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Exploring the Unique Characteristics of Cancer in Adolescents and Young Adults in Tennessee

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by

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ABSTRACT

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Adolescents and Young Adults (AYAs) ages 15-39 years with cancer have received little attention in the medical and health fields, resulting in a lack of progress for this age group. Little is known about the unique biologic, epidemiologic, and psychosocial issues that play an integral role in the AYA cancer journey. The purposes of this study were to use the Tennessee Cancer Registry for all new cancer cases from 2004-2008 to determine 1) the main types of cancer that affect AYAs in TN, 2) the predictors of late-stage diagnosis of melanoma, and 3) the factors that predict a total thyroidectomy for cancer treatment. A total of 8,097 cancer cases were diagnosed in AYAs in Tennessee from 2004-2008. The five main cancer types were breast cancers, melanomas, thyroid cancers, lymphomas, and testicular cancers and accounted for over 50% (N=4,269) of cancers in AYAs in Tennessee during the study period. Females were significantly more likely to be diagnosed with melanomas (age adjusted incidence rate (AIR) 14.01, 95% CI 12.96-15.06) and thyroid cancers (AIR 13.39, CI 12.37-14.42) compared to males (AIR 8.08, CI 7.28-8.88 and AIR 3.50, CI 2.98-4.03, respectively). All cancer types increased with age. Individuals with government insurance (OR 8.41, CI 3.04-23.27) and those 15-19 years of age (OR 6.30, CI 1.74-22.86) had the highest risk of late-stage melanoma. Significant predictors of a using total thyroidectomy for thyroid cancer treatment included regional/distant stage cancer at

diagnosis (OR 2.80, CI 1.34-5.85) compared to localized stage, papillary carcinoma (OR 2.64, CI 1.02-6.83) and papillary adenocarcinoma (OR 3.56, CI1.37-9.19) histology types compared to follicular adenocarcinoma, and residence in non-Appalachian Tennessee (OR 2.07, CI 1.26-3.42) compared to Appalachian TN. An increased awareness of cancer types that affect AYAs in Tennessee will provide a basis for developing public health campaigns for cancer prevention and control in this population. This research serves as a first step in using state-based cancer registries to identify the unique characteristics of cancer in AYAs and will set the stage for future state-based research in this underserved population.

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ACRONYMS AND ABBREVIATIONS

ACA- Affordable Care Act

ACS- American Cancer Society

AYAs- Adolescents and Young Adults

AYAOPRG- Adolescent and Young Adult Oncology Progress Review Group

CDC- Centers for Disease Control and Prevention

DHHS- Department of Health and Human Services

IRB- Institutional Review Board

LLS- Leukemia and Lymphoma Society

LSYAA- LIVESTRONG Young Adult Alliance

NAACR- North American Association of Central Cancer Registries

NCI- National Cancer Institute

NPCR- National Program of Cancer Registries

SEER- Surveillance, Epidemiology, and End Results

TCR- Tennessee Cancer Registry

TCT- Teenage Cancer Trust

TN- Tennessee

TNDOH- Tennessee Department of Health

US- United States

WHO- World Health Organization

CHAPTER 1

INTRODUCTION

Immense progress has been made in the fields of cancer research, care, survival, and awareness; however, there are still underserved populations. Over the past few decades adolescents and young adults (AYAs), defined as those developing cancer between the ages of 15 and 39, have experienced an increased cancer incidence rate from 137.6 new cases per 100,000 in 1975 to 156.1 new cases per 100,000 in 2008 (AYAOPRG, 2006, Bleyer, Budd, & Montello, 2006; Surveillance, Epidemiology, and End Results, 2011a). More than 72,000 AYAs are diagnosed every year with cancer in the United States (Hayes-Lattin, 2011). Additionally, cancer is the leading cause of nonaccidental death in this age group and AYAs have experienced little to no improvement in cancer survival rates when compared to both younger and older age groups (AYAOPRG, 2006).

Little is known about this population and the biologic, epidemiologic, genetic, psychosocial, and economic issues that play a key role in the incidence, mortality, and quality of life of AYA patients (AYAOPRG, 2006; Wu et al.2005). However, research shows that cancer in AYAs has distinct features, with the spectrum of malignant disease in this population being much different than malignancies seen in other age groups (Bleyer, 2002). In addition, the disruption of cancer during this part of the life stage provides patients with unique psychosocial, medical, physical, and educational needs (Bleyer, 2002).

Statement of the Problem

Cancer is the second leading cause of death in America and the first leading cause of death due to disease in AYAs (AYAOPRG, 2006; CDC Fast Stats, 2011). The National Cancer Institute (NCI) estimated that in 2011 there were over one million new cancer cases and more

than 72, 000 of those cases were AYAs, accounting for approximately 6% of all cancers diagnosed (AYAOPRG, 2006; Hayes- Lattin, 2011; NCI, 2011a). The five overall leading causes of cancer incidence in the United States are prostate, female breast, lung, colorectal, and melanoma (NCI, 2011a). In comparison, the leading cancers in AYAs are breast, lymphomas, melanoma, thyroid, and male and female gonadal cancers (AYAOPRG, 2006; Bleyer et al., 2008). However, actual cancer incidence in AYAs varies greatly by age, gender, ethnicity, and geography.

The Tennessee Cancer Registry (TCR) estimates that in 2009 approximately 32,000 Tennesseans were diagnosed with cancer and another 13,000 died from this disease (Li, Li, & Whiteside, 2010). Consistent with United States (US) data, cancer is also the second leading cause of death in Tennessee (TN) (Li et al., 2010). Tennessee has not specifically studied cancer incidence and mortality in the AYA population.

