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Survival of Hodgkin Lymphoma has been enhanced through advances in treatment practices and knowledge of the disease. The inception of the WHO/REAL disease classification system for Hodgkin Lymphoma allows researchers to gain a greater understanding into the differing relative survival probabilities associated with this unique cancer. This study performed a survival analysis to understand the effects of age-at-diagnosis and gender on WHO/REAL subtypes of Hodgkin Lymphoma among the SEER population, 1975-2005. Five-year relative survival differed by Hodgkin Lymphoma subtype by both age-at-diagnosis and gender, when race/ethnicity was controlled for.

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SURVIVAL ANALYSIS OF HODGKIN LYMPHOMA BYAGE-AT-DIAGNOSIS AND GENDER BASED ON WHO/REAL DISEASE CLASSIFICATION, SURVIELLANCE EPIDEMIOLOGY AND END RESULTS DATA 1975-2005

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SURVIVAL ANALYSIS OF HODGKIN LYMPHOMA BYAGE-AT-DIAGNOSIS AND GENDER BASED ON WHO/REAL DISEASE CLASSIFICATION, SURVIELLANCE EPIDEMIOLOGY AND END RESULTS DATA 1975-2005

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Survivors of Hodgkin Lymphoma are living longer than they have in previous decades, and research has shown that survivability may vary based on age-at-diagnosis and gender (*Han et al, 2008)*. The incidence of Hodgkin Lymphoma displays a characteristic bimodal age distribution, which varies based on the level of socioeconomic development of residency (*Mueller & Grufferman, 2006*; *Swerdlow, 2003)*. Peaks in incidence rates of Hodgkin Lymphoma can be seen among those in early adulthood (age 20-29), and then again among the elderly, age 50 and up. Studies have also indicated incidence rates of Hodgkin Lymphoma are slightly higher for males than for females, 3.0 and 2.6 per 100,000 population, respectively, in the United States (*Mueller & Grufferman, 2006*). In contrast, estimated 5-year survival rates of Hodgkin Lymphoma show slightly greater survival rates among women (86%) than among men (82%) (*Mueller & Grufferman, 2006*). Previous studies showed variation of Hodgkin Lymphoma incidence patterns in regards to the gender ratio by age, indicating that women are less likely to be diagnosed with this disease later in life (*Mueller & Grufferman, 2006*; *Glaser et al, 2003)*. However, no published studies could be found which looked at each Hodgkin Lymphoma subtype separately, instead of grouped together. Previous registry coding work of Hodgkin Lymphoma has grouped all subcategories of this disease, which in the U.S. fall under one ICD-code (code 201) ("Overview of SEER Program", 2009). More recently, the third edition of ICD-O-coding incorporated the internationally accepted and utilized WHO/REAL Hodgkin Lymphoma

classification system ("Overview of SEER Program", 2009). Given the heterogeneity of Hodgkin Lymphoma, this new classification system will help researchers to understand the unique characteristics of each subtype of this disease. This study proposes to perform a survival analysis to examine the age-at-diagnosis and gender differences by WHO/REAL subtype of the Surveillance Epidemiology and End Results (SEER) Registry, 1975-2005.

Research Question and Specific Aims

The overall goal of this study is to determine the 5-year survival patterns of Hodgkin Lymphoma patients based on age-at-diagnosis and gender according to newly implemented WHO/REAL classification system. In order to accomplish this goal the following specific aims of this study include the following:

Aim 1: Describe and analyze the survival experience of Hodgkin Lymphoma patients by WHO/REAL subtype based on age-at-diagnosis of SEER Data, 1975-2005.

Aim 2: Describe and analyze the survival experience of Hodgkin Lymphoma patients by WHO/REAL subtype based on gender of SEER Data, 1975-2005.

Significance of the Study

These aims will answer questions regarding the potential differences in survival proportion of Hodgkin Lymphoma classified by the internationally accepted and utilized WHO/REAL classification scheme, based on age-at-diagnosis and gender. Cancer survival is important from a personal, clinical, and public health perspective. Identifying what factors impact survival requires an understanding of how disease is classified and a comprehension of the unique aspects of this classification. This study presents an opportunity to clarify how disease classification and age-at-diagnosis and gender contribute to survival of Hodgkin Lymphoma. The results of this study will provide valuable information for clinicians when

devising treatment options for diagnosed cases of Hodgkin Lymphoma. Armed with greater information regarding survival rates of this disease based on the new WHO/REAL classification system the age-at-diagnosis and gender of the patient may allow for the creation of more effective treatment options. Additionally, future research may be aimed towards looking at additional covariates of survivability, including secondary tumor sites, and potential genetic factors associated with age and gender.

CHAPTER 2

BACKGROUND

Critical Review of the Literature

Biological Description of Hodgkin Lymphoma

Hodgkin Lymphoma was first characterized in the early 1800s. The typifying agent, the presence of Reed-Sternberg Cells (RSCs), is considered one of the central hallmarks of diagnosis of Hodgkin Lymphoma (*Mueller & Grufferman, 2006*; *Swerdlow, 2003; Clarke et al, 2005; Cozen et al, 1992).* While most solid cancers consist almost entirely of tumor cells, Hodgkin tumors contain only about 5 percent cancerous RSCs. The rest are different types of immune cells recruited to fight the tumor, but they are ineffective. The recognition of RCS's within biopsied tissues in the past automatically qualified patients for a singular course of treatment, which has shown remarkable success rates, but among survivors secondary complications from standard treatment protocols have not been notably abated.

Disease Classification Systems

For decades, clinicians and researchers in the U.S. grouped all Hodgkin Lymphoma cases into one group, under ICD code 201. The International Standard Diagnostic (ICD) Classification is the medical coding system used for general health research use. ICD-O is the International Classification for Oncology, which is specific for diagnosis with cancer. Internationally, a number of classification systems were used which created inconsistencies when comparing study results. Since the 1960s, health researchers have observed three main groups of Hodgkin Lymphoma cases based on age-at-diagnosis; the youngest group (under 14 years of age), youths aged 15-34, and older adults (aged 65 and up). These three main groups represent what previous research has suggested as possibly three distinct diseases

with unique etiology and pathogenesis (*Mueller & Grufferman, 2006*; *Clarke et al, 2005; Cozen et al, 1992),* and thereby unique survival rates *(Kuse, Calavrezos, Hinrichs, et al, 1981).*

Originally, the lack of understanding regarding the biological aspects of Hodgkin Lymphoma forced pathologists to classify solely based on morphological characteristics such as the presence or absence of particular cell types, as well as the appearance of the tumor cells *(Lu, 2005).* The advent of the Revised European American Classification of Lymphoid neoplasm (REAL) categorization scheme for all lymphoid neoplasm types occurred in 1994 (*Chan, 2001; Clarke, Undurrage, Haratsy, et al, 2006).* Minor alterations to this scheme resulted in the World Health Organization (WHO) classification system, which was officially adopted worldwide in 2002 *(Chan, 2001; Clarke et al 2006).* This new organization scheme for all lymphoid neoplasms including Hodgkin Lymphoma created disease definitions based not only on morphology of the malignant cells, but also on phenotypic and genotypic aspects of the tumor, as well as clinical components of diagnosis *(Chan, 2001; Clarke et al, 2006, Colgiatti & Schmid, 2002).* The only validation studies which have been performed to determine the reliability of SEER conversion of ICD-O-1 and ICD-O-2 to the third edition (ICD-O-3) have been done through the Non-Hodgkin's Lymphoma Classification Project, where 1,378 cases were correctly classified based on pathological findings *(Clarke et al, 2006).*

The new classification system created two main categories of Hodgkin Lymphoma, Nodular Lymphocyte Predominance Hodgkin Lymphoma (NLP-HL) and Classical Hodgkin Lymphoma (C-HL). The latter category is further divided into subtypes based on morphological and immunogenic characteristics. In short, NLP-HL consists of B-cell

neoplasms which have the ability to produce immunoglobulin mRNA transcripts, and rarely contain Epstein-Barr virus genes or gene products. C-HL consists of B-cell neoplasms of germinal origin which do not produce immunoglobulin mRNA transcripts, and contain Epstein-Barr virus genes and/or gene products in most cases *(Clarke et al, 2006).* Table 2.1 illustrates the new classification of Hodgkin Lymphoma based on REAL/WHO classification schemes.

