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Descriptive Epidemiology of Adult Liposarcoma: A Population-based Study Using SEER and the Combined SEER/NPCR Databases, 2001-2016

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ABSTRACT

DESCRIPTIVE EPIDEMIOLOGY OF ADULT LIPOSARCOMA: A POPULATION-BASED STUDY USING SEER AND THE COMBINED SEER/NPCR DATABASES, 2001-2016

SUZANNE BOCK

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INTRODUCTION:

Rare cancers, affecting 1 in 5 cancer patients, disproportionally contribute to cancer mortality. This research focused on liposarcoma, an understudied rare cancer with unknown risk factors and limited treatment options.

METHODS:

Liposarcoma incident cases were identified from the Surveillance, Epidemiology, and End Result (SEER) program and the combined SEER-National Program of Cancer Registries (CNPCR) for 2001-2016. Incidence rates (age-adjusted and age-specific) and 5-year survival were calculated using SEER*stat. Time trends were determined using Joinpoint.

RESULTS:

SEER liposarcoma cases represented ~30% (n=11,162) of the nationwide pool (n=37,499). Males accounted for ~60% of the cases, 82% cases were identified among whites. Age-adjusted incidence was greater among males vs. females and whites vs. blacks, whereas survival did not differ by sex and race (~80%). The dedifferentiated (57.2%), pleomorphic (64.1%) and retroperitoneal (63.9%) tumors had the worse survival. Liposarcoma rates increased nationwide

by 19% in 2001-2016, with the annual percent increase (APC) of 1.43% (95% CI: 1.12-1.47). The APC was greater for males vs. females (1.67% vs. 0.89%) and retroperitoneal vs. extremity tumors (1.96% vs. 0.58%). The SEER generally overestimated the rates and time trends compared to nationwide data.

CONCLUSIONS:

The comprehensive description of liposarcoma epidemiology reveals increasing incidence of this understudied rare cancer, with greater increases among males, the high-risk subgroup and retroperitoneal tumors, the low-survival subgroup. The time trends suggest an environmental component, which if discovered, may help to prevent liposarcoma. Differences between SEER and CNPCR findings emphasize the need for nationwide cancer surveillance.

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by

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APPROVAL PAGE

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Author's Statement Page

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CHAPTER I

INTRODUCTION

1.1 Rare Diseases

According to the National Center for Advancing Translational Sciences (2017), a rare disease in the United States is defined as a disorder that affects less than 200,000 people. Internationally this accounts for as many as 7,000 different diseases (National Center for Advancing Translational Sciences, 2017). While each rare disease may only affect a relatively small number of individuals, the sum of all these diseases has a far-reaching impact on population health. The National Organization of Rare Disorders (2016) estimates that up to 30 million people or 10 percent of the U.S. population have a rare disease. Globally, this translates to 350 million people (Global Genes, n.d.). Even though rare diseases affect many people worldwide, there is a lack of attention towards the diagnosis and treatment of these uncommon disorders. Often overlooked by pharmaceutical companies, researchers, and the scientific community, a new name emerged for these forgotten diseases, "orphan" (Bolignano & Pisano, 2016). Intending to address the public health issues surrounding orphan diseases, in 1983 Congress passed the Orphan Drug Act. This act gave pharmaceutical companies financial incentives to plan and develop drugs for these forgotten diseases (National Center for Advancing Translational Sciences, 2017). However, to date, there is still more to be done to raise awareness towards these diseases.

The collective impact of rare diseases is far-reaching. The National Organization of Rare Disorders (2016) claims that "there are more Americans who live with a rare disease than all of those who have either HIV, heart disease, or stroke" (p. 2). Despite the sizable number of people affected, rare diseases still lack the attention and funding of more common disorders. Rare diseases can also be challenging to identify. Many times, insufficient knowledge about the 7,000

different rare diseases leads to delays in getting a proper diagnosis. The average time from symptom onset to a correct diagnosis for someone with a rare disorder is six years (Blöß et al., 2017). During this time, patients see many doctors and specialists trying to uncover the source of their symptoms. Even when a doctor is familiar with the disease, heterogeneity of rare diseases can complicate matters (Ronicke et al., 2019). Low incidence combined with many different subtypes for the same disease will often delay diagnosis (Ronicke et al., 2019).

Once a person is diagnosed, treatment for rare diseases is extremely limited. Given the small number of cases associated with rare diseases, animal models and small sample sizes make the development of therapeutic options expensive and difficult (Palmer & Pryde, 2014). According to the National Organization of Rare Disorders (2016), it is estimated that only 5% of all rare diseases have corresponding therapy. Thus, rare diseases burden patients, doctors, and health systems with their lack of treatment options, high costs of existing treatment, and frequent misdiagnosis.

1.2 Rare Cancers

Rare cancers share many of the problems associated with rare diseases such as insufficient knowledge, lack of funding, and limited treatment options. As with rare diseases, rare cancers are also widespread throughout the world. In the European Union, estimates of rare cancers are calculated at 108 new cases per 100,000 people, or 22% of all new annual cancer diagnoses (Gatta et al., 2011). Similarly, in the United States, 20% of all new cancer diagnoses are considered rare (DeSantis, Kramer, & Jemal, 2017). These numbers constitute a substantial proportion of all new cancer diagnoses. Unlike rare diseases, however, rare cancers are often fatal. Population-based research reveals the stark statistics of the rare cancer burden. The five-year relative survival for rare cancers from 2000 to 20007 verses more common cancers in the European Union was 49%

vs. 64% (Gatta et al., 2011). Similarly, in the United States, compared to more common cancers, rare cancer 5-year relative survival among males was (55% vs. 75%) and among females was (60% vs. 74%) (DeSantis, Kramer, & Jemal, 2017).

Heterogeneity of rare cancers further complicates the development of evidence-based guidelines of care. For example, even though sarcomas represent 1% of all adult malignant tumors, included in that 1%, are over 70 different subtypes (Mathoulin-Pelissier & Pritchard-Jones, 2019). Randomized controlled trials for these distinct morphologies are often underpowered, leaving many questions of treatment and care unanswered. Hence, all of the above-mentioned issues – misdiagnosis, limited treatment options, and lack of viable prevention measures – are especially serious for rare cancers, making it one of the most dramatic unresolved public health problems.

1.3 Liposarcoma

Liposarcoma is a rare cancer that forms from mesenchymal cells in the body. It can be found anywhere on the body but is most commonly found in the extremities and the retroperitoneum (Barbetakis et al., 2007). Although liposarcoma is a rare cancer, it is the most common of all sarcomas, accounting for 20% of all mesenchymal tumors (Schwartz, 2019). In 2013, the World Health Organization issued a reclassification of soft tissue sarcomas that redefined liposarcoma into 4 major histological subgroups: atypical lipomatous tumors/well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma (Jo & Fletcher, 2014). This new classification system not only takes into consideration the distinct morphology, but also the genetic make-up of the tumor, helping researchers to determine patterns of disease and treatment options (Blay, 2018).

1.4 SEER and NPCR databases

One way that cancer researchers track cancer incidence and survival statistics is through The Surveillance, Epidemiology, and End Result (SEER) program. The SEER database provides data from 18 registries across the United States, representing approximately 27.8% of the population (SEER, n.d). SEER has been a popular source for population-based cancer-related research for years. Just recently, however, the National Program of Cancer Registries (NPCR) publicly released data that covers 46 states and 97% of the United States Population (Centers for Disease Control and Prevention, n.d.). Combined with the SEER database, this dataset provides cancer statistics covering 100% of the United States population (Centers for Disease Control and Prevention, n.d.). The combined dataset allows researchers to have a larger covered population and thus, a better representation of cancer surveillance in the United States. While both data sources provide useful information, each has specific advantages. Although the SEER database only represents approximately 27.8% of the population, its key advantage is that it contains more detailed information regarding tumor characteristics and estimates of survival. The primary benefit of the combined NPCR (CNPCR), on the other hand, is the broader representation of cancer in the U.S., despite having a more limited number of variables in the dataset.

1.5 Gaps and Purpose of Study

The population-based research of liposarcoma in the U.S. is limited. Previously published analyses of liposarcoma incidence focused on histology (Wu, Qian, & Jin, 2019), targeted therapy (Tseng, et al., 2011) and the relationship between survival and tumor location or treatment (Smith et al., 2012; Gerry, Fox, Spruill, & Lentsch, 2014). This analysis fills the gaps in the literature by not only including the latest and most comprehensive data available, but also by focusing on liposarcoma incidence trends over time.

