TEMPORAL TRENDS IN HODGKIN'S DISEASE MORTALITY, 1940 - 1990

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A thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfillment of the requirements
for the degree of Master of Science

ABSTRACT

This study describes 9,316 patients with Hodgkin's disease from 13 cancer treatment centers who were diagnosed between 1940 and 1987. Temporal trends in Hodgkin's disease mortality were examined over 50 years. Causes of death were compared with those from the general United States population. During this period 4,394 deaths were observed and 69,350 person-years at risk were accrued. Overall, the relative risk of dying for this cohort was 11.5 (95% Confidence Interval (C.I.) 11.3 - 11.7). Patients who did not die from Hodgkin's disease had a relative risk of 2.9 (95% C.I. 2.8 - 3.1) of dying from other causes. This risk differed when specific causes were considered. The relative risk was 1.6 (95% C.I. 1.5 - 1.7) for ischemic heart disease, 6.3 (95% C.I. 4.9 - 7.9) for infections, 0.7 (95% C.I. 0.6 - 0.9) for external causes and 5.2 (95% C.I. 4.7 - 5.7) for second cancers. Proportional hazards analyses indicated that increasing age, and diagnosis before 1965 were significantly related to the increased risk of death. Age was the strongest predictor: patients aged 60 or older experienced 5.6 time the risk of death when compared to patients under age 15. Patients diagnosed before 1965 experienced twice the risk of death of patients who where diagnosed in 1975 or later. Although not statistically significant, females under age 15 who were diagnosed before 1965 had a higher risk of mortality than males the same age. After age 15 the data suggested a protective effect for females. However, this trend was not consistent across all age groups and periods. The decrease in mortality over time is consistent with the progress that has been made in diagnostic and staging techniques, improved medical management and the use of aggressive multimodal therapy for Hodgkin's disease patients in the last 50 years.

RÉSUMÉ

Cette étude décrit 9 136 patients atteints de la maladie de Hodgkin, recrutés dans 13 centres de traitement du cancer, et diagnostiqués entre 1940 et 1987. L'évolution de la mortalité chez ces patients fut déterminée pour une période d'une cinquantaine d'années. Les causes de décès furent comparées avec celles de la population générale des États-Unis. On observa 4 394 décès, pour un total de 69 350 personnes-années à risque. Globalement, le risque relatif de décès pour cette cohorte était de 11.5 (intervale de confiance à 95% [IC - 95%]: 11.3-11.7). Les patients ne mourant pas de la maladie de Hodgkin présentaient un risque relatif de 2.9 (IC - 95%: 2.8-3.1) de mourir d'autres causes. Le niveau de risque variait selon les causes spécifiques de décès. Le risque relatif était de 1.6 (IC - 95%: 1.5-1.7) pour les maladies cardiaques ischémiques, 6.3 (IC - 95%: 4.9-7.9) pour les infections, 0.7 (IC - 95%: 0.6-0.9) pour les causes externes et 5.2 (IC - 95%: 4.7-5.7) pour les deuxièmes cancers. Des analyses de densités proportionnelles montrèrent qu'un âge plus avancé et un diagnostic avant 1965 augmentaient significativement le risque de décès. L'âge était le prédicteur le plus puissant; les patients de 60 ans ou plus démontraient un risque 5.6 fois plus élevé que les patients de moins de 15 ans. Les patients diagnostiqués avant 1965 subissaient un risque de décès deux fois plus élevé que ceux diagnostiqués en 1975 ou après. De façon non statistiquement significative, les filles de moins de 15 ans diagnostiquées avant 1965 présentaient un risque de mortalité plus élevé que les garçons du même âge. Après l'âge de 15 ans, les données suggéraient un effet protecteur pour les femmes. Cependant, cette tendance n'était pas uniforme pour tous les groupes d'âges et d'années de diagnostic. La diminution générale de la mortalité au cours des 50 dernières années correspond aux progrès accomplis au niveau des techniques de diagnostic et de détermination du stade de la maladie de Hodgkin, du traitement, et de l'utilisation d'interventions énergiques faisant appel à plusieurs modalités thérapeutiques.

ACKNOWLEDGEMENTS

The successful completion of this thesis has been possible through the generous assistance and encouragement of a number of individuals.

I would like to thank my thesis supervisor, Dr. J.F. Boivin, who suggested the topic for this thesis. I am grateful for his constant support and advice from the beginning until the completion and for his assistance in the French translation of the abstract.

In addition, I would like to thank the members of my thesis committee, Dr. K. Gray-Donald and Dr. J.I. Williams, for their time, critical advice, and valuable suggestions.

I also wish to Marielle Olivier for her help with the data processing, Carey Levinton for assistance provided during the analysis of the data, and Larry Stevenson for his advice and assistance in preparing tables.

Finally, I would like to thank my family for their love and support.

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CHAPTER ONE

INTRODUCTION AND RATIONALE FOR THIS STUDY

1.1 INTRODUCTION

During the last 30 to 40 years, there have been substantial improvements in survival for patients with Hodgkin's disease (Rubin et al., 1985; Henry-Amar and Somers, 1990; Hoppe RT, 1990). These improvements reflect the use of more accurate staging, the identification of prognostic factors to assist in treatment selection, the refinement of radiation therapy techniques, the development of effective combinations of drugs and follow-up of patients in order to identify complications of therapy. More accurate staging not only has advanced our knowledge of the natural history of the disease but allowed clinicians to adjust treatments to meet the needs of individual patients (Hoppe RT, 1990). The use of modern therapies, such as combination chemotherapy and high-dose radiotherapy have led to high survival rates, particularly for early stages of the disease. There is now evidence that a patient with early stage disease can be cured with a probability as high as 90%; and a patient with advanced stage, with a probability of approximately 70% (Henry-Amar and Somers, 1990). It is difficult, however, to estimate the proportion of the improvement due to earlier diagnosis of the disease, better supportive medical care and improved cancer treatment.

This study examines trends in mortality rates and survival among patients diagnosed with Hodgkin's disease. Three time factors are examined: 1) **age effects**, changes in rates of mortality attributable to age at time of diagnosis of Hodgkin's disease; 2) **period effects**,

changes associated with the time period in which Hodgkin's disease was diagnosed and treated; and 3) **cohort trends**, changes associated with period of birth.

While there have been several studies to examine temporal trends in cancer mortality, no study has specifically examined the effects of age, period and cohort on Hodgkin's disease mortality. Roush et al. (1987) recently used an age-period-cohort model to analyze time trends in Hodgkin's disease incidence. Data from the Connecticut Tumor Registry was used and included patients diagnosed between 1940 and 1979 and was restricted to patients under 65 years of age. Although this was a very comprehensive study of temporal trends in Hodgkin's disease incidence, trends in mortality were not reported.

Several studies have reported on complications after treatment for Hodgkin's disease or examined treatment results and prognostic factors (Boivin et al., 1984; Boivin and Hutchison, 1984; Boivin, 1990; Boivin and Hutchinson, 1992; Tubiana et al., 1984; van Rijswijk et al., 1987; Tucker et al., 1988; Rubin et al., 1985; van der Velden et al., 1988; Loeffler et al., 1988; Axtell et al., 1972; Coltman et al., 1982; Pedersen-Bjergaard et al., 1987; Henry-Amar, 1983; Krikorian et al., 1979). These studies have been done at different centers with differing patient populations and treatment methods making them difficult to evaluate. Furthermore, many of these studies have been characterized by small sample sizes that limit efforts to compare estimates across studies.

The most comprehensive analysis of survival of Hodgkin's disease to date is that by Henry-Amar and his colleagues (1990) which includes the period 1963 to 1990. At an international workshop on Treatment Strategy in Hodgkin's disease held in Paris, France in 1989, sponsored by the European Organization for Research and Treatment of Cancer, a

database of more than 14,000 cases of Hodgkin's disease was established. The objective of this joint analysis was to assess the relevance of parameters commonly used in the management of Hodgkin's disease patients with respect to treatment response and prognosis. The study population includes 14,225 patients from 15 treatment centers across Europe and North America, treated from 1963 to 1987, for whom age, sex, initial clinical stage and survival data were available. In addition, cause of death in 5 broad categories was reported (related to Hodgkin's disease, treatment related without evidence of Hodgkin's disease, second malignancy, intercurrent, or cause unspecified). 9,041 patients (63.6%) presented with Stage I - II disease and 5,184 (36.4%) with Stage III - IV disease. 7.7% were treated in the 1960s, 56.6% in the 1970s and 35.7% in the 1980s. Only patients 15 years of age and older were included. Henry-Amar and Somers (1990) report an overall 10 year survival rate of 68% and 15 year survival rate of 60%. Deaths were more frequently observed in males than in females and the risk of mortality increased with increasing age. Their study revealed better overall long-term survival in patients initially treated in the seventies and eighties compared with those in the sixties for all stages of the disease. While this patient population is somewhat heterogenous the authors consider their series to be representative of what generally happened in various cancer centers throughout the western world.

1.2 OBJECTIVES OF THIS THESIS

This study was the first to consider temporal trends in Hodgkin's disease mortality over a 50 year period. The main objective of this study was to evaluate the effects of age, birth cohort and calendar period on the overall risk of mortality. In addition, changes in patterns of

mortality and improvements in survival over time for various Hodgkin's disease patients were examined. A secondary objective of this study was to describe the causes of mortality and to evaluate the risk of specific causes of death in this study population.

Both internal and external comparisons were made. In the case of external comparisons, the reference population was the general United States population. Internal comparisons were made, the reference population being a subset of the study population. The two variables, 'calendar year' and 'age' are by definition time-dependent. The method of analysis using external comparisons took this type of dependence into account, allowing calendar year and age to change over the duration of the follow-up. In the internal analyses, it is also theoretically possible to take into account this time dependence. For the sake of simplicity and ease of data manipulation however, the variables were defined as 'calendar year of diagnosis' and 'age at diagnosis of Hodgkin's disease'.

The following chapter will provide an overview on the epidemiology of Hodgkin's disease. Changes in treatment methods, diagnostic techniques, staging procedures and prognosis over time will also be discussed. Overall survival will be considered as a measure of the efficacy of all these measures.

Age, period and cohort analysis will be discussed in chapter three. Traditional approaches to these data are reviewed with emphasis on using the trends observed in these methods as a starting point for the derivation of the models. Various approaches to the statistical modelling of these effects are discussed and the identification problems are described.

The sources of the data, the variables and the methods used to ascertain which factors are predictors of increased risk of mortality are described in chapter four. Based on the general

United States population rates, age-specific rates were calculated for ten 5-year calendar period and eighteen quinquennia of age. This permitted external comparisons to be made between the study population and the general United States population. Cox's regression model was used to make internal comparisons.

The data analyses and results are presented in chapter five and the last chapter reviews the results and compares them with those of the European Organization for Research and Treatment of Cancer study. Possible explanations for differences and limitations of this study are discussed.

CHAPTER TWO

HODGKIN'S DISEASE

2.1 INTRODUCTION

Hodgkin's disease is a relatively rare condition accounting for less than 1% of all neoplasms and about 0.3% of all cancer deaths among men and women in the United States and Canada. Of 101,000 new cases of cancer reported in Canada in 1989, 768 (0.76%) of the patients were diagnosed with Hodgkin's disease. The estimated number of deaths from cancer was 52,500 of which 167 (0.32%) were due to Hodgkin's disease (Canadian Cancer Statistics, 1989). These percentages correspond closely to those reported in the United States (Hellman et al., 1989).

Hodgkin's disease is one of a group of lymphoid cancers referred to as lymphomas. The disease was named after Thomas Hodgkin who first described it in 1832. While it has been almost 160 years since it was first described, little was actually known about Hodgkin's disease until the last 35 years. Initially, all lymphomas were classified as Hodgkin's disease until Reed and Sternberg described the multinucleated (Reed-Sternberg) giant cell in some lymphomas in 1898. They are credited with the first definitive descriptions of these cells, as well as other histopathologic features that define Hodgkin's disease as a distinct entity (Kaplan, 1980). Since their discovery, lymphomas that demonstrate the Reed-Sternberg cell have been classified as Hodgkin's disease. This distinction became important as the clinical course, prognosis and treatment are substantially different, although there are numerous superficial similarities.

The cause or causes of Hodgkin's disease remain unknown. Two opposing views of the etiology of Hodgkin's disease have emerged. One hypothesis is that this disease is the result of two etiologic processes. The great variability in the clinical course, in the constitutional symptoms and the histopathology has resulted in Hodgkin's disease being classified at various times as an infectious disease or as a malignant neoplasm (MacMahon 1957; Grufferman and Delzell, 1984; Greenwald et al., 1975). Proponents of the opposing view hold that Hodgkin's disease is a single neoplasm that develops into other forms of malignant lymphoma (Greenwald et al., 1975; Kaplan, 1980).

2.2 ETIOLOGY

The incidence of Hodgkin's disease varies by age, sex and race. In addition, immunologic, infectious, environmental and genetic factors have all been implicated (Fogel et al., 1985).

2.2.1 Gender

While the incidence of Hodgkin's disease is higher for males than for females in all age groups, the sex ratio varies with age. The M/F incidence ratio is highest in the 5-14 age group and lowest in the 15-19 age group (MacMahon, 1966; Grufferman and Delzell, 1984; Gutensohn, 1982). Variation in sex ratio among age groups is greater for mortality than morbidity rates and this indicates that females have a lower incidence and a better prognosis than men. The proposal of an infectious etiology is consistent with the observation that males are far more susceptible to infectious diseases in childhood (Grufferman and Delzell, 1984).

2.2.2 Age

There are bimodal peaks of incidence of Hodgkin's disease related to age in economically developed countries. One peak appears in early adult life (15-34) with the second peak found after the mid-forties. While the early peak in Hodgkin's disease is not understood, Hellman et al. (1989) relate it to the nodular sclerosing type of Hodgkin's disease, the tissue type that is observed commonly in young persons. Cole et al. (1968) believe that the dual peaks in the incidence of Hodgkin's disease support MacMahon's hypothesis that this disease is the result of two etiologic processes: a biologic agent of low infectivity that causes the disease in young adults, and a malignant process similar to that of other lymphomas in the older age group.

2.2.3 Genetic factors

Familial links have been reported in Hodgkin's disease. The risk of Hodgkin's disease in first degree relatives of patients is reported to be up to three times higher than that in the general population (Grufferman and Delzell, 1984; Fogel et al., 1985). While these reports raise the question of genetic susceptibility, other authors give more weight to the influence of common exposure to environmental factors or infectious agents. They base their opinion on the fact that the multiple cases of Hodgkin's disease within a family occur relatively close together in time of onset (Kaplan, 1980).

Racial differences have been reported in the incidence of Hodgkin's disease as well. Blacks and Orientals have lower incidence rates than whites. Although the incidence is lower, blacks have a uniformly poorer prognosis than whites. Japan has lower incidence rates than other developed countries, and there is no young adult peak in incidence (Grufferman and

Delzell, 1984). MacMahon (1957) has observed that Jews appear to be at higher risk for older adult disease than either Catholics or Protestants.

Clearly it is difficult to separate genetic factors from environmental conditions in the study of this disease. It would be of interest to know how much of the racial difference is due to genetic factors and how much to environmental and lifestyle factors.

2.2.4 Possible infectious etiology

The hypothesis of infectious etiology is related to the clinical course of the disease as many Hodgkin's disease patients have unexplained persistent fever, night sweats and weight loss, symptoms associated with infection. There are indications of a possible relationship between the Epstein-Barr virus and nodular sclerosing Hodgkin's disease. Mononucleosis which is due to the Epstein-Barr virus is a predictor of Hodgkin's disease (Grufferman and Delzell, 1984; Cole et al., 1968; Coleman et al., 1977). The relationship is further supported by the consistent finding that Hodgkin's disease cases have higher levels of antibody to Epstein-Barr than controls. Preliminary data suggest that the occurrence of Epstein-Barr infection precedes the development of Hodgkin's disease, although definitive confirmation must await the results of a larger longitudinal study (Roush, 1987).

There have been reports of a strong association between antibodies in Hodgkin's disease patients and a herpes-like DNA virus that was first observed in conjunction with B-cell lymphomas in patients with acquired immune deficiency syndrome (Hellman, 1989). However, all attempts to implicate such a virus in the etiology of Hodgkin's disease have failed so far (Urba and Longo, 1992).

The hypothesis of the infectious process has received further support from the findings of a case-control study that reported the odds of developing Hodgkin's disease in patients under 40 years of age were 2.9 times greater if the individual had a prior tonsillectomy (Vianna et al., 1971; Gutensohn, 1982). It has been hypothesized that tonsils act as a protective barrier against agents responsible for Hodgkin's disease.

The finding is consistent with certain well-established anatomical and epidemiological characteristics of the disease. The most common site of early detection of Hodgkin's disease is in the region of the lymph nodes that drain the pharyngeal tonsils. However, patterns of tonsillectomies have changed in recent years with fewer being performed on very young children. If the hypothesis is true, the age-specific rates for persons under 40 should decline as the frequency of tonsillectomies has declined.

2.2.5 Environmental factors

There are considerable international variations in disease incidence and patterns (Cole et al., 1968; MacMahon, 1966). Hodgkin's disease is more commonly diagnosed in industrialized countries. It is possible that the reported higher incidence is due to superior health services, improved diagnostic techniques or possibly better reporting of cases. Correa et al. (1971) recognized that in economically underdeveloped countries such as Peru, Portugal and Iran, the overall incidence of Hodgkin's disease is lower than in developed countries but incidence before the age of 15 is higher, with only a modest increase throughout adolescence and young adulthood. Roush (1987) suggested that this may bear an etiologic relationship to some event surrounding conception or birth, genetic or environmental.

The link between socioeconomic status and Hodgkin's disease has been reported in several studies (Grufferman and Delzell, 1984; DeLong et al., 1984; Henderson, 1979). Hodgkin's disease patients appear to be in higher socioeconomic classes and have a relatively higher IQ than controls without Hodgkin's disease. Young adults with Hodgkin's disease are more likely to live in developed rather that undeveloped countries, come from smaller families and live in single family homes than controls. Fathers of cases are more likely to be professionals than those of controls (Grufferman and Delzell, 1984).

It has been suggested that the more frequent occurrence of the nodular sclerosing form of Hodgkin's disease in young adults from higher social classes may reflect a combination of non-infectious and infectious elements (Henderson, 1979; Cole et al., 1968). These characteristics are consistent with a disease caused by virus that is widely disseminated under conditions of poor hygiene and which, in the case of early infection, rarely leads to a severe illness. In areas with poor sanitation and underdeveloped countries children are more likely to be exposed to a virus at a very early age and able to develop immunity before adolescence. The theory is that delayed age at infection results in an increased risk of young adult disease and that high socioeconomic status diminishes the risk of childhood disease and thereby increases the risk of young adult Hodgkin's disease (Grufferman and Delzell, 1984; Hellman et al., 1989).

The clustering of cases of Hodgkin's disease has been reported in a number of studies (Vianna et al., 1971; Fogel et al., 1985; Hellman et al., 1989). Whether such clustering of Hodgkin's disease occurs in time and space in a manner consistent with a transmissible agent or whether it is a matter of chance variation has been discussed by a number of investigators. Population-based studies using cancer registries in Connecticut and California have made a rather

convincing argument that the reported clusters have occurred by chance alone (Hellman et al., 1989; Fogel et al., 1985).

Other unexplained factors are associated with the increased risk of acquiring Hodgkin's disease, including increased risk among woodworkers, chemists, rubber workers, printing workers and veterinarians (Grufferman and Delzell, 1984). Detailed information on work exposures in investigations of occupational factors in Hodgkin's disease is severely lacking due to the rarity of the disease.

2.3 DIAGNOSIS AND HISTOPATHOLOGICAL CLASSIFICATION

The single most useful diagnostic test for Hodgkin's disease is a lymph node biopsy. Although the Reed-Sternberg cell is essential to the diagnosis of Hodgkin's disease, it is not absolute proof of Hodgkin's disease because on rare occasions it can be observed in other conditions such as infectious mononucleosis or in lymph nodes receiving drainage from some types of infections, etc. (Hellman et al., 1989). It is the total histologic picture that characterizes Hodgkin's disease.

Pathologists began more than 60 years ago to delineate histopathologic subcategories of Hodgkin's disease that differed not only in morphology but also in prognosis. A major advance occurred in 1966 when Lukes and his colleagues proposed a new histologic classification for Hodgkin's disease that appeared to correlate well with clinical stage and aggressiveness of the disease. Later in the same year (1966), at the Rye Conference, an international meeting addressing problems and management of Hodgkin's disease, the scheme was simplified into the Rye Classification (Table 1). In this classification, Hodgkin's disease is divided into four

categories: 1) **lymphocyte-predominant**, the most favorable prognosis; 2) **mixed cellularity**, which at one time had a less favorable prognosis but more recently, as a consequence of modern therapeutic advances, has improved dramatically; 3) **lymphocyte-depleted**, associated with a poor prognosis and a distinctive clinical picture characterized by a rapidly progressive course; and 4) **nodular sclerosis**, which usually has a good prognosis, particularly in those patients with localized disease (Hellman et al., 1989; Kaplan, 1980).

Nodular sclerosis is the only form of Hodgkin's disease that is more common in women than in men. It occurs most frequently in adolescents and young adults and is unusual in patients over 50 years of age (Hellman et al., 1989).

2.4 CLINICAL STAGING

Once the diagnosis of Hodgkin's disease has been established on the basis of lymph node biopsy and the histologic type, the next step is to determine the extent of disease. Staging is important in that it aids the clinician in determining the aggressiveness of the disease and indicates the extent of treatment required. Hodgkin's disease almost always develops in a lymph node, progresses to immediately adjacent lymph nodes and subsequently to the nonlymphatic tissues (Hellman et al., 1989).

In the 1950s Peters and her group developed the first useful staging system for Hodgkin's disease. They classified patients into three stages. Stage I includes patients with a single site of involvement. Stage II comprised of patients with two or more contiguous sites of involvement, but limited to one side of the diaphragm and Stage III includes those with disease or tumor that involved visceral organs (Hellman et al., 1989).

Whereas clinical staging was predominant prior to 1964, staging procedures continued to evolve. In the early 1960s, Kaplan and his associates began to perform exploratory laparotomies and splenectomies on patients with diagnostically perplexing findings, such as splenomegaly with a normal lymphangiogram, or abnormal liver function tests without other signs of intra-abdominal involvement, or a lymphangiogram that was suspicious but not diagnostic of involvement (Kaplan, 1980). Important information on the natural history of Hodgkin's disease was gained from this procedure. It became evident that Hodgkin's disease was not a focal disease as hidden disease was present below the diaphragm in at least 25% of all patients. Kaplan's group reported that modifications in treatment were made as frequently as 35% of the time as a result of findings of this procedure. From 1969 until the early 1980s, staging laparotomies and splenectomies were regarded as an essential component of the routine evaluation of all previously untreated patients with Hodgkin's disease at most treatment centers (Hellman et al., 1989; Aisenberg, 1979).

By 1969, there were reports of improved prognosis with combination drug treatments for patients with advanced Hodgkin's disease. The importance of these advances led to another international meeting in Ann Arbour, Michigan in 1971. As a result of this conference, clinical staging was further modified (Table 2).

The Ann Arbour staging is based on the observation of disease that spreads contiguously from lymph nodes to adjacent organs does not adversely affect survival. Stages I, II and III, followed by the subscript **E**, denote direct extension of disease into the lymph nodes. Involvement of the spleen is signified by the subscript **S**. Stage IV signifies spread to extranodal areas. Patients with Stage III or IV have a poorer prognosis than those with limited disease

(Stage I or II). On the basis of history and physical findings, the Hodgkin's disease patient will be substaged as **A** or **B**, depending on the presence or absence of fever, night sweats, or weight loss greater than 10 percent of body weight (Hellman et al., 1989).

This staging system is, therefore, an anatomical one that describes the sites of tumor in relation to the diaphragm. It has been the basis for treatment decisions in Hodgkin's disease for more than 20 years (Urba and Longo, 1992).

Following the Ann Arbour recommendations, staging laparotomies were more frequently performed in the 1970s. However, more recently laparotomies have become less popular. Presumably, this is due to more extensive use of combination chemotherapy and the improvements in other diagnostic tests. Urba and Longo (1992) report that a laparotomy is now performed only if radiotherapy is the desired treatment and if the detection of intraabdominal disease would alter the choice of therapy. Improvements in the clinical staging of Hodgkin's disease have contributed to an improved outcome of treatment as the assessment of the extent of disease permits selection of the most effective therapy.

2.5 TREATMENTS FOR HODGKIN'S DISEASE

2.5.1 Introduction

In Hodgkin's disease, the stage of disease at diagnosis is the most important guide to prognosis and treatment. Clinical staging according to the Ann Arbour system and histological classification according to the Rye Conference criteria has allowed clinicians to tailor treatments to meet the needs of the individual patients. Although staging laparotomies are not performed as frequently now as they were in the 1970s, they have played an important role in further advancing our understanding of the disease, particularly in the case of splenic lymphomas (Aisenberg, 1979; Hellman et al., 1989). The remarkable improvement in survival for Hodgkin's disease patients can be attributed to these improved measures of extent of disease, coupled with increasingly refined methods of radiation therapy and the effectiveness of treatment with drug combinations.

2.5.2 Radiotherapy

While radiation therapy as treatment for Hodgkin's disease was reported as early as 1902, therapy was limited by the equipment available. The machines at that time delivered the maximum dose of radiation to the surface of the skin rather than below the skin. This caused extensive skin burns and reactions and thereby limited their usefulness. Nonetheless, interest in radiation treatment continued, although standard treatment was with localized irradiation, usually with palliative intent.

The Swiss radiotherapist, Gilbert, was the first to suspect that Hodgkin's disease spread contiguously and it was he who is credited for laying the foundation for the principles of modern radiation therapy. Despite the availability of only orthovoltage radiation, Gilbert recognized the importance of treating involved disease with the maximum dose possible if cure was the goal of treatment. He was also one of the first to suspect that prophylactic treatment of clinically uninvolved lymph nodes adjacent to the involved sites resulted in a possible cure of patients with early stages of Hodgkin's (Hellman, 1989).

Peters of Princess Margaret Hospital in Toronto followed his technique. In an analysis of survival of 113 patients treated from 1924 to 1942, she reported a five-year survival of 51% and a ten-year survival of 25% for all stages of disease. More impressively, the five-year survival for Stage I was 88% and 72% in Stage II (Kaplan, 1980).

Megavoltage radiotherapy (4-8 MeV) devices were developed in the 1950s. In contrast to orthovoltage x-rays (usually 250 kV), megavoltage x-rays have a 'skin sparing quality' which means the maximum dose is delivered **at least 1 cm** into the skin, thereby eliminating the severe skin reactions. The linear accelerator, which produces megavoltage photons, is considered to be the machine best suited to treat Hodgkin's disease because of the ability to treat extended distances that include multiple lymph node regions (Hoppe, 1980).