Table 2.1 REAL/WHO Classification Scheme of Hodgkin Lymphoma

Classical Hodgkin Lymphoma (C-HL)
Lymphocyte Rich Hodgkin Lymphoma (LR-HL)
Mixed Cellularity Hodgkin Lymphoma (MC-HL)
Nodular Sclerosis Hodgkin Lymphoma (NS-HL)
Lymphocyte depletion Hodgkin Lymphoma (LD-HL)
Nodular lymphocyte predominance Hodgkin Lymphoma (NLP-HL)

Descriptive Epidemiology

Incidence rates of Hodgkin Lymphoma vary by subtype. Classical subtypes of Hodgkin Lymphoma are greater than that of Nodular lymphocyte predominance Hodgkin Lymphoma (2.59 versus 0.08 persons per 100,000 in the United States) (*Glaser et al, 2003).* Developing countries show higher incidence of certain subtypes of Hodgkin Lymphoma, particularly Classic Mixed Cellularity Hodgkin Lymphoma and Classic Lymphocyte Depleted Hodgkin Lymphoma, as compared with Europe and the United States. Incidence is often higher among developed areas worldwide, and Hodgkin Lymphoma cases are most often of the Classic Nodular Sclerosis variety (*Dessain, Spears & Argiris, 2008).*

Hodgkin Lymphoma is considered a rare malignancy overall in the Unites States, accounting for just over 1% of all reported cancers *(Jarrett, 2003).* It is estimated that there

are 7,250 newly diagnosed cases of Hodgkin Lymphoma each year in the United States, with 1,400 deaths due to this disease (*Mueller & Grufferman, 2006*; *Swerdlow, 2003).* In 2002, there were 62,000 incident cases of Hodgkin Lymphoma worldwide (*Dessain, Spears & Argiris, 2008).*

Incidence rates of Hodgkin Lymphoma are highest among the non-Hispanic white population, followed by African Americans and Hispanic whites (*Glaser et al, 2003).* It is hypothesized that these differences in racial distribution of incidence of Hodgkin Lymphoma may be related to socioeconomic status, a known risk factor for this disease (*Han et al, 2008; Glaser et al, 2003; Clarke et al, 2001).* However, this racial distribution does not seem to differ according to Hodgkin Lymphoma subtype.

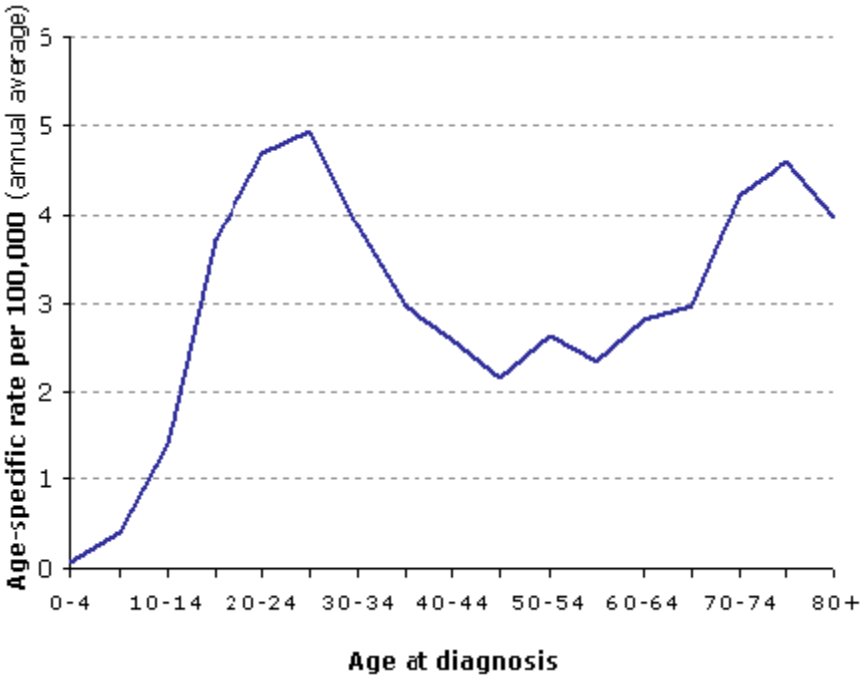

Figure 2.1 Incidence per 100,000 of Hodgkin Lymphoma by Age-at-Diagnosis and Gender, Ontario Cancer Registry, 2006 . (*Ontario Cancer Registry, 2006)*

Within developed countries, Hodgkin Lymphoma is the most common type of cancer among young adults, aged 15-24 (*Jarrett, 2002; Jarrett, 2003).* The bimodal to trimodal distribution of age-at-diagnosis (Figure 2.1) has lead researchers to believe that Hodgkin Lymphoma is not one disease with a singular pathology, but instead a group of conditions which may have unique etiologic backgrounds (*Mueller & Grufferman, 2006*; *Swerdlow, 2003; Clarke, Glaser, Keegan, et al, 2005; Cozen, Katz, & Mack, 1992)*. Populations residing in developing countries experience bimodal peaks , with one occurring in childhood between 0-14 years, and at the second at ages 65 and up (*Swerdlow, 2003; Clarke et al, 2005)* . Conversely, in populations of developed countries the childhood peak is shifted to ages 15-34 (*Jarrett, 2002; Jarrett, 2003).* Researchers have hypothesized that this link may be due to infection with the Epstein - Barr virus (EBV) (*Mueller & Grufferman, 2006*; *Swerdlow, 2003; Jarrett, 2003)* a known risk factor for Hodgkin Lymphoma. Since EBV typically infects teenagers and young adults as *Infectious Mononucleosis*, certain health researchers believe this infection may act as an initiator or a catalyst to the development of Hodgkin Lymphoma in young adults, where Hodgkin Lymphoma among those later in life (65 and up) may be a malignant neoplasm more closely associated with age or cumulative effects of known and unknown exposures (*Mueller & Grufferman, 2006*).

In addition to the unique age-incidence curves of this malignancy, gender differences also exist. Prevalence is slightly higher among males than among females (54% vs. 46% of cases), with similar findings for mortality rates between the two (*Mueller & Grufferman, 2006*; *Swerdlow, 2003).* Table 2.2 indicates the incidence per 100,000 and the 5-year relative survival for the U.S. population. Reasons for this gender disproportion are unknown. Incidence rates of Hodgkin Lymphoma have been shown to differ by gender and grouped

WHO/REAL classification subtypes within a population based cohort study, but have not been confirmed using a nationally representative registry*(Clarke, Glaser, & Prehn, 2001*). A population based case-control study of women of all ages in San Francisco indicated a range of reproductive factors which may play a role in the development of Hodgkin Lymphoma, including an increased risk of disease following miscarriage among women under 35 years of age (OR=5.7, 95% CI 1.2-34.5) (*Glaser et al, 2003*). This study also showed a potential protective effect (OR=0.6, 95% CI 0.4-0.8) for women who ever had children versus women who never had children. These results varied based on number of live births when compared with women with no children (*Glaser et al, 2003).* Reproductive factors, both before and after conception may be playing a role in gender disproportion in later years, as it is hypothesized that hormonal differences may explain differences in incidence and survival of Hodgkin Lymphoma (*Glaser et al, 2003).* This study indicated that the use of exogenous hormones was protective against the onset of Hodgkin Lymphoma, particularly at higher levels of hormone intake. (*Glaser et al, 2003*).

Table 2.2 Hodgkin Lymphoma Incidence and 5-year Relative Survival for the United States, SEER Data 1973-2003

	Incidence per 100,000†	5-year Relative Survival‡
Males	3.0	82%
Females	2.6	86%

† Incidence for 1999 (*Mueller & Grufferman, 2006*)
‡ 5-year Relative Survival for 1992-1998 (*Mueller & Grufferman, 2006*)

Survival

Previous studies have shown an overall 5-year survival rate of Hodgkin Lymphoma in excess of 84% in the United States (*Swerdlow, 2003)* across all reported cases combined. The 2007 SEER Survival monographs indicated survival patterns of Hodgkin Lymphoma have shown variation based on HIV status, age-at-diagnosis, stage at diagnosis, gender, race,

and histological subtype (*Han et al, 2008)*. However, since the implementation of the WHO/REAL classification system, the only study to date to look at 5-year survival by age-at-diagnosis used 45 years of age as the cut-point to dichotomize the variable. Table 2.3 indicates the results of the study performed by Han et al (*2008*) using nationally representative SEER data.

