKinderen et al [1989] found that retinoblastoma patients with a physician delay ≥1 week had a statistically significantly higher death rate (HR=5.1) than patients with shorter delay. Rodrigues et al. [2004] also found that retinoblastoma patients with a delay <6 months had a statistically significant higher 5-year survival rate than patients with longer delay. Conversely, Goyal et al. [2004] did not find any statistically significant differences in event-free survival between patients with <3 months, 3-6 months and > 6 months diagnosis delay. Similarly, Saha et al. [1993] did not find that delay times were predictive of event-free survival even after adjusting for possible confounders. None of the studies has looked at the possible mediating effect of disease severity at diagnosis on the relationship between delay and survival.

In this study, I found that the association between delays and disease prognosis differs by type of delay and for patients diagnosed with leukemias, lymphomas and CNS tumours. For patients with leukemias and lymphomas, diagnosis delay, as well as patient and physician delay, was not associated with disease prognosis. However, diagnosis delay and physician delay had a positive relationship with survival for patients diagnosed with CNS tumours. Conversely, patient delay had a negative relationship with survival. This implies that the correlation between diagnosis delay and disease prognosis is likely to be influenced primarily by the effects of physician delay.

For patients diagnosed with CNS tumours, longer diagnosis delay was associated

with a lower risk of death. When disease severity was taken into account, the influence of this variable decreased but was still statistically significant for patients with the longest delay. This shows that disease severity has a mediating effect on the relationship between survival and delay but it does not fully explain this relationship. The impact of delay on survival must also act via another mechanism, not captured in the present analysis.

Similarly, it was found that longer physician delay was associated with an improved prognosis, even after controlling for empirical confounders. The effect of delay on survival remained statistically significant and even increased when disease severity was considered. Again, these findings show that the effect of delay on survival occurs through another mechanism rather than via the influence that physician delay may have in leading to a more advanced disease severity. It is possible that patients with aggressive, fast-growing tumours may report to health care professionals with more apparent symptoms and advanced disease. The urgency of these cases would lead to a faster diagnosis of the child's illness, but worse prognosis. Alternatively, less aggressive, slow growing tumours may not be noticed quickly and would lead to longer physician delays. Therefore, the underlying biological aggressiveness of the disease and/or characteristics of the affected child likely play a role in the relationship between diagnosis delay and cancer survival.

Conversely, longer patient delay is associated with a greater risk of death, even after accounting for empirical confounders. However, the effect of patient delay on survival was no longer present after adjustment for disease severity. This provides a clue into the role of patient delay in the prognostic pathway for CNS tumour patients. These

findings suggest that the harmful effect of patient delay exists only via the influence that this delay has in leading to a more advanced disease severity at the time when therapy may be initiated. In theory, disease severity is a critical factor due to its upstream effect on survival, in which a long delay would lead to more advanced disease at diagnosis and, in turn, to a greater risk of death. However, it was found in chapter 9 that longer patient delay was associated with a lower disease severity. Another explanation for the observed relationship between patient delay and survival may be the differences in treatment procedures for patients with varying levels of disease severity. It is possible that more aggressive treatment protocols for patients with cancers of greater disease severity may be more effective than the milder treatments given to patients with a lower tumour severity. Alternatively, the biology of the disease may also explain these observations. It has been reported that the greater the indolence of a tumour the more resistant it may be to adjuvant therapy (post-surgical, chemotherapy or radiotherapy) [Chabner, 1982]. Thus, patients with a slow growing tumours (resulting in longer patient delay) may be more resistant to non-surgical treatment and, in consequence, have poorer survival than patients with fast growing tumours.

In addition to the study limitations previously discussed, other concerns should be considered when interpreting the present findings. Firstly, the outcome used in the survival analysis was death from all causes and not specifically from cancer. If some deaths were unrelated to cancer then the results would be biased towards the null. However, it is unlikely that children diagnosed with cancer would die from another disease unrelated to their cancer or its treatment since cancer is the leading cause of disease-related death in such children. Premature death may also have resulted from

non-cancer related events. However, non-disease related deaths (e.g. accident, injury) are doubtful since these patients are likely under closer supervision and care by their parents. Secondly, residual confounding of disease severity may still exist due to the broad categorization of disease severity. However, this is the first study on childhood cancer to attempt the control for the possible confounding or mediating effect of disease severity on the relationship between delay and survival. Further development and progress in the staging of cancers in children and adolescents will certainly refine these groupings and help verify the present findings. Lastly, the completeness of the outcome in TOS might be questioned. However, the overall number of deaths of children diagnosed with cancer recorded in TOS compared favourably to those reported in the CCR of children diagnosed with cancer between 1995-2000 (excluding Quebec and Ontario) (Appendix 5). As a setting-specific limitation, it is possible that this study's inability to find an influence of delays on the survival of leukemia and lymphoma patients may be related to the relatively short delay times afforded by the Canadian healthcare system. It is conceivable that in settings with more extreme delay times a survival effect may eventually be revealed.

The findings of this study emphasize the need for early recognition of cancer symptoms by the patients, their parents and their health care providers while the disease is still in its early stages, followed by immediate diagnostic action. Educational programs aimed at the identification of early symptoms of cancer in children and adolescents before their disease has become advanced would be helpful for the population and primary health care professionals. Further research on the effect of delays on patient survival is needed in order to uncover the other mechanisms behind these relationships.

Nonetheless, it is reassuring to observe that on the basis of the typical delay times experienced in Canada there are no substantial influences on survival of leukemia and lymphoma patients, groups that in combination comprise the majority of childhood cancers.

Table 10.1: Characteristics used in survival analyses of leukemia, lymphoma and CNS tumour patients

Study Population Characteristics	Leukemia N=874	Lymphoma N=360	CNS Tumours N=503
Patient age [Mean (SD)]	6.70 (4.8)	11.9 (4.8)	8.21 (4.8)
Sex [n(%)]			
Female	390 (44.6)	136 (37.8)	233 (46.3)
Male	484 (55.4)	224 (62.2)	270 (53.7)
Body Mass Index [Mean (SD)]	18.30 (10.3)	20.79 (17.7)	18.60 (9.2)
Median income [Mean (SD)]	53 910 (12 780)	54 011 (13,543)	53 318 (14 379)
Population size [Mean (SD)]	31 296 (21 050)	29 974 (21 718)	29 898 (18 990)
First Health Contact [n (%)]			
GP	428 (49.0)	226 (62.8)	174 (34.6)
ER	144 (16.5)	54 (15.0)	164 (32.6)
Other	292 (33.4)	75 (20.8)	150 (29.8)
Region [n (%)]			
Quebec	305 (34.9)	133 (36.9)	174 (34.6)
Atlantic	143 (16.4)	54 (15.0)	117 (23.3)
Prairies	241 (27.6)	112 (31.1)	137 (27.2)
British Columbia	182 (20.8)	58 (16.1)	74 (14.7)
Community Type [n (%)]			
Rural	235 (26.9)	91 (25.3)	134 (26.6)
Urban	588 (67.3)	246 (68.3)	326 (64.8)
Cancer suptype [n (%)]			
ALL	716 (81.9)	--	--
Non-ALL	158 (18.1)	--	--
Hodgkin Disease	--	185 (51.4)	--
Non-Hodgkin lymphoma	--	161 (44.7)	--
Medulloblastoma	--	--	104 (20.7)
Other	--	--	384 (76.3)
Disease Severity			
Low	436 (56.8)	173 (57.5)	221 (80.4)
High	332 (43.2)	128 (42.5)	54 (19.6)
Patient Delay Category [Median (IQR)]	8 (1-21)	11 (2-39)	14 (0-42)
Physician Delay [Median (IQR)]	3 (1-14)	11 (4-41)	16 (4-56)
Diagnosis Delay [Median (IQR)]	19 (9-36)	39 (18-90)	48 (23-119)

Note: Totals are not equal across categories due to missing values.

