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Population based survival analysis of childhood cancer

by
Paul J. Villeneuve

Faculty of Medicine,
Department of Epidemiology and Community Medicine

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ABSTRACT

Purpose: To assess the survival of children diagnosed with cancer between 1982 and 1988 using population based data.

Objectives:

(1) to provide a baseline for one, three and five year survival rates for common forms of childhood cancer

(2) to assess the effect of age at diagnosis and gender as prognostic factors for selected childhood cancers

(3) to assess changes in survival by year of diagnosis between 1982 and 1988

(4) to examine variations in survival by geographic region by comparing cancer specific survival in one region to the remainder of the cohort

Design: Retrospective cohort study

Subjects:

4715 cancer patients diagnosed with cancer prior to age twenty, between 1982-1988, as reported population based cancer registries. Data was not available from the province of Ontario at the time the study was undertaken. Mortality status (up to December 31, 1991) was ascertained by linking subjects to the Canadian mortality database.

Main outcome measures:

Actuarial survival rates and assessment of the role of covariates (ie. gender, age at diagnosis, year of diagnosis) on survival using the proportional hazards model.

Results:

The five year survival rate of children diagnosed with a primary malignancy between 1982 and 1988 was 69%. Among those cancers examined, age at diagnosis was a significant prognostic factor for children diagnosed with leukaemia, neuroblastoma, astrocytoma, ependymoma, and rhabdomyosarcoma ($p < 0.05$). Decreased survival was also observed among older male children with Hodgkin's disease. Infants with leukaemia had a substantially poorer prognosis when compared to children diagnosed after age one. Conversely, those diagnosed with neuroblastoma prior to age one had a considerably improved chance of survival. After adjusting for age and year of diagnosis, females were found to have a markedly higher survival for acute lymphocytic leukaemia, and ependymomas ($p < 0.05$).

Improved survival was observed for children diagnosed more recently with acute lymphocytic leukaemia, acute non-lymphocytic leukaemia and Non-Hodgkin's lymphoma ($p < 0.02$). There was evidence to suggest that survival also improved by year of diagnosis among children with fibrosarcoma ($p = 0.05$), Wilms' tumour ($p = 0.07$) and ovarian germ cell malignancies ($p = 0.06$). Decreased survival was observed among infants diagnosed more recently with neuroblastoma, however, very

few deaths occurred in this age group (n=6). No significant trends in survival were observed for the other forms of childhood cancer examined.

Geographical variations in survival were assessed for children diagnosed with either acute lymphocytic leukaemia, an astrocytoma or Hodgkin's disease. The survival rates among children diagnosed with acute lymphocytic leukaemia or astrocytoma in British Columbia between 1987 and 1988, were found to be significantly higher when compared to the remainder of the cohort ($p < 0.05$).

Limitations of study:

It would be desirable to have information of incident cases from the province of Ontario. Not only would sample size be increased, but more importantly, the analyses would be more representative of the Canadian population. The analysis is also limited due to the absence of other prognostic variables such as staging and treatment information.

Recommendations and conclusions:

Continued follow-up of this cohort should be maintained in order to assess the late effects arising as a result of treatment. The development of a database which includes information on treatment and staging and other prognostic factors would be useful.

The field of pediatric cancer is evolving rapidly through higher incidence and better treatment results. The present study hopes to become a baseline against which future treatment can be compared.

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GLOSSARY OF TERMS AND ACRONYMS

ALL	Acute lymphocytic leukaemia
ANLL	Acute non-lymphocytic leukaemia
BMDP	A commercially available computer software package that performs statistical analysis
CCSG	Children's Cancer Study Group
CCCCP	Canadian Childhood Cancer Control Program
CMDB	Canadian Mortality Database
CNS	Central nervous system
GRLS	Generalized Record Linkage System
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
MCTR	Manchester Children's Tumour Registry
NCIRS	National Cancer Incidence Reporting System
NHL	Non-Hodgkin lymphoma
NWSG	National Wilms' Study Group
POG	Pediatric Oncology Group
SEER	Surveillance, Epidemiology and End Results Program
SMN	Secondary malignant neoplasm
SNS	Sympathetic nervous system
STS	Soft tissue sarcomas

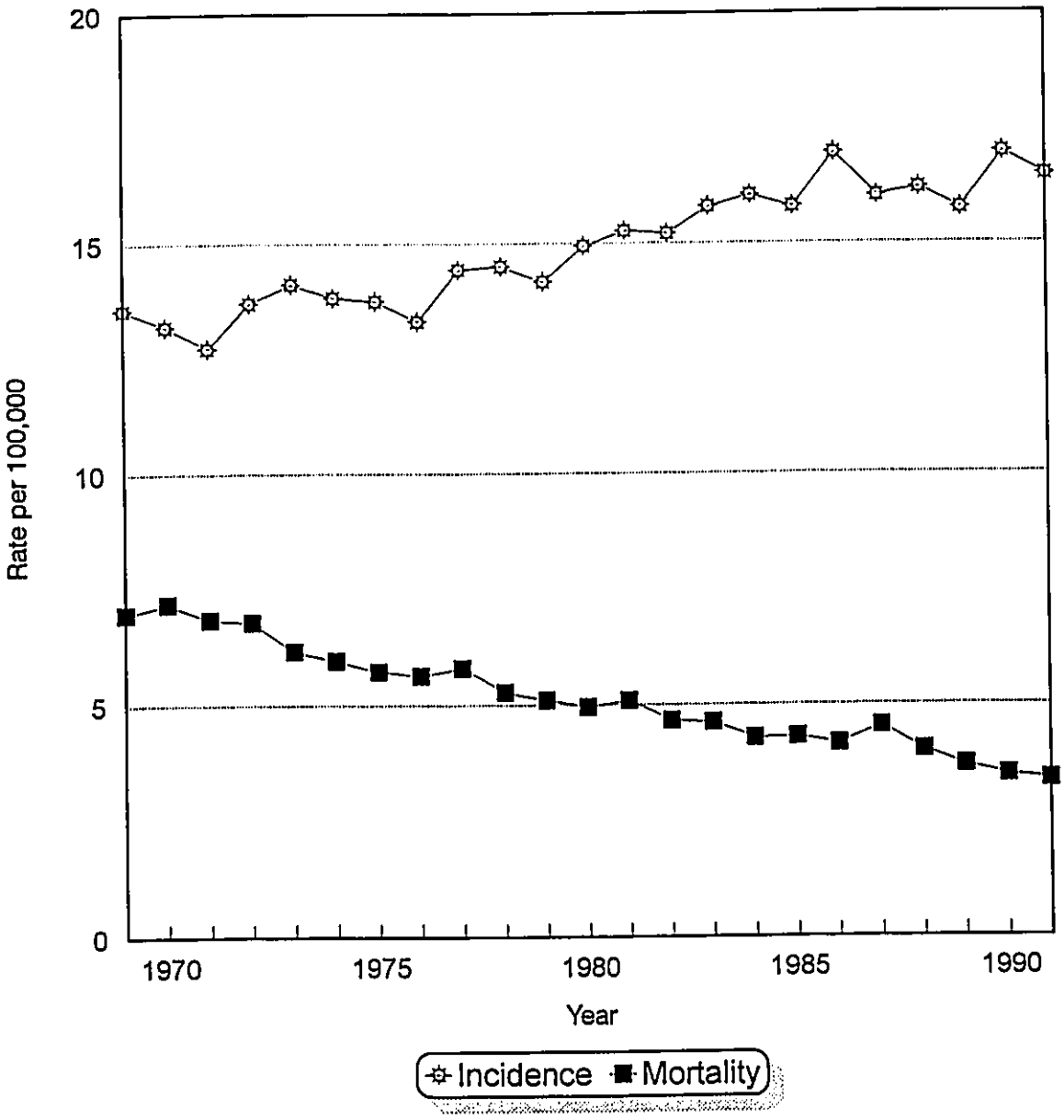
INTRODUCTION

1.1 Overview

The occurrence of cancer in children is relatively rare when compared to adults. In Canada, between 1987 and 1990, approximately 1200 persons under the age of twenty were diagnosed with cancer annually.[1] Over this same period, on average, 230 cancer deaths occurred each year in this age group. In 1991, children with cancer spent approximately 53,000 days in Canadian hospitals.[1]

The incidence of cancer has risen among Canadian children between 1969 and 1991 (Figure 1). Over this period, the age standardized cancer incidence rates of those under age twenty have increased at an average annual rate of 1.2 per cent.[1] Conversely, cancer mortality rates, in this same age group, have declined on average by 3.2 percent annually, over the same time period.[1] These diverging trends in cancer mortality and incidence may be explained by improved diagnostic and/or treatment procedures. Based on the 1991 Canadian mortality and cancer incidence rates, approximately one out of 310 children will develop cancer before age twenty.

Figure 1. Age standardized* cancer incidence and mortality rates, Canadians aged 0-19, 1969-1991



*Standardized to the 1981 Canadian census population

The prognosis of children with cancer has improved dramatically over the past twenty years. These improvements have been ascribed to better diagnostic procedures and to the development of multimodal therapy.[2] This therapy may include various combinations of surgery, radiation therapy and/or multidrug chemotherapy. The five year survival of childhood cancer patients is currently over sixty percent in both the United States and in Britain.[3,4]

The improvements in childhood cancer therapy have not come without a cost. Childhood cancer survivors are susceptible to a number of long term physical and psychosocial side effects. Due to the increasing number of cancer survivors, a greater burden will be placed on the health care system to treat late effects arising from treatment. With reported incident cases of cancer and the subsequent estimation of survival rates, the prevalence of cancer survivors, and thus to some extent, the burden of late effects arising from cancer therapy could be assessed.

Published results of childhood survival using population based data are not common. Population based survival rates have been calculated using data from the national childhood cancer registry in Germany,[5] data collected from the Surveillance, Epidemiology and End Results Program (SEER) in the United States[6] and data from the Manchester tumour registry in Britain.[7] Although considerable data is available through hospital data, such data is often a biased representation from particular referral patterns.

The purpose of this thesis is to examine the survival experience of a cohort of Canadian children diagnosed with cancer. Specifically, variations of survival with respect to gender, age at diagnosis, geographical region and year of diagnosis will be examined. To date, no Canadian population based study has examined the survival of children diagnosed with cancer using a recently developed classification system based on tumour morphology.

1.2 Classification of childhood malignancies

Cancer in children differs significantly from adult cancers both in terms of site of occurrence and in histological type. With the exception of haematopoietic malignancies, studies typically classify cancers by the site of occurrence using the International Classification for Diseases (ICD).[8] This scheme is unsuitable for classifying childhood malignancies. Some common childhood tumours (e.g. neuroblastoma) can occur almost anywhere. The International Classification of Diseases for Oncology (ICD-O)[9] allows for the coding of neoplasms by both morphology and site of occurrence.

The classification system used for the purposes of this study was developed originally for use by the Manchester Children's Tumour Registry (MCTR) and modified slightly for use in an international context.[10] The classification scheme divides tumours into twelve diagnostic groups as follows:

I. Leukaemia
II. Lymphomas and other reticuloendothelial neoplasms
III. Central nervous system and miscellaneous intracranial and intraspinal neoplasms
IV. Sympathetic and allied nervous system tumours
V. Retinoblastoma
VI. Renal tumours
VII. Hepatic tumours
VIII. Malignant bone tumours
IX. Soft tissue sarcomas
X. Germ-cell, trophoblastic and other gonadal neoplasms
XI. Carcinomas and other malignant epithelial neoplasms
XII. Other and unspecified malignant neoplasms

In addition, the more common types of childhood cancer are individually specified. A full description of the main groups and their sub-categories in terms of ICD-O morphology and topography codes are provided in Appendix A.

1.3 Incidence, prognosis and treatment of childhood cancers

The childhood classification scheme developed by the MCTR divides malignancies into a large number of categories. Indeed, some of these forms of cancer are quite rare. This section provides a brief overview of the pattern of incidence, prognostic factors and treatment methods for the cancers examined in this study.

Leukaemia

Leukaemia is the most common form of childhood cancer. This malignancy is a haematopoietic disease in which abnormal poorly differentiated cells replace normal bone marrow elements. The cause for the leukaemic transformation is unknown although genetic, environmental and infectious factors may be involved.[11]

Between 1985 and 1992, leukaemia accounted for approximately twenty seven percent of malignancies among Canadians under age twenty (Figure 2). Acute lymphocytic leukaemia (ALL) accounts for almost three out of four cases of childhood leukaemia.[12,13] The second leading form of leukaemia, acute non-lymphocytic leukaemia, accounted for almost thirteen percent of Canadian incident cancer cases between 1985 and 1992. Chronic myeloid leukaemia and chronic lymphocytic leukaemia are two other forms of leukaemia that are extremely rare in children.

Acute lymphocytic leukaemia (ALL)

ALL is the most common childhood neoplasm. The highest incidence of this malignancy occurs among children in the 1-4 year age group.[14] The presence of more than 25% lymphoblast in bone marrow aspirate establishes the diagnosis.[15] The male female ratio is usually about 1.1:1 to 1.3:1.[14]

The initial leukocyte count has been identified as the most important prognostic factor.[16,17,18] Age at diagnosis has also been found to be a prognostic factor as patients between the ages of two and ten have a better prognosis than teenagers and infants.[15] More than 70% of children diagnosed with ALL in Britain between 1983 and 1988 managed to survive at least five years.[7] The five year survival rate among U.S. children has improved from approximately 25% in 1970 to an estimated 70% in 1989.[19]

The following therapies have been identified as having improved the prognosis of children with ALL:[13]

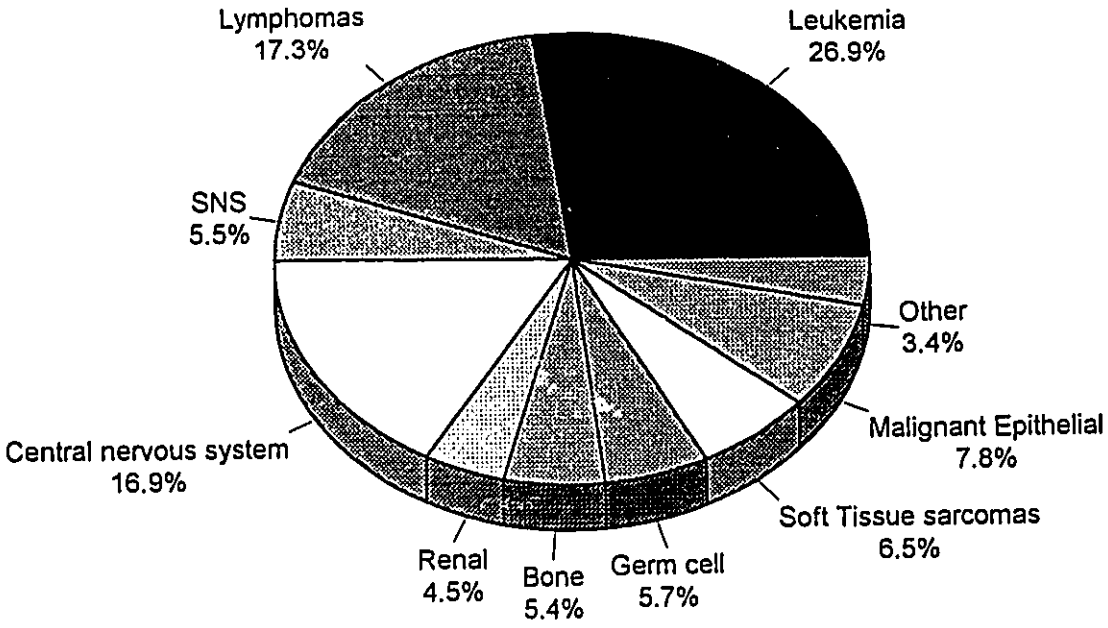
(1) CNS prophylaxis for all patients to prevent CNS relapse

(2) Multiagent chemotherapy with high doses of drugs

(3) Better supportive techniques involving blood products, transfusions, antibiotics and prevention of infection.

Newer developments have included treating relapsed leukaemia with bone marrow transplantation.[20]

Figure 2. Percent distribution of selected cancers, Canadian children, aged 0-19, 1985-1992



SNS=sympathetic nervous system
Source: see reference 1

Acute non lymphocytic leukaemia (ANLL)

ANLL (or acute myelogenous leukaemia) is a heterogeneous group of malignancies caused by a clonal proliferation of primitive myeloid cells.[21] Infiltration of the bone marrow by these cells causes impairment of normal haematopoiesis and results in anemia, granulocytopenia and thrombocytopenia.

The incidence of ANLL is fairly homogeneous prior to age ten and peaks in late adolescence.[21] Genetic abnormalities are present in almost all ANLL. ANLL is treated with aggressive chemotherapy for a relatively short duration, 8-12 months.[13] Approximately 70-90% achieve remission and of these, 35-40% may be cured.[86]

Lymphomas

Lymphomas account for approximately seventeen percent of all childhood malignancies (Figure 2). Hodgkin's disease and Non-Hodgkin's lymphoma (NHL) comprise the overwhelming majority of such tumours.

Hodgkin's Disease

Hodgkin's disease is a malignant lymphoma which usually arises in a single lymph node or anatomic group of lymph nodes.[22] This malignancy presents itself as a painless enlargement and occurs primarily in the lower cervical lymph nodes.[23] An infectious etiology has long been suspected but never confirmed.[11]

Hodgkin's disease typically accounts for approximately 45% of all lymphomas in children.[24] This malignancy is rare before age five and twice as common in males.[14]

The prognosis and choice of treatment is often influenced by the distribution and size of the affected lymph nodes.[13] Second malignancies, muscle wasting, sterility and hypothyroidism are known late effects of treatment.[13] Radiotherapy is the primary means of treatment in older children with localized disease, whereas for more extensive forms of Hodgkin's disease chemotherapy is used.[22] The prognosis of children diagnosed with this malignancy is quite favourable. More than 90% of children diagnosed with Hodgkin's disease are now being cured.[4]

Non-Hodgkin's lymphoma (NHL)

These tumour cells originate from normal lymphocytes and display rapid cell growth. NHL accounts for approximately ten percent of all cancers under age twenty, is most common in the second decade of life, and is unusual under age three.[23] It is different from that found in adults as it is rarely nodular and the range of histology is also much more limited.[66]

The five year survival rate among children who receive modern chemotherapy is approximately 60%.[23] The prognosis is dependent on stage. In most staging system, children with NHL are categorized as having localized disease in favourable sites or with disseminated disease in unfavourable sites. NHL is very similar to ALL

and is distinguished on the degree of infiltration of blood and bone marrow.[66]

Tumours of the central nervous system

These tumours are the third most common form of childhood cancer after leukaemia and lymphomas. Overall, tumours of the central nervous system (CNS) accounted for 17% of Canadian childhood malignancies between 1985-1992 (Figure 2). The most common forms of CNS tumours are astrocytomas (30-50%), medulloblastomas (15-20%) and ependymomas(5-15%).[14] The incidence of these cancers is more common among males and peaks in the first decade of life. These tumours are unique in that they usually remain confined to the CNS.[25]

Astrocytomas

Astrocytomas arise from glial cells. The most common sites of occurrence are the cerebellum followed by the cerebral cortex and then the optic tract.[26] Astrocytomas may also appear in the third ventricle as well as the spinal cord.