Table 2.3 Five-year Relative Survival of Hodgkin Lymphoma by Dichotomized Age-at-Diagnosis, Gender, and Race Group, SEER Data 1973-2003†

Subtype (age group)		5-year Relative Survival		
		Non-Hisp White	Hisp White	Black
Hodgkin Lymphoma (<45)	Male	87.2	81.3	78.6
	Female	91.4	92.2	84.5
Classic	Male	87.0	80.9	78.0
	Female	91.4	92.1	83.9
Nodular Sclerosis	Male	88.6	85.4	80.1
	Female	92.1	93.3	84.9
Mixed Cellularity/	Male	83.4	74.7	79.4
Lymphocyte Depleted	Female	88.3	87.3	81.7
Nodular Lymphocyte	Male	95.3	96.0	96.0
Predominance	Female	92.6	--	96.9
NOS	Male	84.8	73.5	71.2
	Female	88.3	89.3	80.3
Hodgkin Lymphoma (45+)	Male	61.7	50.3	60.7
	Female	59.2	54.9	70.8
Classic	Male	61.1	49.3	59.2
	Female	58.9	54.5	68.2
Nodular Sclerosis	Male	69.7	57.8	64.6
	Female	67.8	66.2	78.4
Mixed Cellularity/	Male	53.9	44.2	52.8
Lymphocyte Depleted	Female	53.3	48.0	54.0
Nodular Lymphocyte	Male	87.2	--	93.5
Predominance	Female	74.9	--	100.0
NOS	Male	58.2	42.8	61.8
	Female	49.4	40.5	67.4

† *Han et al*, 2008

-- indicate cells with less than 10 individuals, and no Relative Survivals could be calculated

Han et al (2008) utilized the new WHO/REAL disease classification to analyze 5-year survival by race of the 1973-2003 SEER registry data and concluded that those individuals classified as non-Hispanic white had greater survival rates than Hispanic whites, blacks, and American Indian/Asian-Pacific Islanders. This study found that individuals diagnosed before the age of 45, and at stage I and IA, had 94.1% and 96.9% survival rates. Conversely, they

found that patients diagnosed before age 45, and at stage IV had survival rates which ranged from 73.1 to 83.1%. The majority of Hodgkin Lymphoma patients are diagnosed at stage II and have an estimated survival rate of 92.5% (*Han et al, 2008).*

Treatment is also hypothesized to play a role in survival of Hodgkin Lymphoma patients (*Han et al, 2008, Clarke et al, 2001).* However, course of treatment is often indicated by stage of diagnosis as well as the presence or absence of B-symptoms, and therefore B-symptoms are a related factor. B-symptoms are a collection of symptoms which appear in lymphoma patients with advanced disease, and are thought to indicate the spread of disease to distant sites (*Clarke et al, 2001).* For example, when Ann Arbor staging is used in evaluating the progression of Hodgkin Lymphoma, treatment is often consistent with Ann Arbor staging. Early stages, such as IA and IIA, are typically given radiation only treatment, and have longer relative survival rates (*Clarke et al, 2001*). Later stages of diagnosis, such as III-IV, as well as IB and IIB stages, involve the use of chemotherapeutic agents, and are indicative of more advanced disease.

Summary

Hodgkin Lymphoma incidence differs by race, gender, and age. In general, White men are more likely to be diagnosed with Hodgkin Lymphoma than White women and Black men, Asian men, and American Indian/Alaskan Native men. With the recent adoption of the WHO/REAL classification of Hodgkin Lymphoma malignancies, it is possible to further explore potential differences of this disease, including survival patterns by age-at-diagnosis and gender. This study presents an opportunity to clarify how disease classification contributes to survival of Hodgkin Lymphoma. Armed with greater information regarding survival rates of this disease, based on the new WHO/REAL classification system, and the

age-at-diagnosis and gender of the patient, the clinician will be able to create a more effective treatment regimen. Additionally, future research may be aimed towards looking at addition covariates of survivability, to include secondary tumor sites, as well as potential genetic factors associated with age and gender.

CHAPTER 3

METHODS

Study Population and Eligibility

Data on survival for Hodgkin Lymphoma were obtained through the Surveillance Epidemiology and End Results (SEER) Registry (1975-2005). SEER is a population-based registry which currently collects cancer data on 26% of the United States population. The SEER registry covers a range of race/ethnicities, including a broad representation of African Americans, Hispanics, Native American/Alaskan Natives, and individuals of Asian descent. Also included in the SEER registry are demographic, diagnosis, and follow-up information *("Overview of SEER Program", 2009).* Eligibility requirements for inclusion into the study included a diagnosis between the years of 1975 to 2005 (when treatment procedures remained relatively consistent) with a histologically classified form of Hodgkin Lymphoma, no previous diagnosis with any malignancy, and who were followed for vital status until December 31, 2005. In addition, participants were excluded from the study if reported histological and pathological diagnoses did not match, in an effort to decrease misclassification of Hodgkin Lymphoma subtypes. Classification of tumor diagnoses by SEER was based on the new ICD-O-3 scheming codes (Table 3.1).

Table 3.1 ICD-O-3 Codes by Hodgkin Lymphoma Subtype

Hodgkin Lymphoma Subtype	ICD-O-3 Codes included†
Classic: Nodular Sclerosis	*9661-9665, 9667*
Classic: Mixed Cellularity	*9652*
Classic: Lymphocyte Rich	*9651*
Classic: Lymphocyte Depletion	*9653-9655*
Nodular Lymphocyte Predominance	*9659*
NOS‡	*9650*

† Codes are inclusive of all classified Hodgkin Lymphoma Cases
‡ Not Otherwise Specified

Survival Analysis

Patients within the SEER registry are followed up for vital status annually, and mortality is verified using the National Center for Health Statistics. Survival time began at the date of diagnosis with Hodgkin Lymphoma, and was counted until one of three events occurred: (1) death (2) censorship due to loss, and (3) censorship due to end of study completion, or survival through the study period.

Statistical Analysis Software (SAS) version 9.1 was used to perform frequency univariate analysis to test for the normalcy of the data by age-at-diagnosis. The distribution of the obtained variables was used to check for anticipated bimodal or trimodal distribution of age-at-diagnosis, as well as to help in determining justifiable categories to best fit the data. Previous literature shows diagnosis age-groupings of Hodgkin Lymphoma typically in one of two manners: (1) a cut-point of 45 years of age, creating a dichotomous age-at-diagnosis variable and (2) 16-year age groupings, beginning with 18-34, and continuing. The analysis portion of this study utilized both the 16-year age groupings, to provide consistency with this work and previously published work, as well as 5-year incremental age-groupings, in order to see the effect of smaller age-groupings on survival of Hodgkin Lymphoma. Frequency procedures for gender (male or female) were used to obtain descriptive statistics of the variables under study. The SEER registry had 100% completeness for each of these variables, and therefore no missing values.

Relative survival for Hodgkin Lymphoma by age-at-diagnosis and gender classified by WHO/REAL classification criteria was analyzed using both SEER*Stat analysis and Kaplan-Meier survival proportion in SAS. Relative survival is a ratio of observed survivors to expected survivors in a set of cancer free individuals (*"Relative Survival", 2007*). This

type of survival statistic helps to show whether the disease of interest, in this case Hodgkin Lymphoma, shortens the life of individuals. Median survival times, with 95% confidence intervals, were compared to look for similarities between survival trends among WHO/REAL subtypes. This form of statistical analysis estimates survival functions based on life-time data (*Han et al, 2008; Kleinbaum, 1996).* Survival curves were estimated based on age-at-diagnosis and gender at 5-years, and incremental years thereafter. The curves were then compared between subtypes using Log-Rank test, (alpha level of 0.05). The Log-Rank comparison based on gender is similar to a Chi-Square test, testing the null hypothesis that there is no overall difference between age groups and gender groups. The Log-Rank comparison, using 2 degrees of freedom for both age-at-diagnosis and gender, based on age-at-diagnosis and gender separately tested the null hypothesis assuming that all survival curves are the same *(Colgiatti & Schmid, 2002)*. A p-value of less than 0.05 of a two-tailed statistical test was considered statistically significant. Hazard ratios were computed using Cox Proportional Hazards modeling to estimate the relative risk of survival after controlling for race/ethnicity. Referent groups were chosen based on those individuals with lowest risk of event, in this case death from Hodgkin Lymphoma. The age-at-diagnosis group used as referent was the 22-27 age group, and the gender referent group was chosen to be females. In order to maintain consistent 5-year age groupings, the first group was set at 18-22, and then followed with 5-year incremental age groups.

Within the SEER registry, there are two separate race/ethnicity variables. One of these variables uses a simplistic categorical denomination of 'White', 'Black', 'Other', and 'Unknown'. This variable showed fewer missing values, and was therefore employed within this analysis.

Methodologic Considerations

Race/ethnicity and stage-at-diagnosis were evaluated as potential confounders within the survival models. With a high degree of missingness (81.4%) of the stage-at-diagnosis variable within the SEER registry for persons included in the study, it was not included within survival models. The remaining 19.6% of individuals with stage-at-diagnosis information were equally distributed among Hodgkin Lymphoma subtypes, and therefore do not indicate selective information of particularly exposure variables.

In calculating hazard ratios using survival data, attending to the assumptions of the proportional hazards regression model is unavoidable. These assumptions include that all events of survival of Hodgkin Lymphoma are considered independent, failure times have similar distributions and hazard ratios are constant over time. These are large assumptions. Consequently, we graphed plots of log-log S(t) against log time to assess for cross-over's and performed the Cox significance test to check whether these assumptions were met in our data. All variables included within the model met the proportional hazards assumption, except for the race/ethnicity variable. The model was therefore relaxed, and the gender variable was used as an interaction term with survival time, in order to meet the required assumptions.

CHAPTER 4

RESULTS

Population Description and Variables of Interest

Between the years of 1975 and 2005, there were 31,711 newly reported cases of Hodgkin Lymphoma to all 17 available SEER registries in the United States. Following the implementation of the aforementioned inclusion/exclusion criteria for this study, 28,892 individuals were eligible to be included in this study.