Table 10.2: Death rates of leukemia patients

	Person-time (months)	Deaths	rate (per 1000)	95% CI (per 1000)	(per 1000)
Overall	26980.5	95	3.52	2.88	4.31
Diagnosis Delay					
under 9	6088.2	25	4.11	2.77	6.08
9 – 18	6429.1	27	4.20	2.88	6.12
19 – 35	6512.7	22	3.38	2.22	5.13
36 and up	7654.3	20	2.61	1.69	4.05
Patient Delay					
under 1	4931.6	21	4.26	2.78	6.53
1 – 7	7943.9	30	3.78	2.64	5.40
8 – 20	6257.1	22	3.52	2.32	5.34
21 and up	7372.7	22	2.98	1.96	4.53
Physician Delay					
under 1	1500.5	5	3.33	1.39	8.01
1 – 2	9289.2	34	3.66	2.62	5.12
3 – 13	8708.5	31	3.56	2.50	5.06
14 and up	7117.2	22	3.09	2.04	4.69

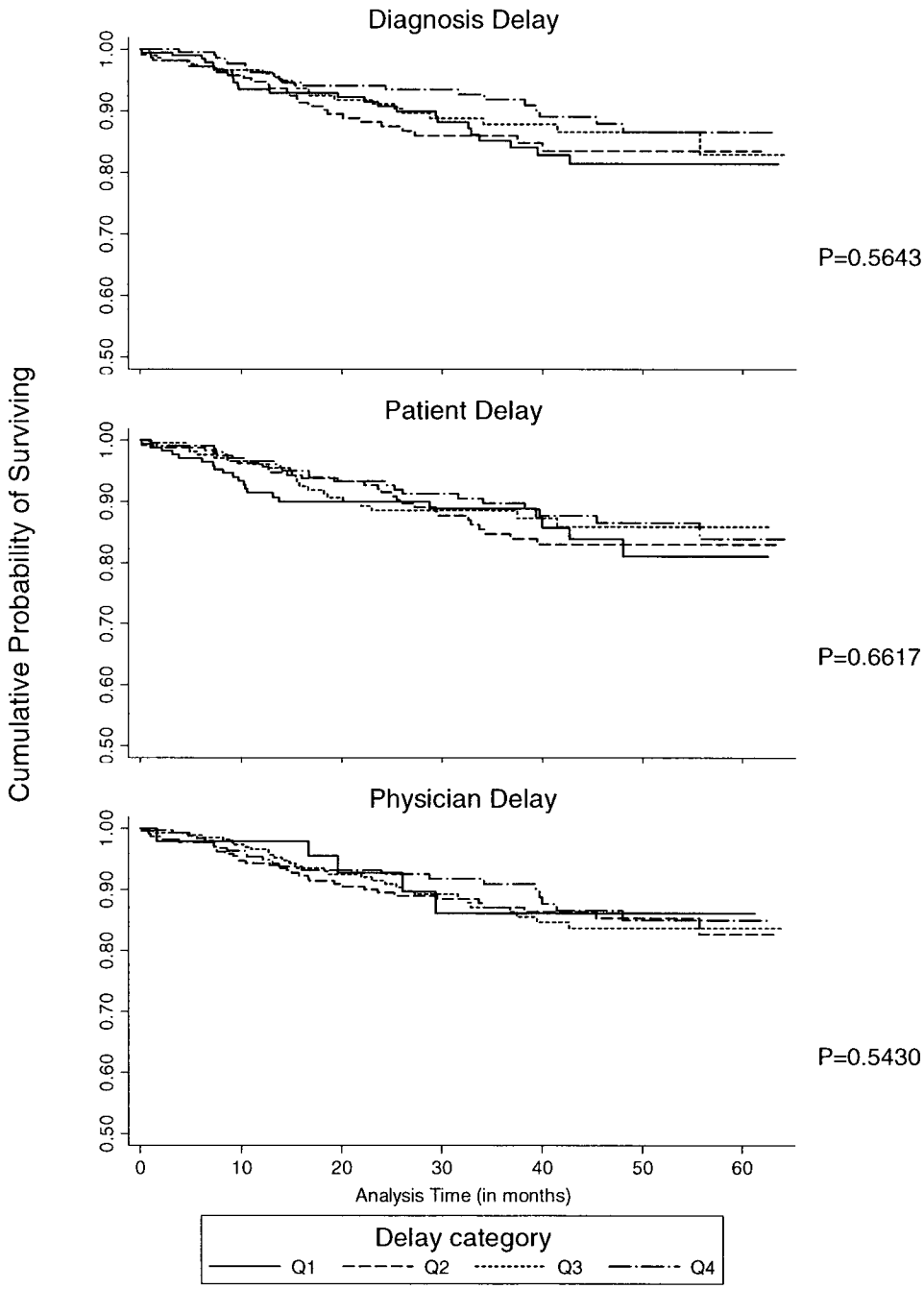
Table 10.3: Death rates of lymphoma patients

	Person-time (months)	Deaths	rate (per 1000)	95% CI (per 1000)	(per 1000)
Overall	10866.645	23	2.12	1.41	3.19
Diagnosis Delay					
under 18	2509.6	5	1.99	0.83	4.79
18 – 38	2412.4	7	2.90	1.38	6.09
39 – 89	2910.3	5	1.72	0.72	4.13
90 and up	2886.9	5	1.73	0.72	4.16
Patient Delay					
under 2	2610.5921	3	1.15	0.37	3.56
2 – 10	2633.3224	8	3.04	1.52	6.07
11 – 38	2799.9013	3	1.07	0.35	3.32
39 and up	2761.8092	9	3.26	1.70	6.26
Physician Delay					
under 4	2262.9	5	2.21	0.92	5.31
4 – 10	2601.3	7	2.69	1.28	5.64
11 – 40	2644.1	7	2.65	1.26	5.55
41 and up	3033.1	2	0.66	0.16	2.64