A large proportion (50-90%) of astrocytomas of the cerebellum and cerebral hemispheres are totally resectable.[27,28,29] The ten year survival rate for these cases is over 80%. Hypothalamic and optic chamatic astrocytomas commonly affect young children. Radiation therapy in these children secures long term survival in 65-80% of such patients.[25] The risk of side effects remains a major source of concern. Recently,

chemotherapy has been introduced in order to delay irradiation thus allowing for normal maturation of the brain. Site of occurrence, age, histology, resectability and response to radiotherapy have been identified as prognostic factors.[26]

Medulloblastomas

Medulloblastomas arise from the cells of the external granular layer of the cerebellum. Presenting symptoms are headaches, emesis and ataxia. A peak of incidence was observed among Canadian children aged 1-4.[30] This tumour may spread to the spinal cord via cerebrospinal fluid.

Prognostic factors for children with a medulloblastoma include: degree of tumour resection, extent of tumour, and dose of radiation to posterior fossa.[31-33] Approximately one-half of patients who receive craniospinal irradiation are cured.[31,32,34] Chemotherapy is often administered to those at greater risk. Specifically, these are children who at diagnosis, have locally extensive and often unresectable tumours in the posterior fossa.[23]

Ependymomas

Ependymomas arise from the ependymal lining of the ventricular system or central canal of the spinal cord and may occur throughout the entire neural axis.[23] Approximately half of these tumours occur before the age of five and more than 90% of these tumours are intracranial.[35]

Ependymomas are first treated by surgery in order to establish a diagnosis and to remove as much of the tumour as possible. Ependymomas have also been shown to be responsive to radiation therapy and chemotherapy. Based on results from several centres, between 40-70% of children with ependymomas are now being cured.[36-38] The survival rate is between 60-70% for low grade ependymomas and 10-30% for anaplastic or high grade tumours.[90-92] Infants have a poorer prognosis, although age has not been found to be a predictor of survival among children older than four.[92-95]

Sympathetic nervous system tumours

Tumours of the sympathetic nervous system (SNS) account 5.5% of all childhood malignancies among Canadians under age twenty (Figure 2). Neuroblastomas are the most common malignancy of the SNS accounting for more than ninety five percent of malignancies.[39]

Neuroblastomas originate in neural crest cells and they typically appear as an abdominable mass among very young children (median age two years).[40] In fact, this is the most common form of cancer in infants under age one with an incidence rate more than double that of ALL the second leading cancer in this age group.[30]

Neuroblastomas occur in several body sites. From a large population based study, 23% occurred in the adrenal glands, 32% in the abdomen, 16% in the thoracic

cavity, 7% in the pelvic region and the remainder (22%) elsewhere.[70] The majority of these cancers have regional lymph involvement or metastases at more distance sites.[71]

Infants, those diagnosed before age one, have demonstrated improved prognosis. Most of these patients do well with minimal therapy. Spontaneous regression of this tumour has been observed in this age group.[13]

Biologic features of tumour cells that are associated with an improved prognosis include: hyperdiploidy in children under two, a normal *N-myc* copy number[40] and lower serum levels of lactate dehydrogenase[41] or ferritin.[42] Treatment procedures include the use of surgery, radiotherapy and chemotherapy. Approximately 90% of children with localized but unresectable tumours can be cured.[41] Fewer than twenty percent of older children with lymph node involvement or metastases experience long-term survival.[43]

Retinoblastoma

This form of cancer is the predominant cancer of the eye in children. Approximately 80% of these cancers occur before age three.[67] This tumour is of particular interest to geneticists as well as epidemiologists. Retinoblastomas are typically slow growing tumours and they may remain contained in the eye for months or even years.

This form of cancer appears as both a hereditable and non-hereditable form. The hereditable form, which accounts for 10-15% of cases, generally presents itself in children under age one with bilateral involvement.[23] Although the mortality rate of this cancer is extremely low, a significant number of treatment related late effects arise. One third of patients with heritable tumours will develop second malignancies, typically osteogenic sarcoma.[68]

Enucleation is curative and it is used primarily in cases of advanced disease in which there is little chance of preserving the child's vision. Administering chemotherapy, radiation therapy, cryotherapy and laser therapy are used in other instances. Prognosis is quite favourable as approximately 90% of patients survive and are free of tumour 5 to 10 years after diagnosis.[44,45]

Renal tumours

Wilms' tumour

Wilms' tumour (nephroblastoma, or renal embryoma) is the most common intraabdominal neoplasm diagnosed during childhood. It generally presents itself as an asymptomatic mass in children under the age of five.[25] These tumours account for more than 90% of all kidney cancers. Hypertension is present in about one quarter of cases.[46] Wilms' tumour has been linked to changes in one or more of several genes.[23]

Treatment has been developed that combines surgery, radiation therapy and chemotherapy and is determined by the stage of the disease. A staging system has been devised by the National Wilms' Tumor Study Group.[88] Histology, tumour specimen weight (>250g), presence of tumour metastases and regional positive lymph nodes have been identified as prognostic factors.[47] The overall prognosis is quite favourable as the long term survival is greater than 80%.[25]

Hepatic tumours

These tumours account for between 0.5-2% of all pediatric malignancies.[72] Hepatoblastoma is of interest in genetic and molecular biological studies and typically occurs among children under age two. Hepatocellular carcinoma is the second leading cancer of the liver among children. The median age of this carcinoma is ten years with most of these cancers arising in adolescents.[72] For both of these hepatic tumours, survival is dependent upon complete resection of the tumour.[96] Serious postoperative complications arise and less than half of the patients with liver cancer survive five years after diagnosis.[73]

Malignant bone tumours

The occurrence of bone tumours is related to the rapid growth that accompanies adolescence and these tumours are rare in the first decade of life. Bone tumours account for 5.4% of childhood cancers (Figure 2). The two principal subtypes are osteosarcoma and Ewing's sarcoma which account for 60-63% and 27-30% of all bone tumours respectively.[24]

Osteosarcoma

Osteosarcoma is thought to arise from bone producing mesenchymal cells. This malignancy produces osteoid or immature bone. Approximately 90% of these tumours arise in the long bones of the extremities.[25]

This malignancy typically occurs during adolescence when growth is quick. The incidence is therefore higher among females between the ages of 10 and 14 and greater in boys thereafter. Persons with the hereditable form of retinoblastoma have an increased risk of osteosarcoma which is unrelated to the use of chemotherapy or ionizing radiation.[68]

Surgical removal of the primary tumour by amputation or local excision with limb salvage is essential for disease free survival.[87] This is preceded and followed with the administration of chemotherapy to control metastases. Five year survival rates are

between 50-60%.[6,7] The most important prognostic factors among patients with osteosarcoma are tumour necrosis evident following preoperative chemotherapy and the presence of lung metastases with a positive diagnosis.[48]

Ewing's sarcoma

Ewing's sarcoma is probably derived from primitive neural or mesenchymal tissue of the medullary cavity.[25] This cancer is highly malignant and is typically found in bony structures and occasionally in soft tissue. The most common sites of occurrence are the femur, pelvis and the tibia.[66]

The incidence of Ewing's sarcoma is rare before five and after twenty.[66] There is a striking geographical variation in incidence rates as the prevalence of this cancer is quite rare in Chinese and Black populations.[14]

Progress has been made in treating this malignancy which was once regarded as fatal. Treatment involves the combined efforts of surgery, radiotherapy and chemotherapy. These tumour cells can be mistaken for neuroblastoma, NHL or rhabdomyosarcoma. Metastatic Ewing's sarcoma or Ewing's sarcoma in the pelvic region have poorer prognosis.[25] Between 50 and 74% of children with the nonmetastatic form of Ewing's sarcoma experience long term survival; less than 40% of those with a metastatic form of the disease survive.[49]

Soft tissue sarcomas (STS)

Soft tissue sarcomas account for 6.5% of all childhood malignancies among Canadians under age twenty (Figure 2). Most childhood STS are rhabdomyosarcomas (52-66%), while fibrosarcomas account for approximately 10%. Other forms of STS include soft tissue Ewing's tumour and neurofibrosarcoma. The occurrence of STS is slightly more common among males.[14]

Rhabdomyosarcomas

Rhabdomyosarcomas are thought to arise from progenitor cells for striated muscle found throughout the body.[69] This cancer has a high metastatic potential through lymphatic or blood vessels. As with Wilms' tumour and neuroblastomas, these tumours can be present at birth. The highest incidence of this cancer occurs prior to age five and there is a slight excess of cases in males.[14]

Rhabdomyosarcomas are most commonly found in the head and neck area (40%), genitourinary tract (20%), extremities (20%), trunk(5%) and retroperitoneum (5%). [50,51]

Up to two thirds of patients survive with multimodal therapy of surgery, chemotherapy and radiotherapy.[23] The primary site of occurrence and the clinical stage are the two most important predictors of survival.[52] The survival rate of children with

stage I or II is approximately 80%.[13] Only 25-30% of those with stage IV are cured.[13] Other prognostic variables include: tumour size, age and tumour cell ploidy.[52,53]

Fibrosarcomas

Fibrosarcomas are spindle cell tumours that are mostly seen at distal extremities.[23] Fibrosarcomas are classified as congenital and postpubertal where the tumour is much more likely to metastasize. The incidence rates of fibrosarcoma and neurofibrosarcoma increase with age. Fibrosarcomas are also common as secondary radiation induced neoplasms.

For the non-metastatic form of fibrosarcoma, age is a significant prognostic factor of survival. The long term survival is 83-92% among children under age 5 and 60% for those above age five.[23] There is no prospective evaluation of patients available to provide an estimate of 5-year survival for the metastatic form although it has been regarded as being quite poor. The standard approach is aggressive surgery. The role of chemotherapy is unclear and is presently under study.

Germ cell tumours

Germ cell tumours are generally more frequent in gonadal sites.[14] Among males, the peak incidence occurs prior to age five whereas in their female counterparts, the occurrence of this form of malignancy is rare before age ten.[14] These tumours account for approximately 2% and 4% of all childhood malignancies among males and females respectively. [14] They occur in a variety of histological patterns.

For non-gonadal germ cell tumours, survival is poorer among children older than eleven, in children where the tumour is in more than one organ or has not been completely removed at time of surgery.[82] Children enrolled in a recent CCSG experienced four year survival rates of 67% and 48% for ovarian and non-gonadal germ cell tumours respectively.[82] Three year survival rates of greater than 95% have been observed among British children diagnosed with testicular germ cell malignancies.[97]

Carcinoma and other malignant epithelial neoplasms

Carcinomas are relatively uncommon in children. Extrinsic factors such as smoking, are likely to be of greater importance for these neoplasms. The site of appearance of childhood carcinoma differs greatly from those of adults. The most common sites of carcinoma among adults are the lung, colon and breast. The more prevalent forms among children are melanoma, thyroid and nasopharyngeal carcinoma.

1.4 Late effects of treatment

Although not a focus of this thesis, it should be recognized that survivors of childhood cancer are susceptible to a variety of late effects as a result of treatment. These effects include short stature, obesity, sterility, deformities, organ failure, hormonal imbalance, psychosocial problems, mental impairments and secondary malignant neoplasms.[2,3,54] The anthracycline group of drugs are well recognized to be cardiotoxic.[3]

Within twenty years of the first diagnosis, secondary cancers occur in 3-12% of children cured for their primary cancer.[2] When matched for age, this risk is 10-20 times higher than that of the general population. Many of these malignancies are bone or soft tissue sarcomas arising within irradiated fields but secondary tumours are also seen at places where radiation has not been administered.[3] Secondary malignant neoplasms (SMN) of a leukaemic nature occur typically 5-7 years after therapy while the risk of solid tumours increases after a latency of ten years.[55] Secondary malignancies respond very poorly to conventional therapy.

1.5 National databases used in this study

The objectives of this research was facilitated with access to national data of high quality. Two national databases were used in this study: the National Cancer Incidence Reporting System (NCIRS) and the Canadian Mortality Database (CMDB).

1.5.1 The National Cancer Incidence Reporting System (NCIRS)

Canada is one of the few countries in the world with a cancer reporting system covering the whole population. This coverage is maintained by autonomous provincial/territorial registries which have provided data to the NCIRS since 1969. With the inclusion of Quebec in 1970, Canada's entire population was covered by cancer registration.[56] The NCIRS is maintained by the Canadian Centre for Health Information at Statistics Canada.

Each provincial/territorial cancer registry annually reports to the NCIRS new primary sites of cancer occurring among its' residents. Cancer registries obtain incidence data from seven main sources (Appendix B). Most registries have direct access to treatment records of cancer patients, death certificates and pathology reports. Registries also receive information from hospital separation records, autopsy reports and medical files.

In 1969, fewer than five per cent of cancers were unknown primaries (ICD 195-199).[57] Currently, eighty-five percent of incidence cancers are microscopically confirmed and two percent are identified by death certificate only. From 1979, morphology was classified in accordance with ICD-O. Manitoba changed to ICD-O in 1982.

As many sources are consulted in maintaining the NCIRS and because of the complex computer systems developed in the reporting provinces, considerable delays occur in the provision of data to Statistics Canada. Since 1981, data have been published approximately five years after time of diagnosis. Improvements in timeliness are occurring and it is hoped that in the future that a lag time of only two or three years will exist.

1.5.2 The Canadian Mortality Database (CMDB)

The CMDB contains information on all recorded deaths from 1950 onwards.[58] The file contains personal identifying information as well as the date, place and coded underlying cause of death. The database is maintained at Statistics Canada, and is regularly updated with death registrations supplied by each province/territory in Canada. Previous analyses have revealed high detection and specificity rates.[59,60] The CMDB is maintained on microfiche and computer tape with source records stored on microfilm at Statistics Canada.

1.6 Record linkage

Record linkage can be defined as the comparison of records on two distinct files in order to determine whether they represent the same individual. In the case of this study, the two files used were (i) the incident cases identified by the NCIRS and (ii) deaths as contained in the CMDB.

The first work involving record linkage was carried out in the 1950's.[83] In the 1970's record linkage became an effective tool in the field of epidemiology where it was used to examine environmental risk factors. With the increasing popularity of record linkage came the development of the Generalized Iterative Record Linkage System at Statistics Canada.[84] Since that time, methodologic improvements have been made to make better use of the discriminating power of the data.[85]

In order to achieve efficient record linkage, three major difficulties must be overcome. The first difficulty, is the inadequacy of personal identifying information. This may make it impossible to match records (individuals). Some personal identifying information is of greater value. For example, knowledge of an individual birth date is usually more helpful in evaluating a possible link than the individual's marital status.

A second difficulty that must be overcome is coding errors. Mistakes often occur in the reporting of personal identifiers. Where discrepancies exist, other variables obtained in the linkage procedure should be examined. The third difficulty is a result of the large number of records involved in record linkage. Theoretically, each record in one file must be compared with each record in the second file. In practice, it is not really necessary, nor efficient, to compare all personal identifiers. To reduce processing and thus related computer costs, linkage rules are not applied to all record pairs. Some records will be rejected as possible links after only some of the rules have been executed.

Algorithms have been developed in an attempt to quantify the probability of a true link. Agreements of initials, birth dates and other personal identifiers will be more common in genuinely linked pairs than in records brought together and rejected as a positive link. Weighting algorithms have been developed which take into account missing values, reversal of initials, and partial matches of two records. Refinements can be made to the weighting process in order to maximize the discriminating power of the identifying information. Some of the methodologic issues in calculating weights have been previously detailed.[84,85]

1.7 Objectives and rationale of study

The impact of cancer on the health of Canadian children has already been discussed. To date, no study has assessed the survival experience of Canadian children with cancer using population based data and the classification scheme developed by the Manchester tumour registry.

The results obtained from this study will be useful for several reasons. Although the period of the study is relatively short, the results may provide some insight as to whether progress has been achieved in treating various pediatric cancers. Second, the results will permit comparisons to be made with population based data from other countries.

Finally, the results achieved in this analysis will be useful in carrying out further research. Cancers with a poor prognosis could be identified for future clinically oriented research. The survival rates estimated from this study could also be used to forecast the prevalence of childhood cancer survivors.

MATERIALS AND METHODS

2.1 Creation of the working file

2.1.1. Steps performed in the record linkage procedure

GRLS, a software package developed Statistics Canada, was used to perform the record linkage in this study.[104] Permission was obtained from the Canadian Centre for Health Information of Statistics Canada and all provincial cancer registries, with the exception of Ontario, to release the data for the purposes of this study. The following subsection describes the steps involved in carrying out the procedure.

Records of childhood cancer incident cases obtained from the NCIRS were internally linked in order to determine which individuals went on to develop secondary malignancies or which cancers were duplicate reportings. Information that was obtained from the NCIRS for each individual, was then linked to the CMDB. Personal identifying information used to assess the link included name, gender, birth date, marital status and province of residence.

A weighted value was calculated for each possible link. The weight is an estimate of the odds that the two records under consideration refer to the same individual. A listing file, which ordered the comparisons by sample weight, was then produced. Statistics Canada provided this listing file which was I then examined in order to determine whether each comparison was an actual link, a non-link or a possible link.

For questionable links, death certificates were also assessed in order to determine whether coding errors were present in the CMDB data. A decision on the status of the link for each comparison was then supplied to Statistics Canada. Finally, a working file was provided by Statistics Canada which was stripped of all non-essential personal identifying information. This included such variables as surname, social insurance number, and death registration number.

The working file included the variables 'date of death', 'underlying cause of death' and 'date of birth' which were retrieved from the Canadian Mortality database. The underlying cause of death was coded using the International Classification System for Diseases, ninth revision (ICD-9).[8] The date of diagnosis, reporting province, tumour morphology and topography, ICD code, as well birth and death dates were retrieved from the cancer incidence file. Morphology and topography were coded according to the International Classification of Diseases for Oncology (ICD-O).[9] Where the linked record differed in terms of recorded birth dates or death dates, death

certificates were examined in order to validate the recorded data. If a discrepancy remained, the date obtained from the mortality database was used as death certificates are typically signed by a relative of the decedent and were therefore considered more accurate.

2.1.2 Ontario cancer incidence data

As previously detailed, incident cases were not obtained for the province of Ontario. At the time of this study, the Ontario Cancer Registry was in the process of improving the quality of its data on childhood cancer due to concerns of overreporting. In addition, several malignancies with unknown morphology were being reassessed. The Ontario Cancer Registry would not endorse the release of its' data until such modifications could take place. It is hoped that future analysis would include these children. It is estimated that Ontario would account for approximately 38% of all Canadian childhood cancer incident cases.[1]

2.2 Creation of analysis file

From the working file, age at diagnosis was calculated for each record. Patients were also grouped into the age intervals 0-1, 1-4, 5-9, 10-14 and 15-19. Where possible, each incident case was classified using the Manchester classification scheme. In cases where topography codes were missing, the corresponding ICD code was substituted where appropriate.