1.6 Research Questions

This analysis begins by examining the distribution and incidence rates of liposarcoma cases by demographic and tumor characteristics. Age-specific incidence rates and time trends of liposarcoma are examined in the mostly unknown etiology of this rare cancer. Next, I compare the nation-wide estimates (combined NPCR and SEER) with those derived from SEER. Lastly, I delve further into liposarcoma by examining SEER only estimates through grade, size, stage, and survival analysis.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Liposarcoma and Gender

The association between gender and liposarcoma has been documented in several lipomatous tumor studies. Dalal, Kattan, Antonescu, Brennan, & Singer, (2006) collected liposarcoma data from Memorial Sloan-Kettering Cancer Center from 1982 to 2005. During that time period, 801 patients were diagnosed with primary liposarcoma of the extremity, trunk, or retroperitoneum. Of those 801 patients, 69% (n=471), were men. Likewise, Hoffman et al. (2007) investigated localized and metastatic myxoid/round cell liposarcoma at MD Anderson cancer center from 1990 to 2010, and their results show, that 119 of the 207 people (57%) identified as having liposarcoma, were men. Vos et al. (2018) collected data on patients diagnosed with liposarcoma extremity cases from 1986 to 2015 at the Erasmus MC Cancer Institute (Rotterdam), and from 1990 and 2015 at the Maria Skłodowska-Curie Institute-Oncology Center (Warsaw). They also found that the majority (51%) of the cases were male.

Higher incident liposarcoma rates among males were not limited to small research institutions. Broader analysis also found this association between liposarcoma incidence and male sex. The National Cancer Intelligence Network examined liposarcoma incidence rates in England from 2007 to 2009, and they found twice greater liposarcoma rates among males vs. females (2013). Similarly, SEER estimates of liposarcoma data collected from 1978-2001, confirmed the majority (59%) of liposarcoma cases identified were males (Toro et al., 2006).

Research regarding survival estimates between men and women has been mixed. Smith et al., showed no sex differences among well-differentiated liposarcoma in the overall and disease-specific survival (2012). However, another study, which examined survival among patients with extremity myxoid liposarcomas, showed males as being a negative survival predictor (Wu, Qian,

& Jin, 2019). For all cancer types overall, the increased cancer risk and poor survival among males have been established by population-based data (Radkiewicz, Johansson, Dickman, Lambe, & Edgren, 2017; Afshar et al., 2018; Ellison, 2016). Thus, more research is necessary to help elucidate the association between gender and liposarcoma.

2.2 Liposarcoma and Race

Research into liposarcoma and race has been clear, with the majority of incident cases found among whites. For example, in a study where researchers used 1973-2009 SEER data to compare head and neck liposarcoma cases to those liposarcoma cases found on other parts of the body, Gerry, Fox, Spruill, and Lentsch (2003), found that 82% of the 318 head and neck liposarcoma cases and 85% of the 9,485 other liposarcoma cases were of white ethnicity. Smith et al. (2011), also used the SEER database to identify 1,266 cases of well-differentiated liposarcoma from 1988-2004. Their results show that the majority, or 72%, of the patients were white. Another study that examined well-differentiated liposarcoma patient characteristics found that 79% of their 62 patients were categorized as being white (Keung et al., 2018). Lastly, Patil and Chamberlain concurred with other research, finding that 1,117 or 82% of the 1,358 patients diagnosed with liposarcoma were white.

2.3 Liposarcoma and Histological Type

Histological type plays an important role in determining the extent of disease, treatment options, and survival statistics of liposarcoma. As mentioned earlier, following the WHO's reclassification, liposarcoma is categorized by four distinct subtypes: atypical lipomatous tumors/well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma (Jo & Fletcher, 2014).

While these subtypes represent a different kind of liposarcoma, each disease is heterogeneous. For example, well-differentiated liposarcoma is considered a low-grade neoplasm with a small probability of metastasis (Patil & Chamberlain, 2013). Since the well-differentiated subtype of liposarcoma is more likely to stay local than other forms of liposarcoma, surgery is often recommended as the primary treatment option (Patil & Chamberlain, 2013). Whereas myxoid liposarcoma, which is defined as a lipomatous mass with myxoid stroma, is radioresponsive and radiosensitive, research suggests a higher response rate with a treatment combination of radiation and chemotherapy (Chowdhry et al., 2018).

Mutations of recurrent well-differentiated tumors can sometimes result in a change in tumor histology. For example, dedifferentiated tumors contain patterns of both well-differentiated and other higher grade nonlipogenic elements (Wang & Lucas, 2018). Although current estimates of more aggressive dedifferentiated nodules arising from recurrent well-differentiated tumors are only around 10% (Wang & Lucas, 2018), their aggressiveness makes this type of liposarcoma more deadly (Wang & Lucas, 2018). Research shows that current five-year survival rates for dedifferentiated tumors are as low as 20% to 40% (Wang & Lucas, 2018). These statistics are not surprising given that dedifferentiated tumors are often higher grade, heterogeneous in nature, and have limited response to current therapy (Wang & Lucas, 2018; Dalal, Antonescu, & Singer, 2008).

2.4 Liposarcoma and Tumor Site

Tumor location can also influence the course of treatment and survival prognosis. For tumors found on the extremities, the primary therapy is surgery followed by adjuvant radiation or chemotherapy (Vos et al., 2019). It has established that patients with extremity well-differentiated liposarcoma have a good prognosis (Vos et al., 2019; Gatta et al., 2017). For example, 191 patients

from a study led by Vos et al. (2019), who were diagnosed with well-differentiated liposarcoma and treated surgically followed by radiotherapy, had a 5-year survival rate of 98%. However, not all patients fare so well. Patients with tumors located in areas where excision is no longer possible, such as retroperitoneum, have lower survival rates (Schwartz et al., 2019). This is because tumors in the retroperitoneum are often larger in size and asymptomatic until they become too big for resection (Schwartz et al., 2019). Studies have confirmed that patients diagnosed with retroperitoneal tumors indeed have low survival rates (Tseng et al., 2011; Smith et al., 2012; Swartz et al., 2019). Hence, retroperitoneal tumors have fewer treatment options and a poorer prognosis.

Tumor site is not the only factor taken into consideration for therapy. Patient and tumor characteristics such as age, comorbidities, tumor grade, size and histology all play a role in treatment decisions (Vos et al., 2008). As mentioned above, histology is one of the most important factors influencing treatment and, ultimately survival. For those diagnosed with dedifferentiated tumors of the retroperitoneum, even if surgical resection is a viable treatment option, recurrence occurs in over 80% of the patients, with 30% to metastatic sites (Dalal, Antonescu, & Singer, 2008). Thus, the limited treatment options for those with recurrent liposarcoma in the retroperitoneum can partially explain this poor outcome.

2.5 Summary of literature review

Highlights from the literature review of previous studies include:

- Rare diseases such as liposarcoma are understudied
- There are no studies that have examined liposarcoma trends using national NPCR datasets
- Liposarcoma incident rates are twice as high for men than women

- Research shows that liposarcoma affects whites more than any other ethnicity
- Liposarcoma histology often determines treatment options and survival rates
- Tumor site also plays a role in survival prognosis.

CHAPTER 3

MANUSCRIPT

INTRODUCTION

A rare disease, by definition, affects a small number of people. Ignored by the pharmaceutical industry as well as epidemiological and clinical research, rare diseases have a considerable impact on public health outcomes. The National Institutes of Health estimates that up to 30 million people or 10 percent of the U.S. population have a rare disease (National Institutes of Health, 2017). Globally, this translates to 400 million people (Global Genes, n.d.). While each specific disease is considered rare, the sum of all rare diseases has a far-reaching impact on population health. Limited treatment options, high costs of existing treatments, and frequent misdiagnosis burden patients, physicians, and health systems (Ronicke, et al., 2019). Moreover, the lack of knowledge about the risk factors for rare diseases makes their prevention unattainable.