Table 10.4: Death rates of CNS tumour patients

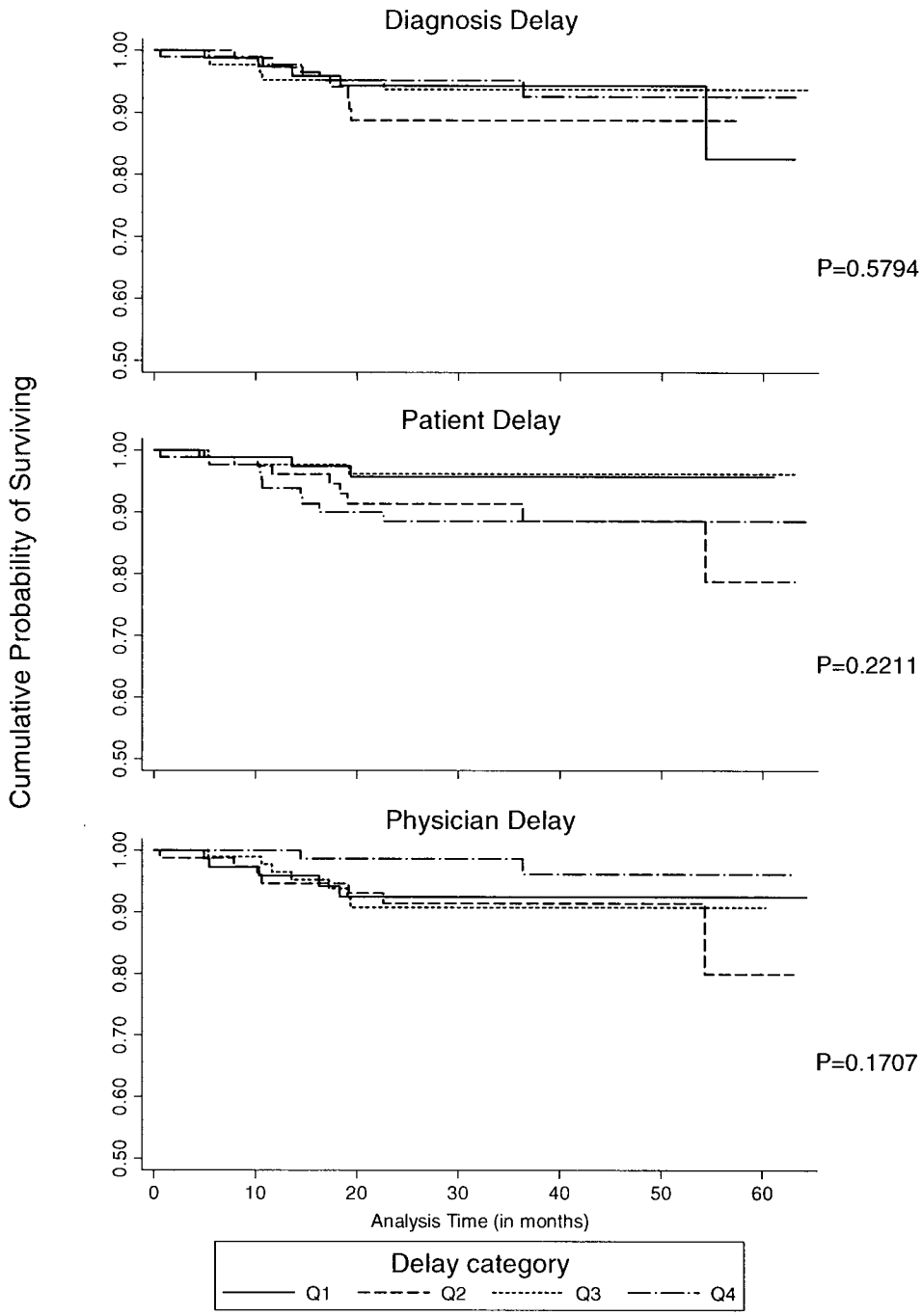
	Person-time (months)	Deaths	rate (per 1000)	95% CI (per 1000)	(per 1000)
Overall	13838.9	89	6.43	5.22	7.92
Diagnosis Delay					
under 23	2824.2	36	12.75	9.19	17.67
23 – 47	3258.6	21	6.44	4.20	9.88
48 - 118	3627.4	22	6.07	3.99	9.21
119 and up	3405.0	10	2.94	1.58	5.46
Patient Delay					
0	2976.5	12	4.03	2.29	7.10
0.1 – 13	3274.2	31	9.47	6.66	13.46
14 - 41	3312.3	26	7.85	5.34	11.53
42 and up	3571.3	19	5.32	3.39	8.34
Physician Delay					
under 4	2579.8	28	10.85	7.49	15.72
4 - 15	3547.9	25	7.05	4.76	10.43
16 - 55	3553.3	20	5.63	3.63	8.72
56 and up	3265.5	14	4.29	2.54	7.24

Figure 10.1: Cumulative probability of survival of leukemia patients by type of delay



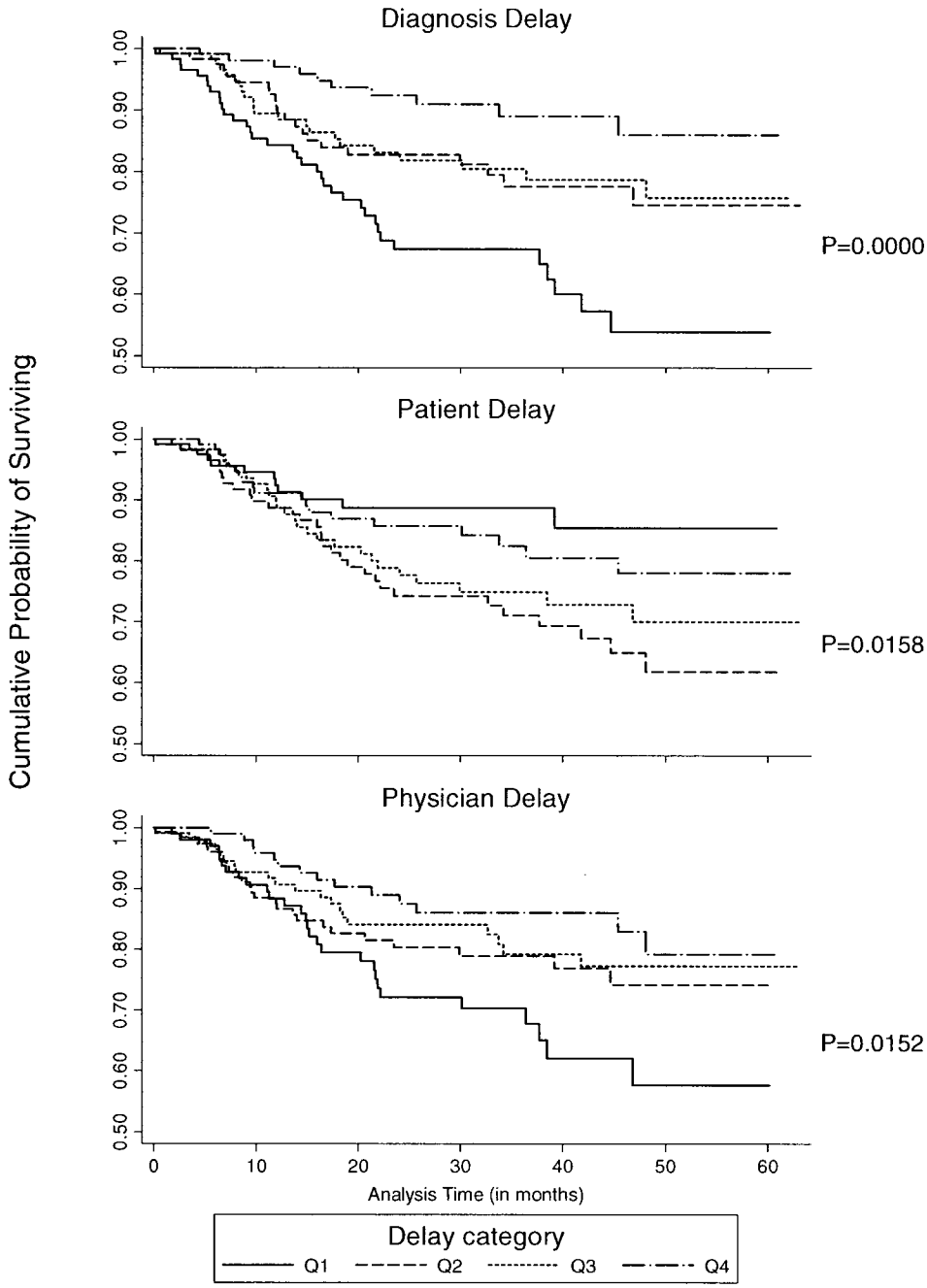
Note: Delay categories are grouped based on the quartiles of the delay (in days)
Diagnosis delay: Q1 (<9), Q2 (9-18), Q3 (18-35), Q4 (36 & up)
Patient delay: Q1 (<1), Q2 (1-7), Q3 (8-20), Q4 (21 & up)
Physician delay: Q1 (<1), Q2 (1-2), Q3 (3-13), Q4 (14 & up)

Figure 10.2: Cumulative probability of survival of lymphoma patients by type of delay