The recording of morphology was incomplete prior to 1982. As a result, survival analysis was restricted among incident cases diagnosed between 1982 and 1988.

Neoplasms that were either benign, a borderline malignancy or in-situ were excluded from the analysis. This behaviour information was available from the fifth digit of the ICD-O code. Further, due to differences in reporting of skin cancers (ICD-9 173) by provinces, these cases were excluded from analysis.

Those children who died of external causes unrelated to cancer were censored at time of death. For example, those who died as a result of a traffic accident would be lost to follow-up at the time of death. Among non-deceased members of the cohort, subjects were censored at the last date of mortality follow-up, December 31, 1991. The

following variables were output for survival analysis by BMDP [a]: sex, type of cancer, age, vital status (1=cancer related death, 0=alive or non-cancer related death), year of diagnosis, province of diagnosis and date censored.

2.3 Statistical methods of survival analysis

Survival analysis may be defined as the use of statistical methods to analyze waiting times, which are times from an initial event to a final event. In this study, the initial event is defined as the date of cancer diagnosis as reported by the NCIRS. The final event is date of death as reported by the CMDB or in some instances the NCIRS. Where no death was observed, the waiting time is said to be censored at the last known point of follow-up, here December 31, 1991.

Three techniques were used to assess the survival experience of childhood cancer subjects. The actuarial life table method was used to produce one, three and five year survival rates. The product limit life table and the proportional hazards model were used to assess the role of covariables on survival for selected cancers. A description of the three methods follows.

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[a] BMDP:commercial statistical software package

2.3.1 The actuarial life table

With an actuarial life table, follow-up of vital status is divided into fixed time interval widths. For this study, these time intervals were specified as three months. It is assumed that loss to follow-up occurs randomly during each interval. For each time interval, the actuarial lifetable provides the investigator with the following information:

- the number of subjects alive at the beginning of the time interval
- the number of subjects that die during the time interval
- the number that are lost to follow-up in each time interval
- the proportion of subjects that manage to survive the interval
- the estimated probability that the subject will not die before or during the time interval

A description of the notation used in the actuarial life table formulas follows. The number of persons at risk at the beginning of the *ith* interval is calculated by :

$$r_i = n_i - \tfrac{1}{2} c_i$$

where n_i=number of subjects at the beginning of the interval
c_i=number of subjects withdrawn or lost to follow-up in the interval

The probability of death during the interval is:

$$q_i = d_i \div r_i$$

where d_i=number of observed deaths during the interval

The probability of surviving the interval, conditional on being alive at the beginning of the interval is thus:

$$p_i=1-q_i$$

The cumulative proportion surviving to the end of the ith interval is estimated by P_{i+1} defined as:

$$P_{i+1}=p_iP_i \qquad \text{where } P_i=1$$

The standard error associated with the survivor function (ie. the cumulative proportion surviving) is obtained from Greenwood's formula:[62]

$$s.e.(P_i) \approx P_i\sqrt{\sum_{j=1}^{i-1}\frac{q_j}{r_jp_j}}$$

There are two important assumptions that must be met when using lifetables. The experience of the subjects with respect to the outcome of interest must not change over the study period. Secondly, life tables assume that the survival experience of patients who are censored is the same as those for whom exact waiting times are known.

2.3.2 The product limit life table

The product limit life table, or Kaplan Meier estimate, is also used to characterize survival. It differs from the actuarial life table in that the estimates of survival are not based on fixed interval widths. The plot of a Kaplan Meier estimate of survival is a stepwise function with decreases occurring at each point in time that a death occurs. The role of the product limit life table in assessing survival is virtually

identical to that of the actuarial life table. The product limit life table does however have the advantage that tests for group differences are not dependent on the selection of time intervals. For this reason, it is the preferred method when there is a small number of cases.

The formula for the cumulative proportion surviving up until time '*t*', using the product life table method is expressed mathematically as:

$$P(t) = \prod_{t_i < t} \frac{N-i+1-\delta_i}{N-i+1}$$

where $\delta_i = \begin{cases} 0 \text{ if } t_i \text{ represents a censored observation} \\ 1 \text{ if } t_i \text{ represents a death} \end{cases}$

and i=1,2...N

The standard error associated with this survival probability is: [62]

$$s.e.(P(t)) \approx \sqrt{\sum_{t_i < t} \frac{\delta_i}{(N-i)(N-i+1)}}$$

In order to test for group differences with the product limit estimates of survival, the Mantel-Cox test statistic (or log rank test) is commonly used. This test statistic gives equal weight to all observations (ie. is independent of the length of the follow-up). The Mantel-Cox test statistic can also be used to assess group differences with the actuarial life table. A detailed description of the mathematical formulae of the Mantel-Cox test statistic is found in Appendix C.

2.3.3 The proportional hazards model

The proportional hazards model is used to determine whether survival is related to one or more continuous or discrete variables. It enables the comparison of survival of two or more groups with varying survival times, some of which may be censored. To be precise, the proportional hazards model evaluates the relationship between the variables of interest and the hazard function. The hazard function is defined as the instantaneous probability of death. The proportional hazards model is sometimes referred to as the Cox model.

The proportional hazards model differs from ordinary regression as the dependent variable modelled is the hazard rate and not survival time. If exact waiting times were known, linear regression could be applied to describe relationship of the covariables on survival time. With censored observations, ordinary regression cannot be used.

Mathematically, the proportional hazards model is expressed as:

$$\lambda(t;x_1,x_2,\ldots x_n)=\lambda_0(t)\exp(b_1x_1+b_2x_2+b_3x_3+\ldots+b_nx_n)$$

where $\lambda_0(t)$ represents the baseline hazard function.
$x_1, x_2, \ldots x_n$ is a set of covariables of interest
$b_1, b_2, \ldots b_n$ are estimated from the data

As illustrated by the preceeding mathematical formulae, survival between groups can be compared without knowledge about the functional form of the hazard functions $\lambda(t;x_1,x_2,\ldots x_n)$ or $\lambda_0(t)$, as long as the two are proportional.

The relationship between the hazard rate and the survivor function can be expressed as:

$$\lambda(t) = -\frac{1}{S(t)} \cdot \frac{d}{dt} S(t)$$

A variable is related to the hazard function if its corresponding parameter estimate is significant. If the parameter estimate obtained from fitting the proportional hazards model is non-positive (ie. $b_1 < 0$), the chance of survival increases as the value of the variable increases. Conversely, when the parameter estimate is positive, the prognosis of the subject decreases as the value of the covariable increases.

The survival of two groups can be compared by the relative hazard (the ratio of two hazard functions). The ratio of two hazards is analogous to the ratio of two mortality rates (or relative risk) except that the hazard rates are instantaneous measures of survival. In our analyses, the relative hazard is used to assess the annual change in risk of mortality among children diagnosed over the period 1982 to 1988. It is also used to assess whether gender or age at diagnosis is associated with survival.

An advantage of the proportional hazards model is that the contributions of variables can be assessed in the presence of other variables. The best model can be identified sequentially by adding or deleting the one variable that has the greatest impact on the residual sum squares. For the stepwise regression performed in this analysis, the level of significance to enter the model was set at 0.10 and the level to remove was set at 0.15.

The proportional hazards model requires the same assumptions to be satisfied as the actuarial and product limit life table. Three additional assumptions are needed:[65]

(i) All of the waiting times must be independent

(ii) All subjects that have the same values for the variables in the regression equation must have the same hazard function

(iii) Subjects with different values for the variables in the regression equation must have proportional hazard functions.

Verifying the assumption of proportionality

There are several different ways to assess whether the assumption of proportionality is met. The easiest way to begin to assess this assumption is to examine plots of the survival curves. Survival curves that cross may indicate instances where the assumption of proportionality is violated.

The assumption of proportionality can formally be tested by introducing a variable which is dependent on time into the Cox model. For example, if we wanted to examine whether gender was a proportional covariate we would fit the following model:

$$\lambda(t) = \lambda_0(t)\exp(\beta_1 z_1 + \beta_2 z_2(t))$$

where z_1 is an indicator variable denoting gender and $z_2(t) = z_1(\ln(\text{time})\text{-constant})$. If the ratio of the two hazards is proportional for any value of survival time, then $\beta_2 = 0$.[62]

When the proportionality assumption is violated, two alternative means exist for comparing survival functions. One way to proceed with the analysis, is to stratify such that cases within each strata conform to the proportional hazards model.[64] The accelerated time failure model is another manner in which the effect of covariates on survival can be assessed. The acceleration time failure model does require the specification of the underlying hazard function. The reader is referred to Kalbfleisch[64] for a detailed overview of the accelerated time failure model.

2.3.4 Assessing the survival of the study cohort

The number of incident cases for each type of cancer was tabulated. One, three and five year survival rates were estimated using the actuarial life table. Survival rates were calculated for all diagnostic groups of the Manchester classification scheme as well as the more common types of childhood cancer.

Differences in survival by gender, age at diagnosis and year of diagnosis

The effect of gender, year and age at diagnosis was assessed for the more common forms of childhood cancer. The effect of these covariables was not assessed for the main diagnostic groups due to the heterogeneity of survival of cancers within groups. Geographical variations in survival were of secondary interest and examined at a later time.

Survival curves were plotted by age group and gender for each cancer using either the actuarial life table or Kaplan Meier estimates of survival. The Kaplan Meier estimate of survival was used for those cancers with smaller sample sizes. These plots enabled a visual assessment of proportionality. Under the assumption of proportionality, the survival curves would not be expected to cross and the logarithm of the survival curves would be parallel. In some instances, an indicator variable was entered to denote a cancer diagnosed in an infant (< 1 year). The creation of this

indicator variable was based on inspection of survival curves by age group as well as results from previous research. In these instances, it was necessary to stratify using this indicator variable to ensure that the assumption of proportionality was satisfied. The assumption of proportionality was formally tested with a time dependent variable as described in the previous section.

Stepwise regression with the proportional hazards model was used in an exploratory manner. The stepwise regression procedure revealed which factors were the most influential predictors of survival. A description of the variables included in the stepwise regression is provided in Appendix D.

Survival curves, by age, were plotted for those cancers where age at diagnosis was associated with prognosis. These curves were plotted using estimates derived from the proportional hazards model. The effect of gender was handled in the same manner. Where both age and gender where significant prognostic variables, survival curves, by age, were plotted for both males and females.

Three year actuarial survival rates were estimated for individual cancers among those diagnosed in 1982/83 and 1987/88. The significance of changes in survival by year of diagnosis, over the period 1982-1988 was tested using both the Mantel-Cox test statistic and the proportional hazards model. The Mantel-Cox statistic tested the survival differences for those diagnosed in the two aforementioned time periods. For

the proportional hazards model, year and month of diagnosis were entered into the model as a continuous variate. The test of significance using the proportional hazards model was adjusted for age and gender and included all diagnosed cases between 1982 and 1988.

Geographical variations in survival

The analysis of geographical variations in survival was performed on children diagnosed in the latter part of the study period (1987-1988). At this time, most Canadian treatment centres were members of one of two collaborative groups: the Pediatric Oncology Group (POG) or the Children's Cancer Study Group (CCSG). Provinces were grouped into four regions (Atlantic, Quebec, Prairies and British Columbia) in order to achieve groups with sufficient sample size to proceed with analysis. It was decided to examine only those cancers in which there was a minimum of fifteen cases per region. This was done as it was recognized that the dataset does not contain all the necessary prognostic factors. As a result, geographical variations in survival were only examined for ALL, Hodgkin's disease and astrocytomas.

Three year survival rates, by region, were calculated for each of these three cancers using the actuarial life table. The survival rates observed in each region were then compared to the remainder of the cohort. This was done using (i) the Mantel-Cox test statistic and (ii) examining the significance of an indicator variable in the

proportional hazards model which denoted the region in which the cancer was reported. The test of significance using the proportional hazards model differed from the Mantel-Cox test statistic in that it was adjusted for the effects of year of diagnosis, age at diagnosis and gender.

RESULTS

All cancers combined

Survival analysis was performed on 4715 incident cases of cancer diagnosed among children under twenty years of age, between 1982 and 1988 (Table 1). A further breakdown of these incident cancer cases by gender can be found in Appendix E.

The actuarial five year survival rate of this cohort was 69% (Table 2). For all cancers combined, a significantly improved survival rate was observed for children diagnosed more recently. The five year survival rate among children with cancer was 67% and 73% for those diagnosed in 1982-85 and 1986-88 respectively (Figure 3). These differences in survival were statistically significant ($p < 0.01$) as measured by the Mantel-Cox test statistic.

Table 1.
Frequency distribution of incident cases of cancer†, by age group, childhood cohort, 1982-1988

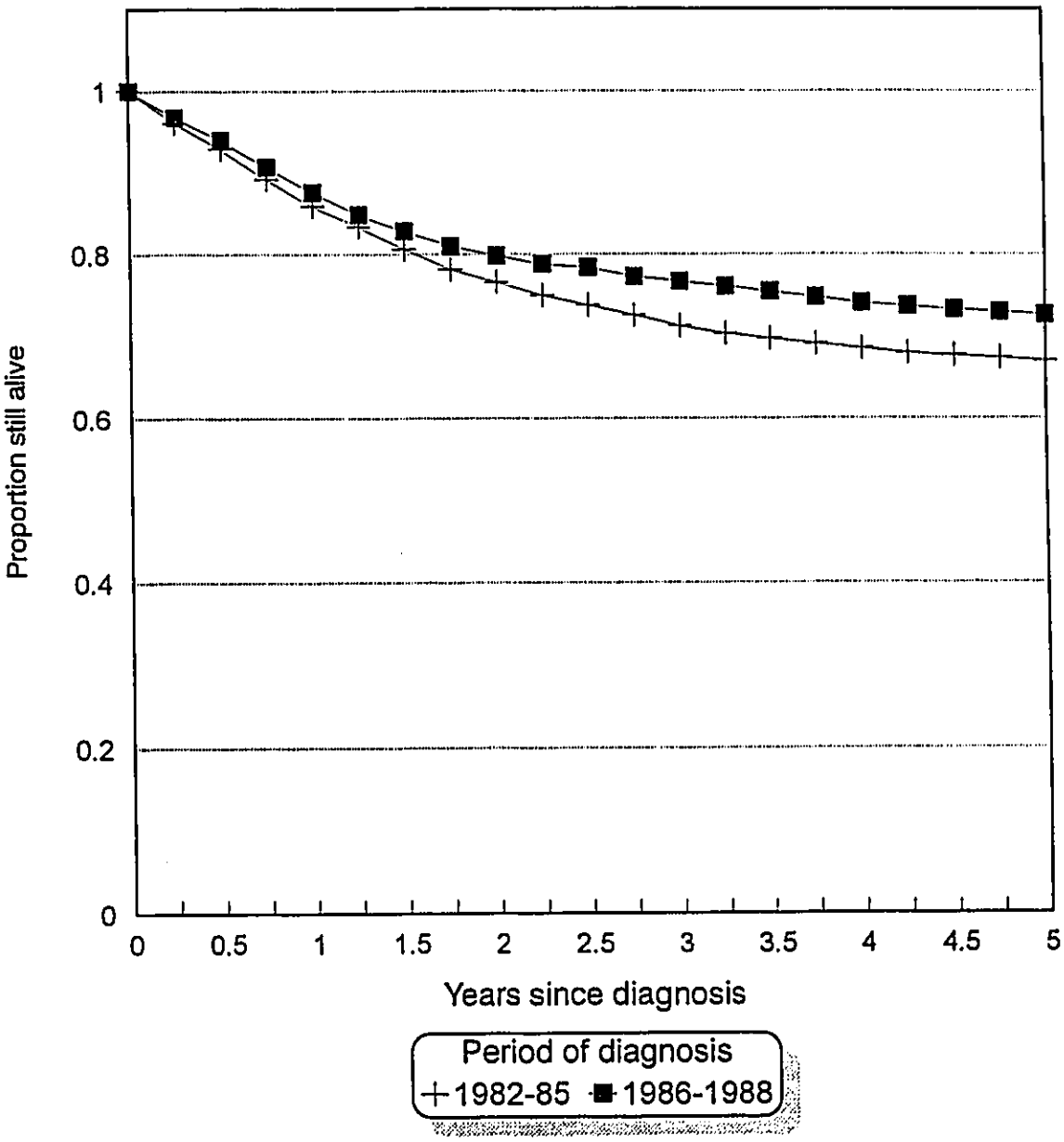
Type of Cancer	Age Group					
	<1	1-<5	5-<10	10-<15	15-<20	Total
Leukaemia	63	572	316	187	180	1318
Acute lymphocytic leukaemia	27	478	264	119	112	1000
Acute non lymphocytic leukaemia	17	46	26	43	43	175
Other leukaemia	19	48	26	25	25	143
Lymphomas	14	65	113	219	380	791
Hodgkin's disease	0	7	43	116	287	453
Non-Hodgkin lymphoma	2	28	43	55	57	185
Central Nervous System	35	206	234	163	150	788
Ependymoma	5	27	16	11	3	62
Astrocytoma	15	70	105	88	93	371
Medulloblastoma	8	46	50	27	18	149
Sympathetic Nervous System	77	120	31	12	9	249
Neuroblastoma and ganglioneuroblastoma	74	115	29	8	4	230
Retinoblastoma	22	56	2	1	1	82
Renal Tumours	43	105	48	11	8	215
Wilms' tumour	38	98	45	9	3	193
Hepatic tumours	13	16	9	3	6	47
Malignant bone tumours	0	9	35	93	111	248
Osteosarcoma	0	1	18	47	64	130
Ewing's sarcoma	0	4	14	37	31	86
Soft tissue sarcomas	20	70	59	80	85	314
Rhabdomyosarcoma	10	53	42	29	34	168
Fibrosarcoma	3	8	7	18	26	62
Gonadal and germ cell	27	34	22	55	135	273
Non gonadal germ cell	12	19	12	15	22	80
Germ cell	11	12	7	35	99	164
Carcinoma and other malignant epithelial neoplasms	6	11	33	58	231	339
Other	9	8	4	9	11	51
All Cancers	329	1282	906	891	1307	4715

†Excludes cases with non-positive survival time, secondary malignancies, and ICD-9 173.