Until recently, AYAs were not seen as a distinct group with specific needs. However, the Adolescent and Young Adult Oncology Progress Review Group (AYAOPRG) have made specific recommendations regarding cancer care, research, and awareness for this population (AYAOPRG, 2006). AYAs with cancer have been described as 'at the edge of no-man's land' and 'the orphans of cancer' (Bleyer, 2011; Hollis & Morgan, 2001). They are identified as a population that falls into a care gap between pediatric and adult health services (Hollis & Morgan, 2001). Due to the distinctive nature of AYA cancer, specific prevention and control strategies should be created to target this population (Wu et al., 2005). Further research needs to be conducted to understand the dynamic needs of this population in order to provide adequate care, interventions, and cancer awareness for AYAs (AYAOPRG, 2006). The purpose of this study is to explore the unique characteristics of AYA cancer in TN. The results from this

research are intended to increase awareness of AYA cancer and to promote public health interventions to reduce the AYA cancer burden.

Research Aims

Research Aim #1- To describe the characteristics of adolescents and young adults who developed cancer in Tennessee during the years 2004-2008, inclusive.

Research Aim #2- To determine the major cancer types that affect adolescents and young adult in Tennessee during the years 2004-2008, inclusive.

Research Aim #3- To evaluate the predictors of late stage diagnosis of melanoma in adolescents and young adults diagnosed in Tennessee during the years 2004-2008, inclusive.

Research Aim #4-To investigate the predictors of a total thyroidectomy as a surgery option in adolescents and young adults diagnosed with thyroid cancer in Tennessee during the years 2004-2008, inclusive.

Tennessee

Tennessee is located in Central Appalachia and is a state that has distinct geographic and demographic variations. It encompasses major metropolitan areas, suburban counties, and several rural communities located in the Appalachian Mountains and the Mississippi Delta region. Only 27 of TN's 95 counties are considered urban and the other 68 are rural (Erwin, Fitzhugh, Brown, Looney, & Forde, 2010). Overall, TN is comprised of roughly 80% Caucasians and less than 20% African-Americans (Erwin et al., 2010). East TN has a relatively homogenous Caucasian population, even in major urban areas like Knoxville (Erwin et al.,

2010). Meanwhile, in West TN the percentage of African-Americans is proportionally higher than the overall state percentage, with figures around 50% (Erwin et al., 2010).

Tennessee has the 22nd highest age-adjusted cancer incidence rate and the 5th highest cancer mortality rate in the nation (Li et al., 2010). Roughly two thirds of cancers in TN could be prevented through life-style changes, mainly through smoking cessation (Li et al., 2010). The TCR Annual Report highlights that the majority of the counties that have high incidence and mortality rates are located in the Appalachian region of TN (Li et al., 2010). This suggests that Appalachian TN residents may be predisposed to developing cancer due to certain lifestyle factors (Li et al., 2010). The TCR reports that for cancer in those less than 20 years of age, the highest incidence rates are found in the 0-4 and 15-19 year old intervals. However, mortality rates are relatively similar for all cancers that are diagnosed prior to age 20 (Li et al., 2010).

Currently in TN, AYAs are categorized into 1) children's cancer (15-19 years old) or 2) adult cancer (20-39 years old). To date, the cancer burden as it relates to AYAs has not been investigated in TN. This research will provide an overview of AYA cancer incidence in TN and provide a more in-depth analysis for two cancers frequently diagnosed in AYAs, melanoma and thyroid cancer. Tennessee is a leader for aspects of cancer prevention and control through the impact of the state-wide TN Cancer Coalition and the comprehensive cancer care provided by St. Jude's and Vanderbilt health systems. Developing a better understanding of overall cancer incidence in the AYA population and identifying the predictors of late-stage melanoma and the characteristics that predict total thyroidectomy as a cancer treatment will assist cancer practitioners in TN to better serve this AYA population.

Definition of Adolescents and Young Adults

The definition of AYAs has evolved through the years and there have been many different definitions based on age, psychosocial development, and societal influences (AYAOPRG, 2006). Adolescence is a complex life stage and seen as a period of psychological and sociological change as individuals progress from childhood dependence to an adult independent status over a 10-12 year period (Hollis & Morgan, 2001; Palmer, Mitchell, Thompson, & Sexton, 2007). It has been observed that young adults face many of the same issues as adolescents (Li et al., 2010).

Adolescence can be considered the continuum of development that occurs from the age of 13 to 23 years, but the exact age range may vary for any specific individual and depends on the individual's needs, circumstances, and development in the context of the requirements of society (Hollis & Morgan, 2001). The variety of different age ranges given for adolescence reflects this wide variation in the rate that individuals progress through adolescence. The World Health Organization (WHO) defines young people as 10-24 years and further divides that into the categories of 1) adolescence for ages 10-19 and, 2) youth for ages 15-24 (WHO, 1986). Society commonly identifies adolescence as the age ranges that coincide with the teen years, ages 13 through 19. Adolescence predominately signifies the transition between childhood and adulthood. This group is neither children nor yet fully adult, do not easily identify with one definition and may be referred to as adolescents, teenagers, young people, or young adults, interchangeably (Whiteson, 2003).

The Adolescent and Young Adult Oncology Progress Review Group (AYAOPRG, 2006) opted to define the AYA population over a relatively wide age range in order to be inclusive of

the entire spectrum of cancer patients that continue to experience a lack of improvement in cancer care and survival (AYAOPRG, 2006). The current AYAOPRG and National Cancer Institute (NCI) definition of AYAs includes individuals diagnosed with cancer between 15 and 39 years of age (AYAOPRG, 2006; NCI, 2012a). The AYAOPRG recognizes that this is not a homogenous group and that developmental differences exist over this wide age range (AYAOPRG, 2006). Although this age range is quite wide, individuals in this age group are unified based on their unique differences in the cancer journey when compared to other age groups (Wolfson, 2010).