Note: Delay categories are grouped based on the quartiles of the delay (in days)
Diagnosis delay: Q1 (<18), Q2 (18-38), Q3 (39-89), Q4 (90 & up)
Patient delay: Q1 (<2), Q2 (2-10), Q3 (11-38), Q4 (39 & up)
Physician delay: Q1 (<4), Q2 (4-10), Q3 (11-40), Q4 (41 & up)

Figure 10.3: Cumulative probability of survival of CNS tumours patients by type of delay



Note: Delay categories are grouped based on the quartiles of the delay (in days)
Diagnosis delay: Q1 (<23), Q2 (23-47), Q3 (48-118), Q4 (119 & up)
Patient delay: Q1 (0), Q2 (0.1-13), Q3 (14-41), Q4 (42 & up)
Physician delay: Q1 (<4), Q2 (4-15), Q3 (16-55), Q4 (56 & up)

Table 10.5: Impact of delay in cancer care on survival of leukemia patients, aged 0-19 years of age

Delay Variable	Crude HR (95% CI)	Model 1* HR (95% CI)	Model 2** HR (95% CI)
Diagnosis Delay Category[a]			
under 9	ref (---)	ref (---)	ref (---)
9 – 18	1.01 (0.6-1.7)	1.07 (0.6-1.9)	1.00 (0.5-1.9)
19 – 35	0.83 (0.5-1.5)	0.86 (0.5-1.5)	0.90 (0.5-1.7)
36 and up	0.65 (0.4-1.2)	0.60 (0.3-1.1)	0.57 (0.3-1.1)
Patient Delay Category[b]			
under 1	ref (---)	ref (---)	ref (---)
1 – 7	0.90 (0.5-1.6)	0.88 (0.5-1.6)	0.88 (0.4-1.8)
8 – 20	0.83 (0.5-1.5)	0.93 (0.5-1.7)	0.96 (0.4-2.1)
21 and up	0.72 (0.4-1.3)	0.89 (0.5-1.6)	0.91 (0.4-1.9)
Physician Delay Category[c]			
under 1	ref (---)	ref (---)	ref (---)
1 – 2	1.11 (0.4-2.8)	1.52 (0.6-4.0)	1.20 (0.4-3.3)
3 - 13	1.07 (0.4-2.8)	1.48 (0.6-3.9)	1.15 (0.4-3.2)
14 and up	0.94 (0.4-2.5)	1.03 (0.4-2.8)	0.80 (0.3-2.4)

*Crude model adjusted for empirical confounders: a) age, population size and cancer subtype; b) income, population size and cancer subtype; c) age, income, region and cancer subtype.
** Model 1 adjusted for disease severity

Table 10.6: Impact of delay in cancer care on survival of lymphoma patients, aged 0-19 years of age

Delay Variable	Crude HR (95% CI)	Model 1* HR (95% CI)	Model 2** HR (95% CI)
Diagnosis Delay Category[a]			
Under 18	ref (---)	ref (---)	ref (---)
18 - 38	1.44 (0.5-4.5)	1.48 (0.4-5.0)	1.31 (0.3-5.6)
39 - 89	0.88 (0.3-3.1)	0.90 (0.2-3.4)	0.97 (0.2-4.5)
90 and up	0.88 (0.3-3.0)	1.35 (0.3-5.2)	1.31 (0.3-6.3)
Patient Delay Category[b]			
Under 2	ref (---)	ref (---)	ref (---)
2 - 10	2.73 (0.7-10.3)	2.01 (0.5-8.1)	2.35 (0.4-13.2)
11 - 38	0.96 (0.2-4.7)	0.65 (0.1-3.3)	0.51 (0.1-4.1)
39 and up	2.93 (0.8-10.8)	2.00 (0.5-8.1)	2.17 (0.4-11.5)
Physician Delay Category[c]			
Under 4)	ref (---)	ref (---)	ref (---)
4 - 10	1.26 (0.4-4.0)	1.59 (0.5-5.4)	1.38 (0.4-5.1)
11 - 40	1.16 (0.4-3.7)	1.89 (0.6-6.4)	1.45 (0.4-5.5)
41 and up	0.31 (0.1-1.6)	0.70 (0.1-4.0)	0.41 (0.0-4.1)

*Crude model adjusted for empirical confounders: a) BMI, health professional and cancer subtype; b) sex, BMI, income, region, population size, community type and cancer subtype; c) sex, BMI, health professional, region, community type and cancer subtype.
** Model 1 adjusted for disease severity

Table 10.7: Impact of delay in cancer care on survival of CNS tumour patients, aged 0-19 years of age

Delay Variable	Crude HR (95% CI)	Model 1* HR (95% CI)	Model 2** HR (95% CI)
Diagnosis Delay Category [a]			
under 23	ref (---)	ref (---)	ref (---)
23 - 47	0.51 (0.3-0.9)	0.60 (0.3-1.0)	0.83 (0.4-1.8)
48 - 118	0.50 (0.3-0.8)	0.52 (0.3-0.9)	0.46 (0.2-1.0)
119 and up	0.24 (0.1-0.5)	0.27 (0.1-0.6)	0.33 (0.1-0.9)
Patient Delay Category [b]			
0	ref (---)	ref (---)	ref (---)
0.1 - 13	2.41 (1.2-4.7)	2.48 (1.3-4.9)	2.15 (0.9-5.4)
14 - 41	1.99 (1.0-3.9)	2.45 (1.2-4.9)	1.96 (0.8-4.9)
42 and up	1.36 (0.7-2.8)	1.59 (0.8-3.3)	1.07 (0.4-3.1)
Physician Delay Category [c]			
under 4	ref (---)	ref (---)	ref (---)
4 - 15	0.67 (0.4-1.1)	0.62 (0.4-1.1)	0.34 (0.2-0.7)
16 - 55	0.54 (0.3-1.0)	0.50 (0.3-0.9)	0.33 (0.1-0.7)
56 and up	0.41 (0.2-0.8)	0.41 (0.2-0.8)	0.37 (0.2-0.9)

*Crude model adjusted for empirical confounders: a) age, BMI, population size and community type; b) age, BMI and region; c) BMI.
** Model 1 adjusted for disease severity

11. CONCLUSION

Few health studies have specifically examined the epidemiology and public health significance of diagnostic and treatment delays in childhood cancer. In the absence of screening for pre-invasive cancers or precursors, useful information for cancer control can be derived from this study. For this study, I had a unique opportunity of working with a national program containing population-based information on children and adolescents diagnosed with cancer accrued over a sufficiently long period and followed up over many years to measure long-term survival. This allowed me to examine the entire scope of the issues concerning delays in the diagnosis of childhood cancer in a detailed study from a national perspective, thus having the weight of evidence that is required for evidence-based decisions.

In this study, I measured and characterized various types of delays in cancer care in Canada and obtained important information on the factors that influence patient and provider delays. This offered an opportunity to isolate the main time segment responsible for lengthening the cancer care pathway taken by children and adolescents. Varying lengths of patient delay and referral delay, across age groups, types of cancers, and Canadian settings, are the main contributors to diagnosis, HCS and overall delay. Also, I extended the current findings in the literature by examining the influence of several parameters on various types of delays. Factors relating to the patient, the parents, healthcare, and the cancer type may all exert different influences on the different segments of the cancer care pathway.

I also examined the relationships between the individual patient and physician delays on disease severity and on prognosis using judicious control for potential

confounding mechanisms and factors. Generally, the findings of this study are contrary to the general belief that delays lead to substantially worse disease severity. The negative association between diagnosis delay and disease severity for lymphoma and CNS tumour patients suggests that tumour biology and the extent of the disease severity may actually be the determinant of the length of delay times and not vice versa. I also found that diagnosis delay, as well as patient and physician delay, was not associated with disease prognosis for patients with leukemia and lymphoma. However, diagnosis delay and physician delay had a negative effect, while patient delay had a positive effect, on survival for patients diagnosed with CNS tumours.