Although some rare diseases are not fatal, rare cancers are. All of the above-mentioned issues – misdiagnosis, limited treatment options, and lack of viable prevention measures – are especially critical for rare cancers, making it one of the most dramatic unresolved public health problems (Gatta et al., 2011; DeSantis, Kramer, & Jemal, 2017; Gatta et al., 2017). Population-based research reveals the stark statistics of rare cancers. In Europe, incidence of rare cancers is estimated as 108 cases per 100,000, or 22% of all new annual cancer diagnoses (Gatta et al., 2011). Likewise, in the U.S., 20% of all new cancer diagnoses are considered rare (DeSantis, Kramer, & Jemal, 2017). Emphasizing the gaps in research and treatment, the 5-year survival for rare cancers is worse as compared to common cancers: 49% vs. 63% in Europe (Gatta et al., 2017), and in the U.S., 55% vs. 75% among males and 60% vs. 74% among females (DeSantis, Kramer, & Jemal, 2017). Heterogeneity of rare cancers further complicates the development of evidence-based guidelines of care. For example, even though sarcomas represent 1% of all adult malignant tumors,

included in that 1%, are over 70 different subtypes (Mathoulin-Pelissier & Pritchard-Jones, 2019). Randomized controlled trials for these distinct morphologies are often underpowered, leaving many questions of treatment and care unanswered, thus, requiring new approaches.

Our interest in liposarcoma was motivated by the anxiety, desperation, and death of our friends and relatives diagnosed with a rare cancer, liposarcoma, a cancer with limited treatment options, and unknown risk factors. We conducted this research to elucidate the extent of liposarcoma burden in the U.S. We believe that change is possible only when the attention of the scientific community and public health advocates focuses on the problem of rare cancers, as it was demonstrated by the HIV/AIDS advocacy movement. Their movement mobilized researchers and the community to discover the causes and treatment for this initially rare disease (Fastercures and HCM Strategists, n.d.). By this contribution, we hope to bring the problem of rare cancers, specifically liposarcoma, to the attention of the scientific community.

Liposarcoma is a malignant mesenchymal tumor (Muratori et al., 2018), accounting for almost 20% percent of all mesenchymal tumors (Barbetakis et al., 2007). It can be found anywhere in the body, but most commonly is found in the extremities and retroperitoneum (Barbetakis et al., 2007). Population-based research of liposarcoma in the U.S. is limited. Previously published analyses focused on histology (Wu, Qian, & Jin, 2019), targeted therapy (Tseng et al., 201), and the relationship between survival and tumor location or treatment (Smith et al., 2012; Gerry, Fox, Spruill, & Lentsch, 2014). Our analysis fills the gaps in the literature by not only including the latest and most comprehensive data available but also examining liposarcoma incidence trends over time.

In this study, we used two publicly available data sources. The Surveillance, Epidemiology, and End Result (SEER) program is the most frequently used population-based cancer incidence

data. The updated dataset provides information on cancer surveillance from 18 registries across the U.S (Centers for Disease Control and Prevention, n.d.; SEER.cancer.gov, n.d.). However, a new publicly released data source called National Program of Cancer Registries (NPCR) has recently become available. This registry covers 46 states and 97% of the U.S. population (Centers for Disease Control and Prevention, n.d). Combined, the SEER and NPCR datasets (CNPCR) provide cancer statistics covering 100% of the U.S. population (Centers for Disease Control and Prevention, n.d). While both data sources provide useful information, each has specific advantages. Although SEER represents ~27.8% of the population, it contains more detailed information on tumor characteristics and estimates of survival. CNPCR, on the other hand, has broader representation of cancer in the U.S., but limited information on tumor characteristics and no information on survival. Our analysis begins by examining liposarcoma distribution by demographic and tumor characteristics as well as estimates of age-adjusted incidence rates. We then present age-specific incidence rates and examine time trends of liposarcoma. Next, we compare the nationwide estimates (CNPCR) with those derived from the SEER. Lastly, using SEER, we delve further into liposarcoma tumor characteristics by examining distribution of cases by grade, size, stage, and survival.

METHODS

Incident cases of liposarcoma between 2001 and 2016 were identified using SEER 18 (November 2018) and the combined NPCR (November 2018) and SEER registry (hereafter referred as CNPCR). Cases were defined by the International Classification for Oncology, 3rd edition (ICD-0-3), codes 8850-8860 with age at diagnoses ≥ 18 years.15 Annual incidence rates were calculated using SEER*Stat software (version 8.3.5) (Surveillance Research Program,

National Cancer Institute, n.d). All rates were expressed per 100,000 person-years and age-adjusted to the 2000 U.S. standard population.

Variables available from SEER and CNPCR datasets

In 2013, the World Health Organization (WHO) issued reclassification of soft tissue sarcomas which redefined liposarcoma into four major histological subgroups: atypical lipomatous tumors/well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma (Jo & Fletcher, 2014). This new classification system not only takes into consideration the distinct morphology, but also the genetic make-up of the tumor, helping researchers to determine patterns of disease and treatment options (Jo & Fletcher, 2014; Blay, 2018). Following the 2013 WHO reclassification (Jo & Fletcher, 2014) liposarcoma histology was categorized as well-differentiated, myxoid, pleomorphic, dedifferentiated and other (round cell, mixed, angiomyoliposarcoma, fibroblastic and not otherwise specified). Tumor site was categorized as retroperitoneal, extremities, or other. Race was categorized as white, black, or other (American Indian/Alaska Native, Asian or Pacific Islander, Hispanic). Age-specific rates were calculated for the following age groups: < 35, 35-44, 45-54, 55-64, 65-74, 75-84, and 85 years and older.

Variables available from SEER dataset

Histologic tumor grade was labeled as low (grade I) and high (grades II, III, and IV). Tumor stage was defined as localized, regional/distant, and unknown. Given the limitation of SEER data in 2016 (retroperitoneal data was not reported), the distribution of stage and frequency of metastasis at diagnosis was described using data from 2001-2015. Relative 5-year survival (proportion of observed cancer survivors to expected cancer-free survivors) was calculated using SEER*stat software (Surveillance Research Program, National Cancer Institute, 2019). The 5-

year relative survival estimates excluded patients with cancer were reported through autopsy or death certificate.

Time trends

Time trends of liposarcoma age-adjusted incidence were examined using Joinpoint regression modeling software, version 4.7 (Joinpoint Regression Program, 2018). Total percent change (PC) for 2001-2016 and annual percent change (APC) were calculated for all cases and stratified by gender, race, and site.

RESULTS

Our analyses identified 11,162 cases of liposarcoma from 2001-2016 in SEER, which constituted 30% of liposarcoma cases identified by CNPCR (n = 37,499). Distribution of liposarcoma by sex was similar in both SEER and CNPCR, with men accounting for approximately 60% of new cases. Liposarcoma was predominantly found in whites, accounting for 82%-86% of all tumors (Table 1). The most common histological subtypes were well-differentiated tumors (33% and 31%), followed by other (21% and 23%), dedifferentiated (20% in both), myxoid (19% in both), and pleomorphic (7% and 8%) tumors in SEER and CNPCR, respectively. Tumors were mostly found in the extremities (39%-41%) and retroperitoneum (21%-22%), with other areas of the body accounting for 39% (Table 2). In general, both SEER and CNPCR showed similar liposarcoma age-adjusted rates, with a slight overestimation by the SEER data. The overall age-adjusted incidence rates were estimated as 1.08 (95% CI, 1.06-1.10) and 1.01 (95% CI, 1.00-1.02) per 100,000 person-years, from SEER and CNPCR, respectively. The incidence rates were nearly twice as high for males as compared to females, which were greatest among whites and lowest among blacks (Table 1).

When examined by tumor characteristics (Table 2), the highest rates were found for well-differentiated tumors (0.31-0.35 cases per 100,000 person-years). Rates of myxoid, dedifferentiated, and the category of other tumors ranged between 0.19-0.23 cases per 100,000 person-years, whereas pleomorphic tumors had the lowest incidence rate (0.08 cases per 100,000 person-years). Compared to CNPCR, SEER also slightly overestimated the rates for tumors found in the extremities, in sites labeled other and in the retroperitoneum.

Age-Specific rates- SEER and CNPCR

As with many other cancers, liposarcoma incidence rates increased with age (Figure 1). The CNPCR data show an increase in incidence among males until age 80-84 years with the peak rate of 4.36 (95% CI, 4.14-4.36) cases per 100,000 person-years. The SEER data show a similar pattern with slightly earlier peak at 75-84 years, estimated as 4.95 (95% CI, 4.58-5.35) cases per 100,000 person-years (Figure 1). Compared to the CNPCR, SEER age-specific rates consistently overestimated liposarcoma incidence among males, with the greatest differences between 75-80 years. Liposarcoma rates for women reached a peak at an earlier age interval in CNPCR (75-79 years) as compared to SEER (80-84 years); however, the difference in age-specific rates at the peak (and overall) was not as pronounced between the two data sources, with the CNPCR estimate of 1.89 (95% CI, 1.79-2.00) and the SEER estimate of 1.97 (1.74-2.22) cases per 100,000 person-years (Figure 1).