Several distinct experiences in the AYA cancer journey are different from those experienced by younger and older populations. These unique experiences include delays in treatment, lack of clinical trials, and balancing treatment schedules with school, work, and young families (LYSAA, 2006). Individuals in the 15-39 year age range are in the reproductive years, so family planning and fertility preservation are both common themes for this population (AYAOPRG, 2006). Individuals at the upper end of this age range have expressed that they identify more with the younger patients than with middle-aged or older patients (AYAOPRG, 2006).

Prior to the AYAOPRG and NCI AYA definition, individuals in this broad age range lacked a home in cancer care and research and were treated according to either pediatric or adult protocols based on their specific cancer diagnosis (AYAOPRG, 2006; Albritton, 2005; Bleyer, 2005; Fernandez & Barr, 2006; LYSAA, 2006). The lack of a separate definition and placement within cancer control and prevention has caused AYAs to be understudied and underserved; the result has been a lack of overall progress for this age group (AYAOPRG, 2006; Albritton, 2005; Bleyer, 2005; Burke, Albritton, & Marina, 2007; Fernandez & Barr, 2006; LYSAA, 2006). The

new formal definition of AYAs will help streamline research, interventions, treatment, and awareness efforts in this population (AYAOPRG, 2006). Unless otherwise specified, the term AYA as used for this study will be as defined according to AYAOPRG and NCI and will refer to individuals in the 15-39 year old range, inclusive.

Cancer in Adolescents and Young Adults

AYA cancer patients have seen a lack of progress in cancer care and outcomes compared to younger children and older adults (Bleyer, 2005). Cancer incidence among AYAs (ages 15-30) in the United States accounts for about 2.0% of all cancers diagnosed, while cancer in individuals under 15 only accounts for 0.8%; however, children's cancers receive exponentially more attention than do those in AYAs (Bleyer et al., 2006). In addition, the 5-year survival rate for AYAs (ages 20-39) in the US has held constant at 70% since 1986 (Bleyer, 2005). Currently, survival rates for AYAs 15-39 vary by cancer type. Of the most commonly diagnosed cancers in AYAs (breast, Hodgkin's lymphoma, thyroid, melanoma, and testicular), survival rates are 80% and higher (Bleyer, 2011). However, acute myeloid leukemia, acute lymphoid leukemia, lung carcinoma, and hepatic carcinoma have survival rates of less that 50% (Bleyer, 2011). Figure 1.1 illustrates the improvements in 5-year survival rates by age from the SEER Database, 1975-1997 (AYAOPRG, 2006).

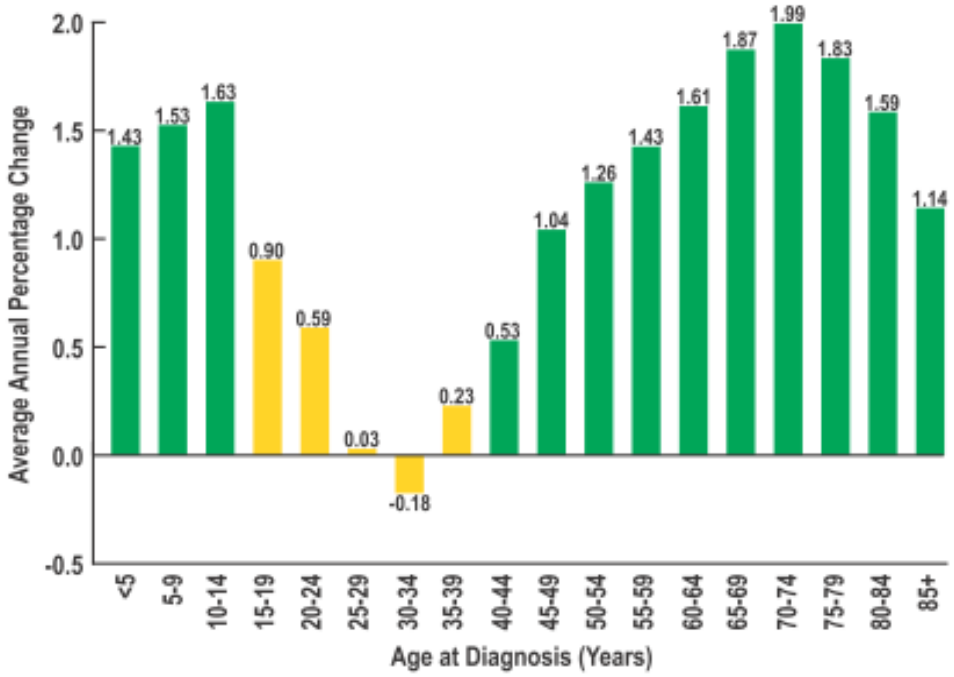

Figure 1.1. Improvements in 5-Year Cancer Survival Rates in the United States by Age

Source: AYAOPRG, 2006.

Figure 1.2 (AYAOPRG, 2006) illustrates the improvements in survival between 1975-1998 for AYAs, children, and older adults in the US. While AYAs have relatively high survival rates, the lack of improvement over the time period, particularly in the 25-39 year age group is concerning. In the 1970s and 1980s, AYAs had drastically higher survival rates than other age groups; however, survival rates have stagnated in this population while they have improved in younger children and older adults (AYAOPRG, 2006). It is not fully understood if the lack of improvement in AYA survival rates stems from the biological differences that exist in AYA cancer, from a lack of research, due to differences in treatment and health services, or due to some other cause (AYAOPRG, 2006; LYSAA, 2006).