I am currently working with the Public Health Agency of Canada and Statistics Canada to obtain information on the status of all of the patients enrolled in the TOS program. This study has helped the Public Health Agency of Canada renew its efforts to re-initiate the CCCSCP and continue with the surveillance and collection of follow-up information of the patients currently enrolled in the program. This will provide more data for my future analyses and strengthen my study findings.

Further research on the effect of delays on patient survival is needed in order to uncover the other mechanisms behind these relationships. The findings of my study support the development of educational programs, for the population and health care professionals, aimed at the identification of early symptoms of cancer in children before their disease becomes severe. Furthermore, the development of more refined and universally adopted staging classification systems for cancers in children and adolescents would greatly benefit future studies on this subject and provide a clearer picture of the impact of delays on disease severity and prognosis.

The information provided from this study may form the basis for new effective policies and programs aimed at eliminating bottlenecks and obstacles in the diagnostic and care trajectories for Canadian children with cancer and for improving their short- and long-term prognosis.

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APPENDICES

Appendix 1: Paediatric cancer centres

1 - BC Children's Hospital – Vancouver

2 - Alberta Children's Provincial General Hospital – Calgary

3 - Cross Cancer Institute – Edmonton

4 - Pasqua Hospital – Regina

5 - Royal University Hospital – Saskatoon

6 - Children's Hospital of Winnipeg

7 - Chedoke-McMaster Hs – Hamilton

8 - Hotel Dieu - Kingston

9 - Children's Hospital of Western Ontario – London

10 - Children's Hospital of Eastern Ontario – Ottawa

11 - Hospital for Sick Children – Toronto

12 - Ste-Justine Hospital – Montreal

13 - Montreal Children's Hospital

14 - Centre Hospitalier de l'Universite de Laval – Ste-Foy

15 - Centre Hospitalier Hotel-Dieu de Sherbrooke

16 - Isaak Walton Killam Children's (IWK) Hospital – Halifax

17 - Janeway Child Health Centre – St-John Nfld

Appendix 2: TOS-CCCSCP Questionnaires

CCCSCP # _____1

NEW PATIENT

PATIENT ID

Informed consent (treatment surveillance) accepted: Yes ☐ No ☐ N/A☐

Consent to be contacted by etiology investigator: Yes ☐ No ☐ N/A☐

Informed consent (long term follow up) accepted: Yes ☐ No ☐ N/A☐

★ Child's Last Name: _____

★ Child's First Name: _____

Hospital Record Number: _____

Provincial Health Insurance Number: _____

★ Sex: Male ☐ Female ☐

★ Birthdate: ____/____/____
(D) (M) (Y)

Institution of initial diagnosis: _____

Was this patient transferred from another clinic? Yes ☐ No ☐

Name of MOTHER or legal guardian Surname: _____

Given Name: _____

Maiden (natal) Name: _____

Mother's date of birth: ____/____/____ ☐ estimated
(M) (D) (Y)

If not mother, relationship to child: _____

CCCSCP # _____2

Name of FATHER or legal guardian Surname:_____

Given name:_____

Father's date of birth: ____/____/____ ☐ estimated
(M) (D) (Y)

If not father, relationship to child:_____

ADDRESS
(To Be Completed At Diagnosis and At Each Follow Up)

Child's Address: Street: _____ City: _____

Province: _____ Postal Code: _____

Child's Phone number: _____

Current address of Mother: ☐ same as child

Street: _____ City: _____

Province: _____ Postal Code: _____

Mother's Phone number: _____

Current address of Father: ☐ same as child

Street: _____ City: _____

Province: _____ Postal Code: _____

Father's Phone number: _____

★ Oncology treatment centre: _____

Name of current physician: _____

★ Data manager name: _____

INITIAL INFORMATION

Date of onset of initial complaint: ____/____/____ (D) (M) (Y) ☐ estimated

Date of first health care contact for complaint: ____/____/____ (D) (M) (Y) ☐ estimated

Which health care professional:

Family Physician (GP)	☐
Paediatrician	☐
Emergency Room Physician	☐
Nurse	☐
Homeopath	☐
Other	☐

if other, please specify: _____

Was anti-cancer therapy given elsewhere prior to referral to the treating institution?

Yes ☐ No ☐ N/A ☐

If yes, then place: _____

and date of first therapeutic intervention: ____/____/____ (D) (M) (Y)

★ Date of first assessment by treating oncologist/surgeon: ____/____/____ (D) (M) (Y)

Initial diagnosis based on pathology report:
Yes ☐ No ☐ Don't know ☐

Initial diagnosis based on diagnostic imaging:
Yes ☐ No ☐ Don't know ☐

★ Date of definitive diagnostic procedure: ____/____/____ (D) (M) (Y)

Procedure:

Autopsy	☐	Radiological	☐
Histological	☐	Clinical	☐
Cytological	☐	Unknown	☐

CCCSCP # _____ 5

★ Initial Diagnosis at treating institution: _____

★ Manchester code: _____
(see list of choices in instructions)

Site of tumour: _____

ICDO T code: _____

★ Morphology/Histology: _____

★ ICDO M Code: _____

Stage: _____ POG ☐ CCG ☐ Other ☐ N/A ☐

If malignancy is ALL, risk: Low ☐ Medium ☐ Standard ☐ High ☐ Very high ☐

If ANLL, risk: M1 ☐ M2 ☐ M3 ☐ M4 ☐ M5 ☐ M6 ☐ M7 ☐

If CNS tumor, WHO histological typing (code): _____

If malignancy is leukemia/ lymphoma: Initial white blood count: _____

CSF positive: Yes ☐ No ☐ N/A ☐

Testicular involvement: Yes ☐ No ☐ N/ A ☐

Metastatic sites:

Lung ☐
Bone ☐
Bone Marrow ☐
Brain ☐
Liver ☐
Lymph nodes regional ☐
Lymph nodes distant ☐
Other ☐
None ☐

Revised Diagnosis (if applicable): _____

☐ True disease conversion

Date of Revised Diagnosis: ____/____/____
(D) (M) (Y)

Manchester code: _____
(see list of choices in instructions)

Site of tumour: _____

ICDO T code: _____

Morphology/Histology: _____

ICDO M Code: _____

Stage: _____ POG ☐ CCG ☐ Other ☐ N/A ☐

If malignancy is ALL, risk:

Low	☐
Medium	☐
Standard	☐
High	☐
Very high	☐

If ANLL, risk:

M1	☐
M2	☐
M3	☐
M4	☐
M5	☐
M6	☐
M7	☐

If CNS tumor, WHO histological typing: _____

If malignancy is leukemia/ lymphoma:

Initial white blood count: _____

CSF positive:

Yes	☐
No	☐
N/A	☐

Testicular involvement:

Yes	☐
No	☐
N/A	☐

Initial extent of disease:

If solid tumor, initial size of tumor in mm: _____ by _____ by _____

If leukemia, % of blast cells: _____ %

Height of child at reference date: _____ cm

or _____ ft _____ in

Weight of child at reference date: _____ kg

or _____ lb _____ oz

CCCSCP # _____ R

Is this a first malignancy? Yes ☐ No ☐ N/A ☐

If not, define prior malignancy (Manchester Code):_____

Date of diagnosis of prior malignancy: ____/____/____ (D) (M) (Y)