Time trends- SEER and CNPCR

The most alarming finding was the increasing rates of liposarcoma from 2001-2016 identified by both SEER and CNPCR (Table 3). Liposarcoma rates are on a continuous upward trend (Supplemental Figure 1). The annual increase of liposarcoma incidence (APC) was estimated as 1.77% (95% CI, 1.21-2.33) and 1.43% (95% CI, 1.12-1.74) and the overall increase (PC) of

liposarcoma was estimated as 27.2% and 19.0 % by SEER and CNPCR, respectively. The sex-differences in time trends were under-estimated by SEER, with males showing 1.3-fold greater APC, whereas CNPCR showed almost twice greater APC in males – the demographic group that is most affected by liposarcoma (Table 3). Stratification by race revealed the fastest growing incidence among those categorized as other, with APCs of 2.68% (95% CI, 1.69-3.68) and 3.16% (1.74, 4.60) estimated from CNPCR and SEER, respectively. Among whites, the increase in incidence was 1.6-fold greater as compared to blacks, as estimated from CNPCR (Table 3). Stratification by tumor site revealed that retroperitoneal and tumors categorized as other increased approximately by 2% a year, whereas tumors arising in extremities increased at a much slower rate, APC=0.58% (95% CI, 0.18-0.98), as estimated from CNPCR (Table 3). Comparing time trend estimates derived from SEER and CNPCR, it is clear that overestimation of the SEER-derived trends was fairly consistent except for the analysis of retroperitoneal tumors: APC was higher as estimated by CNPCR [1.94% (95% CI, 1.40-2.49)] than by SEER [1.36% (95% CI, 0.34-2.40)].

Distribution of liposarcoma by grade, size, stage – SEER

Table 4 depicts the distribution of liposarcoma cases by tumor grade, size, and stage. This table shows that a considerable proportion of tumors (10-19%) had missing data. More tumors were considered low grade (46%), larger in size, ≥ 10 cm (58%), and diagnosed at an earlier stage (59%). Distributions of tumor grade did not differ by sex, race, and site. However, our analysis uncovered a sharp difference in size and stage of the tumors at different sites. Retroperitoneal tumors are diagnosed as larger in size, ≥ 10 cm (75%), and at a more advanced (i.e., regional/distant) stage (45%).

Survival Analysis – SEER

Overall, 5-year relative survival did not differ by sex and race (Table 5). As expected, well-differentiated tumors predicted better survival [95.5% (95% CI, 93.6-96.9)], while pleomorphic [64.1% (95% CI, 59.1-68.7)] and dedifferentiated [57.2% (95% CI, 54.0-60.3)] indicated poorer survival. There was also a sharp difference in survival by site and grade. Tumors located on the extremities had the greatest 5-year survival rates at 89.9% (95% CI, 88.4-91.3), while retroperitoneal tumors were the deadliest [63.9% (95% CI, 61.0-66.7)]. As expected, those diagnosed with low grade tumors survived longer [94.2% (95% CI, 92.7-95.4)] than those with tumors considered high-grade [67.2% (95% CI, 65.1-69.1)].

DISCUSSION

This comprehensive analysis of liposarcoma includes the theoretically representative samples of cancer cases (SEER) and the entire U.S. population (CNPCR). Whereas generalizability of SEER data has been previously questioned (Nattinger, McAuliffe, & Schapira, 1997; Kuo & Mobley, 2016; Pedersen et al., 2019) a direct comparison of cancer rates and time trends between SEER and the nationwide data (to the best of our knowledge) has not been published. Such comparison is especially meaningful for rare cancers because the nationwide data with a larger sample size provide a priori more precise estimates. Thus, one of our main objectives was to derive and compare estimates from the latest data available from SEER and CNPCR. We found reasonably similar estimates of liposarcoma incidence (for all cases) and time trends by examining both datasets, with the SEER-derived estimates being slightly greater as compared to the national data. The subgroup analysis revealed that the SEER-CNPCR differences in incidence estimates were the most pronounced among males aged 60 and older, as demonstrated by the age-specific rates (Figure 1). Such an apparent overestimation of liposarcoma rates was not observed among females (Figure 1). Older males account for the majority of liposarcoma tumors; thus, such

sex-age difference most likely drives the observed over-estimation of liposarcoma incidence by SEER as presented in Tables 1 and 2.

The age-pattern of incidence observed presented a typical (Pedersen et al., 2019) increase followed by a plateau and a decrease at very old age (Figure 1). After age 75-80, cancer incidence is expected to decrease (Harding, Pompei, Lee, & Wilson, 2008); this may reflect increased cellular senescence accompanied by suppression of cellular proliferation – the processes that should slow tumor growth (Harding, Pompei, Lee, & Wilson, 2008). Alternatively, the drop in liposarcoma (or other cancers) incidence at older age reflects poorer cancer detection in the older population (Pedersen et al, 2019).

Since previously published studies focused on specific liposarcoma subtypes, there is no direct comparison for our analysis of liposarcoma demographic, histological subtypes, and tumor site distribution (Wu, Qian, & Jin, 2019). Indirectly, our data can be compared to a study of liposarcoma that examines head and neck to other sites (Gerry, Fox, Spruill, & Lentsch, 2014). Similar to this study, we found (bold) the majority of liposarcoma cases were male (60% vs. 59%), white (86% vs. 82%) and well-differentiated (31% vs. 33%). Likewise, the National Cancer Intelligence Network (NCIN) in the U.K. found twice greater liposarcoma rates among males vs. females (National Cancer Intelligence Network, 2013).

Limited information has been published about liposarcoma time trends. The NCIN reported that liposarcoma incidence in England from 1985 to 2009 had increased.26 These results are consistent with our nationwide findings of rising liposarcoma rates in both sexes (Table 3, Supplemental Figure 1). Thus, males not only have a greater risk of liposarcoma, but the incidence among males increased at a faster rate. The fact that the rates are increasing so quickly in the

subgroup with the greatest risk (males) emphasizes the urgency to better understand the risk factors underlying such time trends.

Comparing time-trends derived from SEER and CNPCR, we found the greatest difference of APC among blacks; specifically, SEER overestimated APC by almost twice as compared to CNPCR for this racial group (Table 3). Thus, nationwide data are particularly important when studying rare cancers among minority subgroups. When stratified by tumor location, the time trends were highly overestimated by SEER for the tumors located in extremities, the least deadly liposarcoma (89.9% survival), whereas for the deadliest tumor – retroperitoneal (63.9% survival) – the SEER estimates were lower (Table 3). Overall, our analysis clearly demonstrates that nationwide data are crucial in deriving a realistic picture of the trends in rare cancers.

Consistent with published results (Smith et al., 2012), the estimates of 5-year survival did not differ between men and women (Table 5). Smith et al. showed no sex differences among well-differentiated liposarcoma in the overall and disease-specific survival (2012). However, another study, which examined survival among patients with extremity myxoid liposarcomas, showed males as being a negative survival predictor (Wu, Qian, & Jin, 2019). For all cancer types overall, the increased cancer risk and poor survival among males has been established by population-based data (Radkiewicz, Johansson, Dickman, Lambe, & Edgren, 2017; Afshar, et al., 2018; Ellison, 2016). Thus, our findings of similar survival among males and females must be confirmed with the more recent data when it becomes available.

Liposarcoma histology also influences survival prognosis. Histological features such as differences in patterns of reoccurrence, metastatic risk, and grade, all influence survival (Tseng et al., 2011; Smith et al., 2012). Our data showed well-differentiated histology as the most common liposarcoma sub-type (33.04%) with the highest 5-year survival of 95.5% (Tables 2 and 5). In

general, well-differentiated liposarcoma has a low probability of metastasis, and therefore, treatment options such as marginal excision will often yield good results (Wang & Lucas, 2018). However, well-differentiated tumors are also known for having a high rate of local recurrence (Wang & Lucas, 2018). Patients with tumors located in areas where excision is no longer possible, such as retroperitoneum, have lower survival (63.9%). Tumors in the retroperitoneum are often larger in size and asymptomatic until they become too big for resection (Schwartz et al., 2019). Hence, retroperitoneal tumors have fewer treatment options and a poorer prognosis. In agreement with published results (Tseng et al., 2011; Smith et al., 2012; Schwartz et al., 2019) our analysis confirms that patients diagnosed with retroperitoneal tumors indeed have the lowest survival rates (Table 5).