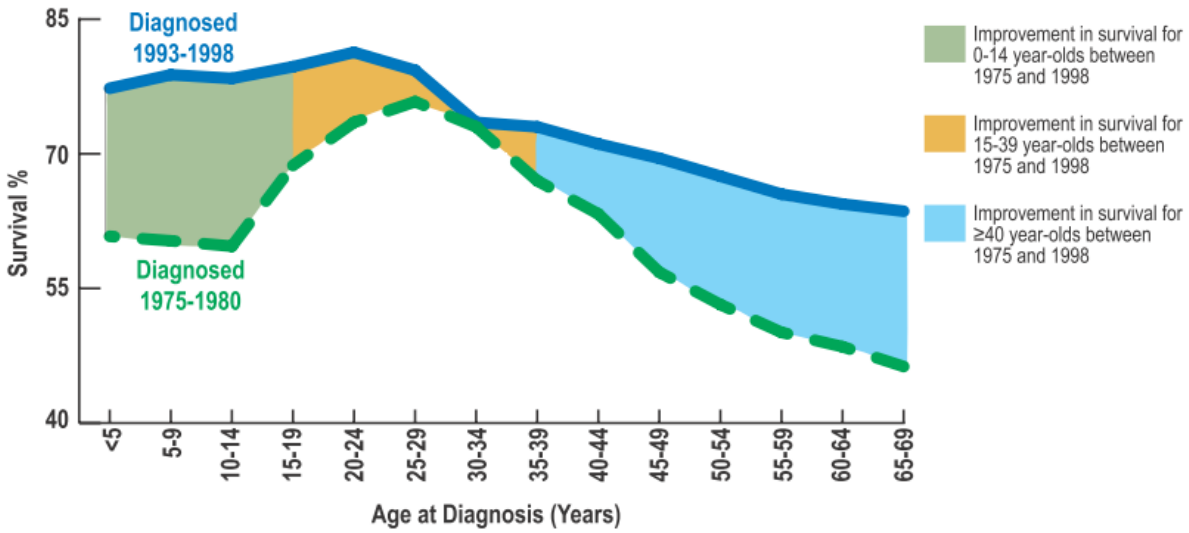

Figure 1.2. Improvement in Cancer Survival in the United States by Age Group, 1975-1998 Source: AYAOPRG, 2006.

The spectrum of tumors seen in AYAs differs from that of childhood or older adults (Bleyer et al., 2008). The majority of these cancers spontaneously occur and are not related to environmental carcinogens or family history (Bleyer, 2007). Roughly 90% of the tumor types exhibited in AYAs stem from 10 groups of cancers: breast, lymphoma, melanoma, ovarian and cervical, thyroid, sarcomas, testicular, colorectal, leukemia, and brain tumors (AYAOPRG, 2006; Bleyer et al., 2008). Figure 1.3 illustrates the composition of cancer types in AYAs (adapted from Bleyer et al., 2008). Bleyer et al. (2008) illustrate the cancer types that occur most frequently in AYAs. Other age groups do not exhibit this distinct pattern of cancer types in terms of the most common cancers.

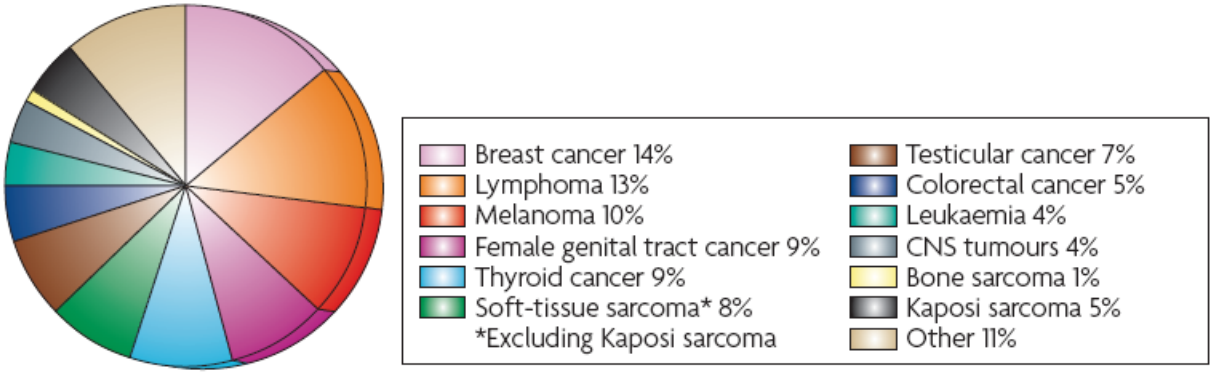

Figure 1.3. Occurrence of the Most Common Types of Cancer in AYAs, 1992-2002 (Adapted from Bleyer et al., 2008).

The incidence of tumor types varies greatly across the AYA age spectrum (AYAOPRG, 2006; Bleyer et al., 2008). Older adolescents (age 15-19) suffer more from lymphomas, germ cell tumors, and leukemias while young adults (age 20-39) have higher levels of carcinomas (AYAOPRG, 2006). The incidence of cancer in the AYA age group has increased consistently over the past 25 years (Bleyer et al., 2006). Males in the 15-29 age range are more likely to be diagnosed with cancer as compared to females (Bleyer et al., 2006). Additionally, Caucasians were more likely to be diagnosed with cancer than other ethnicities (AYAOPRG, 2006; Bleyer et al., 2006). Meanwhile, American Indians and Alaskan natives have the lowest cancer incidence (AYAOPRG, 2006). Figure 1.4 highlights the common cancer types in AYAs broken down by age group (AYAOPRG, 2006).