Is the child registered on a clinical trial treatment protocol? Yes ☐ No ☐ N/A ☐

If no, is the child following a specified treatment protocol? Yes ☐ No ☐ N/A ☐

Identify protocol and treatment arm if CCG or POG: _____

If not CCG nor POG, please specify protocol and treatment arm: _____

_____

Date of first therapeutic intervention at current treating institution: ____/____/____ (D) (M) (Y)

Date of completion of form: ____/____/____ (D) (M) (Y)

Additional comments (can be entered in the utilities option):

CCCSCP # _____ 1

FOLLOW-UP

Routine Follow Up Information (every 6 months)
(please check one for each follow-up)

6 months	☐	12 months	☐	18 months	☐	24 months	☐
30 months	☐	36 months	☐	42 months	☐	48 months	☐
54 months	☐	60 months	☐				

ADDRESS (enter changes if applicable)

Child's Address: Street: _____ City: _____

Province: _____ Postal Code: _____

Child's Phone number: _____

Current address of Mother: ☐ same as child

Street: _____ City: _____

Province: _____ Postal Code: _____

Mother's Phone number: _____

Current address of Father: ☐ same as child

Street: _____ City: _____

Province: _____ Postal Code: _____

Father's Phone number: _____

Oncology treatment centre: _____

Name of current physician: _____

Data manager name: _____

STATUS

Date of last contact in the last 6 month period: ____/____/____ (D) (M) (Y) ☐ Not seen

★ Today's date: ____/____/____ (D) (M) (Y)

Treating institution: _____

Revised diagnosis (if applicable): _____

☐ True disease conversion

Manchester code: _____
(see list of choices in instructions)

Site of tumour: _____

ICDO T code: _____

Morphology/Histology: _____

ICDO M Code: _____

Revised Stage: _____ POG ☐ CCG ☐ Other ☐ N/A ☐

If malignancy is ALL, risk:	Low	☐	If ANLL, risk:	M1	☐
	Medium	☐		M2	☐
	Standard	☐		M3	☐
	High	☐		M4	☐
	Very high	☐		M5	☐
				M6	☐
				M7	☐

If CNS tumor, WHO histological typing (code): _____

Was the patient transferred to another clinic: ☐ Yes ☐ No

Was chromosomal testing performed? ☐ Yes ☐ No ☐ Don't know

If yes, chromosome number: _____ chromosomes

or: ☐ inconclusive karyotyping

Specific congenital abnormality (if applicable):

Translocation: ☐ Yes ☐ No ☐ N/A

if yes, what type: _____

Deletion: ☐ Yes ☐ No ☐ N/A

if yes, what type: _____

Inversion: ☐ Yes ☐ No ☐ N/A

if yes, what type: _____

Other: ☐ Yes ☐ No ☐ N/A

★ **Status over the last 6 months** (Check all that apply):
(at least one status must be checked)

		Date (D/M/Y)
Complete response	☐	_____
		_____
		_____
Partial response	☐	_____
Stable disease	☐	_____
Progressive disease	☐	_____

Status over the last 6 months (con't)

Relapse ☐

Relapse 1: if not leukemia, site:
- Local ☐
- Regional ☐
- Distant ☐

Date: ____/____/____ (D) (M) (Y)

if leukemia:
- Peripheral blood ☐
- Bone Marrow ☐
- CNS ☐
- Testicular ☐
- Other: ☐

if other, specify: _____

Relapse 2: if not leukemia, site:
- Local ☐
- Regional ☐
- Distant ☐

Date: ____/____/____ (D) (M) (Y)

if leukemia:
- Peripheral blood ☐
- Bone Marrow ☐
- CNS ☐
- Testicular ☐
- Other: ☐

if other, specify: _____

Relapse 3: if not leukemia, site:
- Local ☐
- Regional ☐
- Distant ☐

Date: ____/____/____ (D) (M) (Y)

if leukemia:
- Peripheral blood ☐
- Bone Marrow ☐
- CNS ☐
- Testicular ☐
- Other: ☐

if other, specify: _____

Status over the last 6 months (con't):

Death ☐

If yes, date: ____/____/____
(D) (M) (Y)

Was cause disease and/or treatment related? Yes ☐ No ☐ N/A ☐

ICD 10 code (if available): _____

Was and autopsy performed?
Yes ☐ No ☐ Don't know ☐

New Malignancy ☐

If yes: Diagnosis: _____

Manchester Code: _____

Date: ____/____/____
(D) (M) (Y)

Site of Secondary tumour: _____

ICDO T code: _____

Morphology/Histology: _____

ICDO M code: _____

Stage: _____ POG ☐ CCG ☐ Other ☐ N/A ☐

If malignancy is ALL, risk: Low ☐ Medium ☐ Standard ☐ High ☐ Very high ☐

If ANLL, risk: M1 ☐ M2 ☐ M3 ☐ M4 ☐ M5 ☐ M6 ☐ M7 ☐

If CNS tumor, WHO histological typing (code): _____

Status over last 6 months (con't):

If malignancy is leukemia/ lymphoma:

Initial white blood count: _____

CSF positive: Yes ☐ No ☐ N/A ☐

Testicular involvement: Yes ☐ No ☐ N/ A ☐

Metastatic sites:

Lung	☐	Lymph nodes regional	☐
Bone	☐	Lymph nodes distant	☐
Bone Marrow ☐	Liver	☐	
Brain	☐	Other	☐
		None	☐

Height of child: _____ cm

or: _____ ft _____ in

Weight of child: _____ kg

or: _____ lb _____ oz

CCCSCP # _____ 8

CORE TREATMENT INFORMATION

Is patient on treatment currently? Yes ☐ No ☐ Don't know ☐

Initial planned treatment course completed? Yes ☐ No ☐

Don't know ☐

If no, reasons why treatment course not completed:

Death ☐

Physician preference ☐

Moved ☐

No response ☐

Progression ☐

Refusal ☐

Relapse ☐

Too soon ☐

Toxicity ☐

Other ☐

if other, please specify: _____

★ Was chemotherapy administered? Yes ☐ No ☐
N/A ☐

Date: ____/____/____
(D) (M) (Y)

Which of these chemotherapeutic agents have been administered since the last follow up (check all that apply):

5-fluorouracil (5-FU)	☐	Ifosphamide	☐
6-mercaptopurine (6-MP)	☐	L'asparaginase	☐
		Lomustine (CCNU)	☐
6-thioguanine (6-TG)	☐	Melphalan	☐
Actinomycin D	☐	Methotrexate	☐
Adriamycin	☐	Mitomycin C	☐
Bleomycin	☐	Nitrogen Mustard	☐
Busulphan	☐	Prednisone	☐
Carboplatinum	☐	Procarbazine	☐
Carmustine (BCNU)	☐	Taxol	☐
Cisplatinum	☐	Topotecon	☐
Cyclophosphomide	☐	Vinblastine	☐
Cytosine arabinoside	☐	Vincristine	☐
Dacarbazine (DTIC)	☐	VM-26	☐
Daunomycin	☐	Ara-C/IT	☐
Dexamethasone	☐	Hydrocortisone/IT	☐
Epirubicin	☐	Methotrexate/IT	☐
Etoposide (VP16)	☐	Other	☐
Idarubicin	☐	if other, please specify: _____	

Total accumulated dose of anthracyclines: _____

(to be completed at two year follow-up only)

Were biological effect modifiers used: Yes ☐ No ☐ Don't know ☐

If yes, which ones? (check all that apply):

Cyclosporin ☐
Growth factors ☐
Interleukin ☐
Interferon ☐
Retinoic acid ☐
Other ☐
If other , please specify:_____

★ Was surgery performed? Yes ☐ No ☐ N/A ☐

(excluding biopsy and central line insertion and removal)

Procedure Code	Date (D/M/Y)
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