Table 2.
One, three and five year actuarial survival rates, for selected cancers, childhood cohort, 1982-1988

Cancer	1 Yr. Survival Rate (Standard Error)	3 Yr. Survival Rate (Standard Error)	5 Yr. Survival Rate (Standard Error)
Leukaemia	0.858 (0.010)	0.673 (0.013)	0.609 (0.014)
Acute lymphocytic leukaemia	0.913 (0.009)	0.754 (0.014)	0.688 (0.015)
Acute non-lymphocytic leukaemia	0.638 (0.036)	0.356 (0.036)	0.302 (0.036)
Other leukaemia	0.741 (0.037)	0.500 (0.042)	0.433 (0.042)
Lymphomas	0.901 (0.011)	0.836 (0.013)	0.794 (0.015)
Hodgkin's disease	0.978 (0.007)	0.934 (0.012)	0.902 (0.014)
Non-Hodgkin's lymphoma	0.843 (0.027)	0.703 (0.034)	0.621 (0.036)
Central nervous system neoplasms	0.794 (0.014)	0.682 (0.017)	0.642 (0.017)
Ependymoma	0.823 (0.049)	0.677 (0.059)	0.540 (0.064)
Astrocytoma	0.860 (0.018)	0.757 (0.022)	0.729 (0.023)
Medulloblastoma	0.800 (0.033)	0.638 (0.039)	0.578 (0.041)
Sympathetic nervous system	0.783 (0.026)	0.627 (0.031)	0.594 (0.031)
Neuroblastoma	0.787 (0.027)	0.630 (0.032)	0.596 (0.033)
Retinoblastoma	1.0 (0.00)	0.976 (0.017)	0.976 (0.017)
Renal tumours	0.944 (0.016)	0.874 (0.023)	0.859 (0.024)
Wilms' tumour	0.948 (0.016)	0.885 (0.023)	0.869 (0.024)
Hepatic tumours	0.553 (0.073)	0.426 (0.072)	0.404 (0.072)
Bone tumours	0.871 (0.021)	0.641 (0.031)	0.597 (0.032)
Osteosarcoma	0.839 (0.032)	0.607 (0.043)	0.589 (0.043)
Ewing's sarcoma	0.907 (0.031)	0.663 (0.051)	0.570 (0.055)
Soft tissue sarcomas	0.863 (0.019)	0.698 (0.026)	0.656 (0.027)
Rhabdomyosarcoma	0.839 (0.028)	0.643 (0.037)	0.596 (0.038)
Fibrosarcoma	0.903 (0.038)	0.823 (0.049)	0.804 (0.051)
Gonadal and germ cell	0.934 (0.015)	0.843 (0.022)	0.818 (0.024)
Non gonadal	0.863 (0.039)	0.700 (0.051)	0.645 (0.054)
Gonadal			
Testicular	0.980 (0.014)	0.911 (0.028)	0.891 (0.031)
Ovarian	0.952 (0.027)	0.921 (0.034)	0.921 (0.034)
Carcinoma and other epithelial	0.932 (0.014)	0.861 (0.019)	0.842 (0.020)
Other and unspecified	0.863 (0.048)	0.784 (0.058)	0.784 (0.058)
ALL CANCERS	**0.865 (0.005)**	**0.736 (0.006)**	**0.694 (0.007)**

Figure 3. Actuarial survival curves* for all cancers, childhood cohort, by period of diagnosis



* Survival curves estimated using the product limit life table. The Mantel Cox test statistic for group differences was 16.7 (p=0.00)

Leukaemia

The one, three and five year survival rates for children with leukaemia were 86%, 67% and 61% respectively (Table 2). Among children diagnosed with ALL, 69% survived five years after initial diagnosis. The prognosis was much less favourable for those diagnosed with ANLL. Only 30% of children diagnosed with this malignancy survived more than five years.

Age at diagnosis and gender were found to be significant predictors of survival for children with ALL (Tables 3,4). The effects of age on outcome were similar in both sexes. Survival was poorest among infants (ie. diagnosed prior to age one) where less than one out of four survived five years. After age one, survival decreased with increasing age with the most favourable results occurring among those diagnosed prior to age five (Figure 4,5). When adjusted for age, the hazard rate of females was 0.75 times that of males and significant at the two percent level (Table 3).

Table 3.
Results of proportional hazards regression analysis in measuring the effect of gender, for selected cancers, adjusted for age and year of diagnosis†, childhood cohort, 1982-1988

Cancer site	Gender Covariate			
	Parameter estimate of gender covariate‡	Standard error	Relative hazard†	p§
Acute lymphocytic leukaemia	-0.28	0.12	0.75	0.02
Acute non-lymphocytic leukaemia	-0.15	0.18	0.86	0.41
Hodgkin's disease	-0.47	0.31	0.62	0.13
Non-Hodgkin lymphoma	-0.05	0.27	0.95	0.86
Ependymoma	-1.05	0.40	0.35	0.01
Astrocytoma	-0.28	0.20	0.76	0.16
Medulloblastoma	-0.39	0.26	0.68	0.13
Neuroblastoma	0.05	0.21	1.05	0.81
Wilms' tumour	0.06	0.40	1.06	0.88
Osteosarcoma	-0.32	0.28	0.73	0.25
Ewing's sarcoma	0.22	0.34	1.24	0.52
Rhabdomyosarcoma	-0.16	0.25	0.85	0.52
Fibrosarcoma	0.72	0.56	2.06	0.20
Non-gonadal germ-cell	0.21	0.42	1.24	0.60

‡gender was entered in the proportional hazards model as a binary variable (1 = male,2 = female)
§p-value obtained using likelihood ratio test; the reader is referred to section 4.1.5 for a discussion of multiple testing
†The relative hazard is a ratio of the female hazard rate to that of a male adjusted for differences in year and age at diagnosis

Table 4.
Results of proportional hazards regression analysis in measuring the effect of age of diagnosis, for selected cancers, adjusted for gender and year of diagnosis, childhood cohort, 1982-1988

Type of Cancer	Parameter estimate of age covariate	Standard Error of estimate	Relative hazard[‡]	p-value[¶]
Acute lymphocytic leukaemia				
Infants	2.24	0.25	9.35 †	0.00
Diagnoses after age one				
Males	0.08	0.01	1.08	0.00
Females	0.10	0.02	1.10	0.00
Acute non-lymphocytic leukaemia				
Infants	0.99	0.32	2.70 †	0.00
Diagnoses after age one	-0.01	0.02	0.99	0.55
Hodgkin's disease				
Males	0.21	0.07	1.23	0.00
Females	-0.03	0.09	0.97	0.72
Non-Hodgkin lymphoma	0.02	0.02	1.03	0.30
Ependymoma				
Males	-0.10	0.06	0.91	0.07
Females	-0.15	0.08	0.86	0.04
Astrocytoma	0.04	0.02	1.04	0.04
Medulloblastoma	-0.01	0.03	0.99	0.59
Neuroblastoma				
Infants	-2.19	0.44	0.11 †	0.00
Diagnoses after age one	0.01	0.03	1.01	0.75
Wilms' tumour	-0.03	0.07	0.97	0.64
Osteosarcoma	0.00	0.04	1.00	0.91
Ewing's sarcoma	0.02	0.04	1.02	0.56
Rhabdomyosarcoma	0.05	0.02	1.06	0.01
Fibrosarcoma	0.09	0.05	1.09	0.07
Non-gonadal germ cell	0.04	0.03	1.04	0.20
Gonadal germ-cell				
Testicular	0.12	0.09	1.13	0.07
Ovarian	0.05	0.13	1.05	0.68

‡ the relative hazard ratio is the ratio of two hazard rates in which the age at diagnosis differs by one year. The denominator represents the hazard of the older child.

† in this instance, the relative hazard is a ratio of the hazard rate of an infant (ie. diagnosed prior to age one) relative to the hazard rate of a child who is at least one year old when diagnosed.

¶ the reader is referred to section 4.1.5 for a discussion of multiple testing

Table 5.
Results of proportional hazards regression analysis in measuring the effect of year of diagnosis, for selected cancers, adjusted for gender and age at diagnosis, childhood cohort, 1982-1988

Type of Cancer	3 year survival rate[1] 1982-83 (standard error)	3-year survival rate[1] 1987-88 (standard error)	β[2]	s.e. (β)	Relative hazard[3]	p-value[4]
Acute lymphocytic leukaemia						
Infants	0 (0)[5]	0.43 (0.19)[5]	-0.09	0.12	0.91	0.45
Diagnoses after age one						
Males	0.68 (0.04)	0.82 (0.03)	-0.13	0.04	0.88	0.00
Females	0.64 (0.04)	0.88 (0.03)	-0.23	0.05	0.80	0.00
Acute non-lymphocytic leukaemia						
Infants	0.25 (0.22)[5]	0 (0)[5]	0.19	0.15	1.21	0.20
Diagnoses after age one	0.26 (0.07)	0.45 (0.07)	-0.10	0.05	0.90	0.04
Hodgkin's disease	0.91 (0.02)	0.92 (0.03)	-0.02	0.08	0.98	0.77
Non-Hodgkin lymphoma	0.72 (0.06)	0.78 (0.06)	-0.16	0.07	0.86	0.01
Ependymoma						
Males	0.44 (0.17)[5]	0.50 (0.18)[5]	-0.05	0.11	0.95	0.65
Females	0.78 (0.14)[5]	1.0 (0) [5]	0.02	0.20	1.02	0.92
Astrocytoma	0.79 (0.04)	0.75 (0.04)	0.02	0.05	1.01	0.63
Medulloblastoma	0.59 (0.07)	0.60 (0.08)	0.03	0.06	1.03	0.68
Neuroblastoma						
Infants	1.0 (0)	0.87 (0.07)	0.68	0.32	1.98	0.01
Diagnoses after age one	0.42 (0.07)	0.47 (0.08)	-0.06	0.06	0.94	0.29
Wilms' tumour	0.88 (0.05)	0.96 (0.02)	-0.19	0.11	0.83	0.07
Osteosarcoma	0.57 (0.08)	0.74 (0.07)	-0.11	0.07	0.90	0.10
Ewing's sarcoma	0.75 (0.09)	0.68 (0.10)	0.08	0.09	1.08	0.34
Rhabdomyosarcoma	0.60 (0.07)	0.72 (0.07)	-0.06	0.05	0.95	0.38
Fibrosarcoma	0.61 (0.11)	0.95 (0.05)	-0.27	0.14	0.76	0.05
Non-gonadal germ cell	0.56 (0.12)	0.75 (0.11)	-0.09	0.11	0.91	0.41
Gonadal germ-cell						
Ovarian	0.86 (0.07)	1.00 (0)	-0.51	0.33	0.60	0.06
Testicular	0.93 (0.05)	0.86 (0.06)	0.19	0.16	1.21	0.22

[1]survival rates ...culated using the actuarial life table

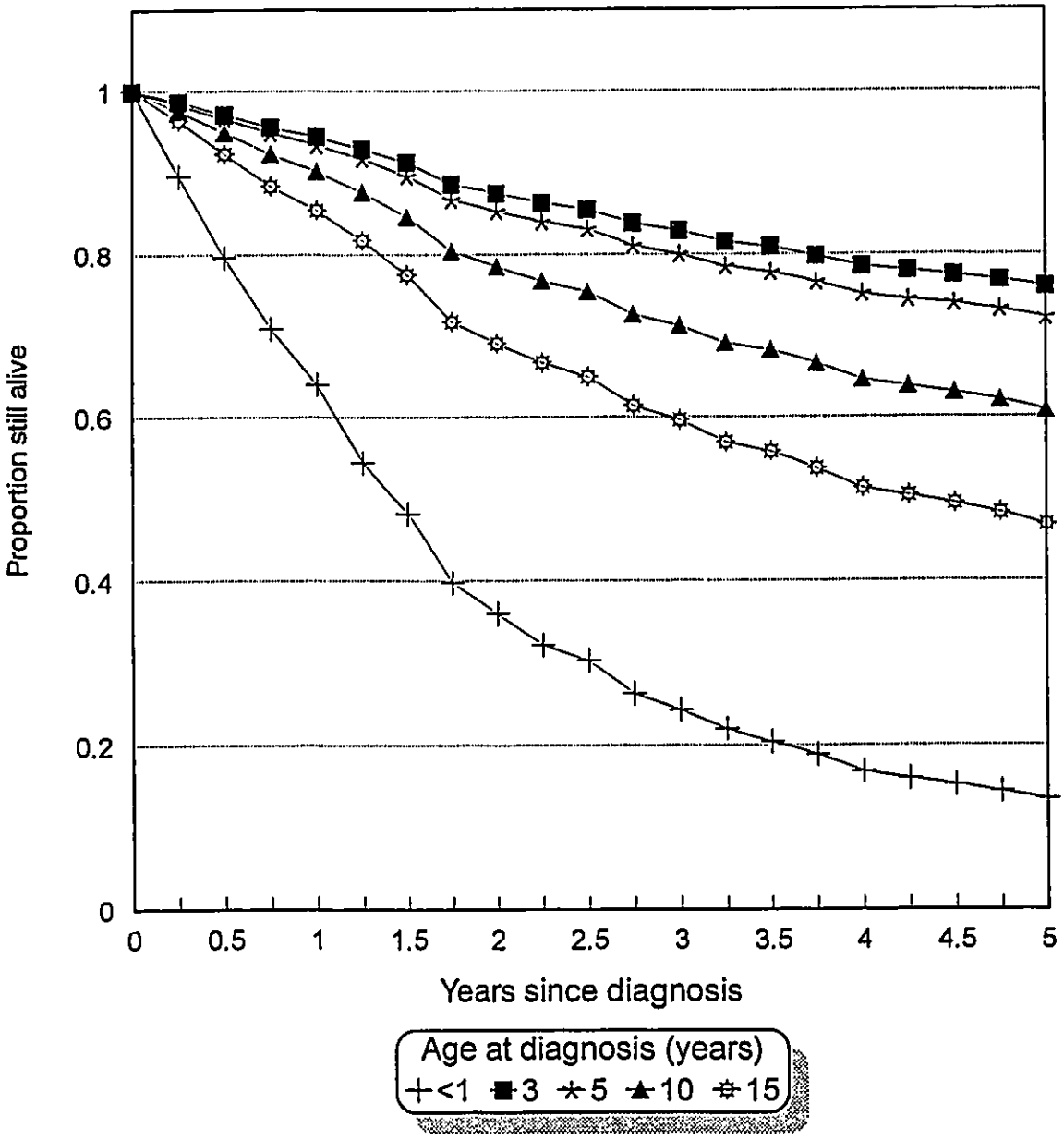
[2]β was estimated using the proportional hazards model and is the coefficient estimate of the year of diagnosis.

[5]survival estimates based on fewer than ten cases

[3]the relative hazard is a ratio of two hazard rates in which the year of diagnosis differs by one. Note the denominator represents the earlier date of diagnosis

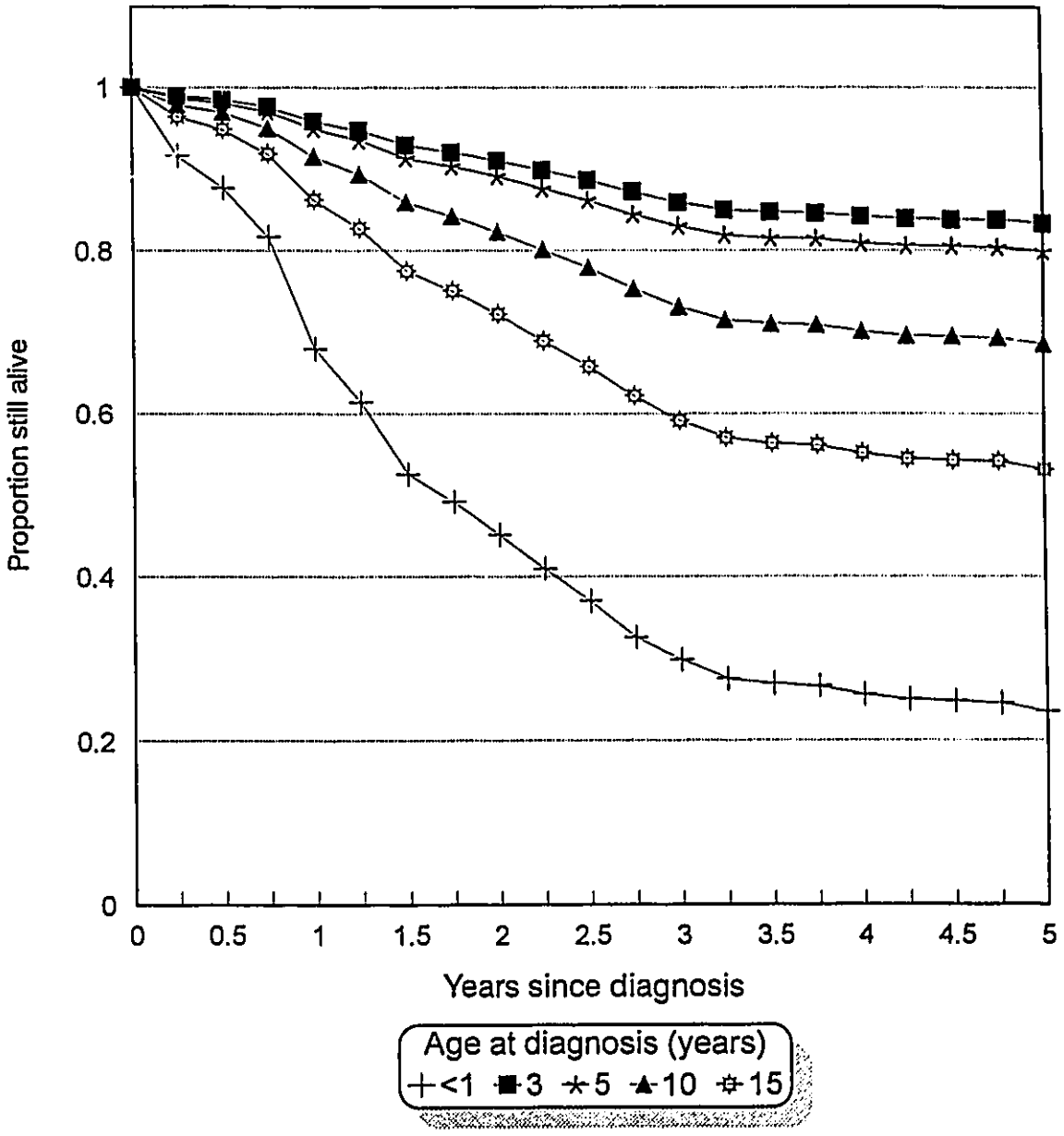
[4]the reader is referred to section 4.1.5 for a discussion of multiple testing

Figure 4. Survival curves* of male children diagnosed with acute lymphocytic leukaemia between 1982 and 1988, by age



*Estimated using the proportional hazards model

Figure 5. Survival curves* of female children diagnosed with acute lymphocytic leukaemia between 1982 and 1988, by age