In 1955, Stanford University Hospital was the first medical centre to install the linear electron accelerator and to treat Hodgkin's disease patients with the megavoltage x-ray beam. Radiotherapists began exploring tissue tolerance and tumor response over a gradually increasing dose which ranged from about 2500 to over 4000 rads, delivered at the rate of 800-1000 rads per week to patients with Stage I or II disease. Encouraged by the results obtained in the first

patients, they extended megavoltage radiotherapy with curative intent to Stage III patients (Kaplan, 1980).

It was Kaplan and his group at Stanford who first studied the possibly curative role of radiation therapy in the treatment of Stage I and II Hodgkin's disease with a randomized controlled clinical trial. From 1962-1967, patients with Stage I or II disease were randomly assigned to treatment with high dose (4400 rads) involved field irradiation (n=45) or high dose extended field irradiation (n=51). Extended fields included the contiguous uninvolved lymph node regions. The results of this trial suggested a benefit in freedom from relapse in the group who received extended field but the results were not statistically significant. Long term survival was similar in the two groups (57% and 53.5% respectively at 20 years). Hoppe et al. (1985) believe that the failure to show a difference is probably related to the fact that patients were staged with clinical studies alone and that it is likely that many had occult disease in subdiaphragmatic sites. It is also possible that the sample size was insufficient, resulting in a Type II error.

Though patients were not stratified by systemic symptoms before randomization, it was observed that patients with systemic symptoms who received involved field radiation did poorly (Rosenberg and Kaplan, 1984). Similar findings were reported by other groups (Haybittle et al., 1985; Hoppe et al., 1985).

A second study tested the curative potential of radiation therapy in Stage III Hodgkin's disease. The standard treatment for Stage III at that time was with palliative radiotherapy, usually low dose involved field radiation. Patients were randomized to receive 1650 rads to the involved field (n=14) or treatment to all of the major lymph node regions above and below the

diaphragm with doses of 4400 rad to involved sites and 3500-4400 rad to uninvolved sites (n=36). This usually required sequential treatment to three regions, including the mantle (encompassing the supradiaphragmatic lymph nodes), the para-aortic lymph nodes and spleen and finally a pelvic field which included both the pelvis and inguinal-femoral lymph nodes.

After three years into the trial it was recognized that the higher dose to all the major lymph node regions was well tolerated and considered safe whereas patients in the lower dose arm were experiencing a high relapse rate (n=12). Although many of these Stage III patients presented with systemic symptoms, the 20-year freedom from relapse after treatment with high doses exceeded 40% as opposed to 14% for those patients who received low doses. This treatment program was the first to demonstrate the curative potential of irradiation for patients with advanced stage Hodgkin's disease (Rosenberg and Kaplan, 1985; Hoppe et al., 1985).

In subsequent years, the techniques of megavoltage radiotherapy were further refined to minimize or eliminate complications such as radiation pericarditis and radiation pneumonitis, which were reported for patients who received mantle therapy. These advances have dramatically altered the prognosis of Hodgkin's disease and have made intensive megavoltage radiotherapy the treatment of choice for all patients with Stage I, II and III-A disease (Hoppe et al., 1985).

2.5.3 Chemotherapy

Iron, cod liver oil, arsenic and vitamins were among the compounds used to treat Hodgkin's disease prior to World War II. Modern drug management of advanced Hodgkin's

disease began following the war after reports of response in patients with advanced disease who were treated with nitrogen mustard (Coltman, 1980).

The period between 1942 and 1963 saw the introduction of a number of new drugs---the alkylating agents, corticosteroids, the folic acid analogs, the vinca alkaloids, and procarbazine, a drug almost specific for Hodgkin's disease (Hellman, 1989). During this time, drugs were used singly or sequentially in the treatment of patients with relatively advanced or recurrent Hodgkin's disease. Each new class of drug demonstrated the capacity to induce partial or complete remission that could be maintained for variable periods of time. However, relapses usually occurred and therapy would be changed to another class of drug where the same cycle of response and eventual relapse were repeated again (Kaplan, 1980; Hellman et al., 1989).

A more aggressive approach involving the use of multiple agents in combination followed. Lacher and Durant were the first to publish data on studies done of combination chemotherapy for the treatment of Hodgkin's disease in 1962 and 1963. Sixteen patients, most of whom had received prior chemotherapy and radiotherapy, were treated with vinblastine plus chlorambucil. A 63% complete response rate was achieved with the average duration of response being 7 1/2 months. The complete response rate and the duration of response were significantly better (clinically) than any previously reported results on the use of single agents for the treatment of advanced Hodgkin's disease (Coltman, 1980).

DeVita and his associates at the National Cancer Institute of the United States were the first to use four agents and combined cyclophosphamide, vincristine, methotrexate and prednisone, in a single cycle in the management of advanced Hodgkin's disease. The results from this pilot study were very encouraging: an 80 percent complete response was achieved in

14 consecutive patients, 12 of them previously untreated. This study led to the development of the four-drug combination **MOPP** (nitrogen mustard, vincristine, procarbazine and prednisone), that was used between 1964 and 1967 at the National Cancer Institute. Each of the agents in this regimen was selected based on its antitumor activity when used as a single agent, and the drugs were given in full dose and according to their optimal schedule with the exception that rest intervals were introduced between cycles to allow marrow to recover. Drugs were also selected to minimize overlapping toxicity to any single organ (Hellman et al., 1989; Coltman, 1980; Kaplan, 1980).

The use of MOPP in 43 consecutive, previously untreated patients with advanced Hodgkin's disease produced an 81 percent complete remission rate which was a four-fold increase over results achieved with the best single agents. This study is considered to be the benchmark against which others have measured their own MOPP experience. These early results of MOPP have been confirmed by others and durable remissions have been maintained in the National Cancer Institute study over the past 20 years (Hellman et al., 1989).

Since then a variety of combinations of drugs, active in Hodgkin's disease, have been studied for the remission induction of advanced disease. The trials have taken three different directions: 1) the development of modifications of MOPP, aimed at retaining efficacy while reducing toxicity; 2) the development of new combinations composed of drugs with different mechanisms of action and known to be non-cross-resistant to the drugs in the MOPP program; and 3) the use of these non-cross-resistant drug combinations in alternating cycles with MOPP or MOPP modifications to avoid early treatment failures and circumvent the development of drug resistance (Hellman et al., 1989). Three of these combinations emerged with side effects

equivalent to MOPP, but because the side-effects were different, they were useful in certain circumstances. One of the best known of these regimens is ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) developed by Bonadonna and his colleagues (1975).

While none of the combinations have proven to be statistically superior to MOPP in terms of response rate, duration, or survival, the studies with MOPP or equivalent regimens have shown that more intensive induction therapy improves disease-free survival. Once a remission has been achieved, however, additional chemotherapy is of no value. Certain prognostic factors can be identified for initial response and for response duration. Factors associated with poor response to chemotherapy include age greater than 40 years, the presence of systemic symptoms, and involvement of more than one extranodal site (Coltman, 1980).

MOPP continues to be the most commonly used regimen. The MOPP program achieves a complete remission rate in up to 80% of previously untreated patients with advanced disease (Stage III or IV) and the remission rates are higher and last longer for asymptomatic patients (Stage IIIA). The regimen has a similar benefit for patients who have relapsed following radiotherapy as for newly-diagnosed patients. Retreatment with MOPP has been reported to achieve long-lasting second remissions in patients whose first MOPP-induced remission exceeded 12 months (Canellos, 1975).

2.5.4 Combined Modality Therapy

The success of the combined drug regimens led to further investigations involving both the use of combination chemotherapy and total lymphoid irradiation in patients with advanced

Hodgkin's disease and limited field low dose irradiation plus adjuvant combination chemotherapy in patients with localized disease (Kaplan, 1980).

The first randomized clinical trials in which irradiation alone, usually total lymphoid irradiation, was compared with total lymphoid irradiation followed by multiple cycles of MOPP combination chemotherapy were initiated at Stanford in 1968. Patients with stages IB, IIB, IIIA and IIIB were included in these trials. The addition of adjuvant chemotherapy after total lymphoid irradiation provided a better freedom from relapse than treatment with total lymphoid irradiation alone. Despite the superior freedom from relapse in the combined modality group, however, there was very little difference in survival, 59% versus 66% after 15 years. Effective salvage therapy with MOPP after failure of initial irradiation explains the lack of a significant survival benefit (Kaplan, 1980; Hoppe et al., 1980; Rosenberg and Kaplan, 1985).

The National Cancer Institute of the United States initiated a study in 1969 in which the opposite sequence was administered. The hypothesis was that early use of chemotherapy would rapidly alleviate systemic symptoms, reduce the volume of tumor masses thereby permitting a reduction of radiation fields and treatment of disseminated disease at a time when its extent was minimal. An important side effect of combination chemotherapy is bone marrow suppression and when combined modality treatment was administered in this sequence, the haematologic tolerance for radiotherapy was very poor (Kaplan, 1980).

In 1974, the Stanford group initiated a new series of clinical trials. For patients with early stage I-IIA disease, a study was designed to compare total lymphoid irradiation with a programme of involved field radiation followed by adjuvant MOPP chemotherapy. The 10-year survival and freedom from relapse was almost identical for each group. Survival was 84% in

both groups and freedom from relapse was 76% and 77%. For patients with stage III and IV disease, the investigators used combined modality therapy but experimented with the sequence of treatment as well different combinations of chemotherapy. The main question being addressed in these trials was whether MOPP could be replaced by a less toxic but equally efficacious combination of drugs. One of the combinations used was PAVe (procarbazine, alkeran and vinblastine). The 10-year survival and freedom from relapse were nearly identical but less toxicity was observed with PAVe (Hoppe et al., 1985; Rosenberg and Kaplan, 1985).

Modifications of technique in combined modality therapy have been explored by other groups who have reported similar findings. By the end of the 1970s, further improvements in freedom from relapse and survival were reported for all stages of Hodgkin's disease, particularly among those patients with advanced disease.

2.5.5 Bone Marrow Transplantation

Patients with relapsed or persistent disease after receiving second-line or salvage therapy are very difficult to treat. Allogenic bone marrow transplantation has been used for relapsed patients with Hodgkin's disease but results have been poor. More recently there has been interest in treating patients with advanced disease with high-dose chemotherapy, with or without radiotherapy, in order to reduce the bulk of the tumor and achieve local control of disease prior to autologous marrow transplant. These techniques are currently being studied in Toronto and other cancer treatment centers (Brandwein et al., 1990).

2.5.6 Treatment Complications

Survival for Hodgkin's disease patients has improved substantially since the 1940s. Because of this long-term survival, late complications of therapy are more frequently reported (Boivin and Hutchison,1984; Boivin, 1990). Since 1972, a growing number of reports have dealt with the long-term consequences of intensive treatment modalities in otherwise cured patients. While some of the complications are minor, others are serious, and sometimes fatal.

Most serious of the late side effects of cancer treatment are the induction of second cancers (Arseneau et al., 1972; Coltman and Dixon, 1982; Rosenberg and Kaplan, 1985; Boivin and Hutchison, 1984; Valagussa et al., 1986). Several of these studies have demonstrated an increased risk of leukemia and solid tumors in patients exposed to radiation therapy. Large increases in risk of leukemia have been observed after chemotherapy. Alkylating agents are associated with leukemia but nitrosoureas are considered to be the worst offender. Those patients receiving more prolonged treatment, or those who receive multiple doses of chemotherapy are considered to be at highest risk (Urbo & Longo, 1992). As the length of follow-up increases, solid tumors related to the use of radiotherapy are the most frequently observed second cancers. Urba and Longo report that by the 15th year after radiotherapy, solid tumors develop in 13% of patients and that the risk continues to increase with time. The majority of these tumors occur in the radiation field.

A number of investigators have reported that the risk of secondary neoplasms increases dramatically whenever combination chemotherapy and extensive radiation therapy are used together (Kaplan, 1980; Hellman, 1989; Krikoran et al., 1979). Other problems encountered in combined modality therapy include an increased risk of cardiomyopathy and heart failure with

the use of adriamycin and radiation over the heart. Patients treated with radiation who subsequently received either bleomycin or adriamycin were reported to be at increased risk for radiation pneumonitis. Increased frequency and severity of bone marrow injury, with complications related to leukopenia and thrombocytopenia, is another clinical problem encountered in combined modality therapy (Kaplan, 1980; Rosenberg and Kaplan, 1985).

There have been reports of increased incidence of coronary heart disease occurring in patients < 40 years of age treated with radiotherapy alone (Boivin et al., 1992; van Rijswijk, 1987).

Both acute toxicities and late treatment complications have become a concern. The major concern during the 1980s at all treatment centers was to modify treatment techniques so as to minimize these complications without compromising rates of freedom from relapse and survival.

2.6 PROGNOSIS

Forty years ago, the median length of life for patients with Hodgkin's disease was 30 months, and the five-year survival rate was estimated to be 13-19 percent (Hellman et al., 1989). Among the first reports that treatment could prolong survival was that published by Peters in 1950. Since that time, there has been evidence of continuing progressive improvement in both survival and freedom from relapse in patients with previously untreated Hodgkin's disease. Whereas at one time the prognosis was extremely poor for patients who had relapsed, today a lasting remission is possible for a large proportion of these patients with the use of MOPP and other combination chemotherapy regimens (Kaplan, 1980). A high proportion of Hodgkin's disease patients are now considered to be permanently cured as a result of new diagnostic techniques, improved staging methods and treatment with modern megavoltage radiotherapy or combination chemotherapy or both. Today the five-year survival rate in asymptomatic stage I and II is approximately 90% and in patients with advanced disease it is approximately 70% (Henry-Amar, 1990; van Rijswijk et al., 1987).

CHAPTER THREE

AGE-PERIOD-COHORT ANALYSIS

3.1 INTRODUCTION

Age, birth cohort and calendar period are three separate time related factors that influence cancer mortality rates. Age-period-cohort analysis can be described as a technique to assess the relative importance of the independent effects of these factors.

Each factor has a different underlying biological interpretation. For instance, birth cohorts may have varying levels of exposure to a particular risk factor which might be expected to produce a change in disease incidence for individuals born at a particular time. Not only are factors at year of birth identified as a **cohort effect**, but so are other factors that affect disease incidence that are related to the year of birth.

A **period effect** is produced when a similar change in disease incidence or mortality is observed for all individuals at a particular time, regardless of age or birth cohort (Holford, 1991). Calendar period values tend to be influenced by late-stage carcinogens (promoters), or diagnostic and therapeutic improvements or changes in coding practices. Any of these influences could affect mortality rates across all age groups (Osmond and Gardner, 1982; Doll, 1971). In the case of Hodgkin's disease for which the etiology remains unknown, Doll and Peto (1981) ascribe the decrease in mortality to be largely due to effective treatment.

The **age effect** follows from variation of mortality rates by age. For most cancers, mortality rates increase exponentially with age. This may reflect the fact that age is a surrogate for cumulative exposures rather than any change in host susceptibility due to the aging process

itself (Breslow, 1985). These three factors, however, are not independent, since definition of any two implies knowledge of the third. The separation of these factors depends on the analysis of several age groups and, in addition, either **a priori** knowledge or increased consistency resulting from an explanation based on a particular factor. An example of **a priori** knowledge is the increased prevalence of congenital deafness in an Australian birth cohort caused by a rubella epidemic (Chronic Diseases in Canada, 1988). Another example would be that of children born during the years when it was not uncommon to prescribe diethylstilbestrol to pregnant women who might face a lifetime risk for certain types of cancer that differs from that faced by children born at another time (Holford, 1991).

Age, period and cohort analysis is completed in two steps. The first involves the graphing of mortality against age and joining points belonging to the same period or cohort. The second step involves the fitting of regression models to quantify the separate effects of age, period and cohort. This type of analysis requires that data be collected over an extended number of calendar years.

3.2 PROBLEMS IN AGE-PERIOD-COHORT ANALYSIS

3.2.1 Identification Problem

Difficulties arise when one attempts to separate age, period and cohort effects because of the linear relationship between age, calendar year and year of birth. When these factors are treated as continuous variables, the mathematical relationship, when mortality is the endpoint, is "(year of birth)+(age at death)=(year of death)" (Kupper et al., 1985). The identification

problem arises when all three of these factors are in the analysis simultaneously. In regression analysis, it is not possible to attribute separate effects to each of these factors due to linear dependence (Holford, 1991).

3.2.2 Misclassification Problems

Misclassification problems arise when age, period and cohort are categorized. The usual way of displaying age-period-cohort mortality data is in a two-way table, as illustrated in Table 3, where the rows represent age and the columns represent calendar period. These rates are generally based on 5-year age and period intervals. The diagonals going from the upper left to the lower right display the mortality patterns for successive groups of patients who were born during the same calendar period and, therefore, form cohorts. This method of defining birth cohort causes some problems. Grouping the data into 5-year intervals results in overlapping sequences of birth periods. That is, there is an overlapping nine-year period in which a birth could have occurred. For example, if one examined the rate for those in the 30-34 age group and the 1940-45 calendar period, the birth cohort would extend from 1906 to 1914. A patient aged 30 who died in 1944 would have been born in 1914 whereas a patient aged 34 who died in 1940 would have been born in 1906. It is important to be aware of the fact that neighbouring cohorts overlap when displayed in this manner as this results in a form of misclassification of the year of birth by as many as 5 years. This would tend to bias the cohort effect towards the null. Similar problems could occur for periods if similar tabulations of rates were broken down by age and cohort (Roush et al., 1987).

The other important characteristic of this relationship between birth cohorts and the diagonals of an age-by-period two-way layout of the data is that the birth cohorts corresponding to the diagonals at the extremes of the table will involve very few data points. Because the earliest cohorts are in the oldest age groups and the latest cohorts are in the youngest age groups, the number of cases available in early and late birth cohorts are reduced in the following ways. Firstly, for early and late birth cohorts, most age groups are not directly represented. Secondly, considering the numbers within each age group, the oldest and youngest age groups will generally have fewer cases relative to the middle age groups. This means that the middle groups are generally better represented (Roush et al., 1987).

In statistical modelling the estimate of the cohort effect would be influenced in two ways. Although age groups for early and late cohorts may not be directly represented, the missing age groups would still be estimated by the model. In addition, the reduced numbers in the earliest and latest birth cohorts would influence the variance and tend to limit statistical power to detect cohort effects (Roush et al., 1987).

3.3 DESCRIPTIVE AGE-PERIOD-COHORT ANALYSIS

The use of graphs is a descriptive technique for examining an array of mortality rates in order to determine if changes in rates over time are due to a period effect, a cohort effect or a combination of the two. Rates, or their transformations thereof, are plotted in various ways as a function of the age, period or cohort groupings.

Kupper et al. (1985) caution that while graphs are helpful in obtaining general impressions about age, period and cohort rate patterns, they do have certain limitations. For instance, the shape of period curves can be affected by varying age effects as well as varying cohort effects. In addition to being somewhat difficult to interpret, a quantitative assessment of age and cohort effects that operate to influence the shape of this period curve cannot be obtained by a simple visual examination of the graph. This quantification can only be achieved through the use of statistical modelling procedures.

3.4 STATISTICAL AGE-PERIOD-COHORT ANALYSIS

3.4.1 Choice of constraint

Since the early 1970s, various approaches for statistical modelling designed to quantify the separate effects of age, period and cohort have been proposed. They all involve some form of regression analysis and usually involve a 3-factor or complete model, a two-factor model, usually age and period or age and cohort or some modification of these two models. Kupper et al. (1985) caution that because the choice of constraint on the parameter estimate has such a major impact on the observed patterns, any interpretations regarding patterns in age, period, and cohort effects must be made very carefully.

A popular approach for choosing a constraint involves a preliminary descriptive examination of patterns in the data to be analyzed. The data-based method utilizes certain observed trends to suggest a possibly realistic constraint. However, Kupper et al., (1985) as well as Holford (1991), believe that such data-dependent procedures can be quite misleading.

3.4.2 Two-factor model

One approach to avoiding the identification problem is to argue that one of the factors is unimportant in which case the two-factor model could provide a reasonable description of the data. If, for example, one adopts the age-period model, the implication is that all the cohort effects are insignificant. In other words, there are no linear or higher order effects due to cohort. Roush et al. (1987) stress the importance of qualifying conclusions implied by eliminating one of the three factors. While the problem of linear dependence may be eliminated, the qualification of the third factor implies that there is no effect, including linear effect, for that factor; and this cannot be specifically tested using the tabulated rates. They recommend that the constraints be made with considerable care because of the large effect they can have on the conclusion. If, for example, the investigator feels that it is not reasonable to assume that a cohort slope is constant for the entire duration, but constant for only a portion of the time, then the parameters should be modified to reflect these new constraints.

3.4.3 Goodness-of-fit criteria

Another method commonly used to decide which of the two-factor models to use is to choose the model goodness-of-fit criteria. Kupper et al. (1985) argue that the adoption of the two-factor model based on goodness-of-fit criteria may not always suggest that one model is significantly better than another and may be invalid when the population effects for one of the factors (age, period, cohort) follows a non-horizontal linear pattern.

The age-period-cohort modelling procedure advocated by Holford (1985) revolves around the statistical concept of "estimability". He proposes that analysts concentrate their discussions

only on the estimable functions such as the curvature component of each effect. While this does not solve the identification problem, he feels that if model fitting is done with care, it can yield important insights into the data and offer some advantages over approaches that simply impose constraints on the parameters.

Ohtaki et al. (1990) introduced a new age-period model that they consider to be free of the identification problem and proposed a method of model fitting to age-period-cohort data through the nonparametric smoothing technique. They derive their model by replacing the cohort-effect term in the ordinary age-period-cohort model by a term of general age x period interaction. It is their view that various types of age x period interaction, including the so-called cohort effect, can be incorporated without suffering from an identification problem.

One of the main reasons that they choose the age-period main-effect model is that the model is easier to handle than the age-cohort main-effect model in parameter estimation. They suggest that since a limited amount of mortality data are available for extremely old or new cohorts, some treatment of missing values is inevitable when the age-cohort main-effect model is adopted whereas such treatment is not required when the age-period main-effect model is used. The essential reason for their choice lies in their belief that recent improvements in medical or public health care, such as advances in developing effective medicines, and introducing screening programs, are equally effective over all age groups.

3.4.4 Coding

Pottern et al. (1980) have described a method of coding which reduces the overlap of neighbouring cohorts. The minimum requirement of this method is that the data be grouped in

no more that one year intervals. Since the date of diagnosis and the age of diagnosis were available for each case in their data set, they were able to calculate the year of birth. Because there were insufficient numbers of cases falling in extreme cohorts, they were not included in the analysis. The advantage of this method is that unique estimates of all the parameters in the complete model can be obtained.

3.4.5 Controlling for age effects

The usual approach to analyzing patient survival in cohort studies is to treat follow-up time as the fundamental time variable, controlling for age and calendar year by stratification. Breslow et al. (1983) and Breslow (1985) suggest that follow-up time is often an inappropriate time variable in cohort studies, the risk being that it could mask the very effects that one is trying to uncover. Because death rates from major diseases rise rapidly with age, they propose that age effects should be controlled as precisely as possible. One approach they suggest is that age be considered as the underlying time variable and to control for secular trends by time-dependent strata consisting of 5-year calendar periods. Thus, those patients who died would be compared with those patients reaching the same age in the same calendar period.

3.5 CONCLUSION

It is difficult to evaluate these modelling approaches proposed by the various researchers. Each of them have recommended that results from application of these age-period-cohort models be considered and interpreted with caution on account of problems of random variation and limitations of the models themselves. Levi et al. (1987) stress the need for careful examination

of the raw data by means of single age-specific rates. Others (Kupper et al., 1985; Holford, 1991) stress that any statistical modelling of age-period-cohort data be carried out in conjunction with a detailed descriptive analysis and graphical displays.

CHAPTER FOUR

METHODS OF ANALYSIS

4.1 GENERAL CONSIDERATIONS

4.1.1. Choice of statistics to measure Hodgkin's disease mortality

In recent years there has been considerable discussion as to which measures best capture the "truth" about recent advances in the control of cancer. Bailar and Smith (1986) disagree with the decision of the National Cancer Institute to emphasize survival because of the bias that can be introduced from standard methods of diagnosis and reporting. They argue that the single best measure of progress against cancer is the age-adjusted death rate associated with all cancers combined, supplemented by age-adjusted rates, and sometimes age-specific rates for specific categories (i.e. sex, race). Not only does this measure remove the effects of changes in the size and age composition of the population, but Bailar and Smith believe that it prevents the selective reporting of data to support particular views, minimizes the effects of changes in diagnostic criteria related to recent advances in screening and detection, and directly measures the outcome of greatest concern --- death.

According to Breslow and Cumberland (1988), the problem with reliance on a single measure of mortality is that the impression conveyed can vary dramatically when the measure is changed. They show calculations that demonstrate how age-adjusted mortality and the measure, Years of Potential Life Lost (YPLL), yield completely different impressions. Furthermore, they believe that reducing results to a single number results in a misleading, unduly negative or unduly positive impression. For example, if one population has higher rates

than another among young persons, but lower rates among the elderly, use of a summary rate would obscure the differences.

Doll (1989) makes a similar argument, suggesting that Bailar and Smith, by taking all ages together, allowed the effects of recent progress to be overshadowed by the effects of changes in behaviour and the prevalence of carcinogenic agents in the distant past, which can manifest themselves only in the old. Rather than rely on a single measure of mortality for the population, they recommend examining age-specific death rates over time, as this permits viewing the dynamics of the mortality trend taking age and changes over time in prevention as well as treatment into account.

This debate over the extent of progress against cancer and how best to measure it led to a request by the Senate Appropriations Committee to the National Cancer Institute to review the adequacy of existing measures of progress against cancer and recommend the most appropriate measures (JNCI, 1990). The committee identified two basic types of measures, direct measures of how cancer affects people and indirect measures consisting of groups of factors that influence the eventual impact of cancer. The most important direct measure that they identified was mortality, particularly the rate of cancer deaths in the population. Other direct measures that they identified were cancer incidence and the duration of survival after diagnosis.

Although the committee recognized mortality as the ultimate measure of progress against cancer, they recommended additional methodologic work on the properties of the various mortality rates. They concluded that survival, the time span from diagnosis to death, was the measure most directly sensitive to changes in detection practices, treatment regimens and advances in medical care (JNCI 1990).

Since incidence rates are not available in the data set used for this thesis, the measures used to assess temporal trends for Hodgkin's disease are mortality and survival statistics. A review of these basic concepts will follow.

4.1.2 Mortality rates

Generally, the analysis of data in cohort studies involves the derivation of rates for a specified outcome among the cohort members during the study period. Rates can be expressed for a total population (crude or adjusted) or for a population subgroup (specific rates).

Crude rates are summary rates based on the actual number of events in a total population over a given period of time. In cohort studies for which people are not each followed up for the same period of time, the crude mortality rate is the estimate of the number of a given population that dies per unit of population time at risk i.e. person-years at risk.

Two generally accepted indices of mortality are either **age-specific** or **age-standardized** rates.