Mutations of recurrent well-differentiated tumors can sometimes result in a change in tumor histology. For example, dedifferentiated tumors contain patterns of both well-differentiated and other higher grade nonlipogenic elements (Wang & Lucas, 2018). Current estimations of more aggressive dedifferentiated nodules arising from recurrent well-differentiated tumors are around 10% (Wang & Lucas, 2018). Five-year survival rates for dedifferentiated tumors can be as low as 20% to 40% (Wang & Lucas, 2018). In our data, the 5-year survival was higher, with approximately 58% for the dedifferentiated sub-type, however, compared to the other histological types of liposarcoma where survival ranges from 96% (well-differentiated) to 64% (pleomorphic), dedifferentiated tumors are the most deadly. These statistics are not surprising given that dedifferentiated tumors are often higher grade, heterogeneous in nature, and have limited response to current therapy (Wang & Lucas, 2018; Dalal, Antonscu, & Singer, 2008). For those diagnosed with dedifferentiated tumors of the retroperitoneum, even if surgical resection is a viable treatment option, recurrence occurs in over 80% of the patients, with 30% to metastatic sites (Dalal,

Antonescu, & Singer, 2008). Thus, the limited treatment options for those with recurrent liposarcoma in the retroperitoneum can partially explain this poor outcome.

CONCLUSIONS

Whereas the U.S. is winning the war on cancer overall, not all population subgroups and cancer patients benefit from the improvements in cancer control and prevention (Siegel, Miller, & Jemal, 2019). Patients with rare cancers are at a disadvantage. We provide comprehensive descriptive epidemiology estimates for the understudied rare cancer, liposarcoma. These findings will serve as a reference for current liposarcoma research; however, it is important for future research to periodically update these estimates as data become available. Our findings emphasize the importance of nationwide data in studying rare cancers such as liposarcoma (Lyu et al., 2019). Currently, SEER data have more tumor (extent of disease such as tumor size, metastasis, etc.) and patient characteristics (place of residence at the time of diagnosis, time to death) as compared to the publicly available NPCR data. In order to make progress in understanding liposarcoma etiology and track progress in treatment, future studies of rare cancers must be based on the nationwide data with the inclusion of as many tumor and patient characteristics as possible. Finally, we demonstrated that liposarcoma incidence is rising, suggesting that non-genetic modifiable risk factors may play a role in the etiology of this malignancy. Identification of such risk factors is necessary for the development of prevention strategies.

Table 4.1 Liposarcoma cases and age-adjusted incidence rates by demographic characteristics, 2001-2016

	SEER		CNPCR	
	Count (%)	Incidence Rate, Cases per 100,000 p-years (95% CI)	Count (%)	Incidence Rate, Cases per 100,000 p-years (95% CI)
All cases	11,162 (100)	1.08 (1.06,1.10)	37,499 (100)	1.01 (1.00, 1.02)
Sex				
Male (ref)	6,803 (60.95)	1.44 (1.41, 1.48)	22,681 (60.48)	1.33 (1.31, 1.35)
Female	4,359 (39.05)	0.79 (0.77, 0.82)*	14,818 (39.52)	0.75 (0.74, 0.77)*
Race				
White (ref)	9,198 (82.40)	1.13 (1.10, 1.15)	32,186 (85.83)	1.04 (1.03, 1.05)
Black	922 (8.26)	0.85 (0.79, 0.91)*	3,235 (8.63)	0.81 (0.78, 0.84)*
Other	1,042 (9.34)	0.95 (0.89, 1.01)*	2,078 (5.54)	1.03 (0.99, 1.08)

* Rate significantly ($p<0.05$) different when compared to the reference category

Table 4.2 Liposarcoma cases and age-adjusted incidence rates by tumor histology and site, 2001-2016

	SEER		CNPCR	
	Count (%)	Incidence Rate, Cases per 100,000 p-years (95% CI)	Count (%)	Incidence Rate, Cases per 100,000 p-years (95% CI)
Histological type				
Well-differentiated (ref)	3,688 (33.04)	0.35 (0.34, 0.37)	11,629 (31.01)	0.31 (0.30, 0.32)
Myxoid	2,094 (18.76)	0.21 (0.20, 0.22)*	6,938 (18.50)	0.19 (0.19, 0.20)*
Pleomorphic	818 (7.33)	0.08 (0.07, 0.09)*	2,922 (7.79)	0.08 (0.08, 0.08)*
Dedifferentiated	2,193 (19.65)	0.21 (0.20, 0.22)*	7,558 (20.16)	0.20 (0.20, 0.21)*
Other[#]	2,369 (21.22)	0.23 (0.22, 0.24)*	8,452 (22.54)	0.23 (0.22, 0.23)*
Tumor site				
Retroperitoneal	2,323 (20.81)	0.22 (0.21, 0.23)*	8,203 (21.88)	0.22 (0.21, 0.22)*
Extremities (ref)	4,531 (40.59)	0.44 (0.43, 0.45)	14,768 (39.38)	0.40 (0.40, 0.41)
Other sites	4,308 (38.60)	0.42 (0.41, 0.43)	14,528 (38.74)	0.39 (0.38, 0.40)

* Rate significantly ($p<0.05$) different when compared to the reference category

[#] Includes round cell, mixed, angiomyoliposarcoma, fibroblastic and not otherwise specified

Table 4.3 Time trends in liposarcoma, 2001-2016

	SEER		CNPCR	
	Total % change	Annual % change (95% CI)	Total % change	Annual % change (95% CI)
All cases	27.16	1.77 (1.21, 2.33)	18.95	1.43 (1.12, 1.74)
Sex				
Males	31.53	1.87 (1.37, 2.37)	21.77	1.67 (1.34, 2.00)
Females	19.95	1.47 (0.68, 2.27)	12.57	0.89 (0.51, 1.26)
Race/ethnicity				
Whites	26.14	1.69 (1.01, 2.37)	19.33	1.40 (1.06, 1.74)
Blacks	14.01	1.62 (0.00, 3.29)	4.38	0.88 (0.02, 1.76)
Other	48.13	3.16 (1.74, 4.60)	30.35	2.68 (1.69, 3.68)
Site				
Extremities	2.80	1.07 (0.29, 1.87)	2.89	0.58 (0.18, 0.98)
Retroperitoneal	28.22	1.36 (0.34, 2.40)	26.03	1.94 (1.40, 2.49)
Other	64.23	2.69 (1.85, 3.53)	34.41	2.02 (1.57, 2.48)

Table 4.4 Distribution of liposarcoma tumors by grade, size, and stage: SEER, 2001 – 20016

	Grade, %			Size, %			Stage, %		
	Low (I)	High (II-IV)	Unknown	<10 cm	≥10cm	Unknown	Localized*	Regional/ Distant*	Unknown*
All cases	45.9	38.7	15.4	31.4	57.5	11.1	59.3	27.5	13.2
Sex									
Males	44.9	40.4	14.7	32.1	56.4	11.6	59.5	26.9	13.5
Females	47.4	36.0	16.6	30.3	59.3	10.4	58.8	28.5	12.7
Race									
White	45.7	38.9	15.4	31.2	57.7	11.1	59.1	28.1	12.7
Black	44.1	37.1	18.8	33.6	55.4	10.8	62.7	24.4	12.9
Other	48.9	38.0	13.1	30.6	57.6	11.8	57.4	25.0	17.6
Site									
Retroperitoneal	44.3	40.9	14.8	16.3	74.7	9.0	42.3	44.7	13.0
Extremities	47.1	38.0	15.0	34.3	57.2	8.5	71.0	18.4	10.7
Other sites	45.5	38.2	16.3	36.3	48.6	15.1	56.1	27.9	15.9

*Due to the lack of reporting of certain cancer variables, stage was tabulated using SEER Historic Stage A (2001-2015).