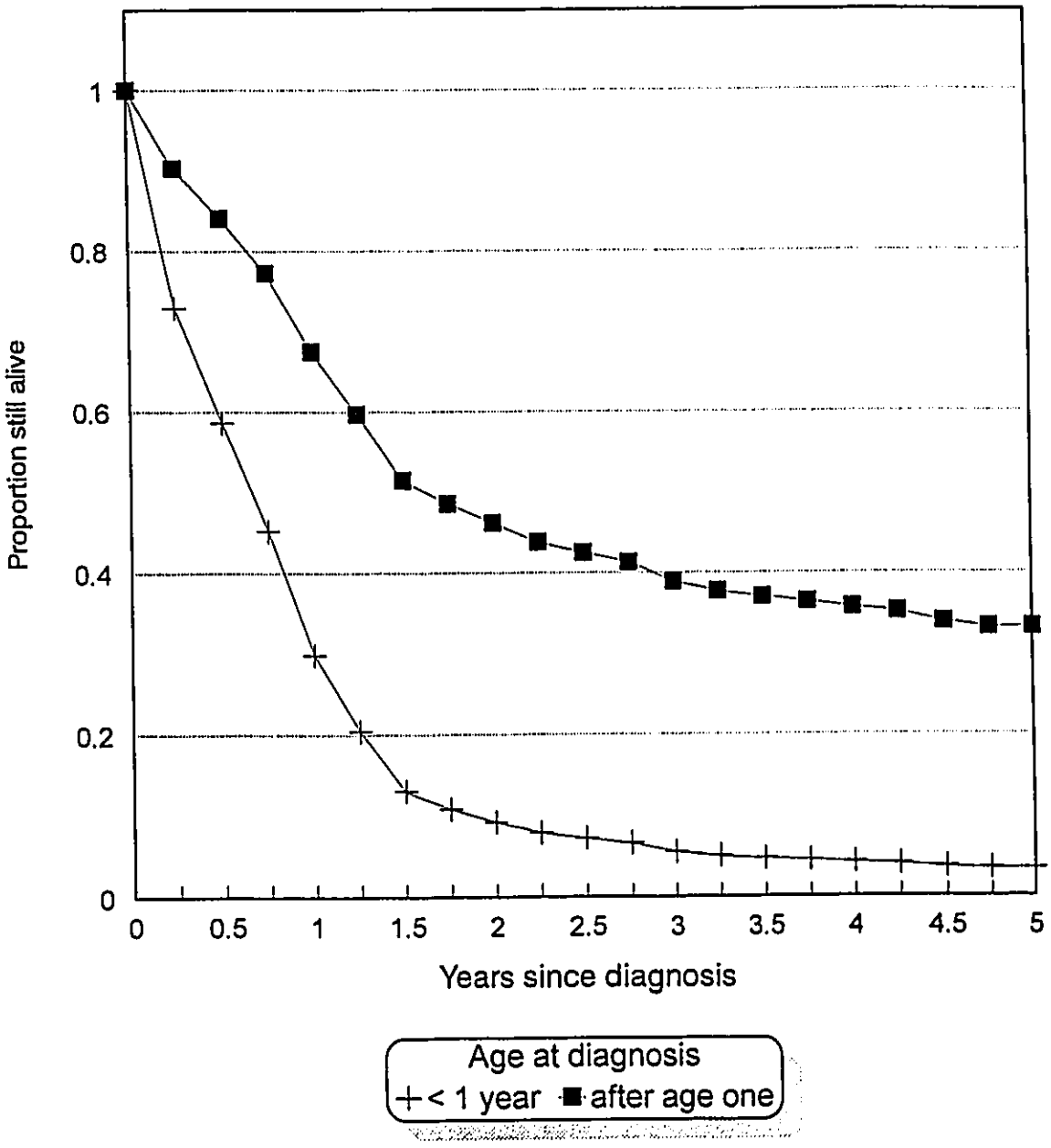


*Estimated using the proportional hazards model

For children with ANLL, age was also a significant prognostic factor. As with ALL, survival was poorest among infants. The presentation of ANLL in this age group was invariably fatal as less than five percent of such cases survived five years after diagnosis (Figure 6). After age one, there were no statistically significant age related differences in survival as the relative hazard was 0.99 ($p=0.55$) (Table 4). Gender was not found to be associated with prognosis ($p=0.41$) (Table 3).

Improved survival was observed among children more recently diagnosed with either ALL or ANLL (Table 5). The five year survival rates among male children diagnosed after age one, improved from 68% in 1982-83 to 82% in 1987-1988. Similar improvements in survival were observed among females were survival increased from 64% to 88% over the same period. For ANLL, the hazard decreased by 10% annually among children diagnosed after age one over the period 1982-1988 ($p=0.04$) (Table 5). Among infants diagnosed with either ALL or ANLL, no statistically significant changes by year of diagnosis were observed.

Figure 6. Survival curves* of children diagnosed with acute non-lymphocytic leukaemia between 1982 and 1988, by age



*Estimated with the proportional hazards model

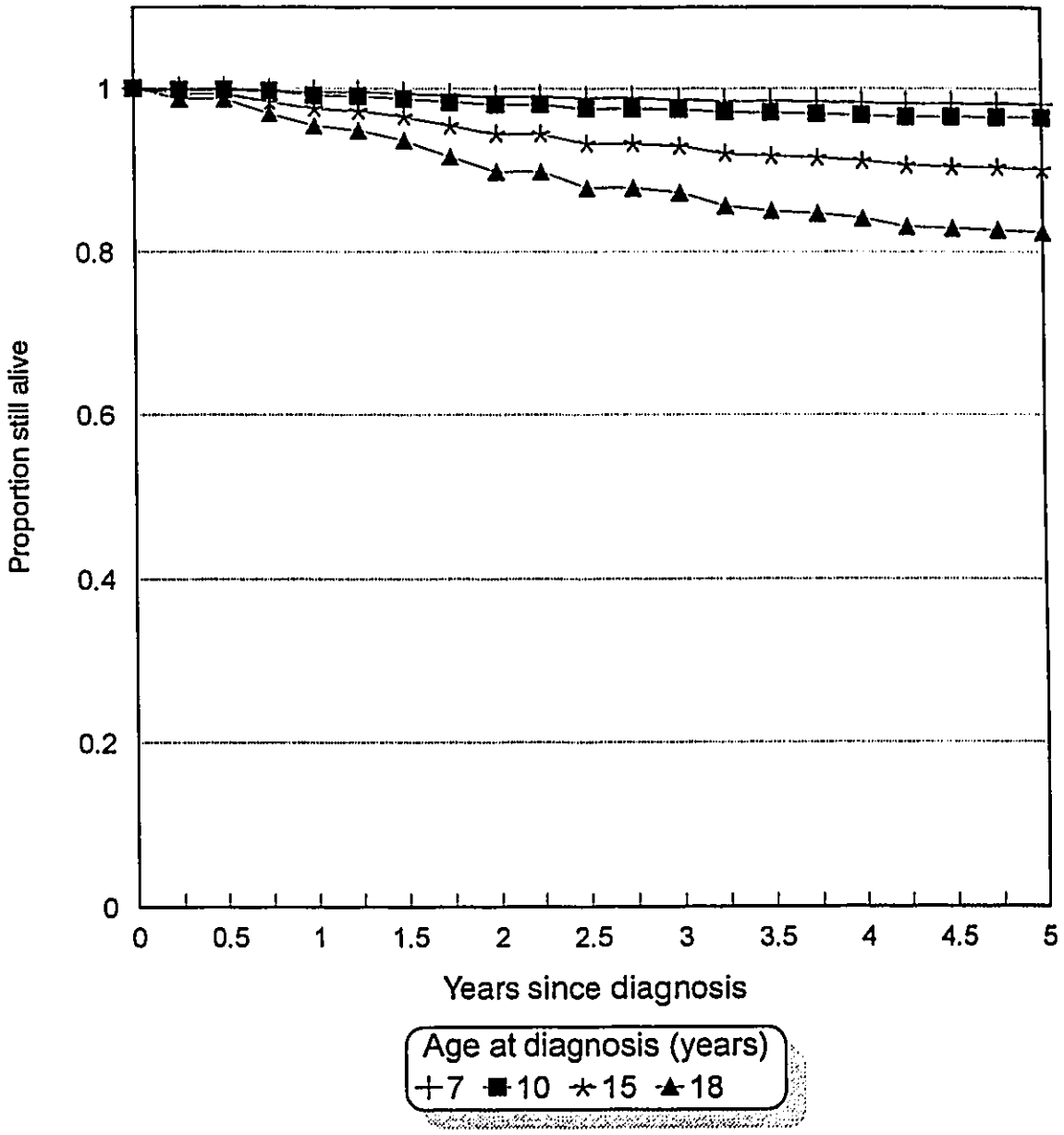
Lymphomas

Among children diagnosed with lymphomas, nearly 80% survived five years after diagnosis (Table 2). Only ten percent of those diagnosed with Hodgkin's disease failed to survive five years. Sixty-two percent of children diagnosed with NHL survived five years after diagnosis.

For males diagnosed with Hodgkin's disease decreased survival was observed with increasing age (Figure 7). The effect of age on predicting survival was not statistically significant among females ($p=0.72$).

Neither age nor gender were found to be significant predictors of survival for NHL. Unlike Hodgkin's disease, year at diagnosis was found to be a statistically significant predictor of survival in the proportional hazards model. As presented in Table 5, the hazard rate among children diagnosed with NHL improved on average by 14% annually over the period 1982-1988 ($p=0.01$).

Figure 7. Survival curves* of male children diagnosed with Hodgkin's disease between 1982 and 1988, by age



*Estimated using proportional hazrds model

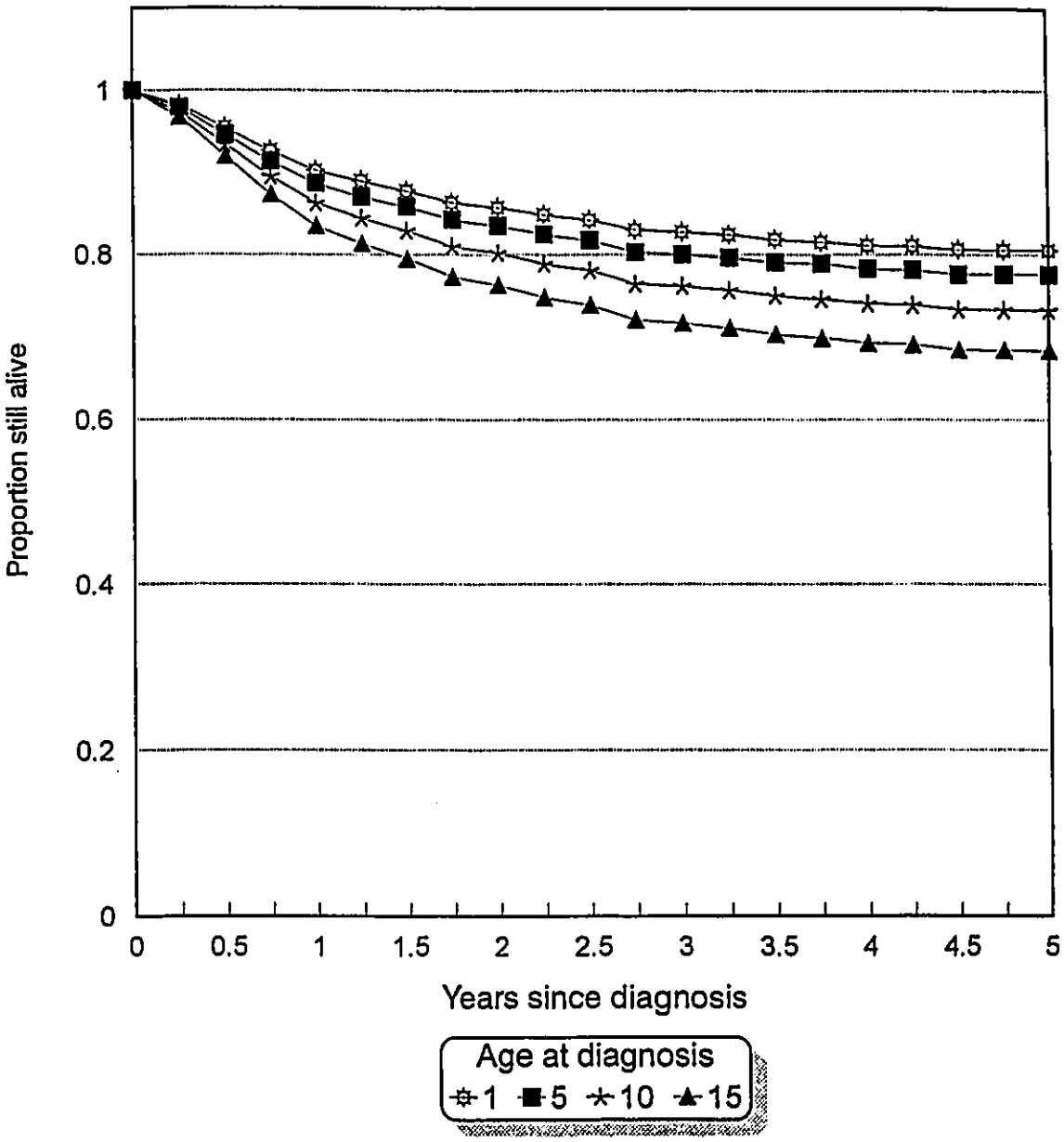
Tumours of the central nervous system

The five year survival rate for children diagnosed with a tumour of the CNS between 1982 and 1988 was 64% (Table 2). The prognosis was similar among those diagnosed with an ependymoma or a medulloblastoma where 54% and 58% respectively managed to survive five years after diagnosis. The survival among children with astrocytomas was more favourable as 73% survived five years.

For children with medulloblastoma, neither age of diagnosis or gender was a significant predictor of survival. Among children with astrocytoma, decreased survival was observed among older children (Figure 8). No changes in survival by year of diagnosis were observed for any of the CNS tumours examined.

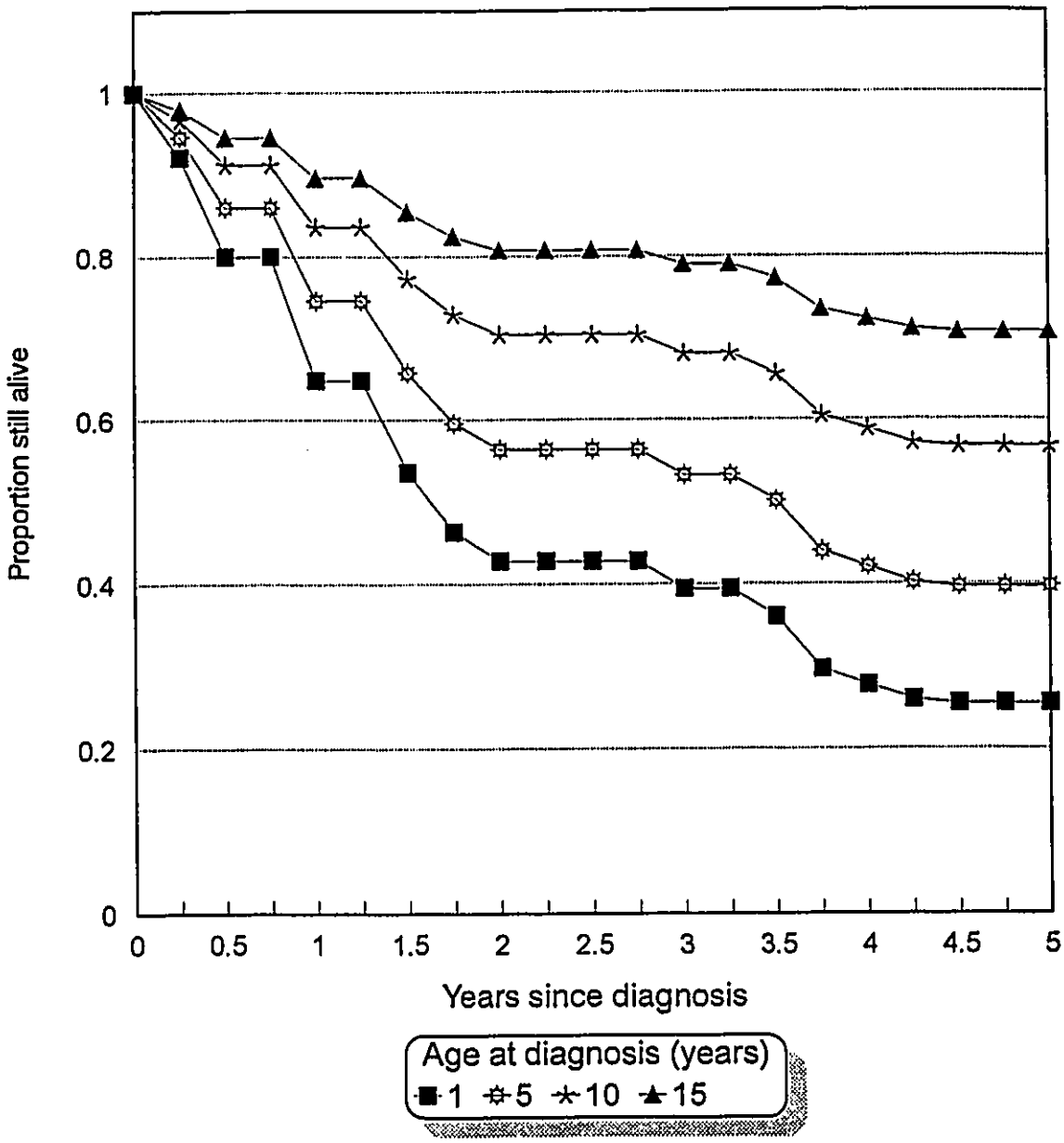
As shown in Table 3, when adjusted for year and age at diagnosis, females diagnosed with ependymomas had a more favourable prognosis than their male counterparts ($p=0.01$). The hazard rate of females was 0.35 times that of males (Table 3). Survival improved among both males and females with increased age (Figures 9,10).