The **age-specific** mortality rates for Hodgkin's disease among United States males, for example, are the mortality rates among males in some particular narrow range of ages. By convention, the 18 five-year age ranges 0-4, 5-9, 10-14, etc. up to 75-79, 80-84 and finally 85 and over, are usually adopted for the calculation of age-specific rates. An examination of mortality rates by age and calendar period would be referred to as an **age-time-specific** rates and would indicate that age and calendar period were important factors. The basic method used to estimate **age-time-specific** mortality is to determine for each individual the amount of observation time contributed to a given *age x calendar period* category and to sum up those

contributions for all cohort members so as to obtain the total number of person-years of observation in that category. These person-years form the denominators of rates the numerators of which are simply the numbers of deaths that are also classified by age and calendar period (Breslow and Day, 1987).

Adjusted or standardized rates are summary rates that have undergone a statistical procedure in order to remove the differences in age composition of the populations being compared. The **age-standardized** Hodgkin's disease rates for United States national data are defined as a weighted average of the 18 separate age-specific rates. Generally, the population (i.e. the US male population) whose age distribution forms the basis of comparison is referred to as the **standard population**.

4.1.3 External comparisons

Analysis of cohort data can involve a comparison of rates in the study population with that of rates in the general population. Cancer rates are known to vary widely according to sex, age and calendar period. The age distribution of the study population can differ from that of the general population and it may evolve with time. In order to control or eliminate the bias that could be introduced by comparison of these rates, the crude rates are adjusted or stratified on an age-sex-time-specific basis (Breslow and Day, 1987). Usually age groups are divided into 5-year intervals (i.e. 0-4, 5-9,...) and 5-year calendar periods (1940-44, 1945-49,...).

The most commonly used methods of standardization are the **direct method** and the **indirect method**. In the **direct method**, the age-sex-time-specific rates for the population being studied are applied to the corresponding group in the standard population in order to obtain the

expected number of deaths in the standard population. These standardized rates are interpreted as the mortality rates that would apply if the age distribution of the study population was the same as the standard population. In the **indirect method,** the age-sex-time-specific rates of the standard population are applied to the corresponding age group in the study population. These are the deaths one would expect to occur under the presumption that the age-sex-time-specific rates of the standard population were the same as those in the study population (Colton, 1974).

The ratio of the total number of deaths observed in the study population to the number that would be expected if the study population had the same specific rates as the standard population is the **standardized mortality ratio (SMR)** (Last, 1988).

4.1.4. Survival analysis

The crude survival rate measures the proportion of patients who survive a specified length of time. This overall rate of survival is not very satisfactory because it contains no information about the duration of follow-up or the quality of life during follow-up, nor does it take into account differences between groups that may be of considerable importance. Another problem, perhaps even more serious, is that it provides no good way to deal with deaths from unrelated causes.

Survival analysis is done when the variable of interest is the length of time to a response, the response being an event that occurs at a specific point in time. In the case of this study, the event is death. A characteristic of survival data is that, at the time of analysis, some patients in the study may not have experienced the event i.e. death. These censored or incomplete observations may arise due to loss to follow-up, withdrawal from the study, or patients may still

be alive at the termination of the study. These censored observations, however, contain useful information. What is known about these patients is that the time to the event (death) exceeds the duration or follow-up. In other words, they provide a lower bound on mortality and are included among the total number of patients at risk of the event (death) up until the time of censoring.

4.1.5 Life Table Analysis

A life-table is a method of summarizing the results of the study by grouping the times to response into time intervals. For each time interval the table includes the number of subjects who are still in the study at the start of the interval, the number who experience the event (death) during the interval, and the number censored (lost to follow-up or withdrawn). From these data, the chance of surviving to any point in time is estimated from the cumulative probability of surviving each of the time intervals that precede it (Benedetti et al., 1988). These time intervals can be any size. If no one dies in a specified interval then the probability of survival for that interval is one. The probabilities of survival in those intervals in which patients experience the event (death) are calculated as the ratio of the number of patients surviving to the number at risk of dying at that time. The two most frequently used life-table methods include the product-limit method given by Kaplan and Meier and the actuarial method (Anderson et al., 1980; Lee,1980).

4.1.6 Requirements and Assumptions for Life-Table Analysis

There must first be a clear indication of the entry date of the study i.e. in our research it is the date of diagnosis of Hodgkin's disease, and the study outcome must be well defined. Not only must it be dichotomous (i.e. dead vs. alive), but it can occur only once (i.e. it must be the first relapse or first febrile episode).

Losses to follow-up should be independent of study outcome. For example, if the subjects who drop out are those doing particularly well or particularly poorly, then their loss will bias the overall results. Life-table analysis assumes that lost subjects have an identical prognosis to those remaining in the study at that time.

The risk of the outcome must be independent of calendar time (Armitage, 1987; Kramer, 1988; Anderson et al., 1980). In other words the risk of the study outcome must remain constant within intervals used in constructing the life table. Risk need not be constant from one interval to the next, but it must remain so within each interval (Kramer, 1988).

4.1.7 The Actuarial Life-Table Method

The most appropriate method of life-table analysis for large data sets is the actuarial life-table method. For each interval the calculated "p" of surviving that interval is one minus the probability of dying, the probability of dying being given by the number of deaths during that interval divided by the number alive at the beginning of the interval minus 1/2 of the number whose data were censored during the interval (assuming that on average, a patient whose data were censored during a certain interval was followed for 1/2 that interval) (Anderson et al., 1980).

Survival distribution is most commonly described by three functions: 1) the survival function, 2) the probability density function, and 3) the hazard function. These three functions are mathematically related.

1. **Survival function**, S(t): Probability that an individual survives longer than time **(t)**.
2. **Probability density function**, f(t): Limit of the probability that an individual dies in the short interval **t** to **(t + delta t)** per unit width.
3. **Hazard function**, h(t): The instantaneous rate of death at a given time **t**. It is sometimes termed the force of mortality or conditional failure rate (Lee, 1980).

4.1.8 Cox's proportional hazards model

For the evaluation of the relative risk from survival data, that may or may not include censored observations, Cox's Proportional Hazard model is commonly used. The model and its variations represent a powerful tool for cohort analysis without requiring an external comparison group or knowledge of baseline rates. An important feature is that the regression coefficients when exponentiated can be interpreted as relative risks with respect to baseline rates.

The proportional hazards model proposed by Cox (1972) incorporates regression-like arguments into life-table analysis. This is a multivariate, non-parametric statistical regression technique that assesses the relative independent contributions of covariates to mortality while allowing for various lengths of follow-up. Cox suggests that the hazard function best describes models in survival analysis.

Whereas in life-table analysis the hazard function gives the probability that a patient dies during a specific time interval, given that she or he lived until the beginning of the interval, in the Cox model, the covariates have a multiplicative, or proportional effect on the probability of dying.

This model presumes that death rates may be modeled as log-linear functions of the covariates. Suppose h(t;z) is the hazard function for an individual with covariate vector **z.** The proportional hazards model is given by:

$$h(t;\mathbf{z}) = h_0(t) \exp(\text{beta}.\mathbf{z})$$

or

$$\ln[h(t;\mathbf{z}) / h_0(t)] = \text{beta}.\mathbf{z}$$

where beta is a vector of regression parameters for individuals, where **z** are the covariates; and where $\mathbf{h}_0(t)$ is the baseline hazard or unknown function of time (Cox, 1972; Cox and Oakes, 1985). The validity of this model is dependent upon two assumptions:

1) **the proportionality assumption** i.e. there is a multiplicative relationship between the underlying hazard function and the log-linear function of the covariates. This means that the ratio of the hazard functions for different levels of an independent variable is a constant function of time (t). In other words, the survival curves for the groups to be compared have similar shape but different levels and that the logarithms of these curves are proportional to one another.

2) **linearity assumption** - the effect of covariates upon the hazard function is log-linear (Cox, 1972; Cox and Oakes, 1985).

Violation of either of these assumptions, proportional hazard or linearity, may result in inaccurate estimates of the relative risk.

The Cox regression coefficients can be used to determine the relative risk between each independent variable and the outcome variable, adjusted for effect of all other variables in the regression equation. A positive regression coefficient increases the value of the hazard function and thereby negatively affects survival whereas a negative coefficient has the reverse interpretation (Hopkins, 1988).

The relative risks can be interpreted as the relative effect on the risk of mortality for patients in a particular category when compared to the referent category. To estimate the relative risk for patients who vary from the referent group on a number of covariates simultaneously the sum of their coefficient estimates are exponentiated as:

$$\exp(\text{beta1}\mathbf{X1} + \text{beta2}\mathbf{X2} + \ldots\ldots \text{beta}p\mathbf{X}p)$$

The likelihood ratio chi-square statistic is used to assess whether an apparent association in the specified model is statistically significant when compared to a baseline model. If significant, the beta differs significantly from zero and the relative risk (exp beta) differs from unity. We used the likelihood ratio chi-square test to determine whether a given model provided a better fit than the baseline model (Lee, 1980). The chi-square has an asymptotic chi-square distribution with degrees of freedom equal to the number of covariates in the model (Hopkins, 1988).

To test whether the proportional hazards assumption holds, PROC PHGLM from the Statistical Analyses System (Version 5) statistical package uses the Z:PH test which is based on the linear correlation between residuals and the rank order of failure time. Non-significant tests indicate no evidence of a major violation of this assumption.

4.2 METHODS OF ANALYSIS FOR THIS STUDY

4.2.1 Source of the data

For the purpose of this study the term 'cohort' should not be confused with that of 'birth cohort'. A review of the literature reveals that there is no common definition for the word 'cohort' (Rothman, 1986; Miettinen, 1985; Last, 1988; Kleinbaum, Kupper and Morgenstern, 1982; Kramer, 1988). In this study, the term **cohort** refers to the 9,316 study subjects who were identified at date of diagnosis of Hodgkin's disease between the years from 1940 to 1987 and followed until the date of death, date of last known survival status or April 1, 1990, whichever came first. This cohort of patients was assembled by Boivin and Hutchison. The purpose of their study was to evaluate the carcinogenicity of radiotherapy and chemotherapy used in the treatment of Hodgkin's disease (Boivin and Hutchison, 1981; Boivin et al., 1984). The data from this study are used to examine trends in mortality in patients with Hodgkin's disease.

4.2.2 Study population

Patients with Hodgkin's disease were identified through records at 13 collaborating cancer centers throughout Canada and the USA. All patients with histologically proven Hodgkin's disease who were diagnosed and registered at the collaborating centers during specific years

were included except: 1) patients who had received substantial treatment for Hodgkin's disease prior to registration at the center and 2) patients seen in consultation but not treated at the collaborating center. The study population included all patients, regardless of gender, stage, histologic type, age and general medical condition. The period of enrolment for each center began with the first year for which the center kept clinical records of excellent quality with good follow-up (Boivin and Hutchison, 1981).

Treatment information and follow-up data were abstracted from the records of the collaborating centers. The following information was obtained for all study subjects: date of birth, sex, date of diagnosis of Hodgkin's disease, date of last known survival status, i.e. alive or dead (Boivin and Hutchinson, 1981). Special attempts were made to locate patients lost to follow-up by writing to family physicians, searching death records at departments of vital statistics, searching records of various hospitals and other similar follow-up methods. Occasionally, these searches led to jails or cemeteries (personal communication from Boivin, 1990).

4.2.3 Mortality data

A copy of the death certificate was solicited for all patients who had died. Not all copies of death certificates included an International Classification of Diseases code for the underlying cause of death. If the rubric was not included, the underlying cause of death was coded according to the format prescribed by the World Health Organization as specified by the Ninth revision of the International Classification of Diseases (1977). The World Health Organization has defined the underlying cause of death as "(a) the disease or injury which initiated the train

of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury."

If the underlying cause was coded according to an earlier edition of the International Classification of Diseases, it was recoded according to the Ninth revision in order to achieve internal comparability of the data. A certified nosologist was consulted in all cases for which the selection process for underlying cause was not clear.

In addition to coding the underlying cause of death for the decedent as many as four conditions contributing to the death, but not related to the terminal condition, were coded. This was done following the same general procedures as for the underlying cause. For the present study, however, only the cause selected as "underlying" was used.

Deaths were grouped into 5 broad categories: infections (ICD-9 codes 001 - 139.8 and 490 - 519.9), ischemic heart disease (ICD-9 codes 410.0 - 414.9), external causes (ICD-9, E-codes E800-E999), malignant neoplasms (ICD-9 codes 140 - 208.9) and a broadly heterogeneous group of "others or unspecified". When the death certificate was missing, the underlying cause of death was attributed to the "other" category.

All deaths due to malignant neoplasms were further grouped into the following categories: Hodgkin's disease (ICD-9 codes 201.0 - 201.9), leukemia (ICD-9 codes 204.0 - 208.9), non-Hodgkin's lymphoma (ICD-9 codes 200.0 - 200.9 and 202.0 - 203.9) and solid tumors (all other malignant neoplasms). If two or more cancers were noted on the death certificate, the site indicated as primary was selected. If there was no statement that clearly indicated the primary site, then the coding rules that require coding to the first site mentioned or, to the defined as opposed to ill-defined site, was selected.

4.2.4 Descriptive age-period-cohort analysis

The first step in this analysis was to compare mortality rates of the study population of Hodgkin's disease patients with that of the general USA population. Using the Person-Years (PYRS) program for cohort study analysis, developed by Coleman et al. (1986), time at risk for death was computed from the date of diagnosis of Hodgkin's disease to the date of death, date of last known survival status or April 1, 1990, whichever came first. The exposure to risk was based on the accumulation of person-years of observation. For each group (specific for age, sex and calendar period), the mortality rate per 1000 person-years at risk was computed as:

$$R = \frac{\text{Observed \# of deaths in group}}{\text{Total person-years at risk in the group}} \times 1000$$

Expected numbers (specific for age, sex and calendar period) were calculated from observed person-years at risk and death rates in the United States population and compared with the observed ones giving an estimation of the standardized mortality ratio (SMR).

Tests of statistical significance and 95% confidence intervals for the standardized mortality ratio were calculated with the use of an accurate asymptotic approximation to the Poisson distribution (Rothman and Boice, 1982). This is based on the assumption that the observed frequency follows a Poisson distribution and that the expected frequency is so stable that it has a variance of zero. If the confidence interval of the standardized mortality ratio does not include 1, and if, for example, the standardized mortality ratio is greater than 1, we would say that the observed number of deaths is significantly higher than one would expect at the 0.05 significance level. All statistical tests and confidence intervals were two-tailed.

Various approaches were used to examine time trends. Graphs of mortality against age and calendar period were plotted for both males and females. Time trends by calendar period and birth cohort were considered for both sexes combined and each sex individually. This was done by plotting age-specific rates against age, first joining points corresponding to the same period and then joining points corresponding to the same birth cohort. To avoid the problem of overcrowded graphs, only half of the data were plotted i.e. every other period and every other cohort. In statistical analyses, however, the entire data set was used.

4.2.5 Survival analysis

The actuarial life-table method was used. Testing for statistical significance of difference among survival curves was determined with the generalized Savage (Mantel-Cox) and the generalized Wilcoxon (Breslow) tests using the BMDP 1L program (1988). Both tests are nonparametric and summarize, at each distinct death time, the differences between the observed and the expected number of deaths derived from the assumption of no difference in the survival experience among the several groups under comparison. The generalized Wilcoxon (Breslow) is considered to be more sensitive to differences occurring in the early stage of the study because it weighs each difference by the total number patients at risk just prior to each death time. Therefore early differences, when there are more patients in the study, weigh more heavily (Rubin et al., 1985; Benedetti et al., 1988).

Median survival is reported rather than mean survival. This is because one or two exceptionally long survivors will greatly affect the mean survival whereas the median time will not be affected.

Because the construction of the right tails of both survival and risk curves depend on the decreasing numbers of patients, the standard errors associated with the curves at long follow-up times can be very high and must, therefore, be interpreted with caution (Rubin et al., 1985).

4.2.6 Cox's proportional hazards model

In order to assess the independent contributions of different variables to the risk of mortality in this patient population while allowing for varying lengths of follow-up, Cox's proportional hazards model (1972) for censored survival data was used. The covariates of interest in this study were sex, birth cohort, age at diagnosis and period of diagnosis. Time from the date of diagnosis to date of death was defined as 'survival' time. Patients who survived to the end of the study were assigned 'censored time', defined as the time from date of diagnosis of Hodgkin's disease to the date of last follow-up. Risks for all cause mortality were estimated for each variable using the proportional hazards modelling routine, PROC PHGLM from the Statistical Analyses System (Version 5) statistical package.

Exploratory univariate survival analysis was done where age, period, birth cohort and sex were considered separately. Initially, these independent variables were finely stratified. When differences in the beta coefficients for different strata were minimal, strata were collapsed to simplify presentation of the data. Age and period were collapsed into categories that reflected the sharp increases in relative risk with increasing age and sharp decreases with successive calendar periods. For the variable sex, males were considered to be the baseline group. For the age and period variables, the baseline groups were ages 2 - 14 and period 1940 to 1964.

After univariate models were fitted for each risk factor, risk factors were added sequentially. Since univariate analyses indicated that age, period and sex were significant predictors of mortality, each of these variables were included in every model. Examination of age-calendar period-sex specific rates and review of the literature support this view. There is no information to suggest that year of birth is in any way associated with Hodgkin's disease mortality and given the identification problems that arise when three factors are included in age-period-cohort modelling, it was decided to exclude birth cohort from these analyses.

The decision to include a risk factor or interaction term in subsequent models was based on the improvement of statistical fit of the other model as well as the change in the beta coefficients of the other variables.

The statistical significance of difference between nested models was determined using a likelihood ratio test obtained from the differences between the log likelihoods. This difference, which is calculated as twice the absolute difference between the two log likelihoods, is approximately distributed as a chi-square statistic with degrees of freedom equal to the difference in the degrees of freedom between the two models. Examining the likelihood ratio statistic enables one to judge whether the evidence favours one model interpretation over another (Breslow and Day, 1987).

Ninety-five percent confidence intervals for the relative risks were estimated as **exp[beta +/- 1.96(SE beta)]** where **beta** is the coefficient from Cox's regression, **exp(beta)** is the estimation of the relative risk and **SE(beta)** is the standard error of the regression coefficient.

CHAPTER FIVE

RESULTS

5.1 DESCRIPTIVE STATISTICS

For the time period 1940 through 1987, 9316 patients with the diagnosis of Hodgkin's disease were ascertained through registration records at 13 collaborating cancer treatment centers in Boston, Montreal, Toronto, Houston, Chicago and New York. Table 4 shows that the calendar time period of diagnosis covered in the study varies somewhat among the collaborating centers, but all cover an interval of at least 17 years. These centers are: the Harvard Joint Center for Radiation Therapy (JCRT) (709 patients diagnosed between 1942 and 1984), the Massachusetts General Hospital (791 patients, 1960-84), the McGill University teaching hospitals (735 patients, 1948-85), Hôpital du Sacré-Coeur (228 patients, 1944-84), Hôpital Maisonneuve-Rosemont (222 patients, 1954-84), Hôpital Notre-Dame (538 patients, 1940-84), Hôpital Saint-Luc (109 patients, 1954-84), Hôpital Sainte-Justine (74 patients, 1946-84), Hotel-Dieu de Montréal (364 patients, 1942-84), the Princess Margaret Hospital (2444 patients, 1940-84), the M.D. Anderson Hospital and Tumor Institute (1179 patients, 1949-87), the Memorial Hospital for Cancer and Allied Diseases (1763 patients, 1948-84) and the University of Illinois Hospital (160 patients, 1967-84). Table 5 lists the distribution of person-years at risk by age and calendar period. More than 69,000 years of follow-up time were accumulated for an average of 7.4 years per person (range 0 - 45 years) and 4394 deaths were observed.

Table 6 shows the distribution of study subjects by age, sex, and year of diagnosis. The majority of patients (69%) were diagnosed with Hodgkin's disease between the ages of 2 and 40 years, and 31 % were over age 40. The greatest number of subjects were in the 20-29 year age group (31%) and the mean age at diagnosis was 34.4 years (median age, 29.5 years), ranging from 2.4 to 98.2 years. More than half the patients were male (57%). More males than females were entered in every age group except the 80+ age group (48% males). 73% and 66% were males in the age 0-9 and 40-49 age groups respectively. Of the 9316 study patients, <1% were diagnosed in the 1940s, 8% in the 1950s, 28% in the 1960s, 44% in the 1970s and 19% since 1980. Table 7 presents survival by interval since diagnosis. At least 55% had a survival in excess of 5 years at the time of analysis (April 1, 1990).

5.2 CRUDE OVERALL MORTALITY RATE

Tables 3, 8 and 9 present mortality rates by age groups and calendar periods. The crude mortality rate was 63.4 deaths per 1000 person-years. The overall rate for males was 70.7 per 1000 person-years and for females it was 54.7 per 1000 indicating that among those patients who develop Hodgkin's disease males have a higher mortality rate than females.

5.3 EXTERNAL COMPARISONS

5.3.1 Male and female rates by age

When male and female age-specific mortality rates are examined, the male/female ratio is lower for males in the 0-14 age group, ranging from 0.4 in the 0 - 9 age group to 0.8 in the

10-14 age group. This indicates that young females, particularly those aged 0-9 years are at a higher risk of dying than young males if they develop Hodgkin's disease. From age 15 onwards the male/female ratio is always larger than unity ranging from 1.08 in the 80-84 age group to 1.5 in the 40-44 age group (Table 3). These sex differences are higher in the 40-49 and 65-69 age groups. A sharp decline in mortality is noted in females between ages 5 and 14, after which there appears to be a plateau until age 40. A similar but less pronounced pattern seems to be present for males. Mortality for both sexes rises steadily after age 40 (Fig. 1).

5.3.2 Male and female rates according to birth cohorts

When age-specific rates are examined as a function of year of birth there appears to be a decline in mortality for both males and females with increasing age and each successive birth cohort has a lower mortality rate at all ages (Fig. 2). Rates for the 1905 birth cohort range from 869.6 in the 40-44 age group to 99.3 in the 80-84 age group. This pattern is clearly inconsistent with our expectation that Hodgkin's disease mortality would continue to increase with age. When birth cohort is on the abscissa (Figure 3), however, the data suggest that at a given age mortality is lower in more recent cohorts, in particular, for 40 year olds born between 1910 and 1945.

5.3.3 Male and female rates by calendar period

When the overall mortality rates for both males and females are examined, they reveal a dramatic and steady decline, ranging from 246.8 in 1940-45 to 30.9 in the period 1985-1987, approximately an eight-fold difference. The male/female ratio is 12.46 for the period 1940-1944

and ranges from 1.53 to 1.19 throughout 1945 to 1987 (Table 3). With the exception of the 1940-1944 period for females, mortality for both males and females shows a sharp and steady decline (Fig. 4). The pattern observed for the years 1940-1944 is difficult to interpret because of the large imprecision in the data: one death was observed in females and five in males (Tables 10 and 11).

When age-specific mortality rates over time are examined, similar trends are observed. Both male and female mortality rates for all age groups have decreased across successive calendar periods, although for all calendar periods mortality rises steadily with age, particularly after age 40 (Figs. 5, 6 and 7). A sharp decline in rates is noted between the periods 1950-1954 and 1955-1959 for all age groups. Mortality rates after 1959 remained fairly constant until the 1965-1969 period, after which time there was a steady decline, particularly for those patients less than 60 years of age. Above age 60, there is no obvious trend.

5.3.4 Conclusion - Descriptive Analysis of Temporal Trends by Examining Mortality Rates

Examination of age-specific mortality rates among patients diagnosed with Hodgkin's disease from 1940 to 1987 shows a strong trend towards declining rates for both males and females with subsequent calendar periods. Rates are higher for males than females except for the age 0-14 year group and rates increase with age for both sexes, particularly after age 40. These trends are consistent with the progress made in diagnostic and staging techniques, improved medical management and the use of aggressive multimodal therapy for Hodgkin's disease patients in the last 40 years. There is no evidence to support the hypothesis that year of birth is independently associated with mortality among these patients. The analysis of rates

by calendar period indicates that the apparent shift seen in age for the birth cohort curves (Figure 2) is essentially an artifact. The dramatic decline in mortality observed for 40 year olds (Fig. 3) from the 1910 to 1945 birth cohorts is likely due to the period in which they were treated.

5.4 OBSERVED TO EXPECTED RATIOS

To determine the extent to which there were a higher number of deaths in the study population than would be expected in the general United States population, standardized mortality ratios were computed for various groups of interest. Overall 4394 deaths were observed, as compared with 382 expected, based on general population mortality rates. The overall standardized mortality ratio is 11.5, which is significantly greater than 1.0 with $p < 0.05$ (95% confidence interval: 11.3 - 11.7) (Tables 12 and 13). Furthermore, the standardized mortality ratio was examined according to gender, different calendar periods and different age groups. The overall standardized mortality ratio for females is 14.2 (CI: 13.9 - 14.6) and significantly higher than would be expected in a normal female population (Tables 10 and 14). A slightly lower overall standardized mortality ratio of 10.2 (CI: 10.0 - 10.4) is observed for males (Tables 11 and 15).

When the study subjects are examined according to age, the standardized mortality ratio is significantly elevated for all age groups except for ages 0-4 years where the observed numbers are very small (n=2). The standardized mortality ratio for both males and females is very high in the younger age groups, ranging from 123.3 (CI: 81.3 - 179.4) in the 5-9 year age group to 18.9 (CI: 17.9 - 20.0) in the 40 - 44 years age group, but it gradually decreases as age increases

(Table 13). This is because the probability of dying at younger ages in the general population is very low. When the standardized mortality ratio is examined as a function of age and sex, it is higher for females across all age groups, particularly in the age 5-9 year group with a standardized mortality ratio of 305.3 (CI: 152.4 - 546.2) for females as opposed to 87.5 (CI: 50.0 - 142.0) for males, a 3.5-fold difference (Tables 14 and 15). As age increases for both sexes, the differences in standardized mortality ratios are smaller particularly after age 40 (Fig. 8). This is because the expected survival rate is higher for women than for men in the younger age groups.

When the standardized mortality ratio is examined according to calendar period, the gender differences remain, although the differences in the standardized mortality ratios are much smaller. The only exception with regards to gender difference and magnitude of the difference is for the 1940-1944 calendar period where the standardized mortality ratio for males is 139 (CI: 45.0 - 324.3) and for females is 26.6 (CI: .7 - 149.9) (Tables 10 and 11). This is probably due to smaller numbers of deaths (1 female, 5 males). For both males and females the standardized mortality ratio shows a sharp and steady decline from 1945 to the 1985-1990 period, ranging from 73.3 (CI: 47.8 - 107.3) to 5.1 (CI: 4.8 - 5.5). This decrease in the standardized mortality ratio reflects the dramatic progress achieved over the last four decades in the diagnosis and management of patients with Hodgkin's disease (Fig. 8).

5.5 SURVIVAL ANALYSIS

Figure 10 illustrates the overall crude survival curve with 95% confidence bands. As the time interval from entry into the study becomes longer, the confidence limits become wider.

This reflects the decrease in confidence in the estimate of the proportion as the size of the population at risk decreases. Overall, the probability of survival at 5 years is 66% and at 10 years is 53% (Table 16). The median survival for all patients is 11.6 years (Table 17).