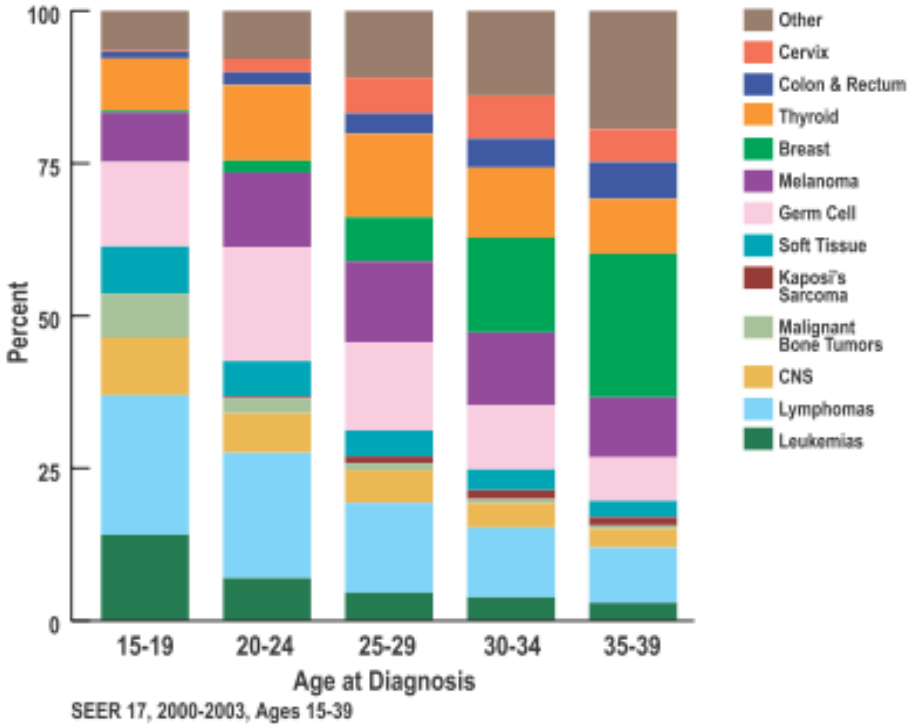

Figure 1.4. Common Types of Cancers Affecting AYAs in the United States by Age Group Source: AYAOPRG, 2006.

Approximately two thirds of the tumor types in AYAs are represented by the following six cancers: breast, lymphoma, melanoma, thyroid, and male and female gonadal cancers (testicular and ovarian cancer, respectively) (Johnson, 2011). This research focuses on five of those leading cancer types: breast, lymphomas, melanoma, testicular, and thyroid.

Breast Cancer

Breast cancer is a cancer that arises from the functional tissue elements of the breast (NCI, 2012b). Over 200,000 new cases of breast cancer are diagnosed in females of all ages each year and approximately 7% of those occur in AYAs (NCI, 2012b; Susan G. Komen for the Cure, 2012). Overall, breast cancer accounts for 14% of cancers in AYAs (Bleyer et al., 2008). The causes of breast cancer are not fully understood; however, several risk factors have been

identified (Susan G. Komen for the Cure, 2012). Risk factors include being a woman, age, family history, genetic mutations, race, lack of physical activity, and consumption of alcohol (NCI, 2012b; Susan G. Komen for the Cure, 2012). Young women (< 45 years of age) diagnosed with breast cancer are more likely to have larger, less hormone sensitive tumors that have spread to the lymph nodes as compared to older women (Anders et al., 2008). Additionally, breast cancer in women under age 45 has unique biological characteristics that are different from older women (Anders et al., 2008). Women diagnosed with breast cancer prior to age 45 tend to have a worse prognosis that is independent of stage at diagnosis and histology type (Bleyer et al., 2008).

Lymphomas

Cancers that arise from the lymphocytes of the immune system are classified as lymphomas (NCI, 2012c). Lymphomas are subdivided into two main types: 1) Hodgkin lymphoma (HL), characterized by the presence of Reed-Sternberg cells, and 2) non-Hodgkin lymphoma (NHL) that includes all other lymphocytic cancers (NCI, 2012c). NHL is more common than HL and is the seventh most common cancer in the US the age-adjusted incidence of NHL has increased by more than 82.5% from 1975-2008 (LLS, 2012). Incidence rates of lymphoma from 1999-2008 were higher for AYAs ages 20-24 as compared to ages 15-19 years, 7.6 and 4.8 per 100,000, respectively (LLS, 2012). Additionally, from 1999-2008 there has been an overall increase in lymphoma for all ages in the AYA population (LLS, 2012). Lymphomas account for 13% of cancers in AYAs (Bleyer et al., 2008). Risk factors for lymphoma are currently unknown (LLS, 2012).

Melanoma

Melanoma is defined by the uncontrolled growth of melanocytes (American Melanoma Foundation, 2006; NCI, 2012d). Early detection and treatment of melanoma generally results in a favorable prognosis (Bleyer et al., 2006). Melanoma is a common and mainly preventable disease; it is the third most commonly diagnosed cancer in AYAs, accounting for 10% of AYA cancers (Bleyer et al., 2008; Plescia, Berman, & White, 2011; Weir et al., 2011). Well known risk factors for melanoma include: overexposure to ultraviolet (UV) radiation from sunlight or artificial sources, family history of melanoma, light hair and skin color, tendency to develop freckles, and immunosuppression (Gilchrest, Eller, Geller, & Yaar, 1999; Lin, Hocker, Singh, & Tsao, 2008; Weir et al., 2011). The incidence of melanoma is highest in Caucasians as compared to all other racial groups, regardless of age (Surveillance, Epidemiology, and End Results, 2011b; Weir et al., 2011). The occurrence of melanomas in AYAs suggest that early risk factors play an important role, especially the potential for gene-environment interactions due to increased UV exposure from sunlight or tanning beds and accumulated lifelong UV exposure (Anderson, Pfeiffer, Tucker, & Rosenberg, 2009; Weir et al., 2011).

Testicular Cancer

Testicular cancer is a cancer that arises from the germ cells in the testes (NCI, 2012e). Because this cancer arises in the germ cells, it is classified as a germ cell tumor. Testicular cancer is usually diagnosed in young or middle aged men and accounts for 7% of all AYA cancer cases (Bleyer et al., 2008; NCI, 2012e). Risk factors for testicular cancer include: cryptorchidism (undescended testicle), race, and personal and family history. However; most men with testicular cancer do not have any of the foregoing risk factors (ACS, 2012). The risk

of testicular cancer is roughly five times higher in Caucasians as compared to African-Americans and three times higher than Asian-Americans (ACS, 2012).