Table 4.5 Five-year survival of patients with liposarcoma: SEER, 2001-2016

	Relative Survival, %
All cases	79.8 (78.6, 80.9)
Sex	
Male	79.0 (77.5, 80.4)
Female	81.0 (79.2, 82.6)
Race	
White	79.5 (78.2, 80.8)
Black	80.9 (76.8, 84.3)
Other	80.9 (77.1, 84.1)
Histological type	
Well-differentiated	95.5 (93.6, 96.9)
Myxoid	85.7 (83.5, 87.7)
Pleomorphic	64.1 (59.1, 68.7)
Dedifferentiated	57.2 (54.0, 60.3)
Other	75.0 (72.4, 77.4)
Site	
Retroperitoneal	63.9 (61.0, 66.7)
Extremities	89.9 (88.4, 91.3)
Other	76.7 (74.7, 78.6)
Grade	
Low Grade (I)	94.2 (92.7, 95.4)
High Grade (II-IV)	67.2 (65.1, 69.1)
Unknown	67.6 (64.4,70.6)

Figure 2.1 Age-specific incidence rates of liposarcoma among males and females as estimated from SEER and CNPCR data for the period of 2001-2016

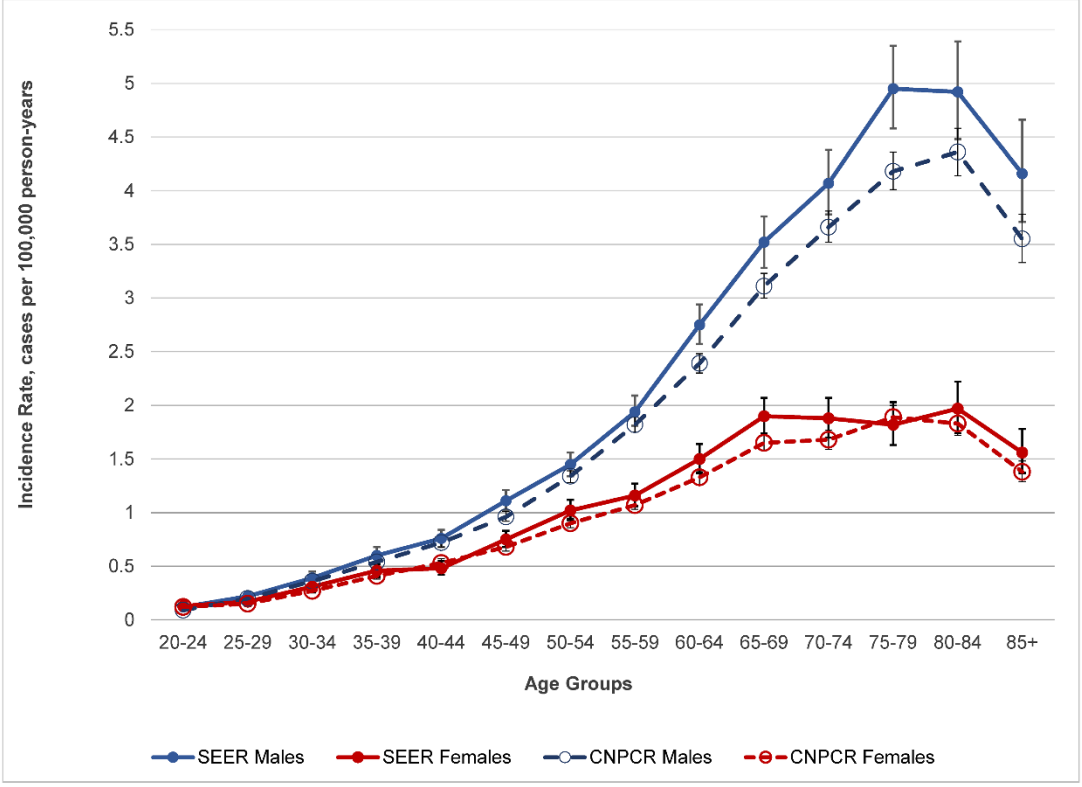


Figure 2.2 Time trends in liposarcoma incidence by sex: CNPCR data, 2001-2016

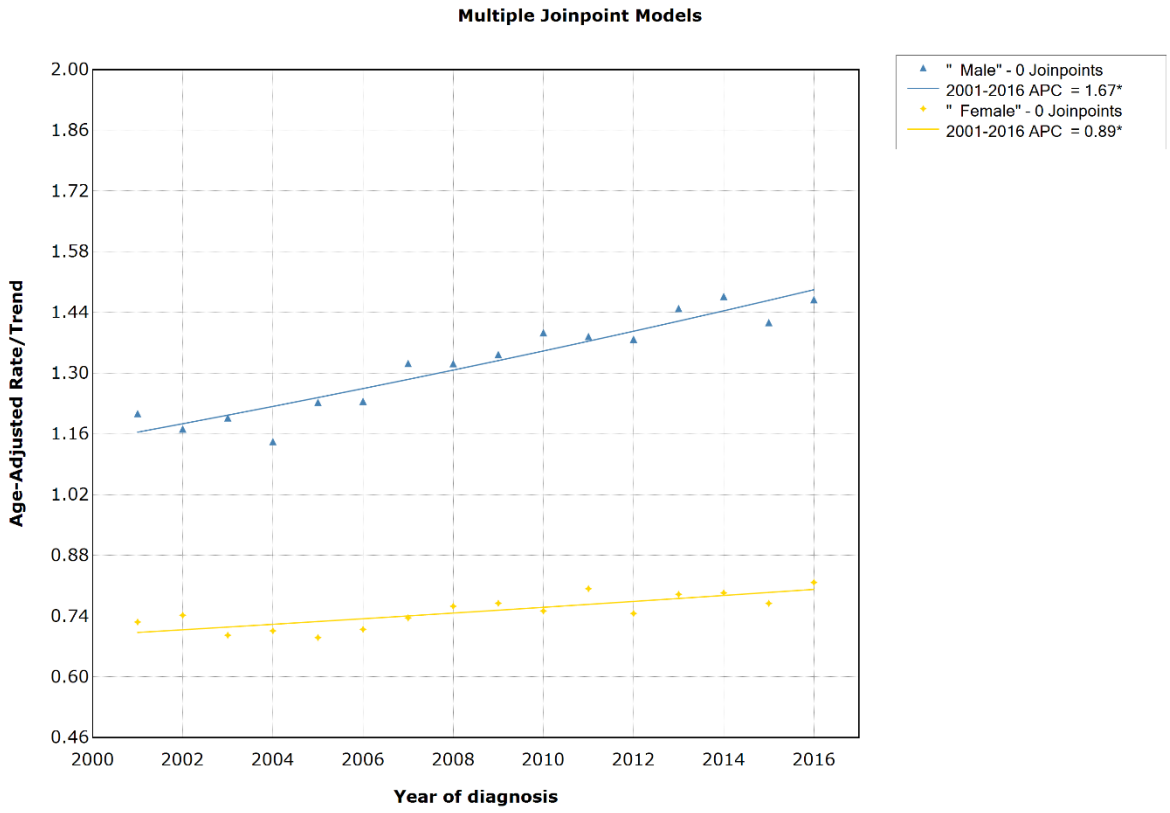


Figure 2.3 Time trends in liposarcoma incidence by race: CNPCR data, 2001-2016

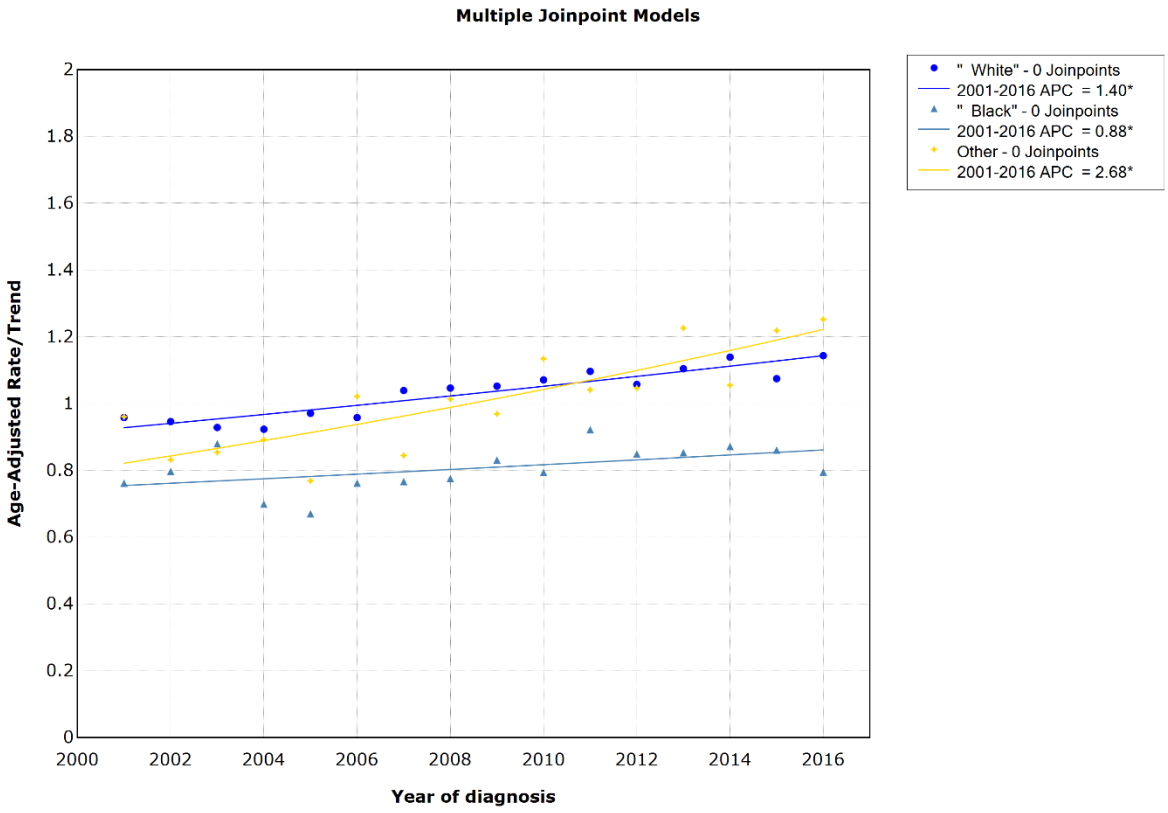
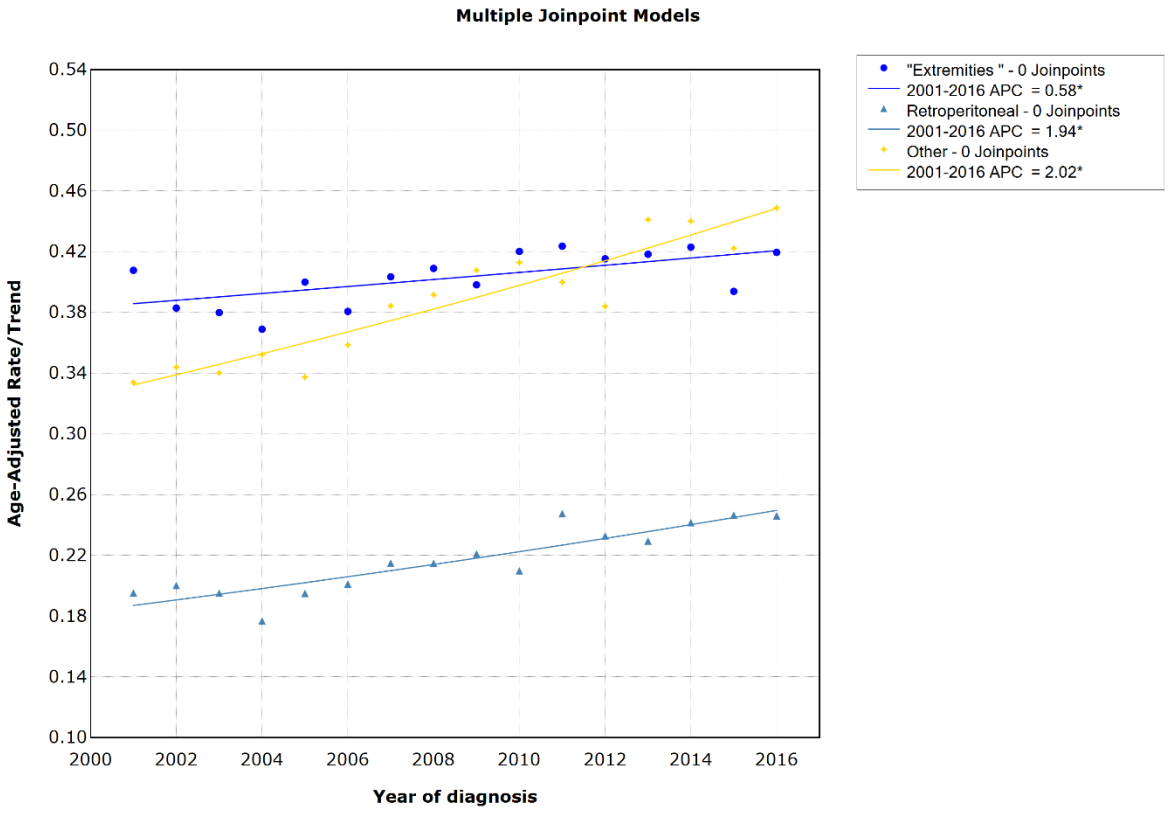


Figure 2.4 Time trends in liposarcoma incidence by site: CNPCR data, 2001-2016



REFERENCES

Afshar, N., English, D. R., Thursfield, V., Mitchell, P. L., Marvelde, L. T., Farrugia, H.,…Milne, R. L. (2018). Differences in cancer survival by sex: a population-based study using cancer registry data. *Cancer Causes*, 29, 1059-1069.

Barbetakis, N., Samanidis, G., Samanidou, E., Kirodimos, E., Kiziridou, A., Bischiniotis, T., & Tsilikas, C. (2007). Primary mediastinal liposarcoma: a case report. *Journal of Medical Case Reports*, 1(161), 1-4. https://doi.org/10.1186/1752-1947-1-161

Blay J. (2018). The theory. An introduction on dedifferentiated liposarcoma. *Cancer and Chemotherapy Reviews*, 13, 3-6.

Blöß, S., Klemann, C., Rother, A. K., Mehmecke, S., Schumacher, U., Mücke, U., Mücke, M., Stieber, C., Klawonn, F., Kortum, X., Lechner, W., & Grigull, L. (2017). Diagnostic needs for rare diseases and shared prediagnostic phenomena: Results of a German-wide expert Delphi survey. *PLoS ONE*, 12(2), e0172532. Available from http://dx.plos.org/10.1371/journal.pone.0172532