Substantial differences are noted across patient subgroups (Figs. 11, 12, 13, 14 and 15). Unadjusted survival for females is significantly higher than that for males. The survival for females is 70% at 5 years and 57% at 10 years, while that of males is 63% and 50%, respectively, and females experience a 4 year greater median survival than males (14.0 years vs. 9.9 years). The median survival for patients diagnosed after 1970 could not be computed because more than half the patients were still alive at the end of the study period. However, the median survival for patients diagnosed after 1967 is 4.2 times greater than that of patients diagnosed before 1967 (19.6 years vs. 4.6 years). Similarly, the median survival for patients under 40 is 4.3 times greater than that of patients aged 40 or older (19.4 years vs. 4.5 years).

5.6 COX'S PROPORTIONAL HAZARDS MODELS

5.6.1 Univariate analysis

Univariate analyses of prognostic factors using Cox's proportional hazards model are shown in Table 18. Male gender, increasing age and early calendar period of diagnosis are all univariately associated with death from any cause.

5.6.2 Comparison of models

Table 19 shows a summary of the Cox regression analyses of the effect of sex and all the other covariates and interaction terms on survival. The log-likelihood and chi-square statistic are presented for each of the models. All of the models have a statistically significant chi square with a p-value of less than 0.00001.

Table 20 presents the results of the likelihood ratio test which tested for statistical significance of difference between the nested models. A significant improvement in fit was obtained with each successive model, 1 through 6. Model 7 did not improve the fit significantly.

5.6.3 Model 3. Sex + Age + Period

The variables sex, age and period were added to the model, one at a time. Table 21 presents estimated coefficients and adjusted relative risks for the multivariate model which includes the variables sex, age at diagnosis and period of diagnosis. The results from this model are generally similar to those described above for univariate analysis, i.e. for gender the adjusted relative risk of 0.79 do not differ very much from the crude relative risk of 0.80. Similarly, the relative risk for age and period, when adjusted for the other two variables do not differ significantly. The interpretation of the relative risks for this model is as follows: if we were to compare two groups of patients, who differ only in gender, but were of the same age and diagnosed in the same calendar period, females would have a risk of 0.79 of dying when compared with males.

5.6.4 Interactions (Effect Modifiers)

Relative risks for various subgroups of the study population were estimated by adding interaction terms to the regression model. Table 22 shows that when the interaction term for age and sex was added to the main effects model, sex was no longer a significant predictor of mortality. This is explained by the relative risk of 1.31 for females under age 15. This indicates an increased risk of dying for young females whereas the relative risks for females across all other age groups suggest a protective effect.

Table 23 indicates that all the significant predictors of mortality from Model 3 remain significant when the interaction term for age and period is added. Patients diagnosed prior to 1965 experience significantly higher mortality than those patients diagnosed in 1965 or later and the risk decreases across successive periods for all age groups. The significant interaction between age and period is explained by the relative risk of 0.90 for patients under age 15 who were diagnosed before 1965. These patients have a higher risk of dying than older patients diagnosed prior to 1965. However, after 1965 the risk of dying increases across all periods with increasing age.

Table 24 presents the regression coefficients and relative risks for the model that includes both interaction terms. The same trends are observed as when each of the interaction terms are included separately. While there continues to be a protective effect for females across most periods and age groups, gender is no longer a significant predictor of mortality. The risk continues to increase with each subsequent age group. The greatest increase in risk is between patients under age 15 and those aged 15-19, with the relative risk increasing from 0.18 to 0.33, a 45% increase in risk. The next substantial increase among age groups is between those in the

40-49 and 50-59 age groups, with the relative risk rising from 0.52 to 0.79, a 34% increase in risk. Although the coefficients change significantly in the final model, period of diagnosis remains an important predictor of mortality, showing a decreasing risk with later periods.

The significant age by sex interaction term suggests that Hodgkin's disease mortality is significantly more favorable for females than males but not across all age groups i.e. females under 15 have a higher risk than males the same age. When the age by period interaction term is examined, we note the trend for younger age groups in earlier periods to have an increased risk of dying whereas after 1970, the risk of dying increases with age. Patients under age 15 experience a strong linear decrease in risk with successive periods. For patients in the age groups 15-19 and 30-39, a curvilinear effect is noted i.e. there appears to be a decreasing risk until 1974 but a slightly increased risk of mortality after 1975. Patients aged 20-29, 40-49 and 50-59 experienced a decreased risk until 1974 after which time the risk of dying plateaued.

In order to further examine the age by period interaction in Model 6, a separate analysis by sex was done. The results are presented in Tables 25 and 26. A breakdown of the age by period interaction term by sex demonstrates a similar trend to that in Model 6 for both sexes under age 15 who were diagnosed between 1965 and 1969. Although not statistically significant, the risk is higher for females than males (1.15 vs 0.80). Females under age 15 appear to have a higher risk than males across all periods: in the 1970-1974 period, the risk is .49 for females vs 0.37 for males and after 1975 it is 0.53 vs 0.30. A similar trend is observed in the 15-19 age group. Across age groups, the risk for males diagnosed between 1965 and 1969 demonstrates an almost perfectly curvilinear effect (0.80 - 0.81) whereas for females there is no consistent pattern. The risk decreases from 1.15 for females under 15 to 0.59 for females ages

20-29, rises to 0.79 for the 30-39 age group and finally drops to 0.65 for females ages 50-59. After 1970 there is no consistent trend for either sex over age 19.

Model 7 includes a sex by period interaction term. On comparing this model with Model 6, the difference between the models, as measured by the chi square, is not statistically significant. In other words, males and females are not found to differ significantly with respect to period of diagnosis. Therefore, the parameters in Model 6 are considered to be reasonable estimates.

5.6.5 Final Model: Sex + Age + Period + Sex by Age + Age by Period

When all of these variables are modeled simultaneously, the regression coefficients in this proportional hazards model are adjusted weights which describe the different attributes of groups of patients. When exponentiated, the coefficients of this regression model are relative hazards. For example, if we compare a group of females who were diagnosed in 1975 or later and between ages 20-29, to the referent group (males, diagnosed before 1965 and between ages 60-99), the relative risk is Exp(-0.122 - 0.930 - 0.644 - 0.235 - 0.913) = 0.06. This means that the referent group has a 17 times higher greater risk of mortality. The relative risk for males between ages 20-29, diagnosed in 1975 or later is Exp(-0.930 - 0.644 - 0.913) = 0.08 , only 2% higher than that for females with the same attributes. Compared with males 65 years of age or older, who were diagnosed before 1965, the relative risk for females is Exp(-0.122) or 0.89 (C.I. 0.77 - 1.02). The protective effect for females is not consistent across all age groups or periods. When we compare females under 15, diagnosed before 1965 to males under 15 in the same period the protective effect for females disappears. Exp(-0.122 - 1.734 + 0.327) vs

exp(-1.734) gives a relative risk of 0.22 for females versus that of 0.18 for males. Similarly, females between ages 2 and 14 who were diagnosed between 1965 and 1969 have a slightly higher risk than males the same age who were diagnosed in the same period. Exp(-0.122 - 1.734 - 0.151 -0.088 + 0.327 vs exp(1.734 - 0.151 - 0.088 gives a relative risk of 0.17 for females vs 0.13 for males. When females under 15, diagnosed between 1975 and 1987 are compared to males under 15 diagnosed in the same period, females have a similar risk. Exp(-0.122 - 1.734 - 0.644 - 0.977 + 0.327) vs exp(-1.734 - 0.644 - 0.977) gives a relative risk of 0.04 for females versus that of 0.03 for males.

5.7 CAUSES OF MORTALITY

4,394 patients died during follow-up. Table 27 gives a distribution of the underlying causes of death coded according to Ninth Revision of the International Classification of Diseases (WHO, 1977). 3,206 (73%) deaths were directly attributed to Hodgkin's disease. 434 (9.8%) were due to second cancers, 68 (1.5%) to infections, 177 (4%) to ischaemic heart disease, 40 (0.9%) to external causes and 152 (3.5%) to other causes. 317 (7.2%) death certificates were missing. In both sexes, the distribution of deaths by cause was similar except for ischaemic heart disease and external causes which were more frequent in males (Table 28). This distribution remained fairly constant until 10 years after diagnosis. For the period extending from 10-19 years after diagnosis females were more likely than males to die from Hodgkin's disease and second cancers but after 20 years there was no difference (Table 29).

Table 30 presents the relative risk of these underlying causes of death. The relative risk or standardized mortality ratio, defined as the ratio of the observed to expected number of

deaths, has been used to compare this cohort of patients to the general population of the United States. Expected numbers were determined from the age-sex-calendar period general United States population rates. Overall, the relative risk of dying for this cohort was 11.5 (95% C.I. 11.3, 11.7). Patients who did not die from Hodgkin's disease had a relative risk of 2.9 (95% C.I. 2.8, 3.1) of dying from other causes. This risk differed when specific causes were considered. It was 1.6 (95% C.I. 1.5, 1.7) for ischaemic heart disease, 6.3 (95% C.I. 4.9, 7.9) for infections, 0.7 (95% C.I. 0.6, 0.9) for external causes and 5.2 (95% C.I. 4.7, 5.7) for second cancers (Table 31).

Standardized mortality ratios by time interval are given in Table 32 for all cause mortality and in Table 33 for all neoplasms. The standardized mortality ratios for both males and females are largest during the first five years after diagnosis. However, the risk for dying among Hodgkin's disease patients remained significantly higher than that of the general population 29 years after diagnosis. When examined by gender, the standardized mortality ratio was significantly higher for females than males for the first 20 years after which time it became more comparable. This is because the expected survival rate is higher for females. The distribution of deaths by cause shows that the majority of deaths due to Hodgkin's disease occurred in the first ten years (Table 34). After 10-14 years the incidence of death due to causes other than Hodgkin's disease was greater than that from Hodgkin's disease. Greater than half the deaths due to Hodgkin's disease occurred in patients less than 40 years of age (Table 35). After age 65, deaths were increasingly attributed to other causes. While the data have demonstrated decreasing mortality with more recent calendar periods, until 1980, greater than 70% of deaths in this patient population continued to be attributed to Hodgkin's disease (Table 36).

434 patients developed second malignancies subsequent to the diagnosis of Hodgkin's disease. Table 31 presents the standardized mortality ratio by interval since diagnosis for all second cancers. Although the findings regarding the standardized mortality ratio differed for the various types of second cancers, in the first twenty years deaths consisted mostly of leukemias and non-Hodgkin's lymphomas for which the frequency observed was significantly higher than that for the general population (Tables 37 and 38). After twenty years, second cancers were attributed to solid tumors (Table 34).

CHAPTER 6

DISCUSSION AND CONCLUSIONS

6.1 INTRODUCTION

The primary purpose of this study was to evaluate the effects of age, birth cohort and calendar period on the overall risk of mortality in a cohort of 9,316 patients diagnosed with Hodgkin's disease between 1940 and 1990. The secondary objective was to describe the causes of mortality and to evaluate the risk of specific causes of death in this study population.

During follow-up 4,394 patients died. When compared with the general United States population matched for age, sex and calendar period, the overall relative risk of dying for this cohort is 11.5 (95% C.I. 11.3, 11.7). Examination of age-specific rates shows a strong trend towards declining mortality rates for both males and females across successive calendar periods. Mortality rates are higher for males than females except for the 2-14 age group and rates continue to increase with age for both sexes, particularly after age 40.

Analyses using Cox's proportional hazards models show that the trends for increased risk in males, decreasing risk with successive calendar periods and increasing risk with age are similar to those observed when comparisons with the United States general population are made. Patients diagnosed prior to 1965 experience significantly higher mortality than those diagnosed in 1965 or later and the risk decreases across successive periods for all age groups. The risk increases with each subsequent age group. The age by period interaction indicates that younger

age groups in earlier periods have an increased risk of dying whereas after 1970, the risk of dying increases with age for both sexes. Trends in Hodgkin's disease mortality are more favorable for females than males but not across all age groups i.e. females under 15 have a higher risk than males the same age. Although not significant, a breakdown of the age by period interaction by sex suggests that the increased risk for females under 15 is higher than that for males across all periods.

The distribution of deaths by cause shows the majority of deaths were related to Hodgkin's disease and occurred in the first 10 years. After 10-14 years the incidence of death due to causes other than Hodgkin's disease was greater than that from Hodgkin's disease. Patients who did not die from Hodgkin's disease had a relative risk of 2.9 (95% C.I. 2.8,3.1) of dying from other causes. A large number of deaths were attributed to second cancers (10%).

6.1.1 Comparison between the present study and the European Organization for Research and Treatment study

Henry-Amar and Somers reported that their study was composed of more than 14,000 patients who were diagnosed between 1963 and 1987. The overall relative risk of dying for this cohort was 7.7 (95% C.I. 7.4, 7.9). Deaths were more frequently observed in males than in females, and an increasing risk in mortality was observed with increasing age at diagnosis for both males and females. The 10- and 15-year survival for their study was 68% and 60%, respectively, as compared with 53% and 44% in the present study, a 15% difference.

The relative risk of dying by 5-year intervals was not as high as that in the present study for the first 14 years. It was 9.8 (0-4 years), 6.0 (5-9 years) and 4.4 (10-14 years) as compared

with 16.1 (0-4 years), 9.4 (5-9 years) and 6.1 (10-14 years) in the present study. However, the relative risk began to increase after 15 years. It increased from 4.5 in the 15- to 19-year interval to 10.5 at 20 years or later whereas in the present study, it was 3.9 and 3.2, respectively. When deaths not related to Hodgkin's disease were considered, the relative risks of dying were 2.1 and 2.9 respectively.

Although similar trends were observed in both studies, there were differences in outcomes. Some of the differences can be explained by the fact that females under 15 years were excluded from their study and by the small number of patients entered prior to 1970, 8% versus 36% in the present study. Since 1970, diagnostic and staging techniques and treatment modalities have markedly improved. This could explain the 15% difference in 10- and 15-year overall survival. Finally, in the Henry-Amar and Somers study, the mortality data was obtained from hospital records as opposed to death certificate data.

6.2 LIMITATIONS

There are several possible sources of bias in the study described in this thesis as observations from 13 cancer treatment centers may not be entirely comparable. Results must be considered and interpreted with caution in light of differences between areas of cancer registration, variations in treatment modalities, host and environmental factors and misclassification of data.

6.2.1 Loss of patients to follow-up

The loss of patients to follow-up is a problem common to all cohort studies. If patients are being differentially lost to follow-up with respect to the risk of death and the covariates of interest, then the estimates of the relative risk may be biased. Tracking a patient for the purposes of death reporting becomes increasingly difficult the longer the patient lives, since his/her likelihood of moving or changing health care providers changes with time. Other administrative problems of tracking a case, such as monitoring medical records or recontacting hospital personnel, also increase over time. In this study 1,274 (13.7%) patients whose last known date of survival was before January 1, 1985 were considered to be lost to follow-up. We must consider the possibility that those patients who were lost to follow-up are different in some unmeasured way that would affect their risk of dying.

6.2.2 Sources of bias associated with age-period-cohort analysis

Statistical age-period analyses quantified the separate effects due to each of the variables and their interactions. One of the reasons that the two-factor model was adopted was to avoid the identification problem that arises due to linear dependence of the three factors. A more essential reason for choosing the age-period model was based on the belief that recent improvements in diagnosis, treatment and health care have been equally effective across all birth cohort groups. Furthermore, visual examination of the graphs suggested that the apparent cohort effect observed in younger age groups from the 1910 to 1945 birth cohorts was related to

treatment period. The results, however, should be interpreted with caution. By adopting anage-period model for these data, the model implies no linear or higher order effects for birth cohort.

6.2.3 Limitations of external comparisons

There are several potential sources of bias associated with external comparisons. Wacholder and Boivin (1987) point out that comparisons may be crude because measurements of covariates of importance usually are not available for the reference population.

Also, characteristics of the study population which are related to death may be different from those of the standard population. Potential biases are introduced by specific referral patterns, treatment practices, local environmental factors, and demographic variation. Therefore, the patterns of risk for Hodgkin's disease and mortality in this study population may differ from that in the general United States population (Boice et al., 1985).

Observational bias may have affected the results of this study. Because these patients have been diagnosed with Hodgkin's disease, they were more likely to have been under closer medical surveillance than persons in the general population. During the first 5 years of follow-up, when patients are at highest risk for a recurrence or metastases and are most closely followed, close medical surveillance could result in the detection of occult tumors, the advancement in the time of diagnosis of some cancers, or the misclassification of a metastatic lesion (Curtis et al., 1985). Furthermore, the frequency of autopsies among cancer patients also would influence the reported number of second tumors (Boice et al., 1985). This raises the possibility that there may have been an underreporting of malignant neoplasms in the general

United States population, thereby causing an overestimation of the relative risk of death due to second cancers in this study population.

6.2.4 Misclassification of diagnosis

Additional sources of uncertainty may have been introduced by changes in diagnostic accuracy and may have affected various age groups differently. Not only has it been reported that non-Hodgkin's lymphoma may be a part of the natural history of Hodgkin's disease but there are sometimes difficulties in resolving the differential diagnosis of advanced cases. These problems appear to be most common among "histiocyte rich" examples of Hodgkin's disease and anaplastic large cell lymphomas (Henry-Amar and Somers, 1990). Furthermore, the disease entity from a diagnostic point of view has changed i.e. lymphomas that may previously have been diagnosed as Hodgkin's disease are now properly diagnosed. Therefore, lymphomas with poor survival that are now excluded from the Hodgkin's disease group would partially account for improved survival in Hodgkin's disease patients.

The diagnosis of Hodgkin's disease was histologically confirmed for all cases in this cohort. However, the possibility of misclassification between Hodgkin's disease and lymphoma in the reference population must be considered.

6.2.5 Early detection

Early detection of Hodgkin's disease may be a contributing factor to variation in survival across patient groups. Systematic differences in earlier detection may exist. For example, patients with more ongoing contact with clinical care may be identified earlier than patients with

poorer access to the health care system. In some instances, early detection of Hodgkin's disease may merely have resulted in shift of time in diagnosis of Hodgkin's disease rather than prognosis. Among more recent cohorts, however, it is likely that the detection of Hodgkin's disease at an earlier and more treatable stage, as opposed to a later and more symptomatic stage, has resulted in a dramatic improvement in survival.

6.2.6 Misclassification of cause of death

Another limitation to this study is one that is common to all epidemiological studies that rely on the use of death certificates. The interpretation of changes in mortality rates can be complicated by changes in disease classification, secular trends in disease diagnosis and in competing causes of death.

While the accuracy of death certificates tends to be high for such characteristics as age, sex and date of death, a major source of bias results from an incorrect cause of death being assigned to the decedent. In completing the death certificate, a physician must choose only one condition as the underlying cause of death. Coding errors may result if the physician is not familiar with the requirements for reporting cause of death and the rules for selecting and coding one cause as primary. Furthermore, depending on the familiarity of the certifying physician with the deceased, there is a tendency to stress malignant neoplasms as the underlying cause of death although the cause of death may be due to other factors than cancer (Bailar et al., 1962; Percy et al., 1981). Therefore, it is likely that the underlying cause of death in this study population may have been attributed to Hodgkin's disease or other cancers when in fact it may

have been caused by some other condition. Conversely, the cancer may have been present but not recognized and the death may have been coded to a nonmalignant condition.

The certified causes of death in the elderly are less reliable for various reasons. The deaths of older patients are not always investigated as aggressively as those for younger patients. On the other hand, since the introduction of medicare and increased hospitalization of the elderly, the accuracy of the information concerning the cause of death may have improved (Doll and Peto, 1981).

Changes in the coding of death following the initiation of a new coding manual could also account for the variation in cancer mortality (Percy et al., 1981). Bailar et al. (1962) report that in the 1930s and 1940s misclassification of Hodgkin's disease and leukemia was very common; in the 1940-48 period, deaths from Hodgkin's disease were coded with a residual category of infectious diseases; and in the 1939-48 period, all lymphomas except Hodgkin's disease were coded with a residual category of malignant neoplasms. Furthermore, the coding of non-Hodgkin's lymphoma on a death certificate may represent misclassification due to the confusion between types of lymphoma.

6.2.7 Missing death certificates

Death certificates for 317 of the 4394 deceased patients were missing for a number of reasons. While some were lost to follow-up, the most common cause was related to those deaths that took place in countries other than Canada and the United States. Although deaths certificates were routinely requested from those countries where deaths were reported they were not always obtainable. A number of certificates had been requested but not yet received for

those deaths reported just prior to the current analysis. Others losses were a result of changes in last name, missing first names (i.e. Mrs. John Smith), differences in spelling of names, or other identification problems (Boivin et al., 1992).

6.3 SUMMARY

There has been an impressive decline in Hodgkin's disease mortality over the last 50 years. The decline is observed in both sexes and across all age groups. These findings reflect improved diagnostic and staging techniques, better radiation technology, more effective drug combinations and the use of combined modality therapy.

Although the overall long-term survival has improved for patients who were initially treated in the seventies and eighties as compared with those initially treated in earlier periods, survivors of Hodgkin's disease continue to be at increased risk of death throughout their lifetime. The results of this study indicate that the overall risk of dying from any cause is significantly elevated for at least 30 years after diagnosis of Hodgkin's disease in comparison with mortality patterns expected from the general United States population matched for age, sex and calendar period.

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Table 1. **Histologic Classification of Hodgkin's Disease and Relationship to Prognosis***

Histology	Frequency	Approximate 5-Year Survival	Comment
Nodular sclerosis	30-50%	70%	Young females
Lymphocyte predominant	5-15%	90%	Usually Stage I or IIA
Mixed Cellularity	30-40%	40%	Intermediate prognosis
Lymphocyte depleted	5-15%	40%	Usually Stage III or IVB

* According to Lukes and Butler (Hellman et al, 1989).

TABLE 2. **Ann Arbour Staging Classification for Hodgkin's Disease***

STAGE I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E).
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaghragm(II_E).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen(III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both(III_{SE})
STAGE IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

The presence or absence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the six months preceding admission are denoted by the suffix letters B and A, respectively. Biopsy-documented involvement of Stage IV sites is also denoted by letter suffixes: marrow = M+; lung = L+; liver = H+; pleura + P+; bone = O+; skin and subcutaneous tissue = D+.

TABLE 3. HODGKIN'S DISEASE. OBSERVED AGE-SPECIFIC, ALL CAUSE MORTALITY RATES FOR MALES AND FEMALES, 1940 - 1990.

RATES PER 1000 PERSON YEARS

AGE	1940 -	1945 -	1950 -	1955 -	1960 -	1965 -	1970 -	1975 -	1980 -	1985 +	MALE/ FEMALE	1940 - > 1990
2 - 4						163.4			106.2		.4	49.3
5 - 9				134.9	110.7	62.7	48.1	28.2	19.6	39.3	.4	48.7
10 - 14			180.7	71.4	100.3	61.2	23.1	22.9		17.9	.8	33.7
15 - 19		144.5	115.0	92.7	99.2	67.3	43.4	24.0	16.4	13.5	1.2	39.4
20 - 24		271.3	199.8	100.4	83.6	78.8	54.4	30.2	24.8	26.6	1.3	45.2
25 - 29		204.9	220.6	165.7	138.6	93.5	48.9	26.6	27.1	24.2	1.4	46.1
30 - 34	249.0	59.9	116.8	142.6	105.1	95.2	66.7	33.1	19.6	25.6	1.2	43.9
35 - 39		234.2	166.9	180.8	125.5	83.4	57.8	35.6	27.2	18.5	1.4	46.3
40 - 44	1591.5	869.6	257.5	190.7	122.5	92.4	73.9	45.6	27.4	18.8	1.5	54.2
45 - 49		261.3	317.1	129.7	150.8	138.9	99.3	57.6	26.6	37.4	1.5	71.9
50 - 54	1217.5	410.6	240.1	181.0	193.6	176.7	108.7	62.1	46.6	29.4	1.3	82.8
55 - 59		387.7	362.9	181.4	207.2	143.1	111.5	86.2	63.4	46.9	1.4	94.9
60 - 64	1902.3	6407.9	676.8	265.1	302.7	239.6	153.7	89.2	102.2	51.4	1.3	130.7
65 - 69			459.8	362.7	417.6	262.8	282.2	128.0	102.0	59.8	1.5	167.7
70 - 74			1241.8	386.4	431.4	230.9	313.7	190.6	143.3	123.6	1.1	206.3
75 - 79			767.3	434.1	670.2	529.5	339.8	215.4	164.4	82.3	1.2	256.5
80 - 84			4150.6	237.3	1765.7	549.6	510.5	294.3	243.3	99.3	1.1	313.5
85 - 99				888.7	1111.5	901.9	369.2	203.6	266.6	395.2	1.3	346.8
TOTAL OBSERVED	6	26	200	227	472	727	933	819	757	227		4394
TOTAL PERSON-YRS	24.3	117.2	887.6	1452.4	3155.6	6405.8	11673.8	17541.4	20736.2	7735.8		69350.0
OVERALL RATE	246.8	221.9	225.3	156.3	149.6	113.5	79.9	46.7	36.5	30.9		63.4
MALE/FEMALE	12.6	1.5	1.6	1.2	1.5	1.3	1.3	1.2	1.3	1.5	1.3	

TABLE 4. CHARACTERISTICS BY CANCER TREATMENT CENTER AMONG 9,316 HODGKIN'S DISEASE PATIENTS DIAGNOSED, 1940 - 1987.

CENTER	CALENDAR PERIOD OF DIAGNOSIS	TOTAL		MALES		FEMALES	
		# of cases	# of person years at risk	# of cases	# of person years at risk	# of cases	# of person years at risk
1. HARVARD JOINT CENTER FOR RADIATION THERAPY	1942-84	709	6063.7	407	3525.8	302	2538.0
2. MASS GEN HOSP	1960-84	791	5934.9	429	3146.3	362	2788.6
3. MCGILL U. TEACHING HOSP	1948-85	735	5262.5	400	2774.9	335	2487.7
4. SACRÉ-COEUR	1944-84	228	1601.2	138	882.8	90	718.4
5. MAISONNEUVE ROSEMONT	1954-84	222	1593.5	139	923.4	83	670.1
6. NOTRE-DAME	1940-84	538	3697.8	323	1952.2	215	1745.7
7. SAINT-LUC	1954-84	109	728.2	71	472.6	38	255.6
8. HOTEL-DIEU	1942-84	364	2124.7	213	1083.7	151	1040.9
9. SAINTE-JUSTINE	1946-84	74	651.2	51	457.1	23	194.1
10. PRINCESS MARGARET HOSPITAL	1940-84	2444	17774.8	1435	9700.8	1009	8074.1
11. NEW YORK	1948-84	1763	12999.7	973	6764.2	790	6235.5
12. HOUSTON	1949-87	1179	9313.6	686	5125.4	493	4188.2
13. CHICAGO	1967-84	160	1604.3	84	876.8	76	727.5
TOTAL		9316	69350.0	5349	37685.7	3967	31664.3

TABLE 5. PERSON YEARS AT RISK IN COHORT OF 9,316 SUBJECTS WITH HODGKIN'S DISEASE, 1940 - 1990.