Thyroid Cancer

Thyroid cancer is one of the most frequently diagnosed cancers in adolescents and young adults (AYAs) and accounts for roughly 10% of all cases (AYAOPRG, 2006; Bleyer et al., 2005; Bleyer et al., 2008; Wu et al., 2005). Thyroid cancer is the fifth most commonly diagnosed cancer in females of all ages (Jemal, Siegal, Xu, & Ward, 2010). Thyroid cancer arises from the thyroid gland located at the front of the lower neck. The thyroid gland uses iodine to produce several important metabolic hormones that are responsible for controlling heart rate, body temperature, metabolism, and the level of calcium in the blood (NCI, 2011b). Risk factors for thyroid cancer include a history of having an enlarged thyroid, family history of thyroid cancer or thyroid disease, specific genetic conditions, exposure to radiation, individuals ages 25-65, being Asian, and being female (NCI, 2011b; PubMed Health, 2011). The prognosis of thyroid cancer is dependent on histology type, size of nodule or tumor, and stage at diagnosis (NCI, 2011b).

The spectrum of cancers that occur in AYAs is a distinctive assortment of tumors and the reasons why these specific cancer types occur more frequently in AYAs compared to other age groups is currently unknown (Hayes-Lattin, 2011). Moreover, the types of cancers that are typically seen in older adults tend to behave differently biologically when occurring in AYAs (Hayes-Lattin, 2011). For example, breast cancers diagnosed in AYAs have gene alterations and behave differently than in older females (LSYAA, 2006). Biological differences in the spectrum of cancers typically seen in AYAs could account for some of the suboptimal outcomes that

AYAs are experiencing; however, additional research is needed to explain this phenomenon (LSYAA, 2006).

Adolescent and Young Adult Cancer Care

AYAs with cancer are currently seen as a distinct group within the national and international health agenda (Morgan, Robert, & Stahlschmidt, 2008). However, this group poses a unique challenge to current health systems and the treatment teams providing care (Palmer et al., 2007). This population falls into a gap within the healthcare setting and is difficult to classify as either pediatric or adult; this results in difficulty in developing an appropriate treatment approach for this age group (Whelan, Dolbear, Mak, Moller, & Davies, 2007). The range of cancer diagnoses and treatments in AYAs is derived from both pediatric and adult oncology practice and specialists must collaborate to deliver what is appropriate for tumor type and the individual patient (Stevens, 2006). The treatment protocols used for AYA patients can vary widely depending on whether pediatric or adult protocols are used and these differences can play a significant role in the outcome of the patient (Bleyer et al., 2008). AYAs seem to have fallen between the cracks in healthcare, being denied the benefits of inclusion in protocols and optimal supportive care (Newburger, Elfenbein, & Boxer, 2002).

In order to best identify the healthcare needs of cancer patients, extensive information must be gathered regarding the biological and psychosocial circumstances during the time when cancer was diagnosed (Zebrack, Bleyer, Albritton, Medearis, & Tang, 2006). Due to the lack of specific biological research on AYA cancers, it is difficult to identify the best course of treatment (LSYAA, 2006). Additional research and increased knowledge of tumor biology could lead to improved treatment protocols for AYAs (LSYAA, 2006). Most health professionals in oncology

are not familiar with caring for AYAs due to the relative rarity of disease in this population. However, these professionals acknowledge that AYAs with cancer are a unique group and have different needs from cancer patients of other age groups (Whelan, 2003).

Little is known about where AYAs receive their initial treatment for cancer (Whelan et al., 2007). Bleyer (2010) states the majority of young AYAs (age 15-19) with cancer are not being referred to the appropriate specialist based on their cancer type. Although specific treatment facilities and teams are occasionally available for young AYAs, they are not always used (Whelan et al., 2007). It has been observed that in medical practice the unique characteristics of AYAs have not been as fully acknowledged as in other arenas, such as the educational and criminal justice systems and the commercial world (Whiteson, 2003). In comparison, childhood cancer has been recognized by the medical profession as a distinct, separate field since the 1950s and adults with cancer became a national priority with the National Cancer Act of 1971 (Bleyer, 2011; National Cancer Act, 1971).

AYAs typically find themselves treated on either a pediatric or adult unit, potentially feeling isolated and having their physical, psychological, and emotional needs being neglected (Brierley et al., 2009). The choice as to whether an AYA patient is cared for by a pediatric or adult oncologist typically depends on the decision made by the referring physician (Bleyer, 2007). During the initial diagnosis process, AYAs may see a variety of practitioners, internists, general practitioners, pediatricians, emergency room physicians, and a wealth of other specialists (AYAOPRG, 2006; Bleyer, 2007). Following a cancer diagnosis, the treatment approach is very inconsistent and AYAs may be treated by adult or pediatric oncologists, or radiation, surgical or gynecological oncologists (AYAOPRG, 2006; LSYAA, 2006).

The decision regarding the setting in which an AYA should be treated should be based on which facility and practitioner will provide the best outcomes for the patient (Bleyer, 2007). Depending on where the AYA patient is referred, the physician chosen to treat an AYA cancer patient may or may not be as familiar with the correct approach to treatment (Albritton, 2005). Specific cancer types such as acute lymphoblastic leukemia (ALL), Ewing's sarcoma, and non-Hodgkin lymphoma have been shown to have better outcomes for AYAs when treated according to pediatric protocols rather than those for adult cancer patients (Bleyer, 2007). Furthermore, treatment protocols for AYAs are not deliberately administered. Younger AYAs who suffer from pediatric tumors do not have explicit provisions for receiving pediatric or adult dosages or schedules of chemotherapy and radiation (AYAOPRG, 2006). Adult oncologists may be less aggressive with chemotherapy dosages compared to pediatric oncologists when treating AYAs because they are used to treating older patients who are not as healthy (Bleyer, 2007). Currently there is a lack of data on AYA outcomes based on treatment teams, protocols, and settings although these factors may distinctly affect overall outcomes (AYAOPRG, 2006).