Bolignano, D., & Pisano, A. (2016). Good-quality research in rare diseases: trials and tribulations. *Pediatric Nephrology*, 31, 2017-2023. DOI 10.1007/s00467-016-3323-7

Centers for Disease Control and Prevention. (n.d.). National Program of Cancer Registries (NPCR). Available from https://www.cdc.gov/cancer/npcr/index.htm

Centers for Disease Control and Prevention (n.d.). NPCR and SEER incidence- U.S. cancer statistics public use database data standards and data dictionary. Retrieved from https://www.cdc.gov/cancer/uscs/public-use/pdf/npcr-seer-public-use-database-data-dictionary-2001-2015-508.pdf.

Chowdhry, V., Goldberg, S., DeLaney, T. F., Cote, G. M., Chebib, I., Kim, J.,…De Amorim-

Berenstein, K. (2018). Myxoid Liposarcoma: Treatment outcomes from chemotherapy and radiation therapy. *Sarcoma*, Article ID 8029157, 1-6 https://doi.org/10.1155/2018/8029157.

Dalal, K. M., Antonescu, C. R., Singer, S. (2008). Diagnosis and management of lipomatous tumors. *Journal of Surgical Oncology*, 97, 298–313.

Dalal, K. M., Kattan, M. W., Antonescu, C., Brennan, M. F., & Singer, S. (2006). Subtype specific prognostic nomogram for patients with primary liposarcoma of retroperitoneum, extremity, or trunk. *Annals of Surgery*, 244(3), 381-391. https://doi:10.1097/01.sla.0000234795.98607.00

DeSantis, C. E., Kramer, J. L., Jemal, A. (2017). The burden of rare cancers in the United States. *A Cancer Journal for Clinicians*, 67,261-272. https://doi:10.3322/caac.21400.

Ellison, L. F. (2016). Differences in cancer survival in Canada by sex. *Health Reports*, 27(4), 19-27.

FasterCures and HCM Strategists. (n.d.). Back to basics: HIV/AIDS advocacy as a model for catalyzing change. Retrieved from www.fastercures.org/assets/Uploads/PDF/Back2BasicsFinal.pdf.

Gatta G., Capocaccia R., Botta L., Mallone, S., De Angelis, R., Ardanaz, E.,…Trama, A. (2017). Burden and centralised treatment in Europe of rare tumours: Results of RARECAREnet—a population-based study. Lancet Oncology, 18, 1022-1039. http://dx.doi.org/10.1016/S1470-2045(17)30445-X.