Figure 8. Survival curves of children diagnosed with an astrocytoma between 1982 and 1988, by age



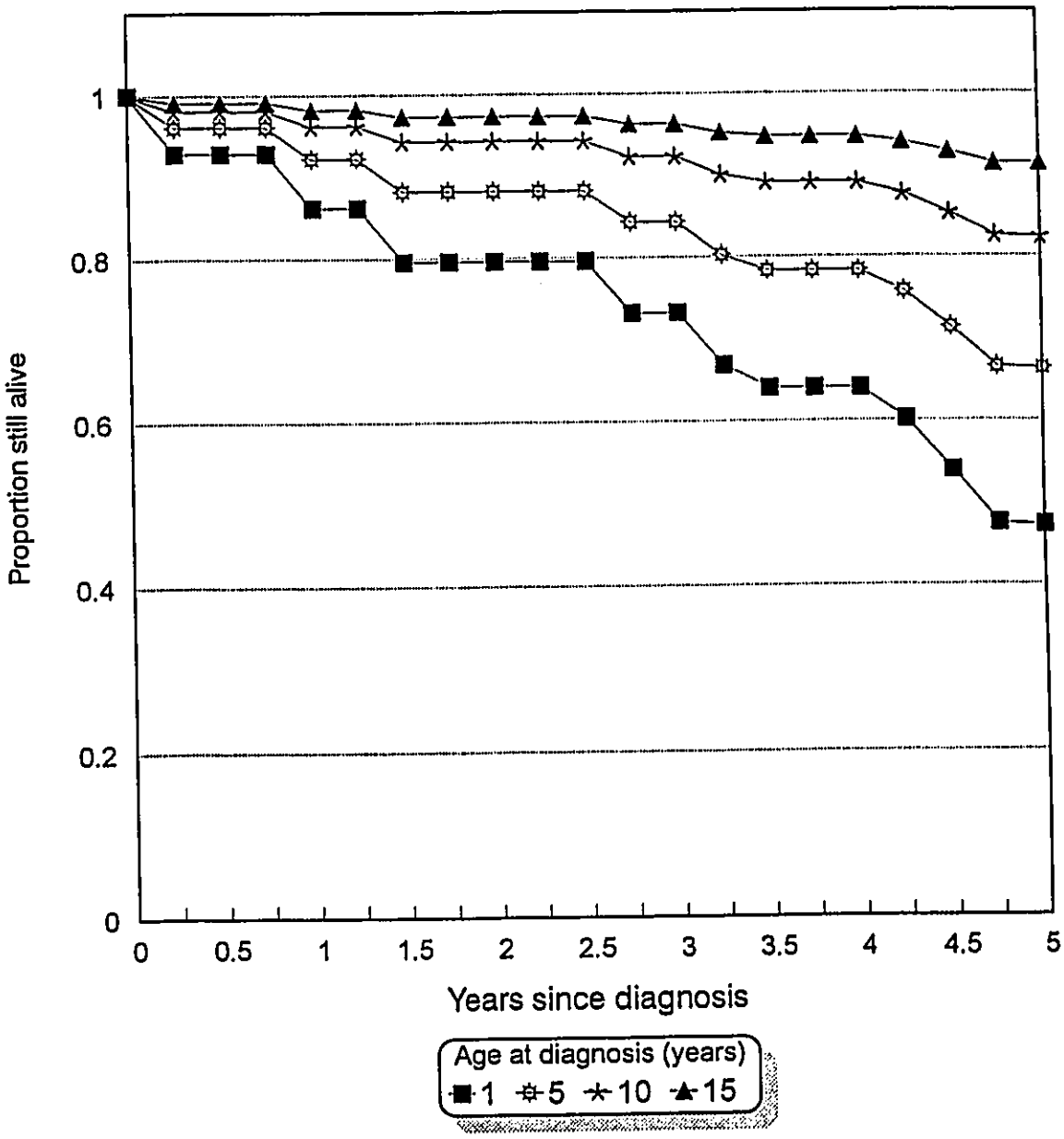
*Estimated using the proportional hazards model

Figure 9. Survival curves* of male children diagnosed with an ependymoma between 1982 and 1988, by age



*Estimated using the proportional hazards model.

Figure 10. Survival curves of female children diagnosed with an ependymoma between 1982 and 1988, by age



* Estimated using proportional hazards model

Sympathetic nervous system tumours

The five year survival rate for neuroblastomas was 60%. The effect of gender was not found to have a significant impact on survival (Table 3). Infants had a substantially higher survival rate. The hazard rate of these cases was one-ninth of those diagnosed after the age of one ($p<0.001$). The five year survival rate of infants was approximately 90% while the corresponding rate of those diagnosed after age one was 46% (Figure 11). After age one, age at diagnosis was not found to be associated with prognosis (Table 4). The prognosis was poorer among infants diagnosed more recently (Table 5).

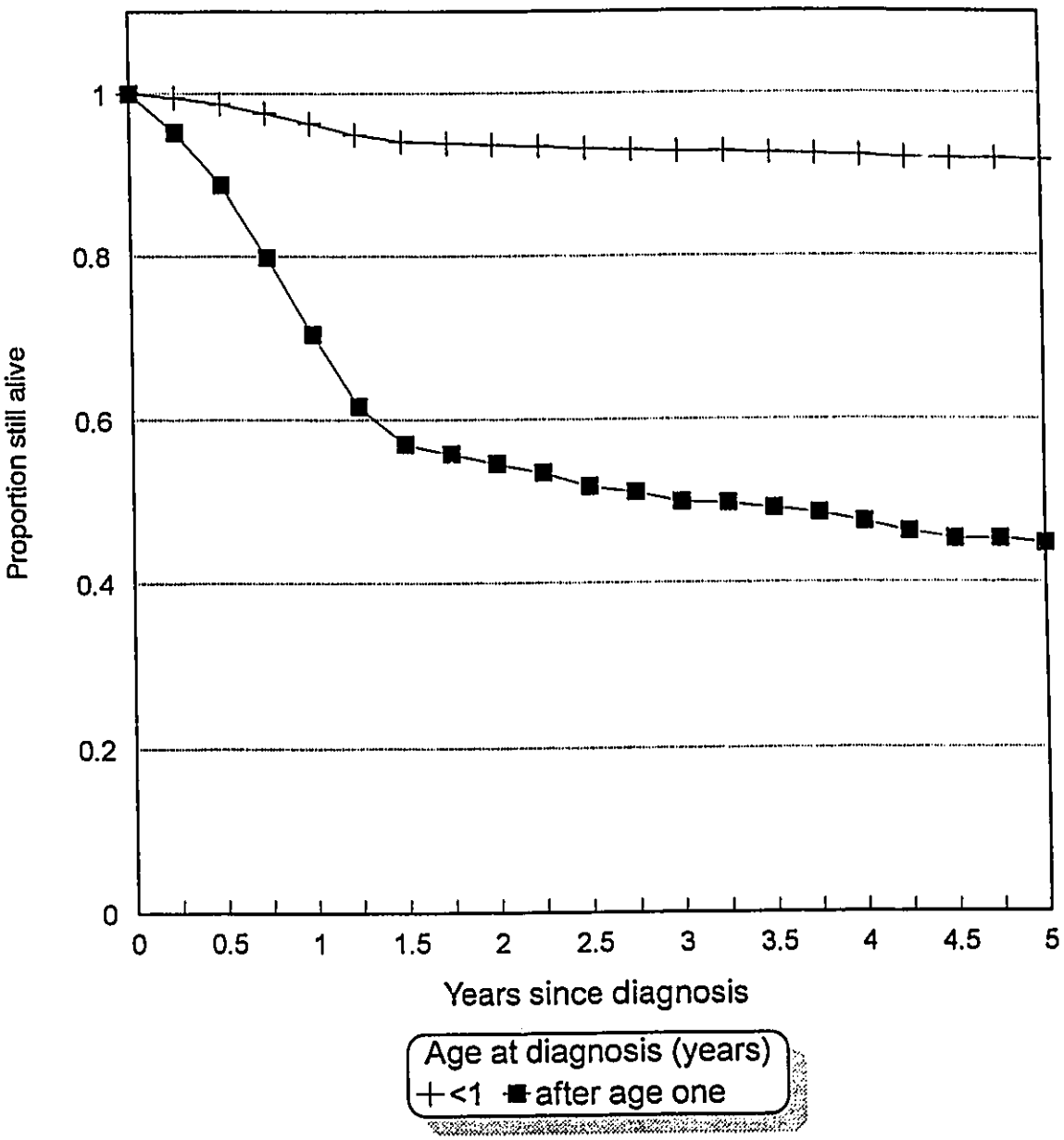
Retinoblastoma

This diagnostic group had the highest survival rate. Only 2 out of 82 cases died during follow-up. The resulting five year survival rate was almost 98% (Table 2). For this reason, no meaningful analysis of differences in survival for the available covariables could be assessed.

Hepatic tumours

The prognosis among children diagnosed with hepatic malignancies was bleak. Only 56% managed to survive one year after initial diagnosis and less than one-third of these patients survived five years post diagnosis (Table 2). Fortunately this cancer was rare with only 47 children diagnosed between 1982 and 1988 (Table 1).

Figure 11. Survival curves* of children diagnosed with a neuroblastoma between 1982 and 1988, by age



*Estimated using the proportional hazards model

Malignant bone tumours

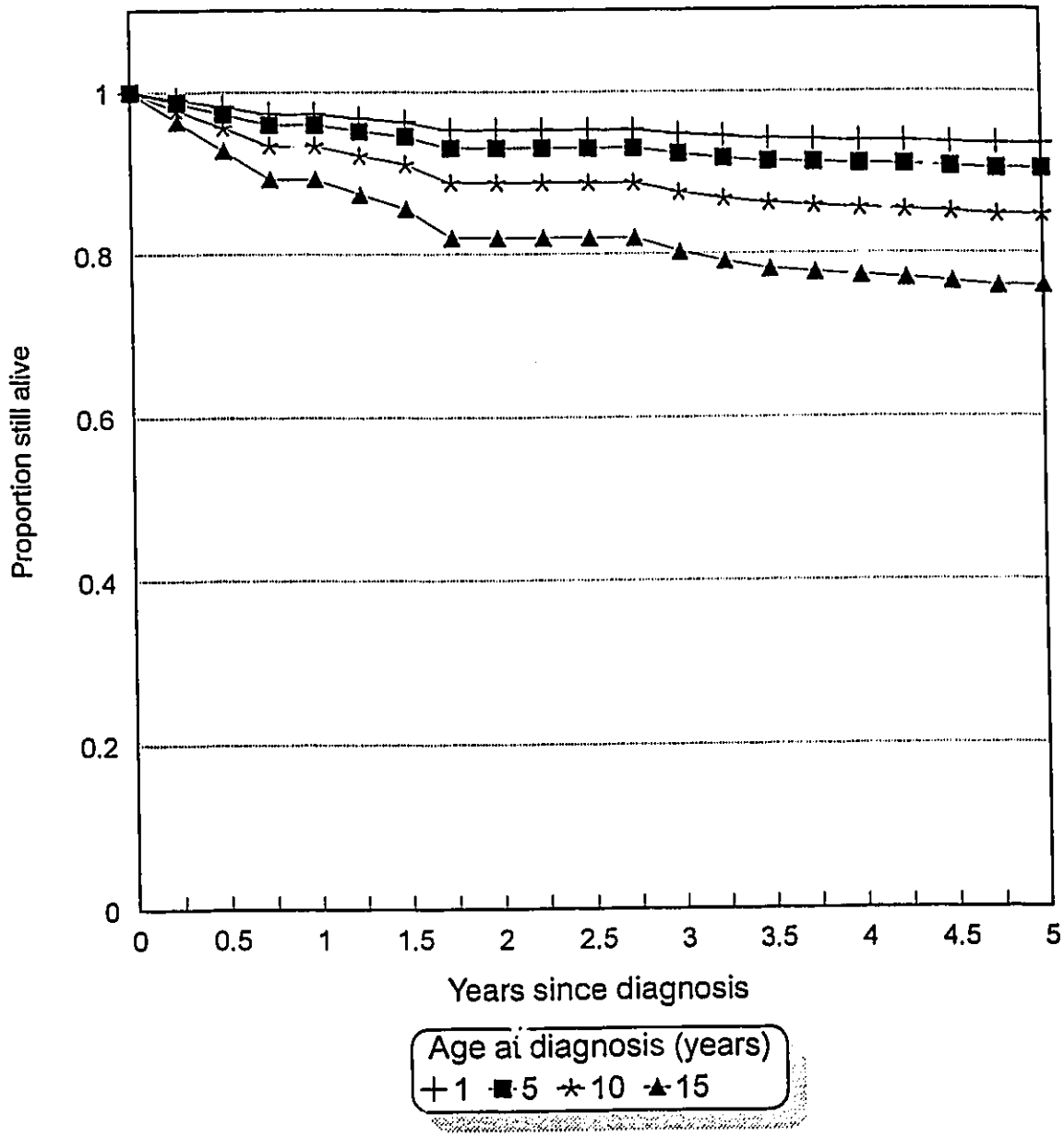
The five year survival rate of children with bone tumours was 60%. The five year survival rate for osteosarcoma and Ewing's sarcoma was 59% and 57% respectively. Among children with osteosarcoma age at diagnosis was not a significant prognostic factor ($p=0.91$) nor was gender ($p=0.25$) (Tables 3,4). Similar findings were observed for those diagnosed with Ewing's sarcoma. Year of diagnosis was not associated with prognosis (Table 5).

Soft tissue sarcomas

Approximately two out of three children diagnosed with a soft tissue sarcoma survived five years of follow-up (Table 2). For those diagnosed a rhabdomyosarcoma the five year survival rate was 60% (Table 2). Children with fibrosarcoma had a more favourable prognosis as the five year survival rate of this cancer was 80%.

Age at diagnosis was associated with the prognosis of children with fibrosarcoma. Decreased survival was observed with increasing age (Figure 12). The hazard rate increased by a factor of 1.09 as age of diagnosis increased by one year (Table 4). As presented in Table 5, the effect of year at diagnosis among children with fibrosarcoma was marginally significant ($p=0.05$). The three year survival rate improved from 61% in 1982-83 to 95% in 1987-88.

Figure 12. Survival curves* of children diagnosed with a fibrosarcoma between 1982 and 1988, by age



*Estimated using proportional hazards model.

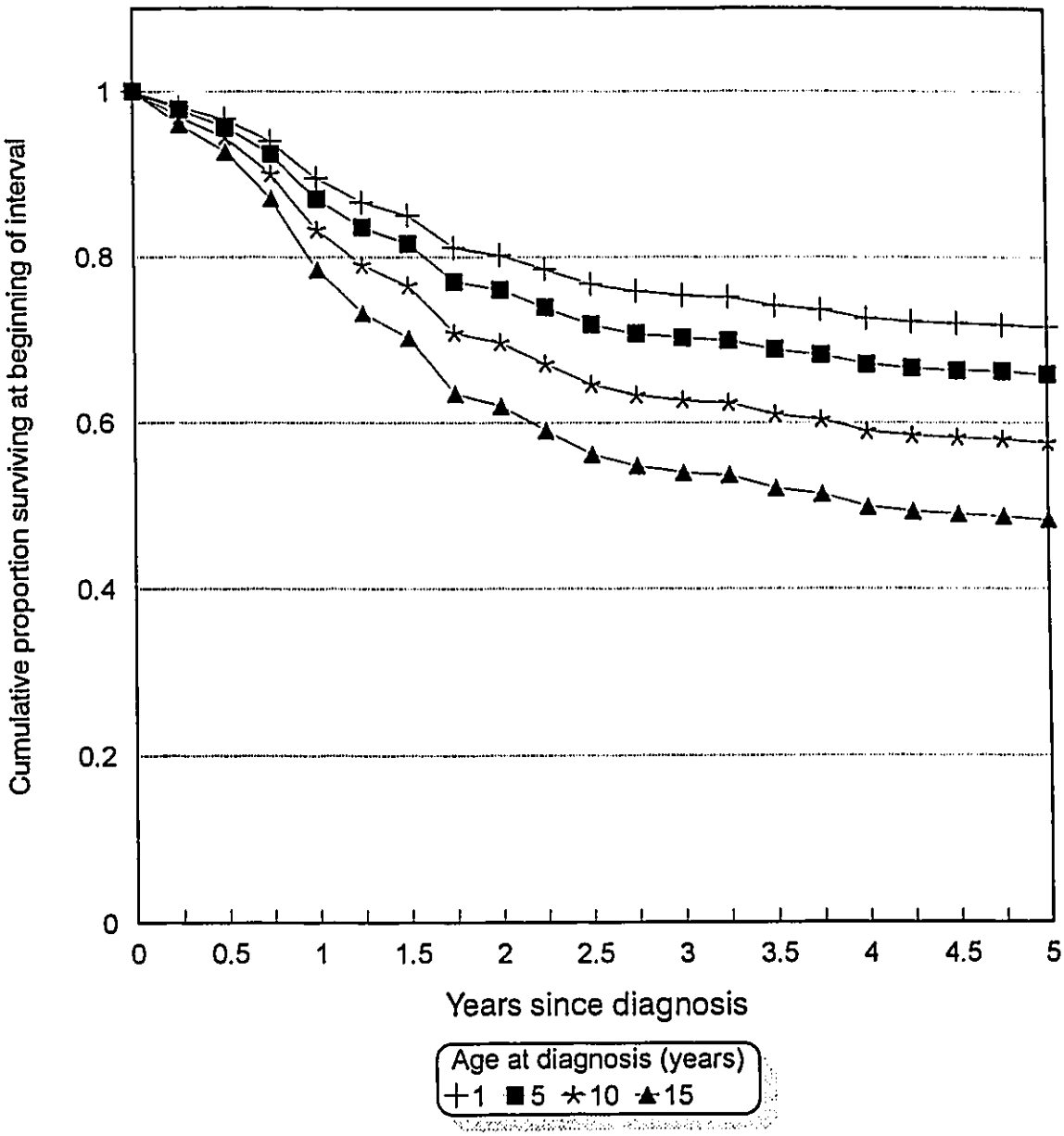
For children with rhabdomyosarcoma, age at diagnosis was a significant predictor of survival (Table 4). As with fibrosarcoma, decreased survival was observed with increased age of diagnosis. Less than sixty percent of those diagnosed after age ten managed to survive five years (Figure 13).

Germ cell tumours

The five year survival rate for germ cell, trophoblastic and other gonadal malignancies was approximately 82% (Table 2). For non gonadal germ cell tumours the five year survival rate was 65%. The five year survival rate for gonadal germ cell malignancies was 89%. Among females, approximately 92% managed to survive germ cell malignancies of the ovary.