PERIOD OF DIAGNOSIS

AGE	1940 -	1945 -	1950 -	1955 -	1960 -	1965 -	1970 -	1975 -	1980 -	1985 -	TOTAL
2 - 4		.5	1.8	4.0	.3	6.1	7.4	8.7	9.4	2.2	**40.6**
5 - 9		4.3	10.8	37.1	45.2	63.8	124.6	141.8	101.9	25.4	**554.9**
10 - 14		3.6	27.7	70.0	139.6	179.7	345.9	436.1	342.1	55.8	**1600.5**
15 - 19	1.0	13.9	52.2	107.9	302.5	579.4	922.0	1168.3	1098.5	222.5	**4468.1**
20 - 24	6.1	18.4	125.1	159.4	370.7	1002.8	1821.2	2381.7	2378.1	675.7	**8939.2**
25 - 29	6.6	24.4	126.9	241.4	425.7	919.5	2023.6	3122.1	3211.9	993.5	**11095.6**
30 - 34	8.0	16.7	145.6	231.4	437.8	808.5	1468.8	2807.1	3516.1	1209.3	**10649.2**
35 - 39		17.1	119.8	171.5	374.5	659.2	1107.0	1739.8	2940.0	1190.1	**8319.0**
40 - 44	1.3	3.5	69.9	104.9	277.7	551.8	947.2	1315.8	1754.7	956.4	**5982.9**
45 - 49		3.8	82.0	100.3	205.6	439.3	785.6	1162.9	1318.2	507.8	**4605.6**
50 - 54	.8	7.3	45.8	71.8	180.8	322.6	607.2	965.9	1158.2	408.2	**3768.5**
55 - 59		2.6	38.6	60.8	125.5	307.6	511.1	742.2	978.7	341.2	**3108.2**
60 - 64	.5	.2	17.7	41.5	115.6	204.5	435.9	616.6	723.8	291.7	**2448.0**
65 - 69		.4	13.1	27.6	86.2	159.8	233.9	453.1	529.3	184.0	**1687.3**
70 - 74		.6	6.4	12.9	37.1	125.6	172.2	236.1	356.0	153.8	**1100.6**
75 - 79			3.9	4.6	22.4	56.7	114.8	143.9	200.7	72.9	**619.9**
80 - 84			.2	4.2	4.0	14.6	37.22	74.8	69.9	50.3	**255.2**
85 - 99				1.1	4.5	4.4	8.1	24.6	48.8	15.2	**106.7**
TOTAL	**24.3**	**117.2**	**887.6**	**1452.4**	**3155.6**	**6405.8**	**11673.8**	**17541.4**	**20736.2**	**7355.8**	**69350.0**

TABLE 6. CHARACTERISTICS OF 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE

	TOTAL	MALES		FEMALES	
		#	% ROW	#	% ROW
	9316	5349	57.4	3967	42.6
AGE AT DIAGNOSIS					
2 - 9	230	168	73.0	62	27.0
10 - 19	1629	849	52.1	780	47.9
20 - 29	2917	1610	55.2	1307	44.8
30 - 39	1612	953	59.1	659	40.9
40 - 49	1064	702	66.0	362	34.0
50 - 59	833	482	57.9	351	42.1
60 - 69	627	364	58.1	263	41.9
70 - 79	340	190	55.9	150	44.1
80 - 99	64	31	48.4	33	51.6
YEAR OF DIAGNOSIS					
1940-1949	79	45	57.0	34	43.0
1950-1959	742	437	58.9	305	41.1
1960-1969	2568	1445	56.3	1123	43.7
1970-1979	4143	2405	58.0	1738	42.0
1980-1987	1784	1017	57.0	767	43.1

VARIABLE	MEAN	S.D.	MINIMUM	MAXIMUM
LENGTH OF FOLLOW-UP (years)				
Overall	7.4	6.3	0	44.9
Males	7.0	6.1	0	39.1
Females	8.0	6.5	.003	44.9
AGE AT DIAGNOSIS				
Overall	34.4	17.3	2.4	98.2
Males	37.7	17.2	2.4	95.4
Females	34.0	17.4	2.7	98.2
YEAR OF BIRTH			1868	1981
YEAR OF DIAGNOSIS			1940	1987
LAST KNOWN SURVIVAL DATE			1943	1990

TABLE 7. LENGTH OF SURVIVAL AMONG 9,316 HODGKIN'S DISEASE PATIENTS, 1940 - 1990.

Age at Diagnosis		0-11 Months	1-4 Years	5-9 Years	10-14 Years	15-19 Years	20-24 Years	25-29 Years	30+ Years	Total
2 - 9	TOTAL	16	62	55	48	28	11	8	2	230
	Males	8	45	44	38	15	10	7	1	168
	Females	8	17	11	10	13	1	1	1	62
10 - 19	TOTAL	80	441	483	327	186	74	23	15	1629
	Males	44	254	240	158	96	35	16	6	849
	Females	36	187	243	169	90	39	7	9	780
20 - 29	TOTAL	165	923	825	580	282	94	25	23	2917
	Males	106	542	449	311	137	41	10	14	1610
	Females	59	381	376	269	145	53	15	9	1307
30 - 39	TOTAL	112	557	469	271	127	54	17	5	1612
	Males	80	344	279	146	65	30	7	2	953
	Females	32	213	190	125	62	24	10	3	659
40 - 49	TOTAL	156	369	245	167	87	26	7	7	1064
	Males	109	247	157	115	53	14	4	3	702
	Females	47	122	88	52	34	12	3	4	362
50 - 59	TOTAL	170	307	199	99	46	10	2		833
	Males	113	184	114	50	15	5	1		482
	Females	57	123	85	49	31	5	1		351
60 - 69	TOTAL	194	259	105	49	12	8			627
	Males	124	147	59	25	5	4			364
	Females	70	112	46	24	7	4			263
70 - 79	TOTAL	149	130	52	6	2	1			340
	Males	75	80	31	3		1			190
	Females	74	50	21	3	2				150
80 - 99	TOTAL	40	17	6	1					64
	Males	22	7	2						31
	Females	18	10	4	1					33
TOTAL		1082	3065	2439	1548	770	278	82	52	9316
TOTAL MALES		681	1850	1375	846	386	140	45	26	5349
TOTAL FEMALES		401	1215	1064	702	384	138	37	26	3967

TABLE 8. AGE-SPECIFIC, ALL CAUSE MORTALITY RATES FOR MALES, 1940-1990.

RATES PER 1000 PERSON-YEARS

AGE	1940 -	1945 -	1950 -	1955 -	1960 -	1965 -	1970 -	1975 -	1980 -	1985 +	1940 - >1990
2 - 4									166.8		34.4
5 - 9				113.4	131.7	44.1	10.8	26.4	12.1	43.7	36.8
10 - 14			172.8	80.7	94.0	60.8	29.2	10.5		22.1	31.2
15 - 19		100.3	155.7	129.0	122.8	75.1	44.5	28.0	13.8	14.7	42.8
20 - 24		226.5	247.2	124.2	110.0	96.9	59.9	36.7	26.8	27.6	51.3
25 - 29		353.6	219.9	184.2	185.3	117.7	57.8	27.9	31.5	21.4	53.0
30 - 34	1667.8	196.7	144.7	153.1	121.4	109.1	67.3	35.6	22.3	27.9	47.8
35 - 39		443.5	244.9	242.6	147.1	84.8	74.9	40.8	27.5	23.2	53.0
40 - 44	1691.5	865.5	324.3	133.7	130.6	103.9	89.0	49.6	34.4	29.4	63.7
45 - 49		712.0	331.8	126.6	168.9	149.2	113.5	60.8	32.9	52.1	85.3
50 - 54		695.7	228.1	180.3	272.5	196.8	109.9	73.0	51.4	36.2	90.7
55 - 59			392.1	255.7	235.8	172.3	141.6	94.9	72.3	56.7	108.9
60 - 64	1902.3	6407.9	866.3	229.5	361.1	297.0	179.3	87.4	108.7	54.1	144.4
65 - 69			438.6	322.8	441.5	259.4	348.0	160.4	143.1	51.0	199.8
70 - 74			867.6	374.9	348.2	226.5	338.2	157.1	178.1	173.8	219.6
75 - 79			880.8		636.8	414.0	371.4	224.0	189.9	131.7	275.5
80 - 84			4150.5	321.0	1486.0	538.4	415.4	379.9	157.9	148.9	323.9
85 - 99				4150.5	794.0	790.0	1773.1	298.9	248.3	395.6	404.2
TOTAL OBSERVED	5	14	123	132	317	430	550	485	462	145	2663
TOTAL PERSON-YRS	7.0	50.9	461.5	783.0	1802.7	3375.8	6161.5	9582.8	11425.3	4035.3	37685.7
OVERALL RATE	718.5	275.2	266.5	168.6	175.9	127.4	89.3	50.6	40.4	35.9	70.7

TABLE 9. AGE-SPECIFIC ALL-CAUSE MORTALITY RATES FOR FEMALES, 1940 - 1990.

RATES PER 1000 PERSON-YEARS

AGE	1940 -	1945 -	1950 -	1955 -	1960 -	1965 -	1970 -	1975 -	1980 -	1985 -	1940 → 1990
2 - 4						362.4					86.7
5 - 9				188.6		108.5	154.6	35.8	51.9		92.0
10 - 14			194.1	49.0	114.0	62.3	14.3	46.6			39.2
15 - 19		257.8	49.9	55.9	71.6	60.1	42.1	19.6	20.2	11.6	35.3
20 - 24		312.5	155.2	80.6	60.6	63.8	48.7	22.7	22.7	25.6	38.9
25 - 29		125.6	221.6	144.0	85.4	70.4	39.9	25.1	21.6	27.1	38.3
30 - 34			95.9	131.8	82.2	80.1	66.1	30.4	16.6	22.8	39.4
35 - 39		159.1	104.9	123.5	99.7	81.4	41.1	30.0	26.9	12.9	38.6
40 - 44		878.0	194.6	247.5	108.4	78.0	50.8	40.7	19.4	6.7	42.3
45 - 49			296.1	134.9	115.2	122.7	77.4	52.4	18.7	20.9	56.6
50 - 54	1217.5	340.7	251.1	182.1	112.3	153.5	106.9	46.1	39.4	21.4	71.8
55 - 59		387.7	330.1	134.1	156.0	114.9	80.0	75.5	51.0	30.9	77.4
60 - 64			323.2	325.7	215.6	179.8	131.8	91.3	93.7	46.8	114.1
65 - 69			509.1	445.3	384.9	266.8	218.6	92.5	62.8	69.7	133.5
70 - 74			2183.9	440.6	566.7	234.6	291.0	225.9	109.9	88.4	193.5
75 - 79			2371.3		748.8	834.1	314.3	205.8	136.3	47.0	235.3
80 - 84					3335.2	569.2	745.2	231.7	345.2	42.6	301.2
85 - 99					1235.0	1567.6	264.5	137.7	275.6	394.7	313.0
TOTAL OBSERVED	1	12	77	95	155	297	383	334	295	82	1731
TOTAL PERSON-YRS	17.4	66.3	426.1	669.4	1352.4	3030.1	5512.3	7958.5	9310.9	3320.5	31664.3
OVERALL RATE	57.6	181.0	180.7	141.9	114.6	98.0	69.5	42.0	31.7	24.7	54.7

TABLE 10. ADJUSTED RELATIVE RISK OF DEATH BY CALENDAR PERIOD, 1940 - 1990.

FEMALES - ALL CAUSES

	OBSERVED	EXPECTED	RELATIVE RISK	95% CONFIDENCE INTERVAL	
1940-44	1	.04	26.6	.7	147.9
1945-49	12	.17	71.0	36.7	124.0
1950-54	77	1.20	64.3	57.4	72.6
1955-59	95	1.98	47.9	43.3	53.5
1960-64	155	5.00	31.0	28.6	33.7
1965-69	297	11.54	25.7	24.3	27.3
1970-74	383	21.20	18.1	17.2	19.0
1975-79	334	29.32	11.4	10.8	12.1
1980-84	295	36.68	8.0	7.6	8.5
1985-90	82	14.42	5.7	5.1	6.4
TOTAL	**1731**	**121.56**	**14.2**	**13.9**	**14.6**

TABLE 11. ADJUSTED RELATIVE RISK OF DEATH BY CALENDAR PERIOD, 1940-1990.

MALES - ALL CAUSES

CALENDAR PERIOD	OBSERVED	EXPECTED	RELATIVE RISK	95% CONFIDENCE INTERVAL	
1940-44	5	.04	139.0	45.0	324.3
1945-49	14	.19	75.3	41.1	126.3
1950-54	123	3.01	40.9	37.4	44.9
1955-59	132	5.34	24.7	22.7	27.1
1960-64	317	13.16	24.1	22.8	25.5
1965-69	430	26.80	16.0	15.3	16.6
1970-74	550	42.69	12.9	12.4	13.5
1975-79	485	63.24	7.7	7.3	8.0
1980-84	462	76.44	6.0	5.8	6.3
1985-90	145	29.80	4.9	4.5	5.3
TOTAL	2663	260.70	10.2	10.0	10.4

TABLE 12. ADJUSTED RELATIVE RISK OF DEATH BY CALENDAR PERIOD, 1940 - 1990.

MALES AND FEMALES - ALL CAUSES

CALENDAR PERIOD	OBSERVED	EXPECTED	RELATIVE RISK	95% CONFIDENCE INTERVAL	
1940-44	6	.07	81.5	29.9	177.4
1945-49	26	.35	73.3	47.8	107.3
1950-54	200	4.21	47.5	44.3	51.2
1955-59	227	7.32	31.0	29.0	33.2
1960-64	472	18.16	26.0	24.8	27.2
1965-69	727	38.35	19.0	18.3	19.7
1970-74	933	63.89	14.6	14.1	15.1
1975-79	819	92.56	8.8	8.6	9.2
1980-84	757	113.12	6.7	6.5	6.9
1985-90	227	44.22	5.1	4.8	5.5
TOTAL	4394	382.25	11.5	11.3	11.7

TABLE 13. ADJUSTED RELATIVE RISK OF DEATH BY AGE, 1940 - 1990.

MALES AND FEMALES - ALL CAUSES

AGE	OBSERVED	EXPECTED	RELATIVE RISK	95%	CONFIDENCE INTERVAL
2 - 4	2	.17	12.0	1.5	43.2
5 - 9	27	.22	123.3	81.3	179.4
10 - 14	54	.61	88.0	76.8	102.0
15 - 19	176	4.62	38.1	35.3	41.2
20 - 24	404	11.53	35.4	33.4	36.9
25 - 29	511	13.60	37.6	36.0	39.3
30 - 34	467	14.03	33.3	31.8	34.9
35 - 39	385	14.92	25.8	24.5	27.2
40 - 44	324	17.16	18.9	17.9	20.0
45 - 49	331	22.24	14.9	14.1	15.8
50 - 54	312	28.99	10.8	10.2	11.4
55 - 59	295	36.69	8.0	7.6	8.5
60 - 64	320	44.32	7.2	6.8	7.7
65 - 69	283	45.58	6.2	5.9	6.6
70 - 74	227	44.63	5.1	4.8	5.5
75 - 79	159	39.66	4.0	3.7	4.4
80 - 84	80	25.27	3.2	2.8	3.6
85 - 99	37	18.01	2.1	1.7	2.5
TOTAL	4394	382.25	11.5	11.3	11.7

TABLE 14. ADJUSTED RELATIVE RISK OF DEATH BY AGE, 1940 -1990.

FEMALES - ALL CAUSES

AGE	OBSERVED	EXPECTED	RELATIVE RISK	95% CONFIDENCE INTERVAL	
2 - 4	1	.04	24.7	.6	137.7
5 - 9	11	.04	305.3	152.4	546.2
10 - 14	20	.13	151.6	92.6	234.1
15 - 19	72	1.11	64.9	57.7	73.6
20 - 24	170	2.68	63.5	58.9	68.8
25 - 29	201	3.41	59.0	55.0	63.4
30 - 34	197	4.18	47.2	44.0	50.8
35 - 39	150	4.79	31.3	28.9	34.1
40 - 44	113	5.30	21.3	19.4	23.6
45 - 49	107	6.05	17.7	16.1	19.6
50 - 54	113	7.85	14.4	13.1	15.9
55 - 59	107	10.43	10.3	9.3	11.4
60 - 64	126	12.67	9.9	9.1	11.0
65 - 69	109	14.35	7.6	6.9	8.4
70 - 74	109	15.79	6.9	6.3	7.6
75 - 79	69	13.53	5.1	4.5	5.8
80 - 84	35	8.89	3.9	3.3	4.8
85 - 99	21	10.32	2.0	1.3	3.1
TOTAL	**1731**	**121.56**	**14.2**	**13.9**	**14.6**

TABLE 15. ADJUSTED RELATIVE RISK OF DEATH BY AGE, 1940 - 1990.

MALES - ALL CAUSES

AGE	OBSERVED	EXPECTED	RELATIVE RISK	95%	CONFIDENCE INTERVAL
2 - 4	1	.13	7.9	.2	43.9
5 - 9	16	.18	87.5	50.0	142.0
10 - 14	34	.48	70.6	59.4	85.4
15 - 19	104	3.51	29.6	26.9	32.9
20 - 24	234	8.85	26.4	24.8	28.3
25 - 29	310	10.19	30.4	28.8	32.3
30 - 34	270	9.85	27.4	25.8	29.2
35 - 39	235	10.13	23.2	21.8	24.8
40 - 44	211	11.87	17.8	16.6	19.1
45 - 49	224	16.19	13.8	13.0	14.8
50 - 54	199	21.14	9.4	8.8	10.1
55 - 59	188	26.26	7.2	6.7	7.7
60 - 64	194	31.65	6.1	5.7	6.6
65 - 69	174	31.23	5.6	5.2	6.0
70 - 74	118	28.84	4.1	3.7	4.5
75 - 79	90	26.13	3.4	3.1	3.9
80 - 84	45	16.38	2.7	2.4	3.2
85 - 99	16	7.69	2.1	1.2	3.4
TOTAL	2663	260.70	10.2	10.0	10.4

Table 16. Overall Survival for Patients Diagnosed with Hodgkin's Disease.

	# at risk	1-yr (SE)	5-yrs (SE)	10-yrs (SE)	15-yrs (SE)	20-yrs (SE)	25-yrs (SE)	30-yrs (SE)	35-yrs (SE)	40-yrs (SE)	45-yrs (SE)
Overall	9,316	.89 (.003)	.66 (.005)	.53 (.006)	.44 (.006)	.38 (.008)	.34 (.01)	.29 (.01)	.24 (.02)	.24 (.02)	.12 (.09)
Females	3,967	.91 (.005)	.70 (.008)	.57 (.009)	.48 (.01)	.43 (.01)	.38 (.02)	.32 (.02)	.30 (.02)	.30 (.03)	.15 (.11)
Males	5,349	.88 (.004)	.63 (.009)	.50 (.008)	.41 (.008)	.36 (.01)	.31 (.01)	.26 (.02)	.20 (.03)	.20 (.03)	—
Age < 40	6,388	.95 (.003)	.75 (006)	.63 (.007)	.55 (.008)	.49 (.01)	.45 (.01)	.40 (.02)	.33 (.03)	.33 (.03)	.16 (.13)
Age =>40	2,928	.77 (.008)	.46 (.01)	.31 (.01)	.23 (.01)	.17 (.01)	.12 (.01)	.08 (.02)	.08 (.02)	—	—
< 1967	2,374	.83 (.008)	.47 (.01)	.31 (.01)	.23 (.01)	.20 (.01)	.17 (.01)	.15 (.01)	.12 (.01)	.12 (.01)	.06 (.04)
=> 1967	6,942	.91 (.003)	.73 (.01)	.62 (.01)	.54 (.01)	.50 (.01)	.49 (.01)	—	—	—	—
< 1970	3,389	.84 (.006)	.50 (.009)	.36 (.008)	.29 (.008)	.25 (.008)	.22 (.008)	.19 (.01)	.16 (.01)	.16 (.01)	.07 (.06)
=> 1970	5,927	.92 (.004)	.76 (.006)	.64 (.007)	.57 (.01)	.53 (.01)	—	—	—	—	—
<= 1959	714	.80 (.015)	.38 (.018)	.24 (.016)	.19 (.01)	.16 (.01)	.14 (.01)	.11 (.01)	.09 (.01)	.09 (.01)	.05 (.03)
1960-69	2,675	.85 (.007)	.54 (.01)	.39 (.01)	.32 (.01)	.28 (.01)	.24 (.01)	.22 (.01)	—	—	—
=> 1970	5,927	.92 (.004)	.76 (.006)	.64 (.007)	.57 (.01)	.53 (.01)	—	—	—	—	—

Table 17. UNIVARIATE SURVIVAL ANALYSIS

Variable	# at Risk	Median Survival (Years)	S.E.
Overall	9,316	11.6	0.31
Females	3,967	14.0	0.63
Males	5,349	9.9	0.34
Age < 40 years	6,388	19.4	0.87
Age > 40 years	2,928	4.5	0.15
< 1967	2,374	4.6	0.15
=> 1967	6,942	19.6	1.92
< 1970	3,389	5.2	0.15
=> 1970	5,927	N.A.	N.A.
<= 1959	714	3.9	0.21
1960-69	2,675	6.3	0.22
=> 1970	5,927	N.A.	N.A.

N.A. = Not Applicable i.e. more than half the patients were still alive at the end of the study period.

Table 18. Univariate Analysis Using Cox's Proportional Hazards Model

Variable	Coefficient	(S.E.)	Relative Risk	95% Confidence Interval Interval	
				Upper	Lower
Age					
2 - 14	-1.958	0.0815	0.14	0.13	0.17
15 - 19	-1.649	0.0603	0.19	0.17	0.22
20 - 29	-1.584	0.0467	0.21	0.19	0.22
30 - 39	-1.310	0.0512	0.27	0.24	0.30
40 - 49	-0.961	0.0535	0.38	0.34	0.42
50 - 59	-0.586	0.0542	0.56	0.50	0.62
60 - 98	**Reference**		**1.00**		
Period					
1940 - 64	**Reference**		**1.00**		
1965 - 69	-0.427	0.0410	0.65	0.60	0.71
1970 - 74	-0.884	0.0413	0.41	0.38	0.45
1975 - 90	-1.194	0.0432	0.30	0.28	0.33
Sex					
Males	**Reference**		**1.00**		
Females	-0.226	0.0309	0.80	0.75	0.85

Table 19. Regression Coefficients, Log-Likelihood and Likelihood Ratio Test Statistics for Cox's Proportional Hazards Models.

MODEL	COVARIATES	-2 LOG-LIKELIHOOD	X^2	d.f.	P Value*
0	None	75406.38			
1	Sex	75352.35	54.03	1	<0.00001
2	Sex + Age	73900.69	1505.69	7	<0.00001
3	Sex+Age+Period	72997.39	2409.00	10	<0.00001
4	Sex+Age+Period+ Age*Sex	72978.96	2427.42	16	<0.00001
5	Sex+Age+Period+ Age*Period	72896.57	2509.82	28	<0.00001
6	Sex+Age+Period+ Age*Sex+Age*Period	72880.13	2526.25	34	<0.00001
7	Sex+Age+Period+ Age*Sex+Age*Period+ Sex*Period	72878.09	2528.29	37	<0.00001

* The actual magnitude of the P-value is not known as the smallest value that the program gives is 0.00001.

Table 20. Comparison of Cox's Regression Models.