Diagnosis and histological classification of WHO/REAL subtypes of Hodgkin Lymphoma were reliable and consistent throughout the SEER database. Only 4.0% of cases were excluded due to lack of diagnostic and histological classification of Hodgkin Lymphoma. Few individuals were excluded due to the lack of specific disease sub typing (2.1%, n=591). Additionally, in order to meet eligibility, individuals must have had matching histological and pathological diagnosis with Hodgkin Lymphoma, which was properly coded within the ICD-O-3 coding scheme. Individuals with listed method of diagnosis confirmation as the following were excluded from the study: positive exfoliate, no positive histology (n=258), positive microscopic confirm, method not specified (n=42), positive laboratory test/marker study (n=5), direct visualization without microscopic confirmation (n=4), radiography without microscopic confirmation (n=26), clinical diagnosis only (n=26), and unknown diagnostic confirmation (n=230). The large majority of those excluded (75.5%) due to lack of proper diagnostic confirmation were of the Not Otherwise Specified (NOS) Hodgkin Lymphoma subtype. The exclusion of these individuals left 28,301 participants to be included within the analysis. Descriptive statistics of the included population can be seen in Table 4.1.

Table 4.1. Descriptive Statistics of Hodgkin Lymphoma Cases included in Study, SEER Data 1975-2005

	Hodgkin Lymphoma	Classic Nodular Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodular Lymph Pred	NOS
n	28301	16722	5386	979	820	693	3701
Mean Age at Diagnosis ±SD	42.6±8.1	37.6±8.3	49.8±9.8	46.5±9	58.3±8.5	43.3±8.2	49.7±10
Gender							
Males	15630	8290	3467	679	522	467	2205
Females	12671	8432	1919	300	298	226	1496
Male: Female Ratio	1.2:1.0	0.9:1.0	1.8:1.0	2.3:1.0	1.8:1.0	2.1:1.0	1.5:1.0
Race							
White	24697	14778	4685	794	724	526	3190
Black	2460	1290	484	130	59	139	358
Other	1000	581	198	45	37	19	120
Unknown	144	73	19	10	0	9	33
Stage-at-Diagnosis							
Localized Only	1136	586	218	75	6	91	160
Regional	2101	1595	224	44	17	40	181
Distant Site/ Node Involvement	1959	1094	320	17	46	36	433
Unknown	23133	13475	4626	830	751	526	2925

Table 4.2 depicts the frequency of Hodgkin Lymphoma Subtypes by WHO/REAL classification for those individuals included in the study, as well as the corresponding ICD-O-3 codes designated for each subtype. The majority of patients diagnosed with Hodgkin Lymphoma were diagnosed with the Nodular Sclerosis Classic subtype (59.1%), with the Mixed Cellularity Classic subtype having the second highest prevalence (19.0%). The other subtypes of Hodgkin Lymphoma are less common, with percentage of diagnosed ranging from 2.5-3.5%.

Table 4.2 Frequency of Hodgkin Lymphoma Subtypes and ICD-O-3 Codes, SEER Data 1975-2005

Hodgkin Lymphoma Subtype	n (% total)	ICD-O-3 Codes included
Classic: Nodular Sclerosis	16722 (59.1)	*9661-9665, 9667*
Classic: Mixed Cellularity	5386 (19.0)	*9652*
Classic: Lymphocyte Rich	979 (3.5)	*9651*
Classic: Lymphocyte Depletion	820 (2.9)	*9653-9655*
Nodular Lymphocyte Predominance	693 (2.5)	*9659*
NOS†	3701 (13.0)	*9650*

† Not Otherwise Specified

Age-at-diagnosis showed no missing values within the SEER data set. With no missing values, the age-at-diagnosis variable was normally distributed (Kolmogorov-Smirnov $D=0.110246$, $p<0.0100$). The mean age-at-diagnosis was 42.6 years of age, and a median of 37.0 years of age for general Hodgkin Lymphoma diagnosis (Figure 4.1). Additionally, an Analysis of Variance (ANOVA) procedure indicated that age-at-diagnosis of Hodgkin Lymphoma subtypes are statistically different than one another ($F=691.45$, $p<0.0001$). Gender also had 0% missing values. There were 15,630 males and 12,671 females within the study population for a 1.25:1.0 male to female ratio; this ratio varied for each WHO/REAL subtype.

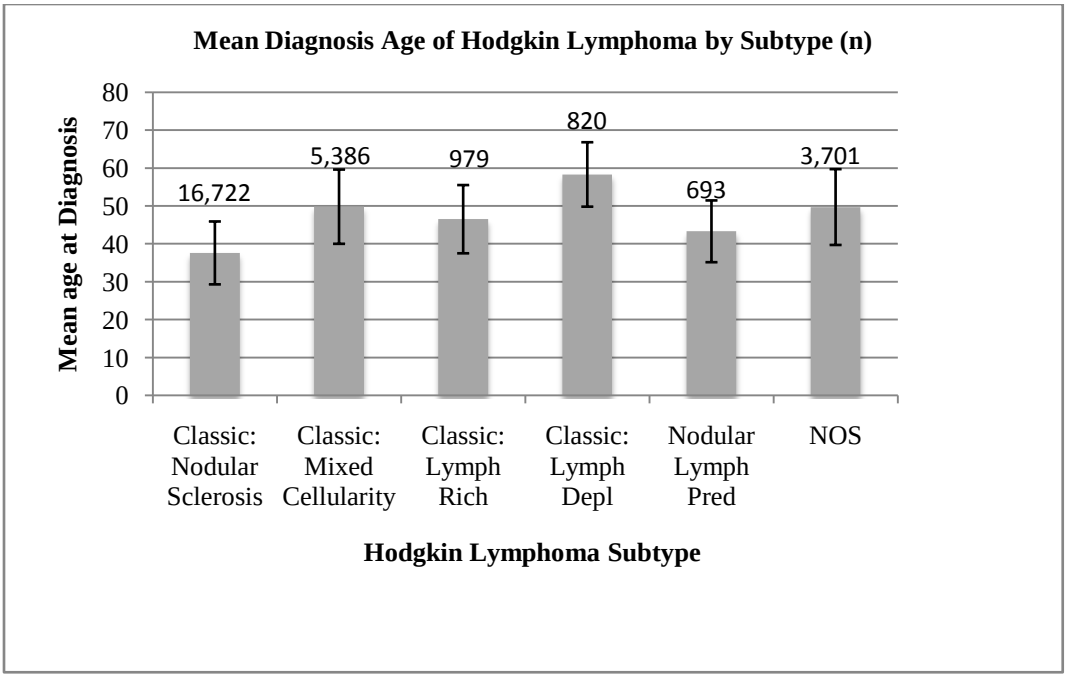

Figure 4.1 Mean Age-at-Diagnosis of Hodgkin Lymphoma by Subtype, SEER Data 1975-2005

Survival Experience among Study Population

The median survival of the included study population was 59 months (95% CI 58-60). The average length of survival for the entire population was 91.7 months (SE±0.5). Duration of median survival among subtypes varied from 19 months for Classic Lymphocyte Depletion Hodgkin Lymphoma to 67 months for Classic Nodular Sclerosis Hodgkin Lymphoma. Of the 28,301 participants in the study, 27,688 individuals died during the study period (1975-2005), while 641 (2.26%) were censored. The Classic Lymphocyte Depletion subtype indicated the highest proportion of censored individuals, with 12.4% of this subtype begin censored through the study period.

Confounding

Analysis of the potential confounder race/ethnicity showed that race/ethnicity is positively associated with the exposure variable, when comparing Whites to non-Whites, and the Nodular Sclerosis Classic Hodgkin Lymphoma Subtype as the referent group, compared with all other subtypes (OR=1.42), and negatively associated with the outcome, survival of Hodgkin Lymphoma (OR=0.89). Race/ethnicity is not an intermediate step in the causal pathway from Hodgkin Lymphoma Subtype to survival of Hodgkin Lymphoma, therefore completing the three criteria to be a potential confounder within this association. When comparing the Betas related to association, only a 6.7% difference is apparent between stratified confounding groups. Although this does not meet the 10% rule for assuming confounding, a priori information indicates a strong relationship between race/ethnicity and survival of Hodgkin Lymphoma. Therefore, all models were adjusted for race/ethnicity during computation. However, all Hazard Ratios were calculated both with and without controlling for the race/ethnicity variable (Appendix, Table A.4).

Survival of Hodgkin Lymphoma by Age-at-Diagnosis

Overall, 20,301 (71.7%) individuals diagnosed with Hodgkin Lymphoma between 1975 and 2005 survived 5-years following diagnosis date. Median survival times were calculated for each Hodgkin Lymphoma subtype based on age-at-diagnosis (Table 4.5). These median survival times differed by age-at-diagnosis. Most of the Hodgkin Lymphoma subtypes indicated a peak median survival time among those diagnosed between ages 23 and 27, with a steady decline thereafter. However, Classic Lymphocyte Depletion Hodgkin Lymphoma showed the highest median survival time among those diagnosed between 48 and 52 years of age.