★ Was radiation therapy administered: Yes (completed) ☐ No ☐
In progress ☐ N/A ☐

If completed:

Date initiated: ____/____/____
(D) (M) (Y)

★ Site (if applicable):

Brain whole	☐	Abdomen-right	☐
Brain partial	☐	Abdomen-left	☐
Cranio-spinal	☐	Hemi-abdomen	☐
Face	☐	Whole abdomen	☐
Neck	☐	Pelvis	☐
Media spinum	☐	Upper limbs	☐
Lung-right	☐	Lower limbs	☐
Lung-left	☐	Testis	☐
Lung-bilateral	☐	Other	☐
		Unknown	☐

★Total dosage: _____

★ Number of fractions: _____

Site:

Brain whole	☐	Abdomen-right	☐
Brain partial	☐	Abdomen-left	☐
Cranio-spinal	☐	Hemi-abdomen	☐
Face	☐	Whole abdomen	☐
Neck	☐	Pelvis	☐
Media spinum	☐	Upper limbs	☐
Lung-right	☐	Lower limbs	☐
Lung-left	☐	Testis	☐
Lung-bilateral	☐	Other	☐
		Unknown	☐

Total dosage: _____

Number of fractions: _____

Site:				
	Brain whole	☐	Abdomen-right	☐
	Brain partial	☐	Abdomen-left	☐
	Cranio-spinal	☐	Hemi-abdomen	☐
	Face	☐	Whole abdomen	☐
	Neck	☐	Pelvis	☐
	Media spinum	☐	Upper limbs	☐
	Lung-right	☐	Lower limbs	☐
	Lung-left	☐	Testis	☐
	Lung-bilateral	☐	Other	☐
			Unknown	☐

Total dosage: _____

Number of fractions: _____

SUPPLEMENTARY TREATMENT INFORMATION

★ Was a bone marrow transplant performed?

Yes ☐ No ☐ N/A ☐

If yes, type of transplant:

- Allogenic ☐
- Autologous ☐
- Matched unrelated donor ☐
- Syngenic (twin) ☐
- Peripheral blood stem cells ☐
- Other ☐

Date: ____/____/____
(D) (M) (Y)

Was transplant related irradiation performed?

- No ☐
- Local irradiation ☐
- Total body irradiation ☐
- Total lymphatic irradiaton ☐
- Don't know ☐

Were other treatments administered?

Yes ☐ No ☐ N/A ☐

If yes, which ones (check all that apply):

- Palliative care ☐
- Laser therapy ☐
- Hormonal therapy ☐
- Other ☐

If other, please specify: _____

Blood components transfusion? Yes ☐ No ☐ Don't know ☐

If yes, type of transfusion:

		Number of transfused units
Red Cells	☐	_____
Platelets	☐	_____
Whole blood	☐	_____
Fresh frozen plasma	☐	_____
Other	☐	_____
Unknown	☐	_____

If other(s), please specify type:

1. _____
2. _____

Did major complications occur?

Yes ☐ No ☐ N/A ☐

Major life threatening infection	☐	Number of episodes:_____
Major bleed	☐	Number of episodes:_____
Organ failure	☐	Number of episodes:_____
Nutritional support (supplemental feeding)	☐	Number of episodes:_____
Febrile Neutropenia	☐	Number of episodes:_____

★ Permanent central lines? (if no, enter 0):

	Portacath	Hickman/Broviac
Number of times removed:	_____	_____
Number of times changed:	_____	_____
Number of times inserted:	_____	_____

Total number of inpatient hospital days at treating institution: _____

Was cancer care given at the treating institution? Yes ☐ No ☐ N/A ☐

Was any cancer care given elsewhere? Yes ☐ No ☐ Don't know ☐

If yes, place(s): 1._____

2._____

Reason:

- Radiation ☐
- Blood transfusions ☐
- Chemotherapy ☐
- Febrile illness ☐
- Toxicity ☐
- Nutritional support ☐
- Other ☐

If other, please specify:_____

Additional comments (can be entered in utilities option):

Appendix 3: Ethical approval

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

September 25, 2007

Dr. Eduardo L. Franco
Division of Epidemiology
Department of Oncology
Gerald Bronfman Centre
546 Pine Avenue West
Montreal Quebec H2W 1S6

RE: IRB Study Number A09-M69-03B

Dear Dr. Franco,

Thank you for submitting an application for Continuing Review for the above-referenced study entitled, *Diagnostic and Treatment Delays in Childhood Cancers in Canada*.

The Study Progress Report underwent review and full Board re-approval for the study was provided on September 24, 2007. The ethics renewal certificate (enclosed) is **valid until September 23, 2008**.

If any study modifications or unanticipated study developments occur prior to the next annual review, including study terminations, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Yours sincerely,

Serge Gauthier, MD
Chair
Institutional Review Board

cc: A09-M69-03B

DATE OF I.R.B. APPROVAL

SEP 2 2007

Faculty of Medicine
McGill University

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Dr. Eduardo Franco Department/Institution: Oncology

IRB Review Number: A09-M69-03B Study Number (if any): _____ Review Interval: Annual

Title of Research Study: Diagnostic and Treatment Delays in Childhood Cancers in Canada

Date of initial IRB approval: Sept. 29, 2003 Date of previous continuing review (if applicable): September 26, 2006

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: √ On Hold: _____ Closed to Enrolment: _____

Interim Analysis: _____ Final Analysis: √ Study Not Activated*: _____

*If the study has not become active at McGill, please provide correspondence to explain, enclosed: _____

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐

MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐ None

McGill hospital(s) where study has not received approval of local Research Ethics Board(s) (if applicable): NA

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed: NA

Number of subjects to be enrolled by the McGill PI: 0

Number of subjects enrolled by the McGill PI to date: 6000 subjects enrolled. This study uses a pre-existing dataset from Health Canada and will not require any further enrolment of subjects.

Number of subjects enrolled by the McGill PI since last review: NA

Have any of these subjects withdrawn from the study?: NA

Has the study been revised since the last review?: No Have the study revisions been approved by the IRB?: NA

Has the consent form been revised since the last review? NA Date of the current consent form: NA

Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

Have there been any serious adverse experiences (SAEs)? NA

Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB? NA

SIGNATURES:

Principal Investigator: _____ Date: September 6th, 2007

IRB Chair: _____ Date: Sept. 24/2007.

DATE OF I.R.B. APPROVAL

SEP 2 2 2007

Faculty of Medicine
McGill University

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Dr. Eduardo Franco Department/Institution: Oncology

IRB Review Number: A09-M69-03B Study Number (if any): _____ Review Interval: Annual

Title of Research Study: Diagnostic and Treatment Delays in Childhood Cancers in Canada

Date of initial IRB approval: Sept. 29, 2003 Date of previous continuing review (if applicable): September 26, 2006

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: √ On Hold: _____ Closed to Enrolment: _____

Interim Analysis: _____ Final Analysis: √ Study Not Activated*: _____

*If the study has not become active at McGill, please provide correspondence to explain, enclosed: _____

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐

MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐ None

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Has the consent form been revised since the last review? NA Date of the current consent form: NA

Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

Have there been any serious adverse experiences (SAEs)? NA

Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB? NA

SIGNATURES:

Principal Investigator: _____ Date: September 6th, 2007

IRB Chair _____ Date: Sept. 24/2007

DATE OF I.R.B. APPROVAL

SEP 24 2007

Faculty of Medicine
McGill University

McGill Faculty of Medicine
Institutional Review Board
-Continuing Review-

Principal Investigator: Dr. Eduardo Franco Department/Institution: Oncology

IRB Review Number: A09-M59-03B Study Number (if any) _____ Review Interval: Annual

Title of Research Study: Diagnostic and Treatment Delays in Childhood Cancers in Canada

Date of initial IRB approval: Sept. 29, 2003 Date of previous continuing review (if applicable): September 26, 2006

INTERIM REPORT (PLEASE CHECK OR SPECIFY)

Current Status of Study:

Active Study: √ On Hold: _____ Closed to Enrolment: _____

Interim Analysis: _____ Final Analysis: √ Study Not Activated*: _____

*If the study has not become active at McGill, please provide correspondence to explain; enclosed: _____

McGill hospital(s) where study is being conducted and has received approval of local Research Ethics Board(s) (if applicable):

JGH: ☐ MUHC/MCH: ☐ MUHC/MGH: ☐ MUHC/MNH-MNI: ☐

MUHC/RVH: ☐ SMH: ☐ Douglas ☐ Other: ☐ None

McGill hospital(s) where study has not received approval of local Research Ethics Board(s) (if applicable): NA

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed: NA

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Number of subjects enrolled by the McGill PI to date: 6000 subjects enrolled. This study uses a pre-existing dataset from Health Canada and will not require any further enrolment of subjects.