Comparison	Likelihood Ratio Test	Degrees of Freedom	P-Value
Model 2 vs Model 1	1451.66	6	<0.001
Model 3 vs Model 2	903.30	3	<0.001
Model 4 vs Model 3	18.42	6	<0.01
Model 5 vs Model 3	100.82	18	<0.001
Model 6 vs Model 3	117.26	24	<0.001
Model 6 vs Model 4	98.83	18	<0.001
Model 6 vs Model 5	16.44	6	<0.001
Model 7 vs Model 6	2.04	3	<0.10

Table 21. Cox Proportional Hazards
Model 3: Age + Period + Sex

VARIABLE	COEFFICIENT	(S.E.)	RELATIVE RISK	95% CONFIDENCE INTERVAL	
				LOWER	UPPER
Sex					
Male	Reference		1.00		
Female	-0.239	0.0311	0.79	0.75	0.84
Age					
2 - 14	-2.038	0.0816	0.13	0.11	0.15
15 - 19	-1.615	0.0604	0.20	0.18	0.22
20 - 29	-1.559	0.0467	0.21	0.19	0.23
30 - 39	-1.360	0.0512	0.26	0.23	0.28
40 - 49	-1.024	0.0536	0.36	0.32	0.40
50 - 59	-0.583	0.0542	0.56	0.50	0.62
60 - 98	Reference		1.00		
Period					
1940-64	Reference		1.00		
1965-69	-0.450	0.0411	0.64	0.59	0.69
1970-74	-0.873	0.0414	0.42	0.39	0.45
1975-90	-1.209	0.0433	0.30	0.27	0.32

Table 22. Cox Proportional Hazards
Model 4: Age + Period + Sex + Age*Sex

VARIABLE	COEFFICIENT	(S.E.)	RELATIVE RISK	95% CONFIDENCE INTERVAL	
				LOWER	UPPER
Sex					
Male	Reference		**1.00**		
Female	-0.072	0.0696	0.93	0.81	1.07
Age					
2 - 14	-2.127	0.1060	0.12	0.10	0.15
15 - 19	-1.535	0.0815	0.22	0.18	0.25
20 - 29	-1.451	0.0608	0.23	0.21	0.26
30 - 39	-1.264	0.0655	0.28	0.25	0.32
40 - 49	-0.958	0.0669	0.38	0.34	0.44
50 - 59	-0.482	0.0707	0.62	0.54	0.71
60 - 98	Reference		**1.00**		
Period					
1940-64	Reference		**1.00**		
1965-69	-0.453	0.0411	0.64	0.59	0.69
1970-74	-0.882	0.0415	0.41	0.38	0.45
1975-90	-1.213	0.0433	0.30	0.27	0.32
Age*Sex					
Females / 2-14 years	-0.268	0.1646	1.31	0.95	1.80
Females / 15-19yrs	-0.193	0.1203	.82	0.65	1.04
Females / 20-29yrs	-0.266	0.0940	.77	0.64	0.92
Females / 30-39yrs	-0.247	0.1044	.78	0.64	0.96
Females / 40-49yrs	-0.165	0.1124	.85	0.68	1.06
Females / 50-59yrs	-0.248	0.1098	.78	0.63	0.97
Males / 60-98yrs	Reference		**1.00**		

Table 23. Cox Proportional Hazards
Model 5: Age + Period + Sex + Age*Period

Variable	Coefficient	(S.E.)	R.R.	95% Confidence Interval Lower	Upper
Sex					
Male	**Reference**		**1.00**		
Female	-0.251	0.0312	0.78	0.73	0.83
Age					
< 15 years	-1.619	0.1312	0.20	0.15	0.26
15 - 19	-1.157	0.1105	0.31	0.25	0.39
20 - 29	-1.018	0.0868	0.36	0.30	0.43
30 - 39	-0.904	0.0899	0.41	0.34	0.48
40 - 49	-0.696	0.0977	0.50	0.41	0.60
50 - 59	-0.298	0.1048	0.74	0.60	0.91
60 - 98	**Reference**		**1.00**		
Period					
1940-64	**Reference**		**1.00**		
1965-69	-0.136	0.1021	0.87	0.71	1.07
1970-74	-0.255	0.0973	0.77	0.64	0.94
1975-87	-0.636	0.0957	0.53	0.44	0.64
Age*Period					
<15yrs/1965-69	-0.102	0.2073	0.90	0.60	1.36
<15yrs/1970-74	-0.863	0.2222	0.42	0.27	0.65
<15yrs/1975-87	-1.004	0.2773	0.37	0.21	0.63
15-19yrs/1965-69	-0.352	0.1633	0.70	0.51	0.97
15-19yrs/1970-74	-0.846	0.1666	0.43	0.31	0.59
15-19yrs/1975-87	-0.731	0.1717	0.48	0.34	0.67
20-29yrs/1965-69	-0.494	0.1313	0.61	0.47	0.79
20-29yrs/1970-74	-0.929	0.1282	0.39	0.31	0.51
20-29yrs/1975-87	-0.915	0.1308	0.40	0.31	0.52
30-39yrs/1965-69	-0.371	0.1429	0.69	0.52	0.91
30-39yrs/1970-74	-0.905	0.1460	0.40	0.30	0.54
30-39yrs/1975-87	-0.739	0.1418	0.48	0.36	0.63
40-49yrs/1965-69	-0.262	0.1496	0.77	0.57	1.03
40-49yrs/1970-74	-0.523	0.1432	0.59	0.45	0.78
40-49yrs/1975-87	-0.577	0.1560	0.56	0.41	0.76
50-59yrs/1965-69	-0.340	0.1542	0.71	0.53	0.96
50-59yrs/1970-74	-0.417	0.1504	0.66	0.49	0.88
50-59yrs/1975-87	-0.401	0.1509	0.67	0.50	0.90
60-98yrs/1940-64	**Reference**		**1.00**		

Table 24: Cox's Proportional Hazards
Model 6: Age + Period + Sex + Age*Period + Age*Sex

Variable	Coefficient	(S.E.)	R.R.	95% Confidence Interval Lower	Upper
Sex					
Male	Reference		1.00		
Female	-0.122	0.0701	0.89	0.77	1.02
Age					
2 - 14	-1.734	0.1458	0.18	0.03	0.24
15 - 19	-1.104	0.1229	0.33	0.26	0.42
20 - 29	-0.930	0.0938	0.39	0.33	0.47
30 - 39	-0.838	0.0970	0.43	0.36	0.52
40 - 49	-0.660	0.1040	0.52	0.42	0.63
50 - 59	-0.235	0.1128	0.79	0.63	0.99
60 - 98	Reference		1.00		
Period					
1940-64	Reference		1.00		
1965-69	-0.151	0.1024	0.86	0.70	1.05
1970-74	-0.278	0.0979	0.76	0.63	0.92
1975-90	-0.644	0.0958	0.53	0.44	0.63
Age*Period					
2-14yrs/1965-69	-0.088	0.2074	0.92	0.61	1.38
2-14yrs/1970-74	-0.882	0.2230	0.41	0.27	0.64
2-14yrs/1975-90	-0.977	0.2774	0.38	0.22	0.65
15-19yrs/1965-69	-0.337	0.1635	0.71	0.52	0.98
15-19yrs/1970-74	-0.825	0.1669	0.44	0.32	0.61
15-19yrs/1975-90	-0.724	0.1719	0.48	0.35	0.68
20-29yrs/1965-69	-0.479	0.1315	0.62	0.49	0.80
20-29yrs/1970-74	-0.916	0.1287	0.40	0.31	0.51
20-29yrs/1975-90	-0.913	0.1308	0.40	0.31	0.52
30-39yrs/1965-69	-0.354	0.1431	0.72	0.53	0.93
30-39yrs/1970-74	-0.883	0.1464	0.41	0.31	0.55
30-39yrs/1975-90	-0.732	0.1418	0.48	0.36	0.63
40-49yrs/1965-69	-0.248	0.1498	0.78	0.58	1.05
40-49yrs/1970-74	-0.501	0.1436	0.61	0.46	0.80
40-49yrs/1975-90	-0.569	0.1561	0.57	0.42	0.77
50-59yrs/1965-69	-0.320	0.1546	0.73	0.54	0.98
50-59yrs/1970-74	-0.396	0.1508	0.67	0.50	0.90
50-59yrs/1975-90	-0.397	0.1511	0.67	0.50	0.90
60-98yrs/1940-64	Reference		1.00		
Age*Sex					
Females / 2-14years	0.327	0.1653	1.39	1.00	1.92
Females / 15-19yrs	-0.152	0.1207	0.86	0.68	1.09
Females / 20-29yrs	-0.235	0.0943	0.79	0.66	0.95
Females / 30-39yrs	-0.198	0.1047	0.82	0.67	1.01
Females / 40-49yrs	-0.111	0.1129	0.90	0.72	1.12
Females / 50-59yrs	-0.180	0.1106	0.84	0.67	1.04
Males / 60-98years	Reference		1.00		

Table 25: Cox's Proportional Hazards Model
Model 6: Stratified by Sex

MALES

Variable	Coefficient	(S.E.)	R.R.	95% Confidence Interval Lower	Upper
Age					
2 - 14	-1.646	0.1641	0.19	0.14	0.27
15 - 19	-1.031	0.1462	0.36	0.28	0.47
20 - 29	-0.914	0.1104	0.40	0.32	0.50
30 - 39	-0.796	0.1118	0.45	0.36	0.56
40 - 49	-0.672	0.1207	0.51	0.40	0.65
50 - 59	-0.247	0.1350	0.78	0.60	1.02
60 - 98	**Reference**		**1.00**		
Period					
1940-64	**Reference**		**1.00**		
1965-69	-0.114	0.1323	0.89	0.69	1.16
1970-74	-0.193	0.1275	0.82	0.64	1.06
1975-90	-0.643	0.1217	0.53	0.41	0.67
Age*Period					
2-14yrs/1965-69	-0.225	0.2688	0.80	0.47	1.35
2-14yrs/1970-74	-0.985	0.2966	0.37	0.21	0.68
2-14yrs/1975-90	-1.192	0.3660	0.30	0.15	0.62
15-19yrs/1965-69	-0.481	0.2244	0.62	0.40	0.96
15-19yrs/1970-74	-0.892	0.2216	0.41	0.27	0.63
15-19yrs/1975-90	-0.805	0.2273	0.45	0.36	0.56
20-29yrs/1965-69	-0.429	0.1706	0.65	0.47	0.91
20-29yrs/1970-74	-0.988	0.1660	0.37	0.27	0.52
20-29yrs/1975-90	-0.935	0.1676	0.39	0.28	0.61
30-39yrs/1965-69	-0.421	0.1841	0.66	0.46	0.94
30-39yrs/1970-74	-0.973	0.1868	0.38	0.26	0.54
30-39yrs/1975-90	-0.740	0.1774	0.48	0.34	0.67
40-49yrs/1965-69	-0.213	0.1883	0.81	0.56	1.17
40-49yrs/1970-74	-0.500	0.1772	0.61	0.43	0.86
40-49yrs/1975-90	-0.530	0.1937	0.59	0.40	0.86
50-59yrs/1965-69	-0.210	0.2034	0.81	0.54	1.21
50-59yrs/1970-74	-0.452	0.1963	0.64	0.43	0.93
50-59yrs/1975-90	-0.377	0.1926	0.69	0.47	1.00
60-98yrs/1940-64	**Reference**		**1.00**		

Table 26: Cox's Proportional Hazards Model
Model 6 - Stratified by Sex

F E M A L E S

Variable	Coefficient	(S.E.)	R.R.	95% Confidence Interval Lower	Upper
Age					
2 - 14	-1.556	0.2187	0.21	0.14	0.32
15 - 19	-1.361	0.1713	0.26	0.18	0.36
20 - 29	-1.208	0.1410	0.30	0.23	0.39
30 - 39	-1.113	0.1510	0.33	0.24	0.44
40 - 49	-0.734	0.1666	0.48	0.35	0.66
50 - 59	-0.412	0.1673	0.66	0.48	0.92
60 - 98	**Reference**		**1.00**		
Period					
1940-64	**Reference**		**1.00**		
1965-69	-0.219	0.1622	0.80	0.58	1.10
1970-74	-0.389	0.1531	0.68	0.50	0.91
1975-90	-0.653	0.1558	0.52	0.38	0.71
Age*Period					
2-14yrs/1965-69	0.136	0.3278	1.15	0.60	2.18
2-14yrs/1970-74	-0.720	0.3404	0.49	0.24	0.95
2-14yrs/1975-90	-0.636	0.4276	0.53	0.23	1.22
15-19yrs/1965-69	-0.161	0.2421	0.85	0.53	1.37
15-19yrs/1970-74	-0.744	0.2547	0.48	0.29	0.78
15-19yrs/1975-90	-0.616	0.2639	0.54	0.32	0.91
20-29yrs/1965-69	-0.530	0.2073	0.59	0.39	0.88
20-29yrs/1970-74	-0.811	0.2044	0.44	0.30	0.66
20-29yrs/1975-90	-0.858	0.2098	0.42	0.28	0.64
30-39yrs/1965-69	-0.238	0.2284	0.79	0.50	1.23
30-39yrs/1970-74	-0.756	0.2364	0.47	0.30	0.75
30-39yrs/1975-90	-0.711	0.2368	0.49	0.31	0.78
40-49yrs/1965-69	-0.335	0.2493	0.72	0.44	1.17
40-49yrs/1970-74	-0.610	0.2563	0.54	0.33	0.90
40-49yrs/1975-90	-0.648	0.2648	0.52	0.31	0.88
50-59yrs/1965-69	-0.433	0.2380	0.65	0.41	1.03
50-59yrs/1970-74	-0.321	0.2357	0.73	0.46	1.15
50-59yrs/1975-90	-0.409	0.2447	0.66	0.41	1.07
60-98yrs/1940-64	**Reference**		**1.00**		

TABLE 27. UNDERLYING CAUSES OF DEATH AMONG 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE, 1940 - 1990.

			%
ALL CANCERS	**3640**		82.8
Hodgkin's Disease		3206	72.96
Non-Hodgkin's Lymphoma		161	3.66
Leukemia		88	2.00
Other Cancers		185	4.21
INFECTIONS	**68**		1.5
Infections & Parasitic Diseases		35	.80
Pneumonia/Influenza		33	.70
ISCHAEMIC HEART DISEASE	**177**	177	4.0
EXTERNAL CAUSES	**40**		0.9
M.V.A.		12	.27
Suicide		18	.41
Poisoning		3	.07
Injury - Accidental/Purposeful		4	.09
Other external		3	.07
OTHER CAUSES	**152**		3.5
MISSING DEATH CERTIFICATES	**317**		7.2
ALL CAUSES	**4394**		**100%**

TABLE 28: DEATH CHARACTERISTICS BY SEX

CAUSES OF DEATH	MALES		FEMALES	
	#	%	#	%
ALL CANCERS	**2185**	**82.1**	**1455**	**84.1**
Hodgkin's Disease	1926	72.3	1280	73.9
Non-Hodgkin's Lymphoma	98	3.7	63	3.7
Leukemia	50	1.9	38	2.2
Other Cancers	110	4.1	74	4.3
INFECTIONS	47	1.8	21	1.4
ISCHAEMIC HEART DISEASE	123	4.6	54	1.2
EXTERNAL CAUSES	30	1.1	10	.6
OTHER	95	3.6	57	3.3
MISSING *	183	6.9	134	7.7
ALL CAUSES	**2663**	**100.0**	**1731**	**100.0**

* Missing death certificates

TABLE 29. CAUSE OF DEATH CHARACTERISTICS BY SEX AND BY INTERVAL SINCE DIAGNOSIS OF HODGKIN'S DISEASE, 1940 - 1990.

TIME SINCE DIAGNOSIS OF HD		MALES		FEMALES	
		#	%	#	%
< 1 yr	All Causes	623	100.0	366	100.0
	All Neoplasms	549	88.1	325	88.8
	Hodgkin's Disease	488	78.3	289	79.0
	Non-Hodgkin's Lymphoma	34	5.4	24	6.6
	Leukemia	6	1.0	3	.8
1-4 yrs	All Causes	1252	100.0	751	100.0
	All Neoplasms	1063	84.9	654	87.1
	Hodgkin's Disease	986	78.8	603	80.3
	Non-Hodgkin's Lymphoma	28	2.2	23	3.1
	Leukemia	20	1.6	10	1.3
5-9 yrs	All Causes	509	100.0	392	100.0
	All Neoplasms	402	79.0	315	80.4
	Hodgkin's Disease	334	65.6	273	69.6
	Non-Hodgkin's Lymphoma	25	4.9	9	2.3
	Leukemia	4	.8	14	3.6
10-14 yrs	All Causes	188	100.0	151	100.0
	All Neoplasms	118	62.8	113	74.8
	Hodgkin's Disease	88	46.8	80	53.0
	Non-Hodgkin's Lymphoma	9	4.8	7	4.6
	Leukemia	-	-	7	4.6
15-19 yrs	All Causes	59	100.0	46	100.0
	All Neoplasms	36	61.0	34	73.9
	Hodgkin's Disease	22	37.3	27	58.7
	Non-Hodgkin's Lymphoma	2	3.4	-	-
	Leukemia		-	4	8.7
20-24 yrs	All Causes	20	100.0	16	100.0
	All Neoplasms	10	50.0	8	50.0
	Hodgkin's Disease	4	20.0	4	25.0
	Non-Hodgkin's Lymphoma	-	-	-	-
	Leukemia	-	-	-	-
25-29 yrs	All Causes	8	100.0	7	100.0
	All Neoplasms	5	62.5	5	71.4
	Hodgkin's Disease	3	37.5	3	42.9
	Non-Hodgkin's Lymphoma	-	-	-	-
	Leukemia	-	-	-	-
≥ 30 yrs	All Causes	4	100.0	2	100.0
	All Neoplasms	2	50.0	1	50.0
	Hodgkin's Disease	1	25.0	1	50.0
	Non-Hodgkin's Lymphoma	-	-	-	-
	Leukemia	-	-	-	-

TABLE 30: CAUSE-SPECIFIC MORTALITY. RELATIVE RISK OF DEATH AMONG 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE, 1940 - 1990.

	MALES				FEMALES				MALES AND FEMALES			
	OBS	EXP	R.R.	95% CI	OBS	EXP	R.R.	95% CI	OBS	EXP	R.R.	95% CI
ALL CAUSES	2663	260.70	10.2	10.0 - 10.4	1731	121.60	14.2	13.9 - 14.6	4394	382.25	11.5	11.3 - 11.7
ALL NEOPLASMS	2185	52.28	41.8	40.9 - 42.7	1455	32.47	44.8	43.7 - 46.0	3640	84.75	42.9	42.3 - 43.7
Hodgkin's Disease	1926	.65	2978.4	2912.4 - 3046.9	1280	.34	3791.9	3685.9 - 3899.7	3206	.98	3257.4	3201.4 - 3315.1
Non-Hodgkin's Lymphoma	98	2.49	39.4	32.0 - 48.9	63	1.23	51.2	39.3 - 65.5	161	3.72	43.3	36.9 - 50.5
Leukemia	50	2.33	21.5	18.7 - 25.1	38	1.27	29.9	25.4 - 35.8	88	3.60	24.5	22.0 - 27.4
Other Ca	111	46.79	2.4	1.9 - 2.9	74	29.40	2.5	2.0 - 3.2	185	76.20	2.4	2.1 - 2.8
INFECTIONS	47	7.18	6.6	4.8 - 8.7	21	3.72	5.6	3.5 - 8.6	68	10.88	6.3	4.9 - 7.9
Infectious-Parasitic Diseases	27	2.11	12.8	8.4 - 18.6	8	1.13	7.1	3.1 - 14.0	35	3.23	10.8	9.1 - 13.1
Pneumonia /Influenza	20	5.07	4.0	2.4 - 6.1	13	2.59	5.0	2.7 - 8.6	33	7.65	4.3	3.6 - 5.2
ISCHAEMIC HEART DISEASE	123	80.64	1.5	1.4 - 1.7	54	29.89	1.8	1.6 - 2.1	177	110.54	1.6	1.5 - 1.7
EXTERNAL CAUSES	30	43.0	.7	0.5 - 1.0	10	11.27	.7	0.4 - 1.6	40	54.43	.7	0.6 - .9
UNRELATED TO HODGKIN'S DISEASE	737	260.05	2.8	2.6 - 3.0	451	121.26	3.7	3.4 - 4.1	1188	381.27	2.9	2.8 - 3.1

TABLE 31: RELATIVE RISK OF DEATH DUE TO SECOND CANCERS AMONG 9,316 HODGKIN'S DISEASE PATIENTS BY TIME SINCE DIAGNOSIS, 1940 - 1990.

TIME SINCE DIANGOSIS (YEARS)	OBSERVED	EXPECTED	RELATIVE RISK	95% C.I.
< 1 yr	97	10.65	9.1	7.4 - 11.1
1 - 4	128	27.77	4.6	3.8 - 5.5
5 - 9	110	21.51	5.1	4.2 - 6.1
10 - 14	63	13.05	4.8	3.7 - 6.1
15 - 19	21	6.68	3.1	1.9 - 4.7
20 - 24	10	2.79	3.6	1.7 - 6.6
25 - 29	4	1.22	3.3	.9 - 8.5
≥ 30 yrs	1	.72	1.4	0.0 - 8.0
TOTAL	434	83.77	5.2	4.7 - 5.7

TABLE 32: RELATIVE RISK FOR ALL CAUSE MORTALITY AMONG 9,316 HODGKIN'S DISEASE PATIENTS BY TIME SINCE DIAGNOSIS, 1940 - 1990.

	ALL CAUSES OF DEATH											
	MALES				FEMALES				TOTAL			
TIME SINCE DIAGNOSIS	OBS	EXPECTED	RELATIVE RISK	95% C.I.	OBS	EXPECTED	RELATIVE RISK	95% C.I.	OBS	EXPECTED	RELATIVE RISK	95% C.I.
< 1 yr	623	37.3	16.7	16.1 - 17.4	366	15.4	22.7	22.5 - 25.0	989	52.7	18.8	17.6 - 20.0
1 - 4	1252	92.9	13.5	13.1 - 13.9	751	39.8	18.9	18.2 - 19.6	2003	132.7	15.1	14.4 - 15.8
5 - 9	509	66.0	7.7	7.4 - 8.1	392	30.3	12.9	12.3 - 13.6	901	96.3	9.4	8.8 - 10.0
10 - 14	188	35.6	5.3	4.9 - 5.7	151	19.7	7.7	7.1 - 8.3	339	55.3	6.1	5.5 - 6.8
15 - 19	59	17.3	3.4	3.0 - 3.9	46	9.7	4.7	4.1 - 5.6	105	27.0	3.9	3.2 - 4.7
20 - 24	20	7.4	2.7	1.6 - 4.2	16	3.9	4.1	2.3 - 6.6	36	11.3	3.2	2.2 - 4.4
25 - 29	8	2.8	2.8	1.2 - 5.5	7	1.5	4.6	1.9 - 9.6	15	4.3	3.5	2.0 - 5.9
≥ 30 yrs	4	1.3	3.1	.9 - 7.0	2	1.1	1.8	.2 - 6.4	6	2.4	2.5	1.3 - 4.3
TOTAL	2663	260.7	10.2	10.0 - 10.4	1731	121.6	14.2	13.9 - 14.6	4394	382.3	11.5	11.2 - 11.8

TABLE 33: RELATIVE RISK OF DEATH: ALL NEOPLASMS AMONG 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE BY TIME SINCE DIAGNOSIS, 1940 - 1990.

	MALES				FEMALES				TOTAL			
TIME SINCE DIAGNOSIS	OBS	EXPECTED	RELATIVE RISK	95% C.I.	OBS	EXPECTED	RELATIVE RISK	95% C.I.	OBS	EXPECTED	RELATIVE RISK	95% C.I.
< 1 yr	549	7.0	78.5	75.3 - 82.0	325	3.7	88.6	83.9 - 93.8	874	10.7	81.7	76.4 - 87.3
1 - 4	1063	17.8	59.7	57.9 - 61.6	654	10.1	64.9	62.4 - 67.5	1717	27.9	61.5	58.7 - 64.5
5 - 9	402	13.4	29.9	28.5 - 31.5	315	8.2	38.2	36.2 - 40.5	717	21.6	33.2	30.8 - 35.7
10 - 14	118	7.6	15.6	14.2 - 17.2	113	5.5	20.4	18.6 - 22.5	231	13.1	17.6	15.4 - 20.1
15 - 19	36	3.8	9.5	8.0 - 11.4	34	2.9	11.7	9.9 - 14.2	70	6.7	10.5	8.1 - 13.2
20 - 24	10	1.7	6.0	2.9 - 11.1	8	1.1	7.0	3.0 - 13.9	18	2.8	6.4	3.8 - 10.2
25 - 29	5	.7	7.2	2.3 - 16.7	5	.5	9.7	3.1 - 22.5	10	1.2	8.2	3.9 - 15.1
≥ 30 yrs	2	.3	6.3	.8 - 22.6	1	.4	2.6	.1 - 14.5	3	.7	4.2	.8 - 12.3
TOTAL	**2185**	**52.3**	**41.8**	**40.9 - 42.7**	**1455**	**32.5**	**44.8**	**43.7 - 46.0**	**3640**	**84.8**	**42.9**	**41.5 - 44.3**

TABLE 34: CAUSES OF DEATH AMONG 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE BY TIME SINCE DIAGNOSIS, 1940 - 1990.

TIME SINCE DIAGNOSIS	TOTAL ALL CAUSES	TOTAL CANCERS	TOTAL HODGKIN'S DISEASE	TOTAL NON-HODGKIN'S LYMPHOMA	TOTAL LEUKEMIA	TOTAL SOLID TUMOURS	TOTAL SECOND CANCERS	TOTAL OTHER	TOTAL UNRELATED TO HD
<1 YEAR	989	874	777	58	9	30	97	115	212
1 - 4	2003	1717	1589	51	30	47	128	286	414
5 - 9	901	717	607	34	34	42	110	184	294
10 - 14	339	231	168	16	11	36	63	108	171
15 - 19	105	70	49	2	4	15	21	35	56
20 - 24	36	18	8	-	-	10	10	18	28
25 - 29	15	10	6	-	-	4	4	5	9
≥ 30 YEARS	6	3	2	-	-	1	1	3	4
TOTAL	4394	3640	3206	161	88	185	434	754	1188

TABLE 35: PERCENTAGE OF DEATHS DUE TO HODGKIN'S DISEASE BY AGE, 1940 - 1990.

AGE	ALL CAUSES #	HODGKIN'S DISEASE		
		#	CUM. MORTALITY	%
2-4	2	0	0	
5-9	27	20	20	74.1
10-14	54	39	59	72.2
15-19	176	136	195	77.3
20-24	404	343	538	84.9
25-29	511	420	958	82.2
30-34	467	380	1338	81.4
35-39	385	299	1637	77.7
40-44	324	245	1882	75.6
45-49	331	218	2100	65.9
50-54	312	223	2323	71.5
55-59	295	202	2525	68.5
60-64	320	218	2743	68.1
65-69	283	173	2916	61.1
70-74	227	142	3058	62.6
75-79	159	87	3145	54.7
80-84	80	44	3189	55.0
85-99	37	17	3206	45.9
OVERALL	4,394	3,206	3,206	

TABLE 36: PERCENTAGE OF DEATHS DUE TO HODGKIN'S DISEASE BY PERIOD, 1940 - 1990.

PERIOD	ALL CAUSES	HODGKIN'S DISEASE	
		#	%
1940 - 1944	6	2	33.3
1945 - 1949	26	22	84.6
1950 - 1954	200	148	74.0
1955 - 1959	227	186	81.9
1960 - 1964	472	379	80.3
1965 - 1969	727	609	83.8
1970 - 1974	933	751	80.5
1975 - 1979	819	581	70.9
1980 - 1984	757	421	55.6
1985 - 1990	227	107	47.1
TOTAL	4,394	3,206	73.0

TABLE 37: RELATIVE RISK OF DEATH DUE TO LEUKEMIA AMONG 9,316 PATIENTS DIAGNOSED WTH HODGKIN'S DISEASE BY TIME SINCE DIAGNOSIS, 1940 - 1990.

	MALES AND FEMALES				
TIME SINCE DIAGNOSIS	OBSERVED	EXPECTED	RELATIVE RISK	95% CONFIDENCE INTERVAL	
< 1 yr	9	.477	18.9	8.6	- 36.0
1 - 4	30	1.260	23.8	16.0	- 34.0
5 - 9	34	.922	36.9	25.5	- 51.6
10 - 14	11	.525	21.0	10.4	- 37.7
15 - 19	4	.099	40.3	11.0	- 103.1
20 - 24	0	0	0		
25 - 29	0	0	0		
≥ 30 yrs	0	0	0		
TOTAL	88	3.283	26.8	21.7	- 32.8

TABLE 38: RELATIVE RISK OF DEATH DUE TO NON-HODGKIN'S LYMPHOMA AMONG 9,316 PATIENTS DIAGNOSED WITH HODGKIN'S DISEASE BY TIME SINCE DIAGNOSIS, 1940 - 1990.