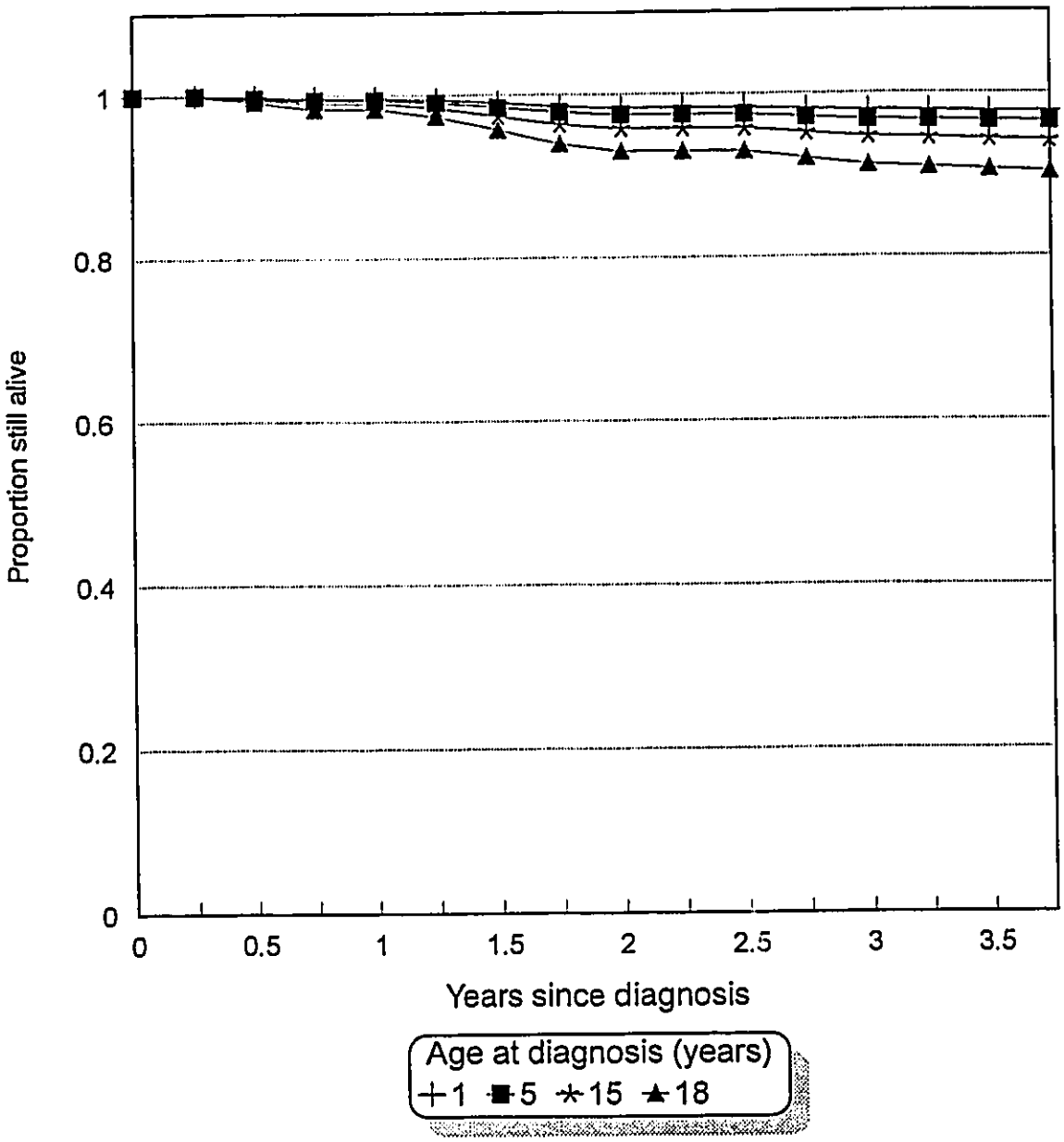
Age at diagnosis was a marginally significant prognostic factor for male children diagnosed with testicular germ cell malignancies (Table 4). Decreased survival was observed with increasing age (Figure 14). Those diagnosed prior to age fifteen were estimated to have a survival rate greater than 90%.

Figure 13. Survival curves* of children diagnosed with a rhabdomyosarcoma between 1982-1988, by age



*Estimated using the proportional hazards model

Figure 14. Survival curves* of children diagnosed with testicular germ cell malignancies between 1982 and 1988, by age



*Estimated using proportional hazards model

Regional variations in survival

Regional differences in survival were examined for children diagnosed with ALL, Hodgkin's disease and astrocytomas between 1987 and 1988. After adjusting for differences in age at diagnosis, gender and calendar year, British Columbia was found to have significantly higher survival rates for children diagnosed with ALL and astrocytomas. The three year survival rate for children diagnosed with ALL in B.C. between 1987 and 1988 was 92% (Table 6). This was statistically significant when compared to the survival of remainder of the cohort over the same period ($p=0.04$).

The prognosis of children diagnosed with Hodgkin's disease was favourable in all regions (Table 7). The three year survival rates ranged from a minimum of 88% in the Maritime region to 96% among children diagnosed in British Columbia.

The regional survival rates varied substantially among children diagnosed with an astrocytoma (Table 8). The three year survival rate among cases reported in B.C. was 95% compared to 76% for the remainder of the cohort. These differences in survival were statistically significant at the one percent significance level.

Table 6.
Three year actuarial survival rates of children diagnosed with acute lymphocytic leukaemia between 1987 and 1988, by region

Region	Cases	3 year survival rate† (standard error)	p-value¥	p-value‡
Atlantic	30	0.77 (0.08)	0.44	0.36
Quebec	113	0.83 (0.04)	0.92	0.95
Prairies	79	0.82 (0.04)	0.18	0.42
B.C.	53	0.92 (0.04)	0.06	0.04
Canada§	276	0.84 (0.02)	--	--

† Survival rate estimated using actuarial life table

¥ p-value generated from Mantel-Cox test statistic which assessed the difference in survival between the specific region versus the remainder of the cohort

‡ p-value generated using proportional hazards model adjusted for age at diagnosis, gender, and year of diagnosis;region was entered as a binary variable in the proportional hazards model (0=specified region, 1=remainder of the cohort).

§ excludes cases from Ontario and includes an additional incident case from the territories

Table 7.
Three year actuarial survival rates of children diagnosed with Hodgkin's disease between 1987 and 1988, by region

Region	Cases	3 year survival rate† (standard error)	p-value¥	p-value‡
Atlantic	17	0.88 (0.08)	0.32	0.42
Quebec	63	0.92 (0.03)	0.95	0.51
Prairies	21	0.90 (0.06)	0.56	0.66
B.C.	25	0.96 (0.04)	0.20	0.13
Canada§	129	0.92 (0.03)	--	--

† Survival rate estimated using actuarial life table

¥ p-value generated from Mantel-Cox test statistic which assessed the difference in survival between the specific region versus the remainder of the cohort

‡ p-value generated using proportional hazards model adjusted for age at diagnosis, gender, and year of diagnosis;region was entered as a binary variable in the proportional hazards model (0=specified region, 1=remainder of the cohort).

§ excludes cases from Ontario and includes an additional 3 incident cases from the territories

Table 8.
Three year actuarial survival rates of children diagnosed with an astrocytoma between 1987 and 1988, by region

Region	Cases	3 year survival rate† (standard error)	p-value¥	p-value‡
Atlantic	16	0.75 (0.11)	0.93	0.88
Quebec	38	0.68 (0.08)	0.27	0.27
Prairies	28	0.71 (0.09)	0.20	0.21
B.C.	22	0.95 (0.04)	0.02	0.01
Canada§	105	0.75 (0.04)	--	--

† Survival rate estimated using actuarial life table

¥ p-value generated from Mantel-Cox test statistic which assessed the difference in survival between the specific region versus the remainder of the cohort

‡ p-value generated using proportional hazards model adjusted for age at diagnosis, gender, and year of diagnosis;region was entered as a binary variable in the proportional hazards model (0=specified region, 1=remainder of the cohort).

§ excludes cases from Ontario and includes an additional 3 incident cases from the territories

DISCUSSION

The goal of this thesis is to assess the survival of children diagnosed with cancer between 1982 and 1988 using population based data. As previously detailed, the objectives of this study include assessing the role of gender, age at diagnosis and year of diagnosis on the prognosis of children with cancer. Further, geographical variations in survival were examined for selected cancers.

The first section of this chapter explores the methodological issues that might limit the interpretation of the findings. The second section compares the results of this study to those obtained from other series of population based incident cancer cases. Trends in survival as well as variations in survival by age at diagnosis, gender and geographic region are also discussed in this section. Finally, possible future trends in the management of pediatric cancers are examined.

4.1 Methodological issues

4.1.1 Quality of the record linkage

Details of the data quality and completeness of the NCIRS is available from Statistics Canada. In particular, item by item tables of availability have been prepared[98] while a thorough examination of major quality indicators has also been performed.[99] Steps have been taken in this thesis to correct for the inconsistent reporting

of some cancers by the provinces. Specifically, benign tumours and skin cancers were excluded from analyses. Provincial cancer registries coordinate their activities in order to provide consistency in their case ascertainment procedures.

The CMDB contains personal identifying information from each death registration in Canada as well as coded underlying cause of death. The linked file provided a clue as to the quality of the coding of the personal identifying information. Birth dates of the NCIRS and CMDB matched on over 97% of the records. Further, there were only ten instances were a death was coded in the NCIRS and no death certificate could be found by the CMDB. Manual examination of the death certificates was performed in order to verify differences in the coding of personal identifying information that were identified by record linkage.

The quality and the completeness of the NCIRS and CMDB has already been discussed. In some instances, the birth dates as recorded by the NCIRS differed from that of the CMDB. For these cases, death certificates could be examined to determine whether the date of birth was incorrectly coded by the NCIRS. The birth dates for those who had not died could not be verified in this manner and it is therefore possible that some cases may in fact be adult cancers. As adults with cancer have a poorer prognosis, the inclusion of these cases may underestimate the survival of children with cancer. The number of these cases should be quite small and the bias should be quite minimal.

It is possible that some death linkages may have been missed and as a result the presented survival rates may be slightly overestimated. A previous study examined the ability of Statistics Canada to detect deaths among a cohort of refinery workers using the CMDB. It found that Statistics Canada was able to detect 93.1% of deaths occurring between 1974 and 1983. Deaths that occurred outside of the country were more likely to be missed as only 30% were detected.[58]

It is probable that the detection rates are higher for this cohort. This can be attributed to detailed collection of personal identifiers by the provincial cancer registries which facilitates the record linkage process. In addition, most cancer registries follow the vital status of recorded incident cases and even fewer deaths would be missed with this additional information. Other reasons which might yield higher detection rates among this cohort when compared to the occupational cohort include: record linkage over a more recent period (ie. 1982 to 1988) and adults are much more mobile than children and consequently, it is likely that a greater proportion of adults die outside of the country. Finally, Statistics Canada has further developed its' expertise in the record linkage process as it has now performed record linkage on numerous studies in recent years.

4.1.2 Diagnostic methods

Among this cohort, the most common methods of diagnosis were histological (71%), cytological (10%), radiological (7%) and clinical (4.1%). Approximately one percent of cases were diagnosed by means of an autopsy and the diagnosis method was unknown in six percent of the cases. Those patients with a non-positive survival time were excluded. The resulting effect of these excluding these malignancies overestimates the true survival of the cohort. As there were only 72 such cases observed in this cohort (1.5% of all cases), this bias is very small.

The diagnostic procedures used were fairly consistent by region. With the exception of Quebec, Manitoba and New Brunswick, each province diagnosed more than 90% of childhood cancers by histology or cytology. In Quebec and Manitoba, 58% and 72% of childhood malignancies respectively, were diagnosed in this manner. However, unlike the other provinces who report the most confirmed method used to establish a diagnosis, Quebec and Manitoba report the first method of diagnosis. In New Brunswick, a substantially higher proportion, almost 20% of the cases, were diagnosed clinically.

4.1.3 Absence of data of potential interest

Preferably, information on other cancer specific prognostic factors would have been collected by the NCIRS. Some of these factors have already been identified in earlier in this report (Section 1.3). Unfortunately, these factors were not available for this cohort and the potential effects of these factors could not be controlled for. The results given in this report should be interpreted cautiously as they presuppose that the manifestation of these prognostic variables is homogeneous across the age, gender and year of diagnosis strata. These factors are seldom available for analysis in population based data and are only typically studied in smaller study groups.

Information of treatment procedures would be useful in identifying the therapy which would maximize the chances of survival. We would also be able to tease out whether improvements in survival that were observed for some cancers were a result of refined treatment procedures, earlier diagnosis or simply an artefact of the data. It is widely acknowledged that treatment procedures have changed greatly over the last decade.

Finally, at the time this study was undertaken, data was not available from the province of Ontario. Since that time, a linked file was made available which contains information of childhood cancer cases diagnosed in Ontario between 1985 and 1991. Preliminary analyses of this dataset provide estimates of survival that are similar to

those obtained from the cohort used in this study. We are still awaiting clearance from the province to publish these results.

4.1.4 Appropriateness of the proportional hazards model

The proportional hazards model assumes that children diagnosed with the same form of cancer and who are identical with respect to gender, age and year of diagnosis will have the same underlying hazard function. As discussed earlier, there are other prognostic factors that are missing. The use of the proportional hazards model will be more robust where sample size is larger. The use of the proportional hazards model is preferred over lifetables as the effect of several variables can be assessed simultaneously and it also allows for the use of continuous variables.

The other alternative would have been to use an accelerated time failure model. The disadvantage of these models is that assumptions have to be made regarding the distribution of the underlying baseline hazard function.

4.1.5 Multiple testing

Some researchers have voiced concern about how p-values are interpreted when multiple comparisons are made. When many comparisons are made, false positive associations are possible simply by chance. For example, when 1000 comparisons are

performed at a five percent level of significance, one would expect 50 positive associations to arise simply by chance. An approach to handling this problem is to make the test of significance more stringent either by changing the significance level or by inflating the *P*-values by some factors which is dependent on the number of comparisons made. However, this approach has been rejected by Rothman[100] as creating more problems than it might possibly solve and was not used in the present study.

4.2 Interpretation of findings

4.2.1 Comparison to other population based results

The survival of this cohort is similar to results observed in other population based series from Britain, the United States and West Germany (Table 9). The survival rates from the United States are based on SEER data which represents about ten percent of the U.S. population found in 11 population based registries distributed throughout the United States.[89] Published rates for children in Britain include children who lived in England, Scotland, or Wales and who were under age 15 at the time of diagnosis. These children were identified by national cancer registration schemes, from entries into the Medical Research Council leukaemia trials and from the register of patients treated by the United Kingdom Children's Cancer Study Group.[7]

Most Canadian paediatric cancer treatment centres belong to one of two cooperative study groups based in the United States. These two groups, the Paediatric Oncology Group (POG) and the Children's Cancer Study Group (CCSG) represent 90% of all paediatric oncologists in the U.S. As a result of this collaboration, one would expect that the future survival rates of Canadian children would be similar to those of American children.

Survival rates for neuroblastoma are also available from Japan and Finland. The five year survival rates are 57% and 67% for Finnish[74] and Japanese[75] children respectively. The improved prognosis among Japanese children is due to their mass screening program which is aimed at detecting neuroblastoma among infants.

Table 9.
Actuarial survival rates for childhood cancers in Canada, Britain, the United States and West Germany

Cancer	Five year survival			
	Canada‡	United States†	Britain†	W.Germany§
Acute lymphoblastic leukaemia	69	72	70	76
Acute non-lymphocytic leukaemia	31	30	34	38
Hodgkin's disease	90	88	91	93
Non Hodgkin's lymphoma	62	69	71	73
Central Nervous system tumours	65	59	57	49
Retinoblastoma	98	-	-	93
Wilms tumour	88	87	81	84
Bone tumours	59	56	51	-
Osteosarcoma	59	-	-	65
Ewing's sarcoma	58	-	-	44
Rhabdomyosarcoma	59	-	-	50
Malignant germ cell	81	-	-	71
Neuroblastoma	60	55	40	48

‡cancer cases diagnosed between 1982 and 1988;excludes cases reported by the province of Ontario
† cancer cases diagnosed between 1983 and 1988
§cancer cases diagnosed between 1980 and 1982

Source: see reference (7)

4.2.2 Trends in survival

Attempts are continually being made in an effort to reduce the health impact of childhood cancer. These include efforts to improve diagnosis, treat and identify risk factors for the incidence childhood cancer.

Survival among children with cancer improved dramatically with the introduction of radiotherapy as well as chemotherapy. A few decades ago, only 20% of children with cancer were being cured.[103] Since that time, treatments have been refined and new drugs have been evaluated through the results obtained from successive series of clinical trials. The population based survival rates presented in this thesis, reflect some of the progress that has been made from these trials.

Children with cancer are treated by paediatric medical centres which have developed specialized programs of treatment and research on childhood cancers. The Canadian centres participate in trials conducted by the POG and CCSG which have resulted in improved survival for its patients. At the Ste-Justine treatment centre in Montreal, recent improvements in survival have been observed after collaborative efforts with a paediatric centre in Boston.[76]

Survival among children with ALL improved over the study period. For children with ALL, much of the improved survival can be explained by ability to administer more intensive chemotherapy.[65] Ongoing research in bone marrow transplant may have also contributed to some of the increase in survival. Bone marrow transplantation has been shown to improve survival among children in their second or subsequent remission.[101]

The improved survival among children with ANLL is not entirely surprising as many of the best methods of treatment of ANLL are investigational.[65] Treatment of very young children differs from older children. Children over age three tolerate drugs better than adults and the dose of chemotherapy is calculated by body surface area whereas in younger children it is calculated using body weight. Improvements in the diagnosis of ANLL have occurred because of recent knowledge gained in using monoclonal antibodies to determine cell surface antigens of ANLL cells.[23] The prognosis of children with ANLL remains quite poor. POG is currently undertaking a study which is examining autologous bone marrow transplant in the first remission to intensive chemotherapy.[23]

In recent years, many advances towards understanding Non-Hodgkin lymphoma have been made on an immunological, cytologic and molecular level.[23] Recent gains have been made in the survival of children with *T* or *B* cell derived NHL.[13] Improved survival in children diagnosed with NHL was observed among U.S children between

1980 and 1990.[77] Among these children, survival improved from approximately 60% in 1980 to an estimated 75% in 1990. These findings support the results obtained in this study where the survival of those diagnosed with NHL between 1982 and 1988 was found to have improved significantly. Studies are ongoing in an attempt to reduce toxicity from treatment as well as determining optimal drug combinations for those with advanced forms of NHL.

Survival of children with Wilms' tumour has also improved in British and American children diagnosed over the last decade. The effectiveness of various treatments have been studied with clinical trials undertaken by the National Wilms' Study Group (NWSG) in the United States. Currently, the NWSG is conducting a study in order to further refine the chemotherapy for different prognostic groups to reduce the late effects of treatment.[23]

There were several cancers in which no improvements in survival by year of diagnosis were observed. This may be a result of the short period of the study. In addition, for those cancers with a more favourable prognosis, any marginal improvements in survival would be difficult to ascertain given the sample size and absence of other variables of interest.

For some cancers, the focus of new treatment is to reduce the risk of possible late effects. Even though survival rates might not have improved, successful improvements in treatment may have occurred. For example, surgical and treatment advances have permitted a greater proportion of limbs to be salvaged among children with bone tumours.[49] Treatment of children with Hodgkin's disease is now being designed with the goal of reducing long-term morbidity in good-prognosis patients and intensifying treatment in poor prognosis patients.[25]

Poorer survival was observed among infants diagnosed more recently with neuroblastoma. This result should be interpreted cautiously as only six deaths were observed in this age group of children with neuroblastoma. The significance of year of diagnosis may be attributed to not being able to control for other known risk factors. These include histopathology, serum markers, tumour cell ploidy and N-myc oncogene amplification.[23]

The ratio of mortality rates to incidence rates (MIR) can serve as a crude indicator of disease prognosis. The fact that a significant improvement in survival was observed in such a short time window (1982-1988) is encouraging. The MIR as presented in Appendix F support these findings. Between 1982 and 1988, the MIR declined from 0.31 to 0.25.

4.2.3 Variations in survival by gender and age at diagnosis

The findings on the effect of age at diagnosis as a prognostic factor are consistent with previous studies. These cancers include ALL, ANLL, neuroblastoma, Hodgkin disease, astrocytoma, ependymoma and rhabdomyosarcoma. In some cases, age is correlated with another prognostic variable such as staging in Hodgkin's disease.

Gender is not typically a recognized as a predominant prognostic factor for childhood malignancies. The results of these analyses support this. Where gender related differences in survival did exist, females fared better. The result showing a gender related difference for children diagnosed with an ependymoma is surprising. The hazard rate of females was 0.35 times that of males after adjusting for age and period of diagnosis. Positive prognostic factors that have previously been identified include: successful tumour resection, older age, caucasian race and higher radiation dose.[78,79] One study found that females had a poorer prognosis.[80] Unfortunately, our analysis is unable to control for all prognostic variables although the power of the gender effect warrants further investigation.