Calculated 5-year relative survival probabilities by subtype of Hodgkin Lymphoma diagnosis by age-at-diagnosis group are presented in Table 4.3. The most commonly diagnosed subtype of Hodgkin Lymphoma, Classic Nodular Sclerosis had high relative survival probabilities among those diagnosed in young age groups, maintaining greater than 80.0% relative 5-year survival through age 52 years. Three of the five classified forms of Hodgkin Lymphoma (excluding NOS), indicate a slight increase in relative survival from the youngest age group (18-22) to the second youngest age group (23-37). Nodular Lymphocyte Predominance Hodgkin Lymphoma maintains relatively high 5-year relative survival rates despite the age-at-diagnosis, with a range of 91.7% for youngest age group through 72.7% for the oldest age group.

According to the observed results presented in Table 4.3, all 5-year relative survival probabilities of Classic subtypes of Hodgkin Lymphoma are statistically different by age-at-diagnosis group. A general visual inspection of the survival curves show marginal differences between most of the Hodgkin Lymphoma subtypes by age-at-diagnosis, with the Classic Lymphocyte Depletion showing the most visually different median survival times between age groups.

Table 4.3 Five-year Relative Survival of Hodgkin Lymphoma Patients Based on WHO/REAL Subtype by Age-at-Diagnosis, SEER Data 1975-2005

Age-at-Diagnosis Group	Classic Nodl Scler		Classic Mixed Cellularity		Classic Lymph Rich		Classic Lymph Depl		Nodular Lymph Pred		NOS	
	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv
18-22	2690	90.5	422	91.6	76	94.2	28	58.1	58	91.7	272	87.7
23-27	2985	91.3	491	89.1	92	94.4	39	64.6	74	94.7	363	90.0
28-32	2654	89.7	441	85.8	110	94.5	46	68.8	85	91.2	329	82.0
33-37	1970	89.6	427	82.8	84	98.7	47	54.0	84	90.7	329	79.0
38-42	1495	89.8	406	81.9	92	89.7	39	77.4	78	92.0	300	72.5
43-47	1095	84.4	394	76.3	87	86.5	40	51.7	51	95.5	260	71.8
48-52	775	82.9	387	67.8	88	92.8	49	41.8	63	95.9	215	77.0
53-57	642	75.3	386	67.9	66	83.5	58	48.3	53	88.5	224	70.6
58-62	546	68.4	362	59.0	66	76.0	70	45.6	46	92.5	251	54.2
63-67	522	64.3	391	59.8	63	56.6	70	26.1	37	86.9	248	47.2
68+	1348	44.0	1279	46.0	155	57.4	334	20.4	64	72.2	910	34.0
Log-Rank χ^2	673.5 p<0.0001		523.7 p<0.0001		77.3 p<0.0001		47.2 p<0.0001		17.4 p=0.0667		152.3 p<0.0001	

Adjusted hazard ratios of age-at-diagnosis categories for each subtype of Hodgkin Lymphoma are shown in Table 4.4. For all Hodgkin Lymphoma subtypes, as the age-at-diagnosis group increased, the risk of event, death from Hodgkin Lymphoma also increased.

Table 4.4. Adjusted Hazard Ratios (95% Confidence Intervals) of Hodgkin Lymphoma Subtypes by Age-at-Diagnosis, SEER Data 1975-2005

	Classic Nodl Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodl Lymph Predominance	NOS
18-22	0.76	0.64	0.53	0.57	0.88	0.79
	(0.72-0.80)	(0.63-0.81)	(0.40-0.71)	(0.32-1.01)	(0.59-1.30)	(0.66-0.94)
23-27†	1.00	1.00	1.00	1.00	1.00	1.00
28-32	0.96	0.71	0.77	0.76	0.82	1.23
	(0.95-1.01)	(0.63-0.81)	(0.60-0.98)	(0.50-1.15)	(0.59-1.15)	(1.08-1.40)
33-37	1.05	0.83	1.00	0.78	0.76	0.94
	(0.98-1.12)	(0.73-0.95)	(0.76-1.31)	(0.45-1.30)	(0.54-1.08)	(0.78-1.10)
38-42	1.23	1.03	1.21	1.08	0.91	1.19
	(1.13-1.33)	(0.90-1.18)	(1.01-1.46)	(0.69-1.70)	(0.62-1.33)	(0.98-1.45)
43-47	1.39	1.18	1.27	1.14	0.99	1.34
	(1.27-1.52)	(1.02-1.36)	(0.93-1.75)	(0.62-2.11)	(0.65-1.51)	(1.07-1.69)
48-52	1.56	1.37	1.38	0.64	1.06	0.99
	(1.40-1.74)	(1.17-1.61)	(1.04-1.84)	(0.38-1.07)	(0.74-1.52)	(0.78-1.25)
53-57	1.23	1.57	1.45	0.76	1.31	1.09
	(1.09-1.39)	(1.35-1.83)	(1.02-2.06)	(0.49-1.17)	(0.82-2.12)	(0.85-1.38)
58-62	1.43	1.58	1.63	1.73	1.25	1.36
	(1.25-1.64)	(1.33-1.88)	(1.11, 2.40)	(1.15-2.58)	(0.78-2.01)	(1.05-1.75)
63-67	1.97	1.95	1.74	1.17	1.74	2.28
	(1.71-2.28)	(1.64-2.32)	(1.11-2.79)	(0.65-2.11)	(1.04-2.93)	(1.72-3.03)
68+	2.70	2.67	2.34	2.70	2.54	2.21
	(2.37-3.06)	(2.35-3.03)	(1.70-2.32)	(1.86-3.91)	(1.25-5.08)	(1.82-2.69)

† Referent Group
*Adjusted for Race (Categorical: White, Black, Other, Unknown)

Survival of Hodgkin Lymphoma by Gender

Median survival times based on gender were also calculated and presented in Table A.2 (Appendix). Classic Nodular Sclerosis and Classic Mixed Cellularity both maintained relatively similar median survival times between genders. However, Classic Lymphocyte Rich indicated a discrepancy of 23 months between males and females. Additionally, males maintained the highest median survival when diagnosed with Classic Lymphocyte Depleted Hodgkin Lymphoma (158 months), with the lowest median survival of Nodular Lymphocyte Predominance Hodgkin Lymphoma (117 months). Females shared the lowest median survival subtype with males, Nodular Lymphocyte Predominance Hodgkin Lymphoma (116

months), with the highest median survival of those diagnosed with Classic Nodular Sclerosis Hodgkin Lymphoma (147 months).

Table 4.5. Median Survival (months) (95% Confidence Intervals) of Hodgkin Lymphoma Subtypes, by Age-at-Diagnosis, SEER Data 1975-2005

	Classic Nodl Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodl Lymph Predominance	NOS
18-22	173 (166-179)	187 (168-207)	204 (186-227)	192 (124-282)	120 (96-141)	160 (136-182)
23-27	161 (157-167)	192 (180-202)	161 (136-183)	166 (136-201)	108 (81-132)	168 (156-188)
28-32	148 (143-153)	182 (163-199)	169 (136-196)	225 (147-262)	137(110-152)	150 (127-172)
33-37	143 (137-150)	164 (149-178)	147 (124-170)	194 (138-270)	132(105-149)	140 (127-155)
38-42	133 (126-138)	148 (138-162)	158 (138-191)	156 (92-226)	123 (93-154)	118 (103-143)
43-47	114 (121-130)	139 (124-154)	138 (107-169)	165 (101-239)	115 (93-131)	110 (89-130)
48-52	113 (107-120)	120 (112-141)	125(101-143)	206 (155-287)	106 (85-141)	135 (109-158)
53-57	120 (110-132)	108 (102-123)	123 (105-165)	162 (139-250)	101 (74-137)	125 (109-153)
58-62	114 (107-125)	124 (108-131)	117 (98-148)	118 (101-169)	122 (78-159)	96 (84-162)
63-67	110 (94-114)	106 (99-115)	107 (84-147)	137 (124-172)	92 (78-129)	86 (80-93)
68+	87 (83-95)	95 (89-98)	89 (74-101	112 (90-124)	93 (71-105)	101 (88-109)

Five-year relative survival probabilities for Hodgkin Lymphoma subtypes by gender were not statistically different between males and females within Hodgkin Lymphoma subtypes (Table 4.6). Log Rank Chi Square test does not indicate that any of the calculated 5-year relative survival of WHO/REAL subtypes of Hodgkin Lymphoma differs by gender. Subtype Classic Nodular Sclerosis demonstrated a nearly 5% difference in relative survival between males and females. Similarly, Nodular Lymphocyte Predominance indicated a marginal difference (3.9%) between the genders in regards to Relative 5-year survival of Hodgkin Lymphoma.