	MALES AND FEMALES			
TIME SINCE DIAGNOSIS (YEARS)	OBSERVED	EXPECTED	RELATIVE RISK	95% C.I.
< 1 yr	58	.49	118.4	89.9 - 153.1
1 - 4	51	1.31	38.9	29.0 - 51.2
5 - 9	34	1.02	33.3	23.0 - 46.6
10 - 14	16	.62	25.8	14.7 - 42.0
15 - 19	2	.12	16.6	1.6 - 61.0
20 - 24	0	0	0	-
25 - 29	0	0	0	-
≥ 30 yrs	0	0	0	-
TOTAL	161	3.72	43.3	37.0 - 50.4

Mortality Rates By Age
Males And Females - All Causes

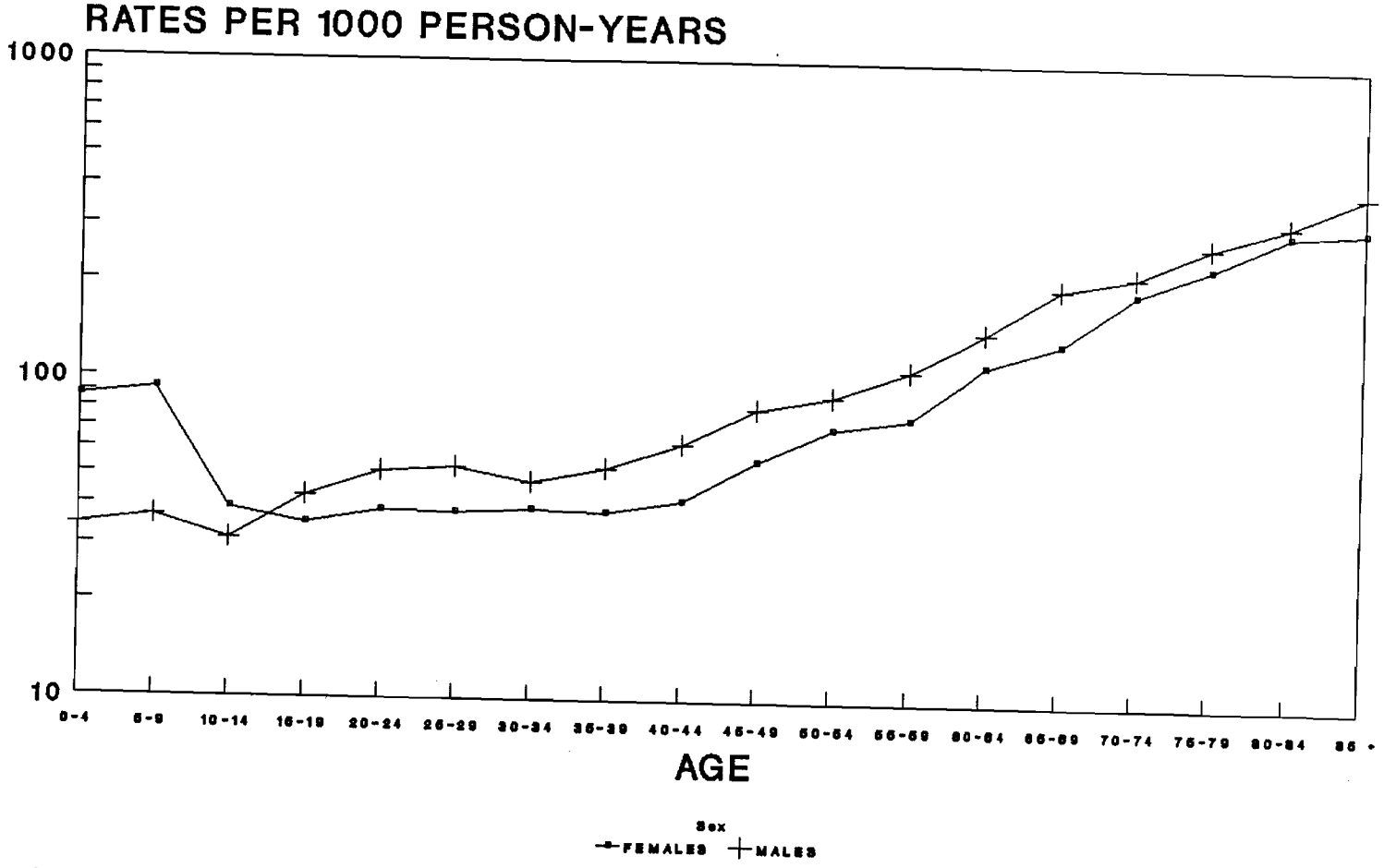

Fig. 1. Hodgkin's Disease.
Age-Specific Mortality Rates for Males and Females, 1940-1990.

Mortality Rates By Age
By Birth Cohorts - All Causes

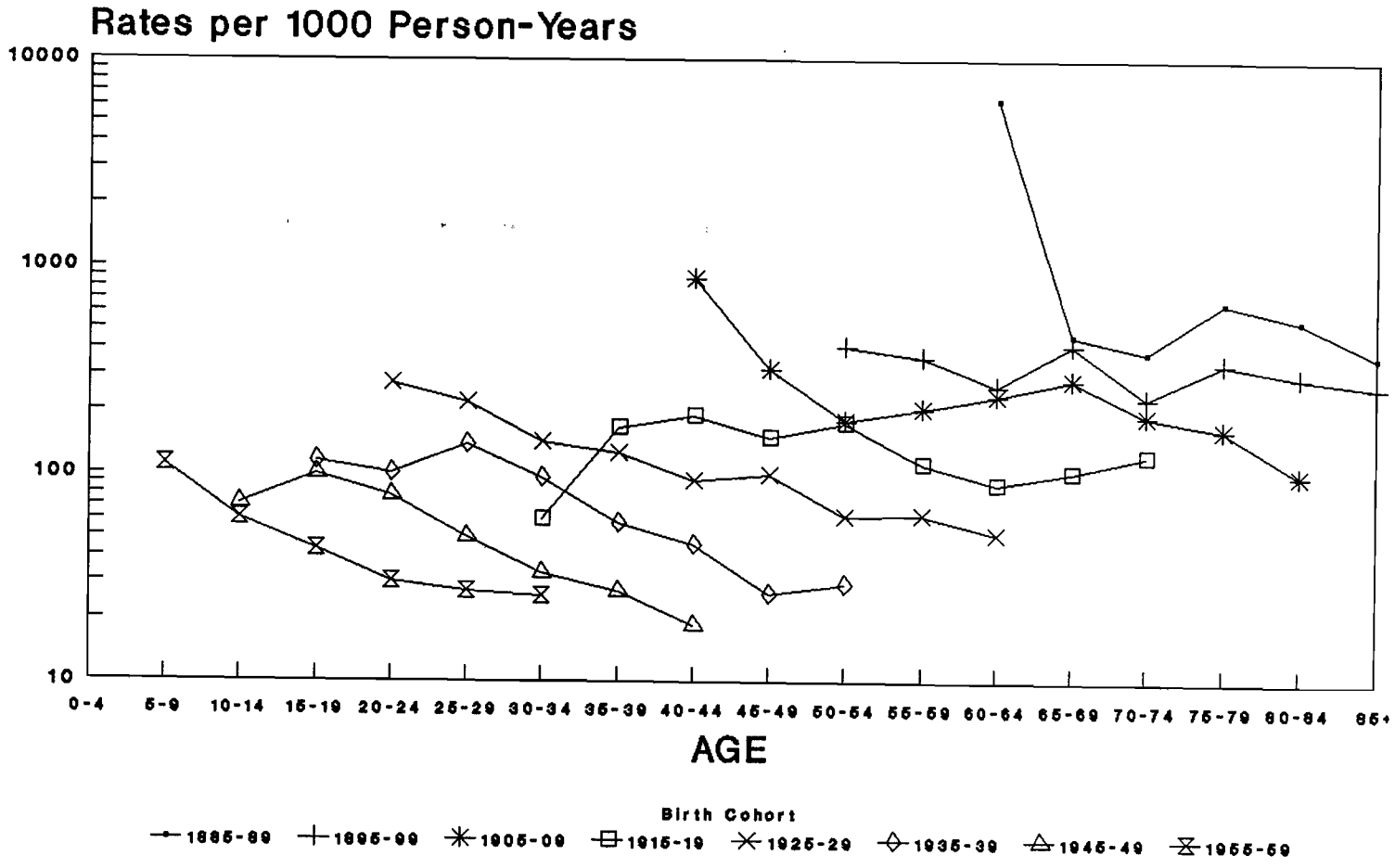

Figure 2. Hodgkin's Disease.
Age-Specific Mortality Rates for Males and Females, 1940-1990.

Mortality Rates By Birth Cohort
Males and Females

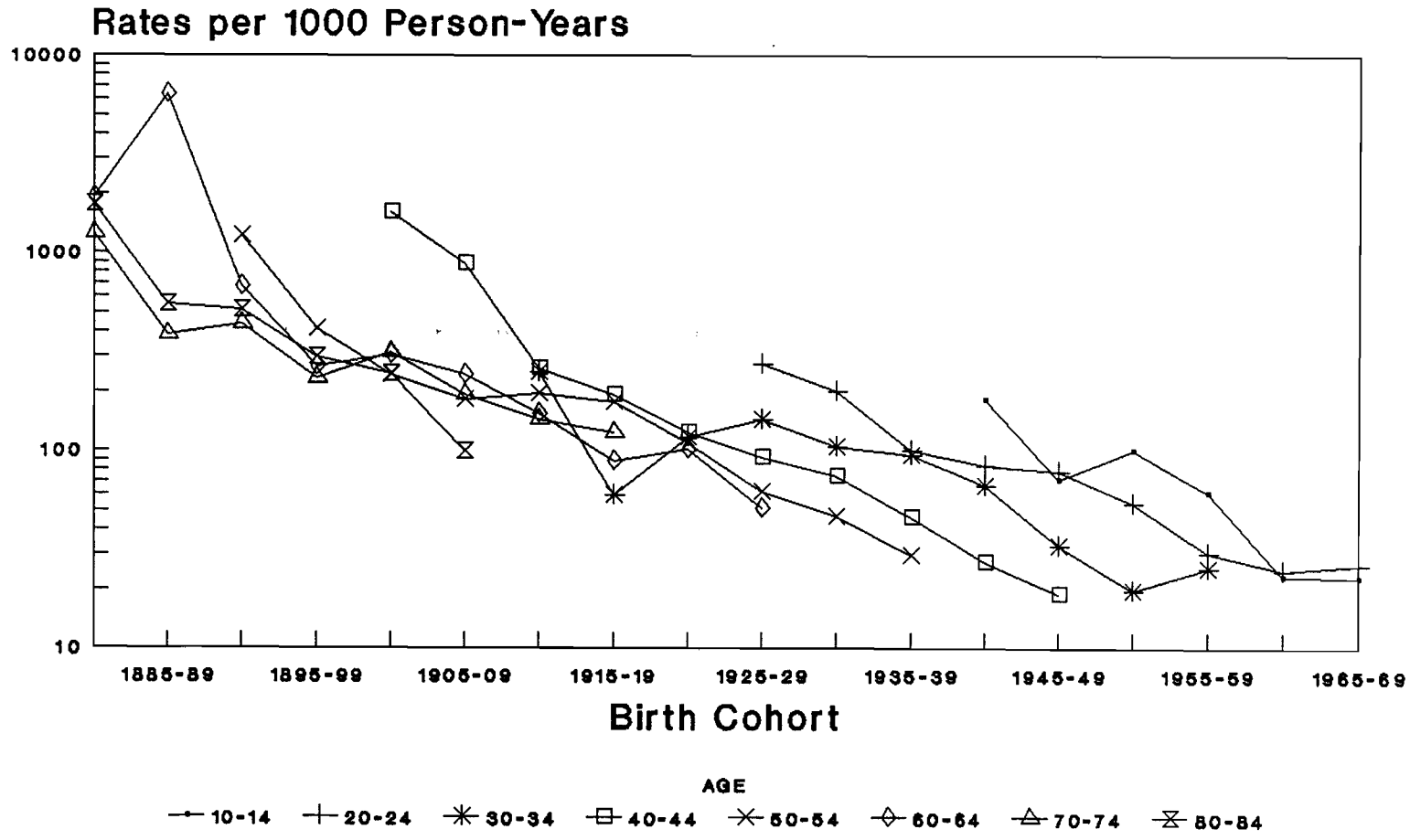

Figure 3. Hodgkin's Disease.
Age-Specific Mortality Rates for Males
and Females, 1940-1990.

Mortality Rates By Calendar Period
Males and Females - All Causes

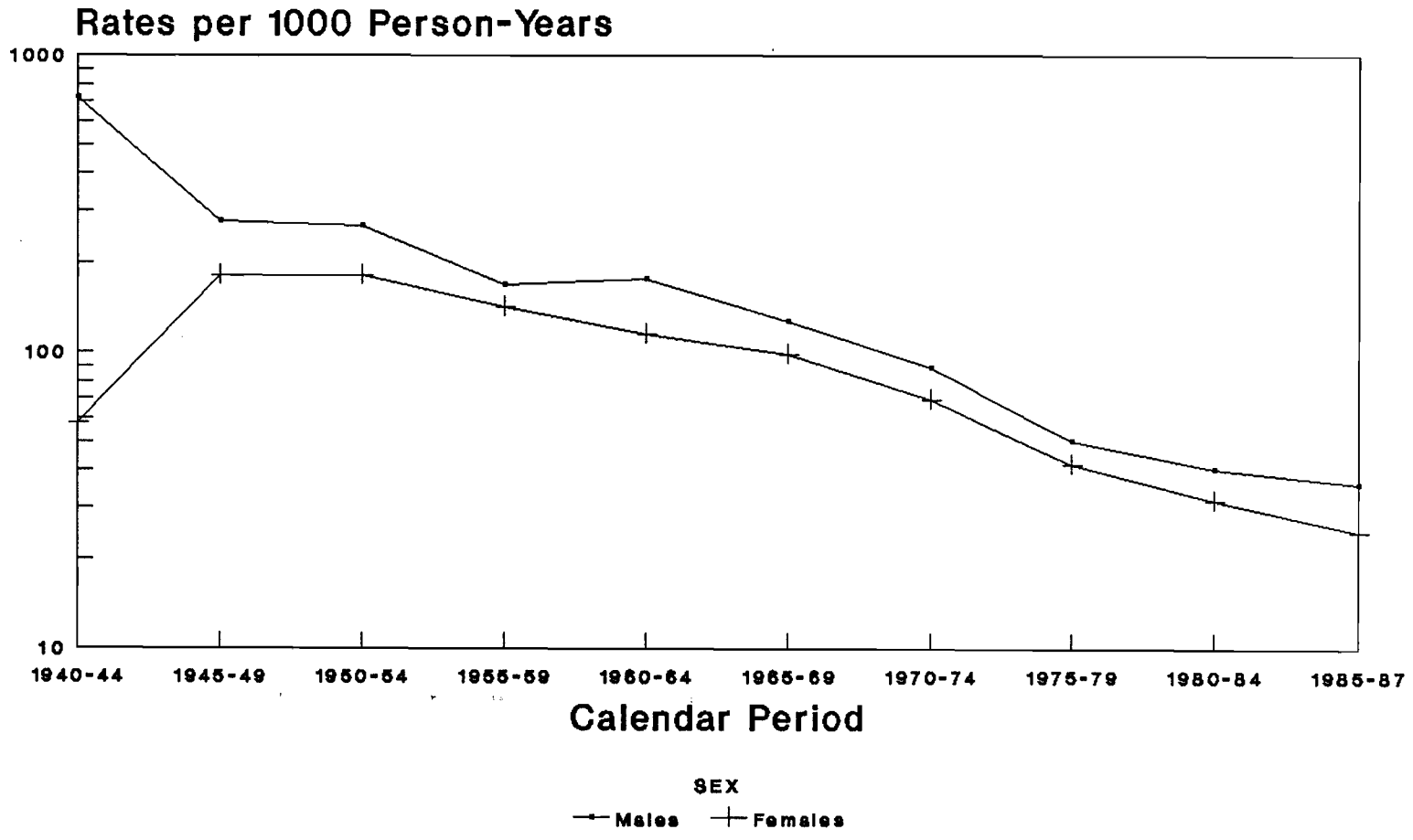

Figure 4. Hodgkin's Disease.
Mortality Rates For Males and Females
1940-1990.

Mortality Rates By Calendar Period
By Age Groups - All Causes

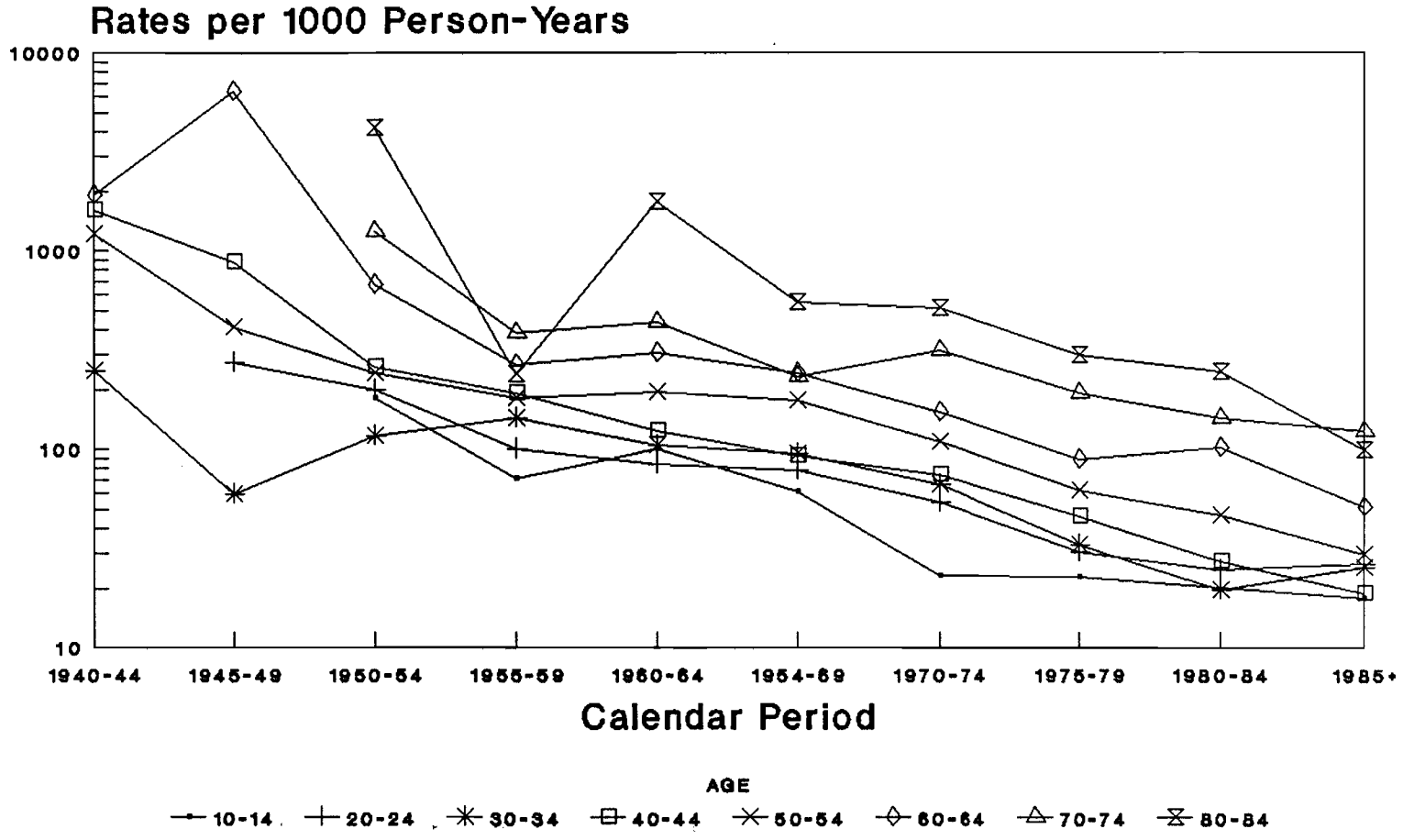

Figure 5. Hodgkin's Disease.
Age-Specific Mortality Rates For Males
And Females, 1940 - 1990.

Mortality Rates by Calendar Period
By Age Groups - All Causes - Females

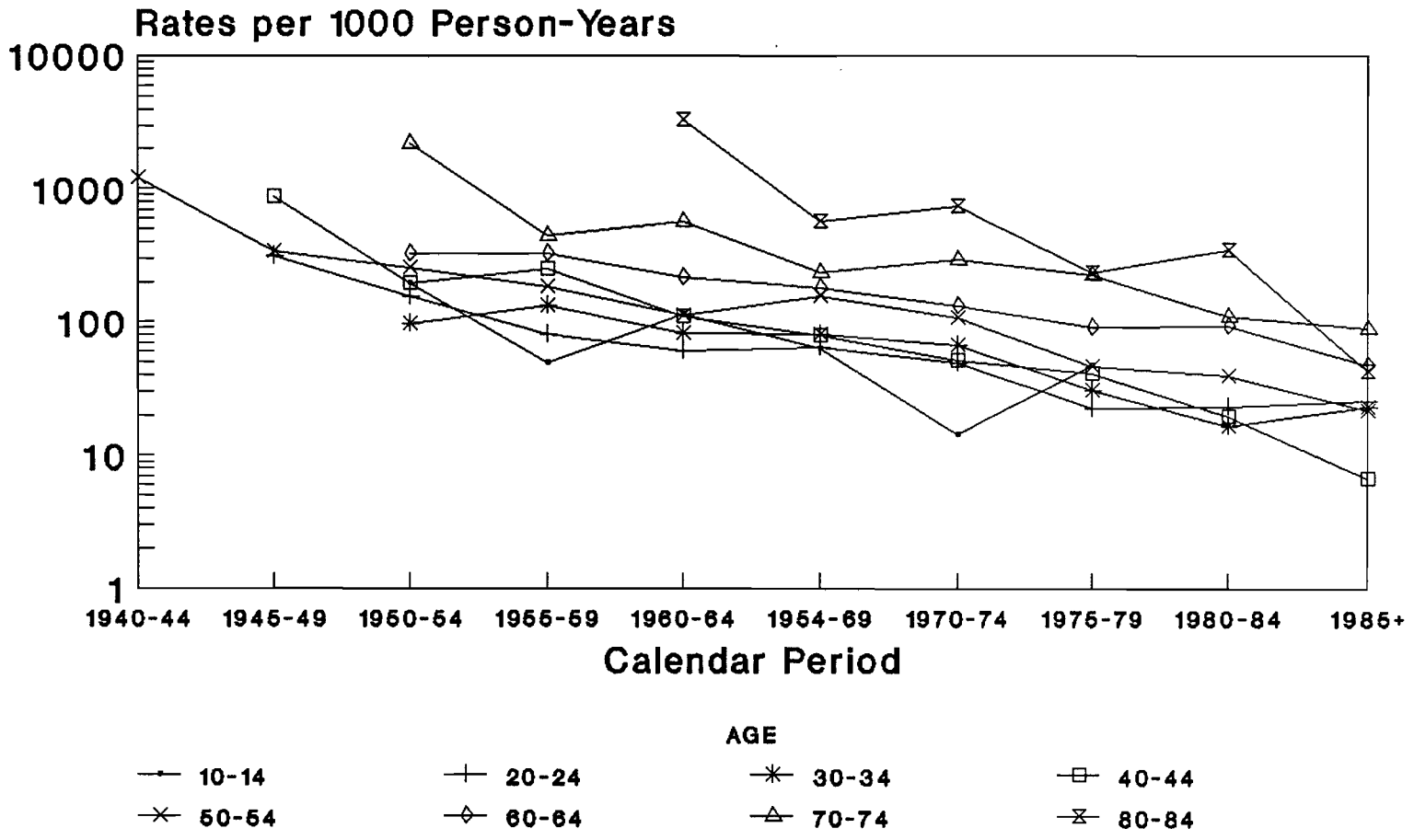

Figure 6. Hodgkin's Disease.
Age-Specific Mortality Rates For
Females, 1940-1990.

Mortality Rates By Calendar Period
By Age Groups - All Causes - Males

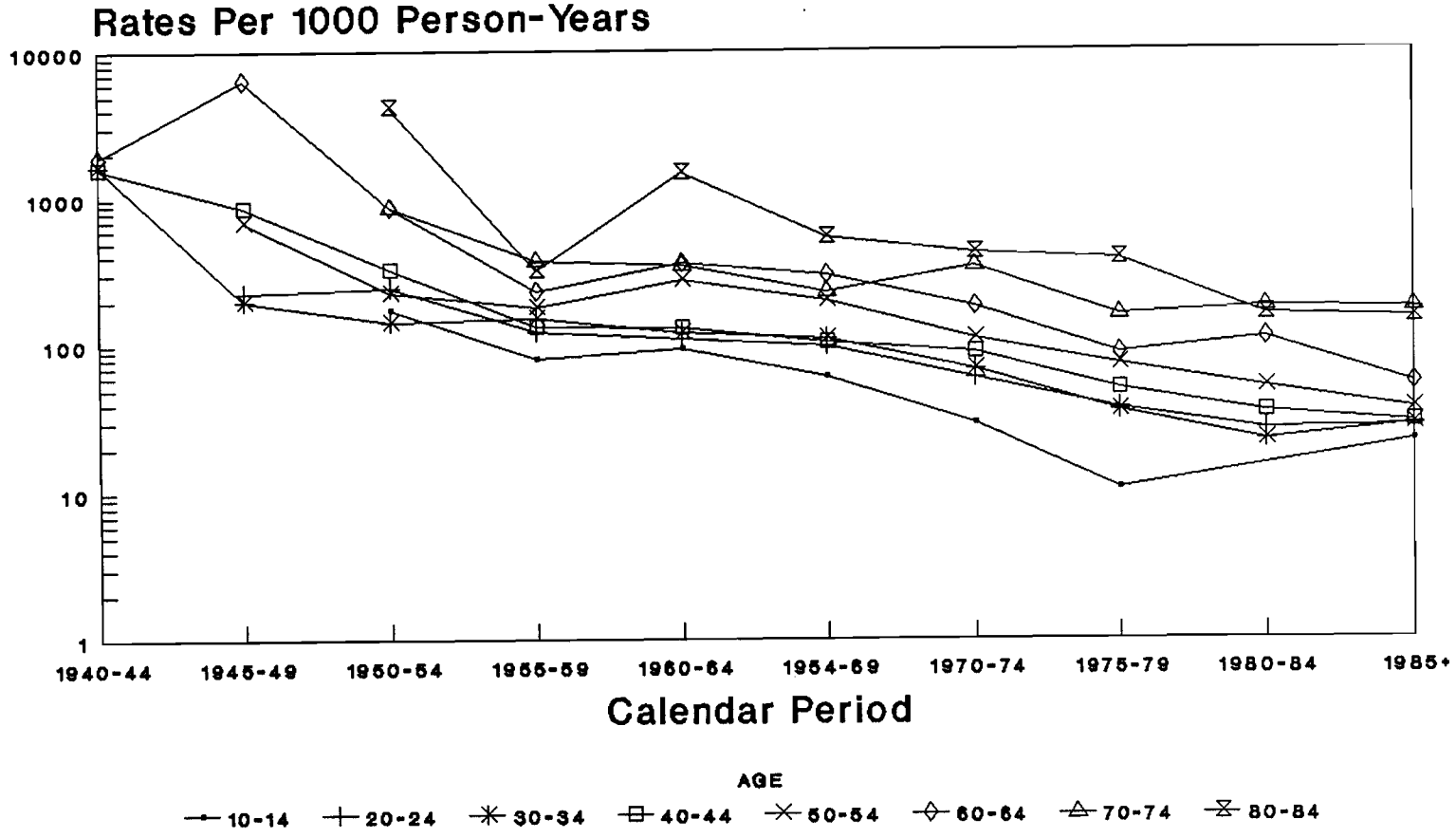

Figure 7. Hodgkin's Disease.
Age-Specific Mortality Rates For Males,
1940-1990.

Relative Risk of Death By Age
Males and Females

Figure 8. Hodgkin's Disease. R.R. of Death Among 9,316 Patients, 1940 -1990.