Awareness is increasing that AYAs fall into a care gap between pediatric and adult cancer services (Bleyer, 2011; Hayes-Lattin, 2011; Smith, 2004). However, there is still a need for AYA cancers to receive much more national attention regarding the approach to cancer treatment and care. Internationally, AYAs have received more attention, particularly in the United Kingdom. The United Kingdom's Teenage Cancer Trust (TCT) has made more specific provisions for AYA (ages 13-24) cancers by providing age-specific cancer treatment and care for AYAs administered by a treatment team trained in AYA cancer management (Bleyer, 2007; TCT, 2011). The TCT found that AYAs have better survival rates when treated by practitioners who specialize in AYAs with care provided by a multi-disciplinary treatment team in a distinct

AYA cancer unit (TCT, 2011). This model has recently been adopted by the government to be replicated throughout the United Kingdom (Bleyer, 2007).

The appropriate care setting and treatment team will vary for AYA cancer patients on a case by case basis (Bleyer, 2007). However, distinct treatment protocols, teams, and care settings should be established to provide optimal care for AYAs with cancer in the US (LSYAA, 2006). Ideally, AYA oncology should be seen as a separate field from pediatric and adult oncology with separate training programs, clinical trials, and research (Bleyer, 2007).

Barriers to Progress in Adolescent and Young Adult Cancer

Progress in the field of AYA cancer has been stagnant due to a variety of reasons, which include a lack of research and awareness. However, a multitude of additional factors specific to this age range also play a role in the barriers to progress. Health insurance issues, delayed diagnoses, the lack of participation in clinical trials, and the dynamic psychosocial needs of this age group are important factors that influence AYA cancer survivorship in the United States (LSYAA, 2006).

Insurance

Due to the uniqueness and transitional issues of this age group, AYAs are the most underinsured of any age group in the US (Siegal, 2011). Based on the lack of insurance, AYAs are likely to have delays in cancer diagnosis and as a result to be diagnosed with later stage disease (Martin et al., 2007). The lack of insurance plays a vital role in the difficulty of having healthcare access for AYAs (AYAOPRG, 2006).

Various factors contribute to the lack of insurance in the AYA population. Provisions in the Affordable Care Act (ACA) may eventually assist with the lack of insurance in this population. The ACA has made obtaining healthcare coverage easier for young adults by allowing coverage on their parents' policy extending to age 26 (DHHS, 2011). Nonetheless, AYAs are currently still lacking consistent health coverage. Prior to the ACA policy in 2010, AYAs that were not currently enrolled in school or over age 23 were no longer insured on their parents' insurance plan (AYAOPRG, 2006). In addition, state-based health insurance through Medicaid discontinues coverage at age 19 (AYAOPRG, 2006). Furthermore, many AYAs over 26 are not employed at companies that offer health insurance plans (Siegal, 2011). In general, many AYAs are not able to afford individual health insurance and if they can afford it, many must choose high deductibles, further limiting the available health care resources (AYAOPRG, 2006).

Following a cancer diagnosis, AYAs that are uninsured or underinsured will find themselves with major debts for medical procedures they are required to pay out of pocket (AYAOPRG, 2006). Another problem is that a cancer diagnosis during the AYA life stage may have continued impact on an individual's ability to obtain health insurance and increase future insurance rates because of a pre-existing condition (AYAOPRG, 2006). Lack of insurance or inadequate insurance creates a multitude of negative outcomes for AYAs, including delayed diagnosis, late stage diagnosis, and these can result in a need for increased treatments and therapies with an overall increased likelihood of negative outcomes (Martin et al., 2007).

Delayed Diagnosis

Delays in diagnosis occur more frequently in AYA cancer patients than in other age groups (Martin et al., 2007). Individuals in the AYA age range are typically healthy; therefore, cancer

symptoms are often overlooked and AYAs are likely to experience misdiagnosis of their cancer systems (AYAOPRG, 2006; LSYAA, 2006). Cancer symptoms in AYAs are usually attributed to stress or fatigue and disregarded for months and possibly years (AYOPRG, 2006). Based on the distinctive cancer types that occur in AYAs, the signs and symptoms also have unique characteristics that differ from those of children or older adults (Bleyer, 2007).

The general symptoms of AYA cancers include: mass in the neck, testis, breast, or other body part, swelling of the lymph glands, constant fatigue, or neurological deficit (Bleyer, 2007). Unfortunately, because many AYAs do not have a primary care physician due to lack of insurance or a transition of care from providers they may not know where to seek treatment should these symptoms arise (AYAOPRG, 2006; Bleyer, 2007; LSYAA, 2006; Siegal, 2011). Because the lack of regular care in the AYA population plays a role in delayed diagnosis and resultant poor prognosis, AYAs should be aware that self-exams and detection play a vital role in decreasing diagnostic time (Bleyer, 2007).

AYAs may minimize the importance of symptoms and delay seeking medical care due to a belief that they are invincible (AYAOPRG, 2006; Albritton, 2005; Bleyer, 2007). In general, society does not believe that young people in this age range are likely to be diagnosed with cancer, so AYAs may not be advised to see a physician and symptoms may be overlooked (Siegal, 2011). AYAs may also feel uncomfortable in seeking medical care for symptoms that involve genitalia or the colon/rectum (AYAOPRG, 2006).