Table 4.6 Five-year Relative Survival of Hodgkin Lymphoma Patients Based on WHO/REAL Subtype by Gender, SEER Data 1975-2005

	Classic Nodl Scler		Classic Mixed Cellularity		Classic Lymph Rich		Classic Lymph Depl		Nodular Lymph Pred		NOS	
Gender	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv	n	5-yr Rel Surv
Males	8290	82.2	3467	71.8	679	86.0	522	41.2	467	91.7	2205	65.5
Females	8432	87.1	1919	69.5	300	82.9	298	40.8	226	95.6	1496	69.0
Log Rank χ^2	1.89 p=0.17		0.03 p=0.86		1.61 p=0.20		0.41 p=0.52		0.39 p=0.53		1.79 p=0.18	

Adjusted Hazard Ratios for Hodgkin Lymphoma subtypes by gender indicated varying results across subtypes (Table 4.7). The Classic Lymphocyte Rich subtype showed the greatest difference between the genders, indicating that males have 1.13 times the risk of death than females. None of the confidence intervals for the calculated hazard ratios indicated statistical significance, as each of the confidence intervals spanned the null value.

Table 4.7 Adjusted Hazard Ratios† (95% Confidence Intervals) of Hodgkin Lymphoma Subtypes by Gender, SEER Data 1975-2005

	Classic Nodl Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodl Lymph Predominance	NOS
Male	0.97 (0.93-1.01)	1.01 (0.93-1.10)	1.13 (0.93-1.37)	1.09 (0.83-1.44)	1.11 (0.86-1.44)	0.92 (0.82-1.03)
Female	1.00	1.00	1.00	1.00	1.00	1.00

†Adjusted for Race/Ethnicity (Categorical: White, Black, Other, Unknown)

CHAPTER 5

DISCUSSION

The new classification system for Hodgkin Lymphoma organizes this disease into two broad groups, with distinct clinical features and treatment regimens. The highest incidence rates of Hodgkin Lymphoma subtype found within Westernized nations is Classic Nodular Sclerosis, which is most common among adolescents and young adults (*Dessian, Spears, & Argiris, 2008*). The present study found 59% of cases to be Classic Nodular Sclerosis. Classic Mixed Cellularity Hodgkin Lymphoma and Classic Lymphocyte Rich Hodgkin Lymphoma follow similar diagnosis and treatment paths, but have a sharp contrast in incidence within this study population (19% versus 3.5%). These proportions fall well within the published reports for Hodgkin Lymphoma subtypes (*Dessian, Spears & Argiris, 2008*). Additionally, the study population in this study had similar gender incidence ratios as have been noted previously. The overall male: female incidence ratio was observed to be 1.25:1.0, similar to the 3.0 to 2.6 male to female incidence ratio reported by Han et al (*2008*). This similarity between the study population and previous research indicates that the study population is representative of those used previously in respect to Hodgkin Lymphoma Subtype distribution and gender ratios. However, the study population did not exhibit the characteristic bimodal age-at-diagnosis distribution noted in studies to date (*Clarke et al, 2006; Glaser et al, 2003; Han et at, 2008).* Although the major peak of adolescent to young adult incidence of Hodgkin Lymphoma is similar to that of previously published literature, the late in life peak does not cause the data set to be non-normally distributed.

The present study found that survival for Hodgkin Lymphoma varies by age-at-diagnosis within each WHO/REAL subtype alone but not by gender. Previous research has indicated that these factors play a role in the survival of this disease (*Clarke et al, 2001; Han et al, 2008; Mueller & Grufferman, 2006*), whether independently or jointly with other prognostic factors.

McMahon hypothesized in 1966 that Hodgkin Lymphoma is not a single disease, but in fact two separate diseases which can be split between those diagnosed in early adulthood and those diagnosed late in life (*Clarke et al, 2001*). This hypothesis has been built upon an attempt to understand the potential differences in etiology and therefore survival of Hodgkin Lymphoma. The results of the present study indicate that the 5-year relative survival of Hodgkin Lymphoma remains relatively stable (89.8% to 91.3%) up to 42 years of age within the most common subtype of Hodgkin Lymphoma in the US. Following 42 years of age-at-diagnosis, 5-year relative survival decreases at upwards to 5% per 5-year age grouping. These results remain consistent with McMahon and similar researchers' hypotheses that individuals diagnosed before 45 years of age have a unique form of Hodgkin Lymphoma when compared with individuals diagnosed at 45 and later. As another point of evidence, older individuals diseased with Hodgkin Lymphoma have shown increased presence of B symptoms, which have been related to poorer survival in previous studies (*Mueller & Grufferman, 2006; Swerdlow, 2003).* Conversely, Clarke et al (*2001*) suggests that stage at diagnosis is most closely related to survival of Hodgkin Lymphoma among those diagnosed in youth and that those diagnosed at younger ages are more likely to be diagnosed at more favorable stages. The results of this study coincide with these patterns, as subtypes of Hodgkin Lymphoma, except Classic Lymphocyte Depleted Hodgkin Lymphoma, maintained

considerably higher proportion of 5-year survival in younger cases than those diagnosed late in life.

Estimated hazard ratios for Hodgkin Lymphoma subtypes by age-at-diagnosis groups indicate that the rate of death of those individuals diagnosed later in life (after 45 years of age) ranges from 1.37 to upwards of 2.5 times the rate of death of those aged 23-27 at diagnosis for three of the four Classic Hodgkin Lymphoma subtypes. Many factors could be playing a role in this increase in rate. Older individuals are more likely to have certain co-morbid conditions that have been associated with incidence and survival of Hodgkin Lymphoma. Rheumatoid arthritis, ulcerative colitis, and lupus are all conditions which can be associated with increased age, and have also been associated with incidence and survival of Hodgkin Lymphoma (*Mueller & Grufferman, 2006*). Aging is known to play a role in decreased immune supervision and functioning, and is believed to be the link between these conditions and the role of Hodgkin Lymphoma (*Clarke et al, 2001*). This immune deregulation is a hallmark of Hodgkin Lymphoma, as the disease is known to express unusually high levels of certain cytokines, chemokines, and associated immune receptors (*Mueller & Grufferman, 2006*), and is known to be involved with tumor instigation and rapid succession (*Clarke et al, 2001*). The role of the immune system in the incidence and survival of Hodgkin Lymphoma among those diagnosed later in life, as well as chronic inflammation, and a lifetime of DNA damage, may play a role in the age-related decrease in survival of Hodgkin Lymphoma in this study.

Additionally, researchers have hypothesized that decreased survival proportions among those diagnosed later in life may be due to the role of clinicians and physicians in designing therapy regimens. Han et al (*2008*) suggest that those diagnosed late in life may be

put into more aggressive treatment procedures, thereby potentially overwhelming their aged body and immune system, leading to lower survivability of Hodgkin Lymphoma .Moreover, the decrease in immune capability both from the implemented treatment protocol, as well as the nature of Hodgkin Lymphoma disease itself may be further facilitating death among those late in life.

Although the current study indicated no statistically significant association between survival and gender, gender-related environmental factors such as occupational exposures, smoking, and alcohol use may play a role in survival of patients with Hodgkin Lymphoma (*Han et al, 2008*). Additionally, research has shown that gender in association with age-at-diagnosis may play a role in the survival of Hodgkin Lymphoma. For example, males are more often diagnosed with Hodgkin Lymphoma at less favorable stages particularly when diagnosed in young adulthood, as well as with the presence of B-symptoms later in life, and with a co-morbid condition of HIV/AIDS (*Han et al, 2008)*. Clarke et al (*2001*) proposed that survival of Hodgkin Lymphoma among males differs by age-at-diagnosis, with those diagnosed in young adulthood more likely to have poorer prognosis and lower survival. The results of this study showed that certain subtypes of Hodgkin Lymphoma diagnosed in males did have as much as a 10% difference in 5-year relative survival when compared with females among the younger age groups (Table A.4, Appendix) Subtypes with large differences between male and female relative survival were Classic Nodular Sclerosis (10%), the most common subtype of Hodgkin Lymphoma in the US, Classic Lymphocyte Rich Hodgkin Lymphoma (10%), and Classic Lymphocyte Predominance (26%). The Classic Lymphocyte Predominance subtype showed great variation between males and females in 5-year relative survival across nearly all age groups. Little previous research has been

conducted on age-specific gender differences in Hodgkin Lymphoma; this should be an area for future research.

The gender disproportion in both incidence and survival of Hodgkin Lymphoma has been considered on the basis of genetic, hormonal, and metabolic influences which may differ between the sexes (*Mueller & Grufferman, 2006*). Familial aggregation, particularly among males, has been associated with incidence of Hodgkin Lymphoma among young adults (*Clarke et al, 2001*). Perhaps this aggregation is indicative of genetic alterations or susceptibility to Hodgkin Lymphoma, which leads to decreased survival among males of younger age groups.