R.R. of Death by Calendar Period
Males and Females - All Causes

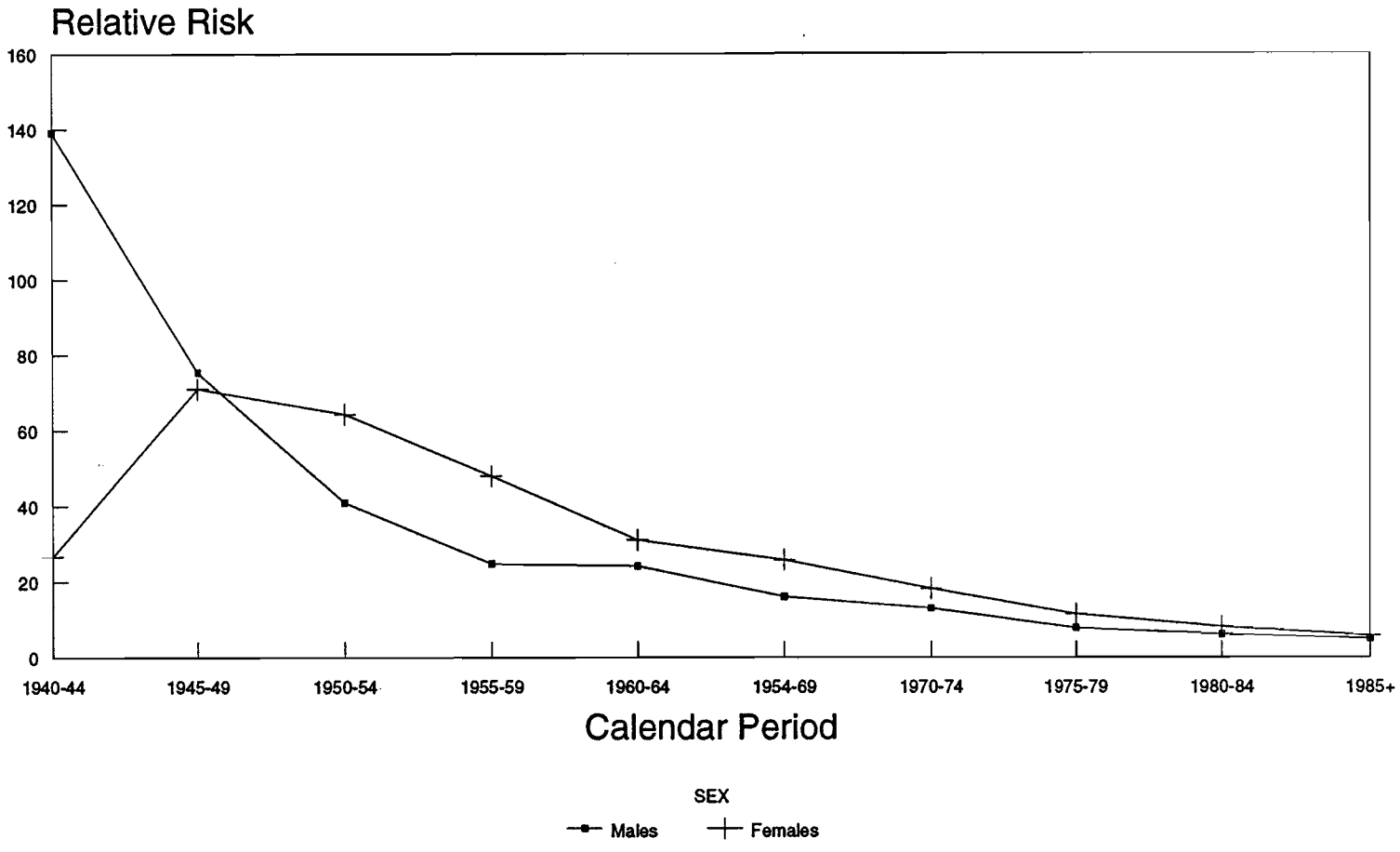

Figure 9. Hodgkin's Disease. Relative Risk of Death Among 9,316 Patients, 1940-1990.

ACTUARIAL SURVIVAL CURVE
Males and Females - All Causes

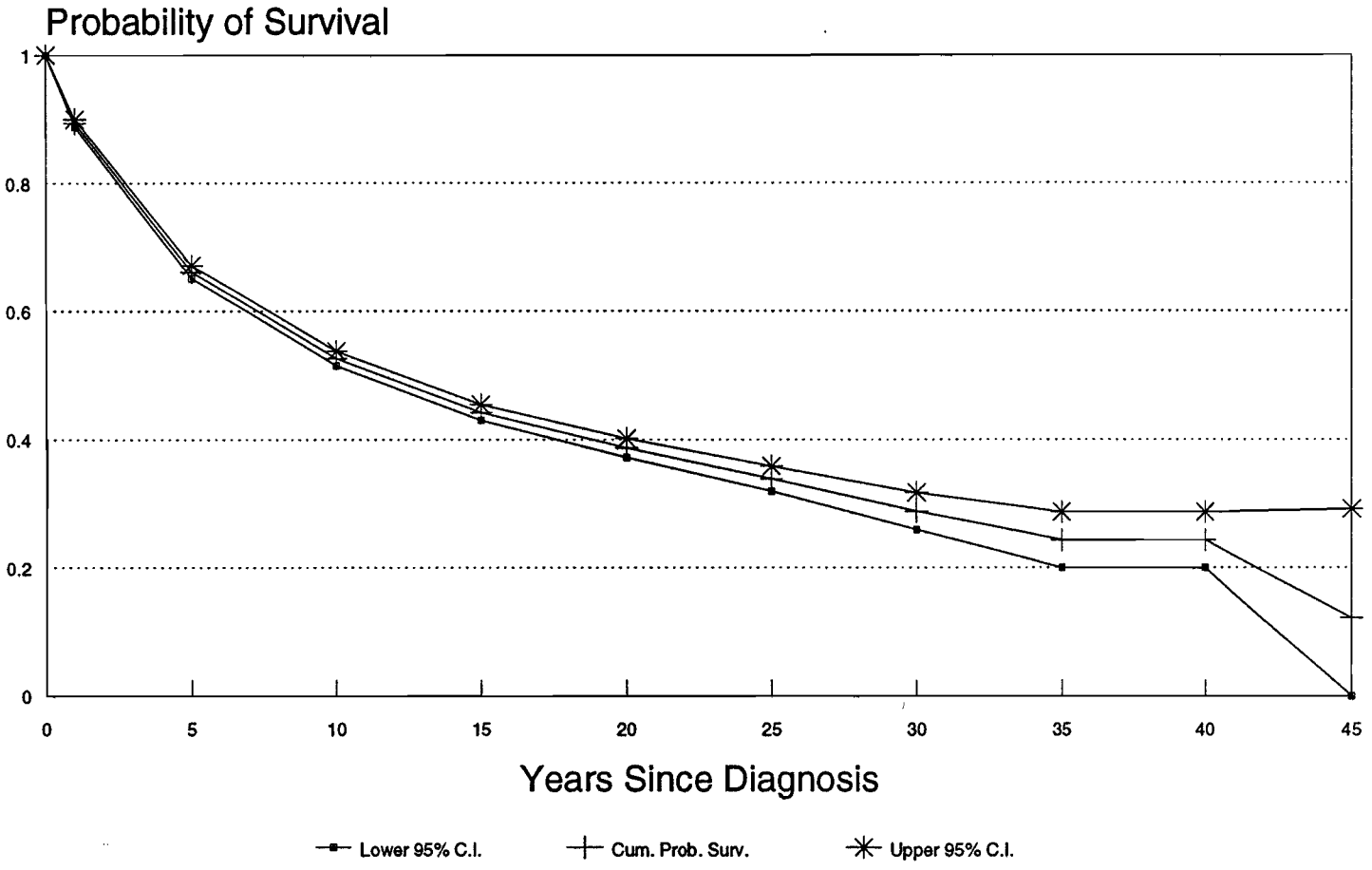

Figure 10. Crude Overall Survival for 9,316 Patients Diagnosed with Hodgkin's Disease, 1940 - 1990.

ACTUARIAL SURVIVAL CURVES BY SEX

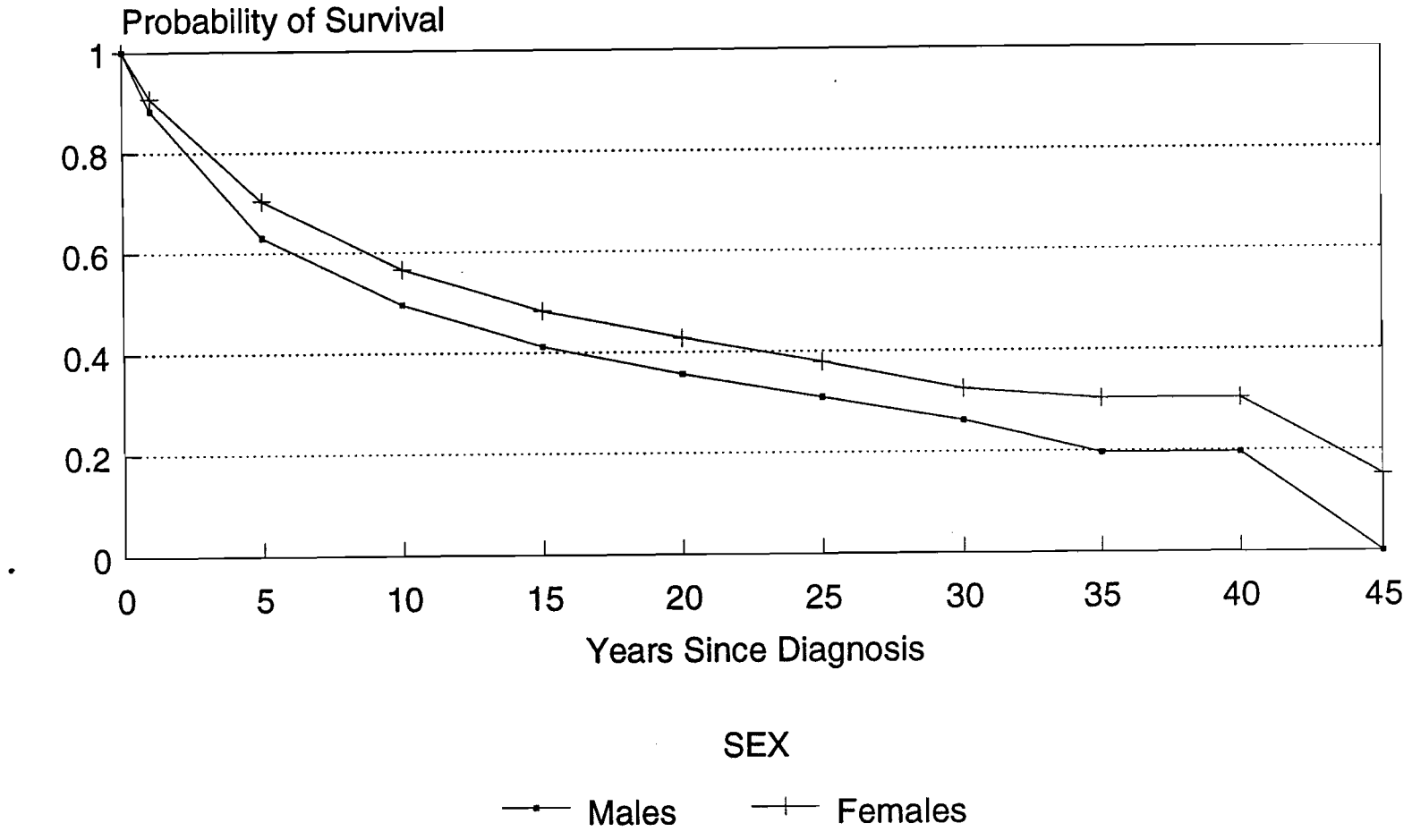

Fig. 11. Survival by Sex (Females:3,967 Patients; Males: 5,349 Patients), 1940 - 1990.

ACTUARIAL SURVIVAL CURVES
BY PERIOD OF DIAGNOSIS

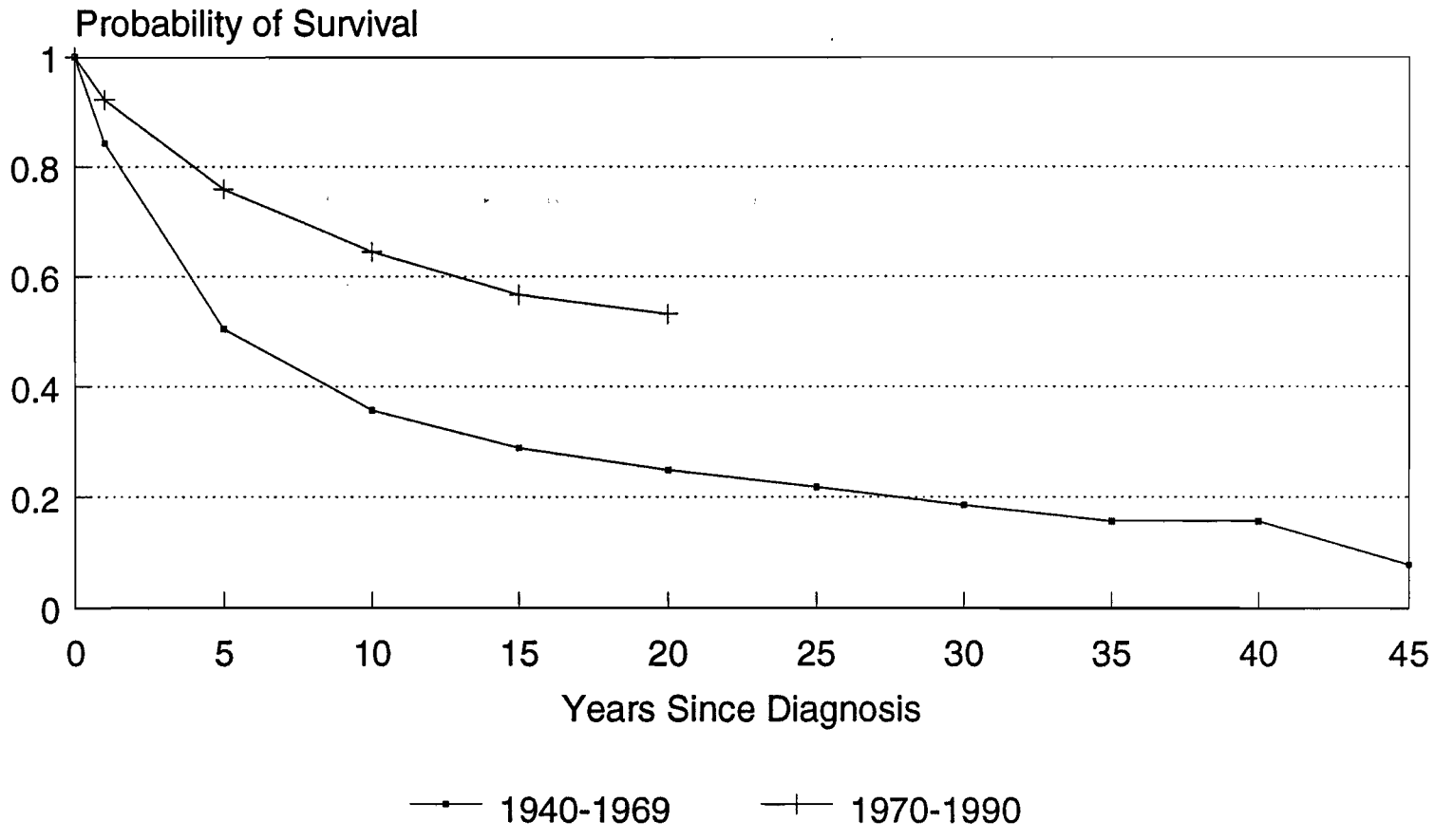

Figure 12. Hodgkin's Disease. Survival by Period of Diagnosis (1940-69: 3,389 pts; 1970-1990: 5,927 pts).

ACTUARIAL SURVIVAL CURVES
BY PERIOD OF DIAGNOSIS

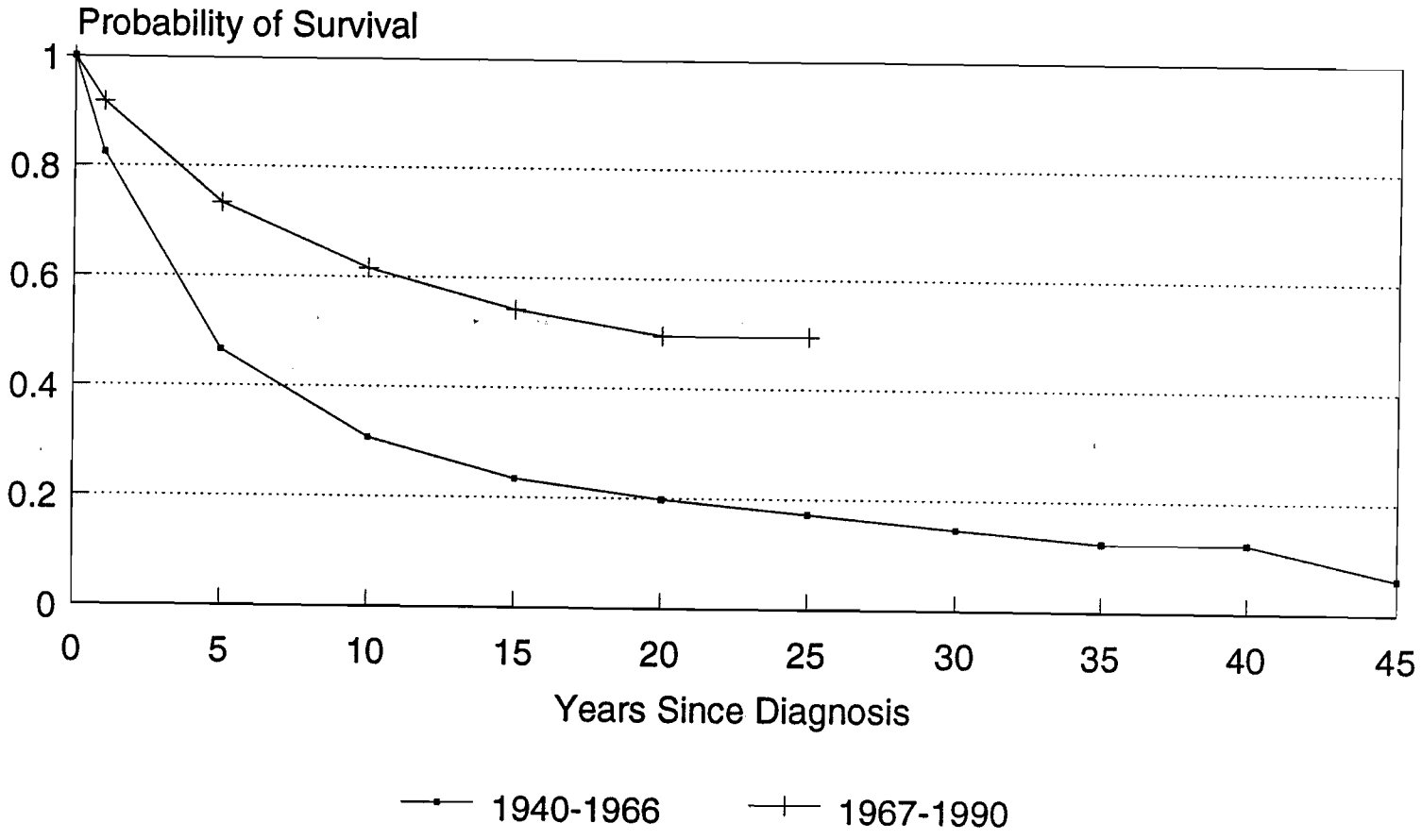

Figure 13. Hodgkin's Disease. Survival by Period of Diagnosis (1940-66: 2,374 pts; 1967-1990: 6,942 pts).

ACTUARIAL SURVIVAL CURVES
BY PERIOD OF DIAGNOSIS

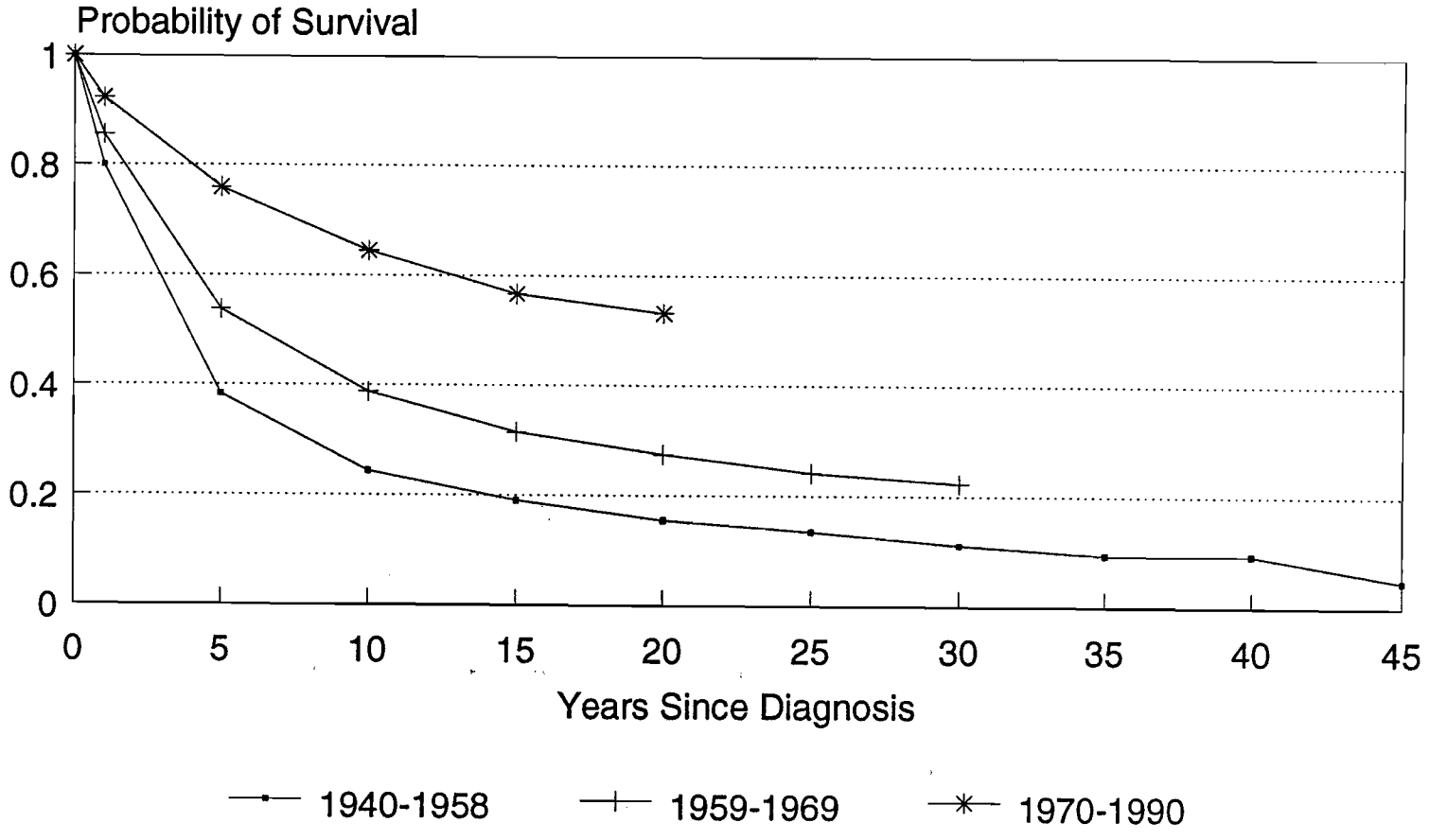

Figure 14. Hodgkin's Disease. Survival by Period of Diag. (1940-58: 714 pts; 1959-69: 2,675 pts; 1970-90: 5,927 pts).

ACTUARIAL SURVIVAL CURVES
BY AGE AT DIAGNOSIS

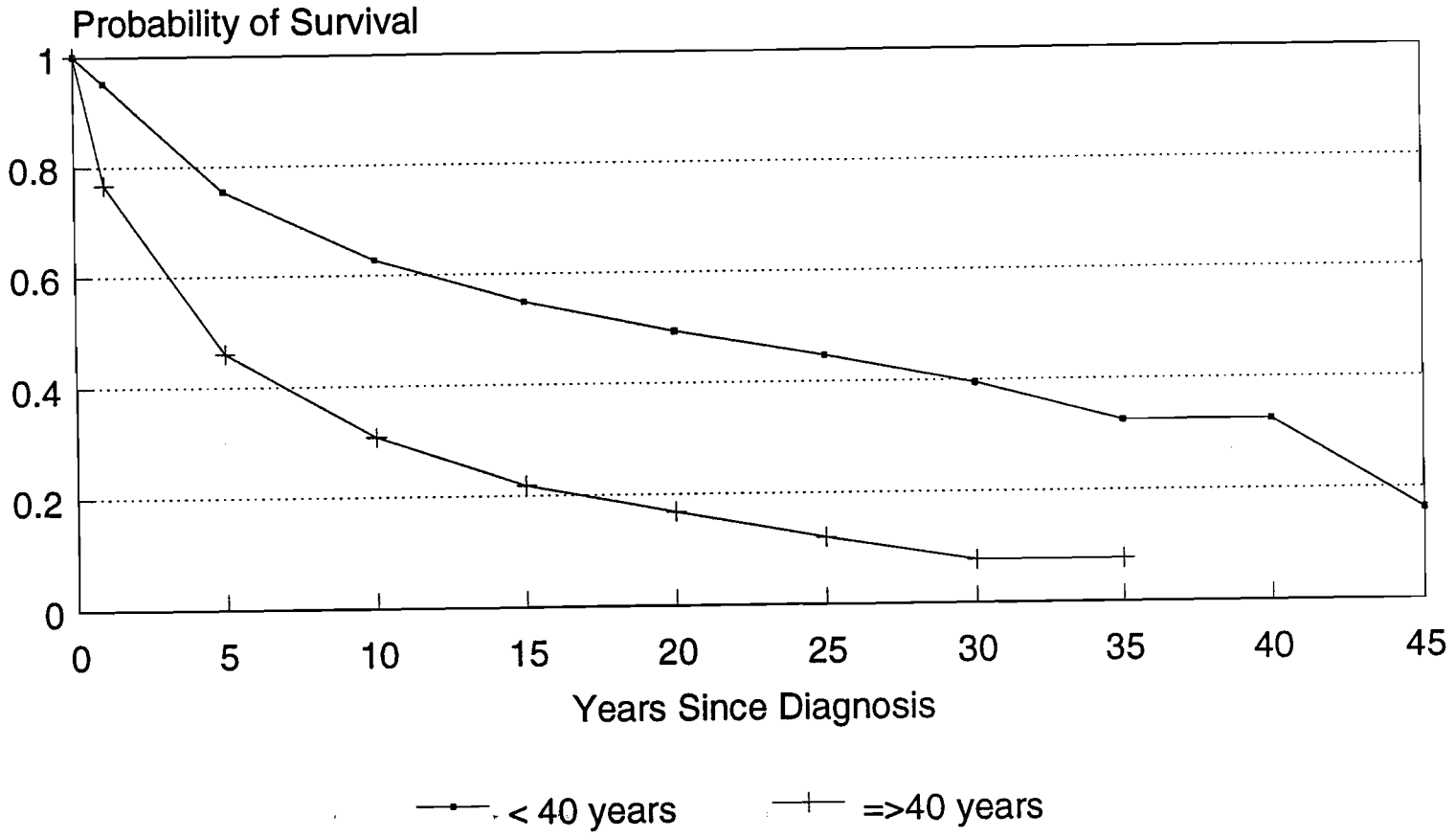

Figure 15. Hodgkin's Disease. Survival by Age at Diagnosis (<40 yrs: 6,388 pts; =>40 years: 2,928 pts), 1940 - 1990.