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Have any of these subjects withdrawn from the study? NA

Has the study been revised since the last review?: No Have the study revisions been approved by the IRB?: NA

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Are there new data since the last review that could influence a subject's willingness to provide continuing consent?: No

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Have all serious adverse experiences (SAEs) and safety reports relevant to the study been reported to the IRB? NA

SIGNATURES:

Principal Investigator: _____ Date: September 6th, 2007

IRB Chair: _____ Date: Sept. 24/2007.

Appendix 4: TOS staging systems outline and disease severity grouping

ICCC	Diagnosis	Staging and Grading System	Disease Severity
Leukemia	Lymphoid leukemia (ALL)	**COG Risk Group Classification**	
		Infant-standard: Age >3 months and <1 year; absence of MLL gene rearrangement (MLL-) or CNS/testicular involvement.	Low
		Infant-high: <1 year; MLL gene rearrangement or CNS or testicular involvement or < 3 mo	High
		Low: 1 to 9 yrs; WBC count <50,000/μL; absence of adverse translocations, absence of CNS disease and testicular disease, and the presence of either the TEL/AML1 translocation or trisomy of chromosomes 4 and 10.	Low
		Standard: 1 to 9 years; WBC count <50,000/μL but do not fall into the low or high risk category	Low
		Medium: Ddo not fall into either the standard or high risk categories.	Low
		High: absence of favorable translocations; presence of the following: CNS or testicular leukemia or MLL gene rearrangement or unfavorable age and WBC count.	High
		Very high: 1 of the following factors present: t(9;22) Philadelphia chromosome (BCR/ABL), Induction failure: >25% M3 marrow on day 29 or M2 or M3 marrow on day 43, Hypodiploidy (DNA index <0.95, 44 or less chromosomes).	High
	Acute myeloid leukemia (AML); ANLL; Unspecified and other specified leukemias	**FAB System**	
		M0: Acute myeloblastic leukemia without differentiation	High
		M1: Acute myeloblastic leukemia with minimal differentiation	High
		M2: Acute myeloblastic leukemia with differentiation.	High
		M3: Acute promyelocytic leukemia hypergranular type.	Low
		M4: Acute myelomonocytic leukemia with/without eosinophilia	High
		M5: Acute monocytic leukemia with/without differentiation.	High
		M6: Acute erythroid leukemia	High
		M7: Acute megakaryocytic leukemia	Low

Cancer Type	Diagnosis	Staging and Grading System	Disease Severity
Lymphoma	Hodgkin disease	**American Joint Committee on Cancer Staging System***	
		I, IE: Cancer is found in one group of lymph nodes.	Low
		II, IIE: Cancer is found in two or more lymph node groups on the same side of the diaphragm	Low
		III, IIIE, IIIE, IIIES: Cancer is found in lymph node groups on both sides of the diaphragm	High
		IV: Involvement of one or more organs that are not part of the lymph system.	High
		Or	
		Ann Arbor Classification	
		I: Single lymph node region or single extra-lymphatic organ or site.	Low
		II: Two or more lymph node regions on the same side of the diaphragm or localised involvement of extra-lymphatic organ or site.	Low
		III: Involvement of lymph node regions on both sides of the diaphragm possibly accompanied by localised involvement of extralymphatic organ or site.	High
		IV: Disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.	High
	Non-Hodgkin lymphoma; Burkitt's lymphoma; Unspecified lymphomas	**St-Jude / Murphy Staging System**	
		I: Single tumour or single anatomical area (mediastinum and abdomen excluded).	Low
		II: Single tumour with regional node involvement.	Low
		III: Two single tumours on opposite sides of the diaphragm.	High
		IV: Any of the above findings with initial involvement of the central nervous system, bone marrow, or both.	High
		Or	
		Ann Arbor Classification (same as above)	

* E: Cancer not part of the lymph system but next to an involved area of the lymph system; S: Cancer is found in the spleen.

ICCC	Diagnosis	Staging and Grading System	Disease Severity
CNS Tumours	Ependymoma; Astrocytoma; Other -gliomas; Other specified intracranial and intraspinal neoplasms; Unspecified intracranial and intraspinal neoplasms; Primitive neuroectodermal tumours	**Surveillance Epidemiology and End Results (SEER) Summary Stage** In situ: Malignant cells within the cell group from which they arose. Localized: Malignancy limited to the organ of origin Regional: Extension beyond the limits of the organ of origin. Distant: Distant metastases. Tumour cells have begun to grow at the new location. or **Chang M-Stage** M0: No metastases M1: Microscopic evidence of tumour cells in the cerebrospinal fluid M2: Macroscopic nodular seeding (metastasis) in cerebellum, cerebral subarachnoid space, or in supratentorial ventricular system M3: Macroscopic nodular seeding (metastasis) in spinal subarachnoid space M4: Metastases outside the central nervous system	 Low Low High High Low Low Low High High
	Medulloblastoma	**Modified Chang M-stage system:** combination of "T" staging & "M" staging T1: Tumour <3 cm in diameter T2: Tumour >3 cm in diameter T3: Tumour >3 cm in diameter with spread T4: Tumour >3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum M0: No evidence of metastasis M1: Tumour cells found in cerebrospinal fluid M2: Tumour beyond primary site but still in brain M3: Tumour deposits in spine area that are easily seen on MRI M4: Tumour spread to areas outside the CNS	Disease severity was classified based on the 'M' staging. Low Low High High High

Appendix 5: Comparison of mortality counts Canadian cancer registry

	Canadian Cancer Registry* (CCR)							Treatment Outcomes and Surveillance** (TOS)							
Province	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**TOTAL**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**TOTAL**	**% in TOS**
NFLD	2	2	6	6	7	4	27	2	2	5	5	6	4	24	0.9
P.E.I.	0	0	0	1	1	1	3	0	0	0	0	0	0	1	0.3
N.S.	2	4	4	7	3	9	29	2	5	4	8	1	5	25	0.9
N.B.	0	4	6	5	9	4	28	0	1	3	3	6	5	18	0.6
Man.	4	3	13	12	4	9	45	3	3	10	10	4	13	43	1.0
Sask.	2	11	7	9	12	14	55	2	11	8	10	12	13	56	1.0
Alta.	10	11	33	9	28	21	112	11	10	26	11	31	18	107	1.0
B.C.	7	20	34	25	26	24	136	5	16	24	19	22	18	104	0.8
Yukon															
Nwt	0	1	1	2	2	1	7		0	1	1	1	0	3	0.4
Total	27	56	104	76	92	87	442	25	48	81	67	83	76	381	0.9

Note: Cases diagnosed between 1995-2000
*QC not in CCR; ** Data does not include POGO.