Although the current study presented many interesting findings, there are limitations which must be taken into consideration. First, one of the major assumptions when performing survival analysis is that death is assumed to be related to the condition under analysis, in this case Hodgkin Lymphoma subtype. This study was not able to verify that cause of death was in fact related to diagnosis with Hodgkin Lymphoma. However, death due to other factors would decrease rather than over-estimate survival probabilities. Secondly, survival analysis also assumes that survival times of censored individuals are identical to survival times of non-censored. This study observed a 2.26% proportion of censored individuals. If this assumption is not true, the estimated survival probabilities could be biased upward or downward, according to the degree of misclassification of censored individual survival times. Additionally, consistency within treatment patterns should be assumed in order for survival results to be valid. Due to high survival rates of Hodgkin Lymphoma, treatment regimens have not changed greatly over the past several decades. Finally, stage at diagnosis and race were selected as potential confounders. First, stage-at-

diagnosis within the SEER dataset for Hodgkin Lymphoma yielded a high number of missing and/or unknown values. Nearly 81% (n=23,013) individuals within the study population lacked the SEER 2001 Summary Stage information with which to perform a review of the potential confounded relationship, and therefore utilize this variable to adjust within the analysis. Although the literature indicates that additional variables may be involved as potential confounders of the association between Hodgkin Lymphoma subtype and survival of Hodgkin Lymphoma, this study chose to analyze only the two variables to keep the model as parsimonious as possible.

Factors which may be playing a role in influencing the results of this study include the inability to control for stage-at-diagnosis. Nearly 81% individuals within the study population lacked the SEER 2001 Summary Stage information with which to perform a review of the potential confounded relationship, and therefore utilize this variable to adjust within the analysis. Since individuals diagnosed with later stages (III and IV) tend to have decreased survival overall, survival probabilities may be underestimated as all patients were treated the same in regards to stage-at-diagnosis. Additionally, the inability to control for co-morbid conditions such as immuno-suppression diseases like Rheumatoid arthritis and HIV/AIDS, may be underestimating estimated survival probabilities.

Despite study limitations, there are many interesting results which may help physicians and clinicians in the future. Armed with a greater understanding of survival probabilities of Hodgkin Lymphoma by age-at-diagnosis and gender, targeted treatment regimens may be created to help increase survival chances for patients. Future studies of Hodgkin Lymphoma may wish to focus on the unique differences between the subtypes which are evident within the results presented here. Perhaps etiology plays a role in the

survival of Hodgkin Lymphoma, which could be further extrapolated by taking each subtype into consideration separately, as well as involving previous known risk factors for disease, including the role of the Epstein Barr Virus and suspected molecular markers. The research areas of Hodgkin Lymphoma are wide open, and this study hopes to help lay a foundation to advance the survival of Hodgkin Lymphoma patients in the future.

In summary, this study concluded that survival of Hodgkin Lymphoma by WHO/REAL subtype differed by age-at-diagnosis alone, but not by gender alone. Future work to further investigate these two factors together may provide a greater understanding of the effects of age-at-diagnosis and gender on survival of Hodgkin Lymphoma by WHO/REAL subtype.

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APPENDIX

ADDITIONAL FIGURES AND TABLES

Table A.1 Median Survival (months) (95% Confidence Intervals) of Hodgkin Lymphoma Subtypes, by Age-at-Diagnosis, SEER Data 1975-2005

	Classic Nodl Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodl Lymph Predominance	NOS
18-22	173 (166-179)	187 (168-207)	204 (186-227)	192 (124-282)	120 (96-141)	160 (136-182)
23-27	161 (157-167)	192 (180-202)	161 (136-183)	166 (136-201)	108 (81-132)	168 (156-188)
28-32	148 (143-153)	182 (163-199)	169 (136-196)	225 (147-262)	137(110-152)	150 (127-172)
33-37	143 (137-150)	164 (149-178)	147 (124-170)	194 (138-270)	132(105-149)	140 (127-155)
38-42	133 (126-138)	148 (138-162)	158 (138-191)	156 (92-226)	123 (93-154)	118 (103-143)
43-47	114 (121-130)	139 (124-154)	138 (107-169)	165 (101-239)	115 (93-131)	110 (89-130)
48-52	113 (107-120)	120 (112-141)	125(101-143)	206 (155-287)	106 (85-141)	135 (109-158)
53-57	120 (110-132)	108 (102-123)	123 (105-165)	162 (139-250)	101 (74-137)	125 (109-153)
58-62	114 (107-125)	124 (108-131)	117 (98-148)	118 (101-169)	122 (78-159)	96 (84-162)
63-67	110 (94-114)	106 (99-115)	107 (84-147)	137 (124-172)	92 (78-129)	86 (80-93)
68+	87 (83-95)	95 (89-98)	89 (74-101	112 (90-124)	93 (71-105)	101 (88-109)

Table A.2 Median Survival (months) (95% Confidence Intervals) of Hodgkin Lymphoma Subtypes, by Gender, SEER Data 1975-2005

	Classic Nodl Sclerosis	Classic Mixed Cellularity	Classic Lymph Rich	Classic Lymph Depl	Nodl Lymph Predominance	NOS
Male	141(92-215)	145(95-215)	147(98-208)	158(106-238)	117(81-163)	125(80-203)
Female	147(95-216)	142(90-216)	124(20-195)	144(95-236)	116(79-154)	140(87-204)

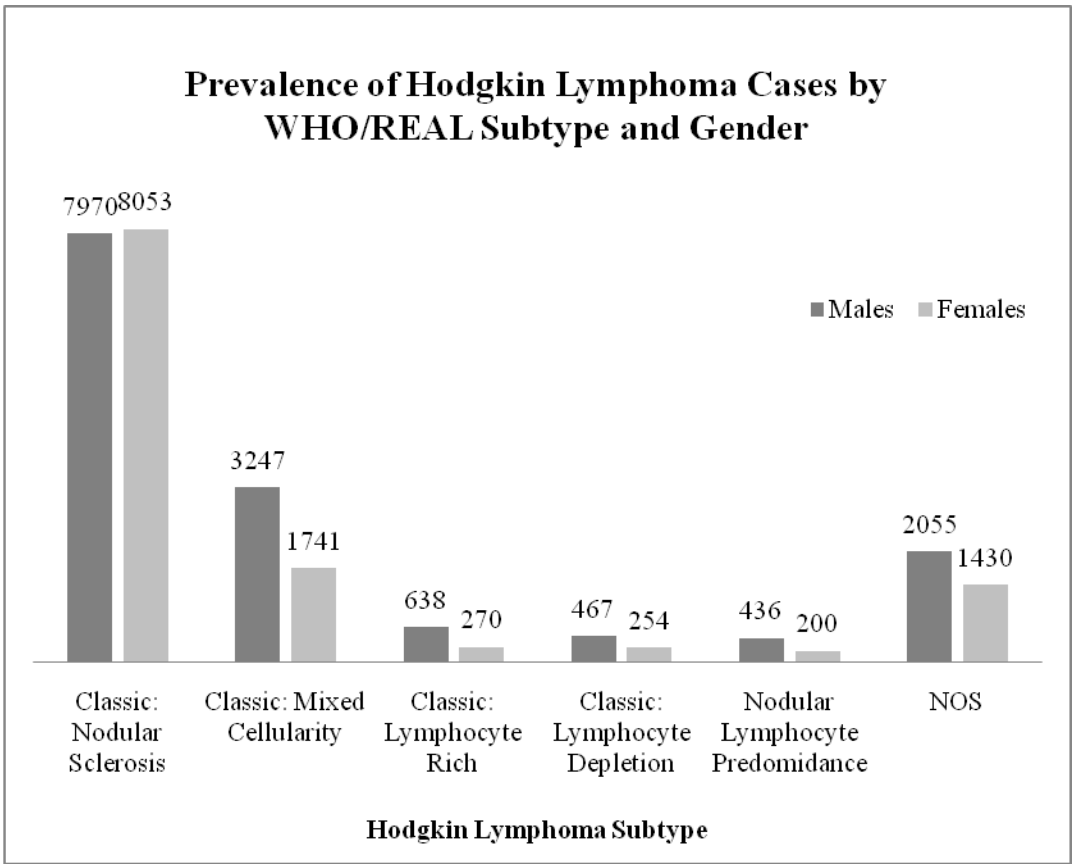

Figure A.1. Prevalence of Hodgkin Lymphoma Cases by WHO/REAL Subtype and Gender.