Gatta, G., Maarten van der Zwan, J., Casali, P. G., Siesling, S., Dei Tos, A. P., Kunkler, I., Otter,

R.,…Capocaccia, R. (2011). Rare cancers are not so rare: The rare cancer burden of Europe. *European Journal of Cancer Prevention*, 47, 2493-2511. https://doi.org/10.1016/j.ejca.2011.08.008.

Gerry, D., Fox, N. F., Spruill, L. S., & Lentsch, E. J. (2014). Liposarcoma of the head and neck: Analysis of 318 cases with comparison to non-head and neck sites. *Head Neck*, 36,393-399. https://doi.org/10.1002/hed.23311

Global Genes (n.d.). Rare Diseases Facts and Statistics. Retrieved from https://globalgenes.org/wp-content/uploads/2015/12/2016-WRDD-Fact-Sheet.pdf

Harding, C., Pompei, F., Lee, E. E., & Wilson, R. (2008). Cancer suppression at old age. *Cancer Research*, 68(11), 4465–4478. doi: 10.1158/0008-5472.CAN-07-1670.

Hoffman, A., Ghadimi, M. P. H., Demicco, E. G., Creighton, C. J., Torres, K., Peng, T.,…Pollock, R. E. (2013). Localized and metastatic myxoid/round cell liposarcoma. Clinical and molecular observations. *Cancer*, 119(10), 1868-1877. https://doi.org/10.1002/cncr.27847

Jo, V. Y., & Fletcher, C. D. M. (2014) WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. *Pathology*, 46(2), 95-104.

Joinpoint Regression Program, Version 4.6.0.0 - April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.

Keung, E. Z., Ikoma, N., Benjamin, R., Wang, W., Lazar, A. J., & Feig, B. W. (2018). The clinical behavior of well differentiated liposarcoma can be extremely variable: A retrospective cohort study at a major sarcoma center. *Journal of Surgical Oncology*, 117, 1799–1805.

Kuo, T., Mobley, L. R. (2016). How generalizable are the SEER registries to the cancer

populations of the USA? *Cancer Causes Control*, 27(9), 1117-1126.

Lyu, H. G., Haider, A. H., Landman, A. B., & Raut, C. P. (2019). The opportunities and shortcomings of using big data and national databases for sarcoma research. *Cancer*, 125(17):2926-2934. doi: 10.1002/cncr.32118.

Mathoulin-Pelissier, S., Pritchard-Jones, K. (2019). Evidence-based data and rare cancers: The need for a new methodological approach in research and investigation. *European Journal of Surgical Oncology*, 45, 22-30.

Muratori, F., Frenos, F., Bettini, L. Matera, D., Mondanelli, N, Scorianz, M.,...Campanacci, D. A. (2018). Liposarcoma: Clinico-pathological analysis, prognostic factors and survival in a series of 307 patients treated at a single institution. Journal of Orthopaedic Science, 23(6), 1038-1044. https://doi.org/10.1016/j.jos.2018.06.008

National Cancer Intelligence Network (NCIN). (2013). Liposarcoma: incidence and survival rates in England. NCIN data briefings. Retrieved from http://www.ncin.org.uk/publications/data_briefings/liposarcoma_incidence_and_survival_rates_in_england.

National Center for Advancing Translational Sciences. (2017, November 30). Retrieved from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.

Nattinger, A. B., McAuliffe, T. L., & Schapira, M. M. (1997). Generalizability of the surveillance, epidemiology, and end results registry population: Factors relevant to epidemiologic and health care research. *Journal of Clinical Epidemiology*, 50(8), 939-945.

National Center for Advancing Translational Sciences. (2017, November 30). Frequently asked

questions. Retrieved from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.

National Organization for Rare Disorders. (2016, June 14). Rare Disease Facts. Retrieved from http://cdn.rarediseases.org/wordpresscontent/wp-content/uploads/2014/11/NRD-1008-FactSheet_5.pdf

Palmer, M. J., & Pryde, D. C. (2014). Orphan Drugs and Rare Diseases. Cambridge: Royal Society of Chemistry. Retrieved from http://search.ebscohost.com.ezproxy.gsu.edu/login.aspx?direct=true&AuthType=ip,shib&db=nlebk&AN=937195&site=eds-live&scope=site

Patil, S. & Chamberlain, R. S. (2013). Determinants of long-term survival in well differentiated extremity and retroperitoneal liposarcoma: A population-based outcomes study of 1,358 patients from the SEER database (1973-2008). *Journal of Surgical Research*, 197(2), 305.

Pedersen, J. K., Rosholm, J., Evertz, M., Engholm, G., Lindahl-Jacobsen, R., & Christensen, K. (2019). Declining cancer incidences at the oldest ages: Hallmark of aging or lower diagnostic activity? *Journal of Geriatric Oncology*, 10, 792-798. https://doi.org/10.1016/j.jgo.2019.02.001.

Radkiewicz, C., Johansson, A. L. V., Dickman, P. W., Lambe, M., Edgren, G. (2017). Sex differences in cancer risk and survival: A Swedish cohort study. *European Journal of Cancer*, 84, 130-140. https://doi.org/10.1016/j.ejca.2017.07.013.

Ronicke, S., Hirsch, M. C., Türk, E., Larionov, K., Tientcheu, D., & Wagner, A. D. (2019). Can a decision support system accelerate rare disease diagnosis? Evaluating the potential impact of Ada DX in a retrospective study. *Orphanet Journal of Rare Diseases*,14(69),1-

12. https://doi.org/10.1186/s13023-019-1040-6

Schwartz, P. B., Vande Walle, K., Winslow, E. R., Ethun C. G., Tran T. B., Poultsides, G.,…Abbott, D. E. (2019). Predictors of disease-free and overall survival in retroperitoneal sarcomas: A modern 16-year multi-institutional study from the United States Sarcoma Collaboration (USSC). *Sarcoma*. Article ID 5395131: 1-8 https://doi.org/10.1155/2019/5395131.

Schwartz, R.A. (2019). Medscape. Liposarcoma. Retrieved from https://emedicine.medscape.com/article/1102007-overview#a4.

SEER.cancer.gov. (n.d.). List of SEER registries. Retrieved from https://seer.cancer.gov/registries/list.html

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *A Cancer Journal for Clinicians*, 2019, 69(1):7-34. Epub 2019/01/09. https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551. PubMed PMID: 30620402.

Smith, C. A., Martinez, S. R., Tseng, W. H., Tamurian, R. M., Bold, R. J., Borys, D., & Canter, R. J. (2012). Predicting survival for well-differentiated liposarcoma: The importance of tumor location. *Journal of Surgical Research*, 175,12-17. doi: 10.1016/j.jss.2011.07.024

Surveillance Research Program, National Cancer Institute. SEER*Stat Software. Version 8.3.5. Bethesda, MD: National Cancer Institute; 2019

Toro, J. R., Travis, L. B., Wu, H. J., Zhu, K., Fletcher, C. D. M., & Devesa, S. S. (2006). Incidence patterns of soft tissue sarcomas, regardless of primary site, in the Surveillance, Epidemiology and End Results program, 1978-2001: an analysis of 26,758 cases. *International Journal of* Cancer, 119, 2922-2930.

Tseng, W. H., Martinez, S. R., Do, L., Tamurian, R.M., Borys, D., & Canter, R. J. (2011). Lack

of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: A SEER analysis. *Journal of Surgical Research,* 168(2), 173-180. https://doi.org/10.1016/j.jss.2011.02.004.

Vos, M., Grunhagena, D. J., Kosela-Paterczykc, H., Rutkowskic, P., Sleijferb, S., & Verhoef, C. (2019). Natural history of well-differentiated liposarcoma of the extremity compared to patients treated with surgery. *Surgical Oncology*, 29, 84–89.

Vos, M., Kosela-Paterczyk, H., Rutkowski, P., van Leenders, G. J. L. H., Normantowicz, M., Lecyk, A.,….Grunhagen, D. J. (2018). Differences in recurrence and survival of extremity liposarcoma subtypes. *European Journal of Surgical Oncology,* 44(9), 1391-1397 https://doi.org/10.1016/j.ejso.2018.03.028.

Wang, G. Y., & Lucas D R. Dedifferentiated liposarcoma with myofibroblastic differentiation. (2018). *Archives of Pathology and Laboratory Medicine*, 142, 1159-1163.

Wu, J., Qian, S., & Jin, L. (2019). Prognostic factors of patients with extremity myxoid liposarcomas after surgery. *Journal of Orthopedic surgery and Research,* 14(90),1-8. https://doi.org/10.1186/s13018-019-1120-2.