For children with ALL, survival has been found to be better among females in previous studies when adjusting for other prognostic factors.[13] Perhaps parents may be more likely to bring female child with symptoms of leukaemia (ie. fever, irritability) to a physician at an earlier date a male child.

4.2.4 Geographical variations in survival

In British Columbia, higher survival rates were observed among reported incident cases of Hodgkin's disease, ALL, and astrocytomas. Unfortunately, no information on treatment procedures used on these children was available. It is possible that the more favourable prognosis associated with B.C. children may be due to the early participation of B.C. treatment centres in the CCSG. B.C. treatment centres joined the CCSG in 1969 and are likely to have benefitted from expertise on the diagnosis, staging, treatment and support of the child with cancer, as well as expertise in clinical trials methodology.

The MIR presented in Appendix G support the findings on geographical variations. The MIR was lower for British Columbia children for all cancers combined and leukaemia. The MIR suggests that the prognosis for Ontario children diagnosed with cancer is better than most other regions.

4.2.5 Future trends

In the past decade several advances in biology have occurred. Insights have been gained on recombinant DNA technology, monoclonal antibodies, molecular genetics and cytokines and cellular drug resistance. The application of these findings in the design of future clinical trials may lead to further improvements in survival.

Although efforts have been directed at improving the prognosis of children with ANLL and older children with neuroblastoma the results so far have been disappointing. Overall, most children with cancer are now being cured and many advances will undoubtedly be in minimizing the late effects of treatment and in reducing costs of treatment.

Health Canada is currently developing a database intended to provide a focus for more detailed studies of risk factors, treatment and outcomes. This initiative, the Canadian Childhood Cancer Control Program will also establish a tumour bank in order to provide a resource for researchers studying the molecular biology of childhood cancer.

Improvements in survival of adults with cancer have not been as dramatic as those observed among children. The success of clinical trials in treating paediatric cancer should serve as a lesson in the management of adult cancer. In the U.S., approximately 60% of children with cancer are recruited for clinical trials compared to 3% of adults. Given the prevalence of cancer in the adult population, even subtle improvements in survival will have a dramatic effect.

SUMMARY OF RESULTS AND RECOMMENDATIONS

5.1 Summary of results

The following are the key findings derived from this study:

1. The five year survival rate for childhood malignancies diagnosed between 1982 and 1988 among the assembled cohort of children was 69%.

2. Females had a markedly improved survival rate for acute lymphocytic leukaemia, and ependymomas after adjusting for age and year of diagnosis.

3. Age at diagnosis was a significant prognostic factor for leukaemia, neuroblastoma, rhabdomyosarcoma and fibrosarcoma.

4. When adjusted for differences in age and gender, significant improvements in survival were observed among children diagnosed with leukaemia, non Hodgkin's lymphoma, and fibrosarcoma ($p \leq 0.05$).

5. Children diagnosed with either acute lymphocytic leukaemia or astrocytoma in 1987-88 in British Columbia had a significantly improved prognosis compared to the remainder of the cohort.

5.2 Recommendations

This cohort of children should continue to be followed in order to examine long-term survival rates (ie. > 10 years). The addition of Ontario data would allow for nationally representative survival rates to be calculated. Finally, if feasible, future survival rates should control for information on staging, treatment procedures used as well as other important prognostic factors that vary by type of cancer. The Childhood Cancer Control Program that has been initiated by Health Canada should produce such data. It is probable that more changes in survival have occurred already among children diagnosed after 1988. Survival rates of these children should be calculated and compared against the survival experience of this cohort.

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APPENDIX A

CLASSIFICATION SCHEME FOR CHILDHOOD CANCER

Diagnostic Group	ICD-0 M-code First 4 digits	ICD-0 M-codes 5th digits	ICD-0 T-code
I. Leukaemias			
a) Acute lymphocytic leukaemia	9821,9824	3	
b) Other lymphoid leukaemia	9820,9822,9823,9825,9850	3	
c) Acute non-lymphocytic leukaemia	9840,9841,9861,9864,9866, 9891,9894	3	
d) Chronic myeloid leukaemia	9863	3	
e) Other and unspecified leukaemia	9800-9804,9810,9830,9842, 9860,9862,9865,9870-9890, 9892,9893,9900-9940	3	
II. Lymphomas and other reticuloendothelial neoplasms			
a) Hodgkin's disease	9650-9662	3,6,9	
b) Non-Hodgkin's lymphoma	9591,9062-9642,9590-9701	3,6,9	
	9750	3,6,9	
c) Burkitt's lymphoma	9590,9600,9601	3,6,9	
d) Unspecified lymphomas	9722	3,6,9	
e) Histiocytosis X	(also SNOMED morphology codes 77860,77910,77920)		
	9710-9721,9730-9741	3,6,9	
f) Other reticuloendothelial neoplasms			
III. Central nervous system and miscellaneous intracranial and intraspinal neoplasms			
a) Ependymoma	9383,9390-9394	0,1,3,6,9	
b) Astrocytoma	9380	3,6,9	192.0
	9381,9400-9441	3,6,9	
c) Medulloblastoma	9470-9480	3,6,9	
d) Other glioma	9380	3,6,9	191.0-191.9, 192.1-192.9
	9382,9384,9442-9460,9481	1,3,6,9	
e) Miscellaneous intracranial and intraspinal neoplasms	8270-8281,8300,9350-9362,9505,9530-9539	0,1,3,6,9	
	9060-9102	0,1	191.0-192.9, 194.3,194.4
	800-8004	3,6,9	191.0-192.9, 194.3,194.4
	9990	0,1,3,6,9	191.0-192.9 194.3,194.4

Diagnostic Group	ICD-0 M-code First 4 digits	ICD-0 M-codes 5th digits	ICD-0 T-code
IV. Sympathetic nervous system tumours			
a) Neuroblastoma and ganglio-neuroblastoma	9490,9500	3,6,9	
b) Other	9680,8693-8710,9501-9504,9520-9523	3,6,9	
V. Retinoblastoma	6510-9512	3,6,9	
VI. Renal tumours			
a) Wilms' tumour	8970	3,6,9	
b) Renal carcinoma	8010-8041,8043, 8140,8230,8231, 8260	3,6,9	155.0,155.1
	8160-8180	3,6,9	
c) Other and unspecified malignant renal tumours	8000-8004,9990	3,6,9	155.0,155.1
VII. Hepatic tumours			
a) Hepatoblastoma	8970	3,6,9	
b) Hepatic carcinoma	8010-1041,8043,8104, 8230,8231, 8260	3,6,9	155.0,155.1
	8160-8180	3,6,9	
c) Other and unspecified malignant hepatic tumours	8000-8004,9990	3,6,9	155.0,155.1
VIII. Malignant bone tumours			
a) Osteosarcoma	9180-9190	3,6,9	
b) Chondrosarcoma	9220-9230	3,6,9	170.0-
	9240	3,6,9	170.9,199.9
c) Ewing's sarcoma	9260	3,6,9	
d) Other and unspecified malignant bone tumours	8812,9250,9261-9330, 9370	3,6,9	170.0- 170.9,199.9
	8000-8004,8800,8801, 8803,9990		170.0-170.9

Diagnostic Group	ICD-0 M-code First 4 digits	ICD-0 M-codes 5th digits	ICD-0 T-code
IX. Soft-tissue sarcomas			
a) Rhabdomyosarcoma, embryonal sarcoma and soft-tissue Ewing's tumour	8900-8920,8991	3,6,9	
	9260	3,6,9	140.0-169.9 171.0-195.8
b) Fibrosarcoma, neurofibrosarcoma, and other fibromatous neoplasms	8810,8811,8813-8832,9540, 9560	3,6,9	
c) Other soft-tissue sarcoma	8840-8895,8990,9040-9044, 9120-9170,9251,9581	3,6,9	
	9240	3,6,9	140.0-169.9, 171.0-195.8
	8800-8804	3,6,9	140.0-169.9
X. Germ-cell, trophoblastic and other gonadal neoplasms			
a) Non-gonadal germ-cell and trophoblastic neoplasms	9060-9102	3,6,9	140.0-182.8 183.2-185.9 187.1-199.9
b) Gonadal germ-cell and trophoblastic neoplasms	9060-9102	3,6,9	183.0,186.0, 186.9
c) Gonadal carcinoma	8010-8041,8043,8140, 8230,8231,8260,8310,8440, 8480,8481	3,6,9	183.0,186.0, 186.9
	8381,8441-8471	3,6,9	
	8600-8650,9000	3,6,9	183.0,186.0, 186.9
d) Other and unspecified malignant gonadal tumours	8000-8004,9990		
XII. Other and unspecified malignant neoplasms			
	8930,8950,8951, 8990,8991,9020, 9050-9053,9110, 9580	3,6,9	
	8000-8004,9990	3,6,9	140.0-154.8, 156.0-169.9, 171.0-182.8, 183.2-185.9, 187.1-188.9, 189.1-190.9, 193.9-194.1 194.5-199.9

Source: adapted from reference (14)

APPENDIX B

Information sources used by the provincial agencies that supply information to the NCIRS

Province or territory / Province ou territoire

SOURCE	●	●	●	●	●	●	●	●	●	●	●	●
Cancer agencies / Organismes du cancer	●	⊙	⊙	⊙			●	●	●	●	●	●
Pathology laboratories / Laboratoires de pathologie	●	⊙	⊙	⊙			●	●	●	●	●	
Hematology laboratories / Laboratoires d'hématologie	●	⊙	⊙	⊙			●		●	●		
Death certificates / Certificat de décès	●	⊙	⊙	⊙			●	●	●	●		●
Hospitals / Hôpitaux	●	⊙	⊙	⊙		●		●		●		●
Autopsy / Autopsie	●	⊙	⊙	⊙			●	●	●	●		
Medicare / Assurance-maladie			⊙	⊙								

- British Columbia / Colombie-Britannique
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- Quebec / Québec
- New Brunswick / Nouveau-Brunswick
- Prince Edward Island / Île-du-Prince-Édouard
- Nova Scotia / Nouvelle-Écosse
- Newfoundland / Terre-Neuve
- Northwest Territories / Territoires du Nord-Ouest
- Yukon

Source: see reference 57.

APPENDIX C

The Mantel-Cox (log-rank) test statistic

This is a method for an overall comparison of life tables. This test statistic is calculated from small intervals of analysis (such as single days or period in which one death occurs). The Mantel-Cox test statistics is suitable for analyzing data in more common longer intervals providing that the proportion dying within any interval is small (less than 10%).[81]

Let

O_{xm} number at risk for the period beginning at time x in group m
O_{xn} number at risk for the period beginning at time x in group n

Then the expected number of deaths in group m for the period beginning at time x is:

$$E(d_{xm}) = \frac{O_{xm}}{O_{xm}+O_{xn}}(d_{xm}+d_{xn})$$

Similarly,

$$E(d_{xn}) = \frac{O_{xn}}{O_{xm}+O_{xn}}(d_{xm}+d_{xn})$$

Under the null hypothesis of no group differences, the square of the difference between total observed deaths and total expected deaths divided by the total expected deaths summed for two groups is approximately λ^2 with one degree of freedom.

For groups m and n this can be expressed mathematically as

$$\lambda_1^2 = \frac{[\sum_x d_{xm} - \sum_x E(d_{xm})]^2}{\sum_x E(d_{xm})} + \frac{[\sum_x d_{xn} - E(d_{xn})]^2}{\sum_x d_{xn}}$$

In general, if k life tables are being compared to see if they differ by more than chance we can compute

$$\lambda_k^2 = \sum_{i=1}^{k} \frac{(OBS_i - EXP_i)^2}{EXP_i}$$

where i represents the ith life table OBS_i is the oberved umber of deaths and EXP_i is the expected number of deaths.

APPENDIX D

Description of the covariables used in the proportional hazards model

In our analysis the following variables representing the covariates were entered into the regression equation:

AGE: continuous variable denoting age at diagnosis

INF: indicator variable which was set to one if age at diagnosis occurred prior to age one, zero otherwise

SEX: was coded one for males and two for females

YR: year of diagnosis coded as a continuous real variable between 2 and 9 (1982-1988); note:month of diagnosis was used to gain further precision

APPENDIX E

Frequency distribution of incident cases of cancer†, by age group, childhood cohort, females, 1982-1988

Type of Cancer	Age Group					
	0-<1	1-<5	5-<10	10-<15	15-<20	Total
Leukaemias	31	261	123	85	64	564
Acute lymphocytic leukaemia	12	214	100	50	37	413
Acute non lymphocytic leukaemia	9	18	13	20	20	80
Other leukaemia	10	29	10	15	7	71
Lymphomas	8	15	26	76	182	307
Hodgkin's disease	0	0	7	45	152	204
Non-Hodgkin lymphoma	1	5	13	13	16	48
Central Nervous System	12	85	108	76	182	307
Ependymoma	1	11	7	7	2	28
Astrocytoma	5	36	53	40	36	170
Medulloblastoma	4	13	22	12	5	56
Sympathetic Nervous System	31	50	14	6	5	106
Neuroblastoma and ganglioneuroblastoma	28	47	12	4	1	92
Retinoblastoma	13	27	1	1	0	42
Renal Tumours	25	59	25	7	5	121
Wilms' tumour	23	57	23	5	1	109
Hepatic tumours	4	5	3	1	3	16
Malignant bone tumours	0	3	21	41	42	107
Osteosarcoma	0	0	9	27	24	60
Ewing's sarcoma	0	2	10	10	13	35
Soft tissue sarcomas	7	31	29	32	33	132
Rhabdomyosarcoma	4	25	18	13	11	71
Fibrosarcoma	1	1	4	5	13	24
Gonadal and germ-cell	10	19	16	37	40	122
Non gonadal germ-cell	10	13	7	3	7	40
Germ cell-Ovarian	0	3	7	29	24	63
Carcinoma and epithelial	4	4	14	27	156	205
Other	6	6	2	4	5	23
All cancers	151	565	382	393	588	2079

Frequency distribution of incident cases of cancer†, by age group, childhood cohort, males, 1982-1988

Type of Cancer	Age Group					
	0-<1	1-<5	5-<10	10-<15	15-<20	Total
Leukaemias	32	311	193	102	116	754
Acute lymphocytic leukaemia	15	264	104	69	75	587
Acute non lymphocytic leukaemia	8	28	13	23	23	95
Other leukaemia	9	19	16	10	18	72
Lymphomas	6	50	87	143	198	484
Hodgkin's disease	0	7	36	71	135	249
Non-Hodgkin lymphoma	1	23	30	42	41	137
Central Nervous System	23	121	126	87	97	454
Ependymoma	4	16	9	4	1	34
Astrocytoma	10	34	52	48	57	201
Medulloblastoma	4	33	28	15	13	93
Sympathetic Nervous System	46	70	17	6	4	143
Neuroblastoma and ganglioneuroblastoma	46	68	17	4	3	138
Retinoblastoma	9	29	1	0	1	40
Renal Tumours	18	46	23	4	5	94
Wilms' tumour	15	41	22	4	2	84
Hepatic tumours	9	11	6	2	3	31
Malignant bone tumours	0	6	14	48	52	182
Osteosarcoma	0	1	9	20	40	70
Ewing's sarcoma	0	2	4	27	18	51
Soft tissue sarcomas						
Rhabdomyosarcoma	6	28	24	16	23	97
Fibrosarcoma	2	7	3	13	13	38
Gonadal and germ-cell	17	15	6	18	95	151
Non gonadal germ-cell	2	6	5	12	15	40
Germ cell-Testicular	11	9	0	6	75	101
Carcinoma and epithelial	2	7	19	31	75	134
Other	3	12	2	5	6	28
All cancers	178	717	524	498	719	2636

APPENDIX F

Annual age standardized cancer incidence and mortality rates, Canadians aged 0-19, 1982-1988

Year	Mortality Rate	Incidence Rate	M/I
1982	4.66	15.21	0.31
1983	4.62	15.79	0.29
1984	4.28	16.04	0.27
1985	4.30	15.79	0.27
1986	4.16	16.95	0.25
1987	4.53	16.02	0.28
1988	4.02	16.19	0.25

APPENDIX G

Age standardized cancer incidence† and mortality rates, by region, Canadians aged 0-19, 1982-1988

Region	Type of Cancer								
	All cancers			Hodgkin's disease			Leukaemia		
	Mortality	Incidence	M/I‡	Mortality	Incidence	M/I	Mortality	Incidence	M/I
Canada	4.37	15.98	0.27	0.09	1.61	0.06	1.62	4.13	0.39
Quebec	5.15	16.31	0.32	0.11	1.68	0.07	2.10	4.78	0.44
Ontario	4.16	17.36	0.24	0.07	1.69	0.04	1.41	4.23	0.29
B.C.	3.61	15.72	0.23	0.11	1.86	0.06	1.26	3.80	0.33
Atlantic	3.82	12.21	0.31	0.12	1.42	0.08	1.30	3.07	0.42
Prairies	4.42	15.45	0.29	0.09	1.31	0.07	1.70	3.82	0.45

† rates are per 100,000 persons, standardized to 1981 Canadian census population
‡ ratio of the mortality and incidence rates which provides a crude indication of disease prognosis

Source: Personal communication. Laboratory Centre for Disease Control. Health Canada

APPENDIX II

Results of stepwise regression in measuring the effects of gender, age and year of diagnosis on survival, for selected cancers, childhood cohort, 1982-1988

Type of Cancer	Variables‡	Parameter Estimates	Standard Error	exp(β)	p
Acute lymphocytic leukaemia	age	0.09	0.01	1.09	0.00
	inf	2.24	0.25	9.35	0.00
	diagy	-0.15	0.03	0.86	0.00
	sex	-0.28	0.12	0.75	0.02
Acute non-lymphocytic leukaemia	inf	1.13	0.27	3.08	0.00
Hodgkin's disease	age	0.11	0.05	1.12	0.02
Non Hodgkin's lymphoma	diagy	-0.15	0.07	0.86	0.02
Ependymoma	age	-0.12	0.05	0.88	0.01
	sex	-1.06	0.35	0.42	0.01
Astrocytoma	age	0.04	0.02	1.04	0.03
Medulloblastoma	NS	--	--	--	
Neuroblastoma	inf	-2.23	0.42	0.11	0.00
Wilm's tumour	diagy	-0.19	0.11	0.83	0.07
Osteosarcoma	diagy	-0.11	0.06	0.90	0.08
Ewing's sarcoma	NS	--	--	--	
Rhabdomyosarcoma	age	0.06	0.02	1.06	0.01
Fibrosarcoma	diagy	-0.26	0.14	0.77	0.06
	age	0.09	0.06	1.10	0.04
Non-gonadal germ cell	NS	--	--	--	
Gonadal germ cell					
Ovarian	diagy	-0.54	0.33	0.58	0.05
Testicular	age	0.10	0.08	1.11	0.10

‡a description of the variables is given in Appendix D.