Table A.3 Unadjusted and Adjusted† Hazard Ratios of Hodgkin Lymphoma by Subtype and Age-at-Diagnosis, SEER Data 1975-2005

	Classic Nodl Scler		Classic Mixed Cellularity		Classic Lymph Rich		Classic Lymph Depl		Nodular Lymph Pred		NOS	
	HR	HR†	HR	HR†	HR	HR†	HR	HR †	HR	HR†	HR	HR†
18-22	0.76	0.76	0.64	0.64	0.53	0.52	0.57	0.56	0.88	0.87	0.79	0.79
23-27‡	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
28-32	0.96	0.96	0.71	0.72	0.77	0.78	0.76	0.77	0.82	0.84	1.23	0.79
33-37	1.05	1.05	0.83	0.84	1.00	0.99	0.78	0.78	0.76	0.77	0.94	0.93
38-42	1.23	1.23	1.03	1.04	1.21	0.90	1.08	1.08	0.91	0.97	1.19	1.17
43-47	1.39	1.38	1.18	1.17	1.27	1.26	1.14	1.13	0.99	0.99	1.34	1.35
48-52	1.56	1.59	1.37	1.39	1.38	1.41	0.64	0.65	1.06	1.08	0.99	0.97
53-57	1.23	1.25	1.57	1.58	1.45	1.44	0.76	0.76	1.31	1.28	1.09	1.09
58-62	1.43	1.45	1.58	1.58	1.63	1.61	1.73	1.72	1.25	1.03	1.36	1.37
63-67	1.97	1.97	1.95	1.97	1.74	1.78	1.17	1.19	1.74	1.68	2.28	2.31
68+	2.70	2.69	2.67	2.65	2.34	2.35	2.70	2.71	2.54	2.71	2.21	2.22

† Adjusted for Race (Categorical: White, Black, Other, Unknown)
‡Reference Group

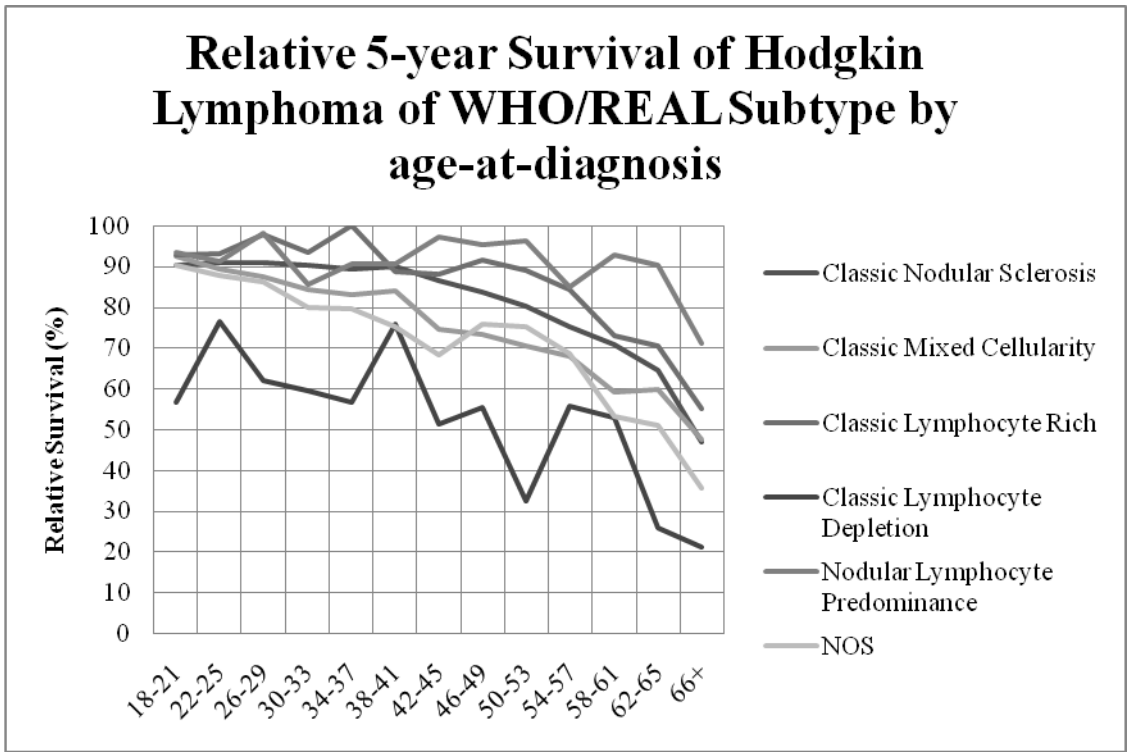

Figure A.2 Relative 5-year Survival of Hodgkin Lymphoma of WHO/REAL Subtype by Age-at-Diagnosis, SEER 1975-2005.

Table A.4. Five-year Relative Survival of Hodgkin Lymphoma by Subtype, age-at-diagnosis and gender, SEER 1975-2005

	Classic Nodl Scler		Classic Mixed Cellularity		Classic Lymph Rich		Classic Lymph Depl		Nodular Lymph Pred		NOS	
	M	F	M	F	M	F	M	F	M	F	M	F
18-22	90.3	100	92.5	89.8	96.9	84.8	54.2	83.5	90.3	100	87.5	86.3
23-27	97.8	94.2	90.2	86.2	94.0	95.3	54.5	82.0	97.8	94.2	85.8	93.6
28-32	91.3	90.1	82.6	93.4	94.2	94.8	64.6	90.9	91.3	90.1	73.4	84.4
33-37	89.5	93.8	80.3	83.6	98.2	100	45.4	87.5	89.5	93.8	71.0	88.4
38-42	91.2	94.5	80.1	86.0	89.1	90.4	79.0	66.8	91.2	94.5	67.9	75.8
43-47	97.3	91.5	74.4	81.2	82.3	100	42.5	66.2	97.3	91.5	65.6	81.6
48-52	95.3	95.5	66.4	79.1	92.4	93.6	36.3	71.5	95.3	95.5	74.7	74.8
53-57	91.5	82.0	68.3	65.9	80.1	92.3	40.6	58.8	91.5	82.0	67.8	62.5
58-62	90.6	92.6	60.0	57.5	76.4	74.9	34.0	60.6	90.6	92.6	41.8	49.9
63-67	81.1	91.9	57.7	64.0	58.9	52.3	32.1	13.2	81.1	91.9	43.6	42.9
68+	55.2	80.5	46.0	44.0	57.5	60.2	25.3	14.3	55.2	80.5	30.4	36.0

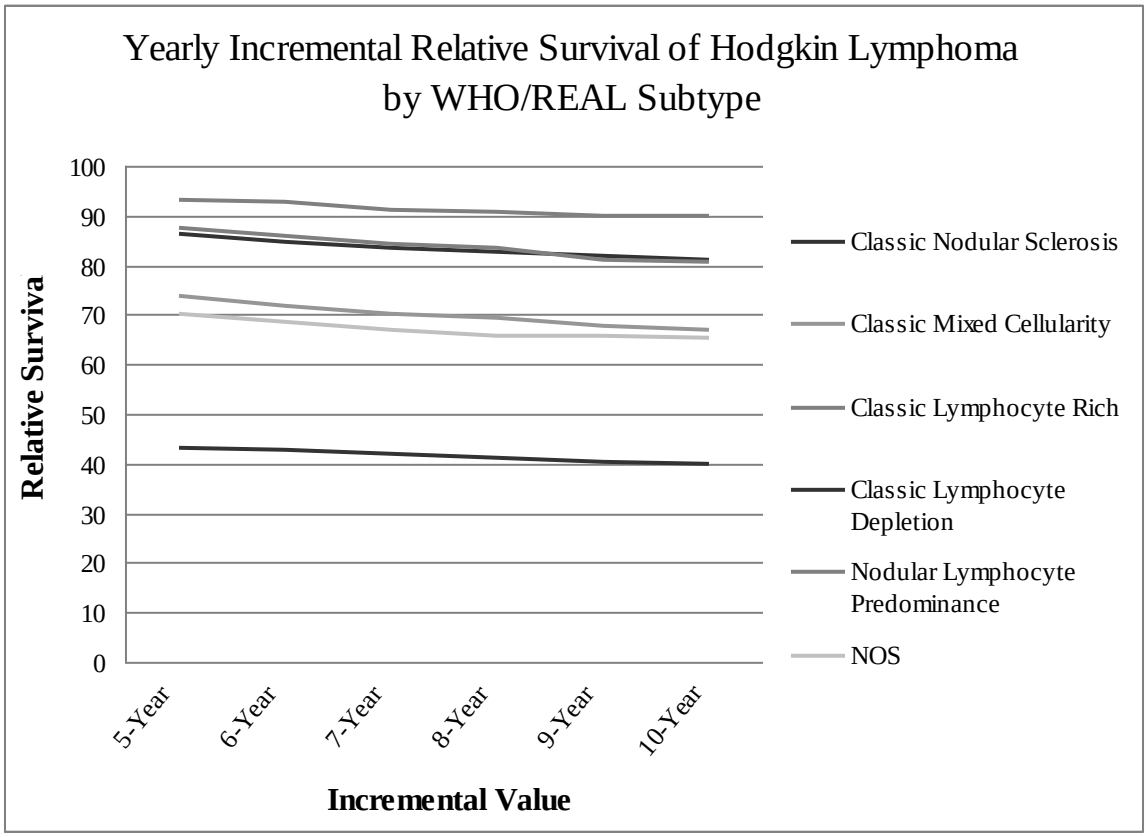

Figure A.3 Yearly Incremental Relative Survival of Hodgkin Lymphoma by WHO/REAL Subtype, SEER Data1975-2005