The interval between symptom onset and diagnosis increases with age, almost double the time frame for younger AYAs, ages 15-19, when compared with children under age 15 (AYAOPRG, 2006). As has been discussed, delays in diagnosis for AYAs stem from provider

and patient lack of knowledge. Physicians should be more aware of cancer symptoms and how they persist in AYAs (LSYAA, 2006). Meanwhile, AYAs must be proactive about their medical care and receive routine exams.

Clinical Trial Participation

Although cancer research and clinical trials have resulted in marked improvements of survival rates in cancer patients, AYAs have not had much benefit from these gains due to low rates of access and participation in clinical trials (Burke et al., 2007). Limited numbers of clinical trials target AYA-specific cancers, resulting in little increased understanding regarding the behavior of AYA cancers (Burke et al., 2007). It is not clear whether AYAs are not participating in clinical trials due to a lack of trials for their age range, patient refusal to enroll, or a lack of physician referral of AYAs to trials (Johnson, 2011).

AYAs would benefit from the conduct of clinical trials targeting their age group and this should be a critical public health target (Bleyer et al., 1997). Although only 2% of AYAs with cancer were given the opportunity to enroll in a clinical trial, over 50% of pediatric oncology patients (under age 15) received treatment as part of participating in a clinical trial (AYAOPRG, 2006; Bleyer, 2011). Participation in clinical trials rapidly declines after the age of 14 (Bleyer et al., 2006). Research shows that roughly 14% of AYA patients diagnosed with non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), acute lymphoblastic leukemia (ALL), germ cell cancer and osteo-Ewing and synovial sarcomas are enrolled in clinical trials during treatment (Parsons, Harlan, Seibel, Stevens, & Keegan, 2011). However, that percentage declines rapidly with age with 15-19 year olds having 34.3% participation, declining to only 8.8% for 20-24 year olds, and eventually only 3.7% for ages 35-39 (Parsons et al., 2011).

Adolescents and young adults are underrepresented in national tumor banks, resulting in a lack of opportunity for tumors samples to be studied retrospectively (Burke et al., 2007). AYAs would benefit from the collection and investigation of tumor specimens in order to better understand AYA-specific biological features (Pollock & Birch, 2008). Less than 60% of the expected numbers of tumor samples from AYAs are sent to the Cooperative Human Tissue Network, limiting the ability of research that can be done retrospectively to study and identify the characteristics of AYA tumors (Burke et al., 2007). While there are several explanations for the insufficient amount of clinical trial research for AYAs, it is clear that there is a lack of trials available for AYAs and that this group should be targeted for participation (Johnson, 2011).

Psychosocial Needs

When the burden of cancer is added during this distinct life stage, AYAs experience extreme challenges in their growth and development (Bleyer et al., 2006). The necessary and critical changes that occur during adolescence and young adulthood may be interrupted, accelerated, or reversed by the cancer experience (Lewis, Fallon, Dongen-Melman, & Barr, 2002). The AYA years can be among the most difficult years of life in regard to self-identity, maturity, and autonomy. These formative years involve a series of developmental stages during which the individual gains personal identity, independence, sexual and emotional maturity, self-esteem, and future life opportunities (Mulhall, Kelly, & Pearce, 2004). This period of development is susceptible to disturbance, as AYAs make the transition from childhood into older adulthood while developing physically, psychologically, sexually, and socially (Evan, Kaufman, Cook, & Zeltzer, 2006). Disruption of the development from childhood to adulthood associated with developing cancer can severely impact an individual.

AYA cancer was once seen as an acute, invariably fatal disease, but is now regarded as a chronic illness (Smith, 2004). Many AYAs diagnosed with cancer will be cured, often after intensive, toxic, and life-changing treatment (Whelan, 2003). Cancer diagnosis during adolescence and young adulthood exacerbates the difficulties of transitioning from childhood to adulthood (AYAOPRG, 2006). Furthermore, a patient's stage of life is directly associated with how he or she understands, processes, and copes with a diagnosis of cancer (Palmer et al., 2007). While a diagnosis of cancer is difficult during any life stage, the impact of cancer on AYAs seems to be greater than other age groups. This age group consists of individuals with particular emotional, social, and psychological problems, with diverse levels of maturity and differing needs (Clerici et al., 2008).

A cancer diagnosis during the AYA life stage raises particular concerns because of the impact on normal development, disruption of school and social activities, loss of self-identity, and dependence on family and caregivers (Mulhall et al., 2004). The multitude of challenges and changes that occur during adolescence make young people susceptible to additional pressures and stressors even without a cancer diagnosis (Palmer et al., 2007). Following the transition from child to adulthood, AYAs are expected to emerge with a positive sense of self-worth, an established identity, comfortable body image, and the ability to form relationships (Hollis & Morgan, 2001). Unfortunately, the diagnosis and treatment of a potentially terminal illness such as cancer does not allow AYAs to progress through the developmental process normally.

AYA cancer patients may not have a normal body image due to such reasons as surgical scarring, weight fluctuations due to treatment, or loss of hair due to chemotherapy (AYAOPRG, 2006). Isolation from their peers during cancer treatment severely limits the development of

social skills and sexual identity (Evan et al., 2006). Other areas that may be impacted include achieving emotional independence from their parents and developing a decision making process that is uniquely their own (Evan et al., 2006). For most AYAs, the cancer diagnosis is the first time they have faced their own mortality (AYAOPRG, 2006).

Summary

The combination of adolescence or young adulthood with a diagnosis of cancer provides a unique situation that requires a specific model of care. The developmental processes experienced by AYA cancer patients differ from the experience of children or older adults with cancer. AYAs have a variety of distinct healthcare needs that must be understood and addressed while providing cancer treatment (AYAOPRG, 2006). The needs of AYA cancer patients are dynamic and comprise physical, psychological, social, and educational needs. Often, these needs are overlooked, leaving AYAs anxious about obtaining information regarding their cancer, treatment and treatment options, peer relationships and psychosocial support, as well as other important general information. Hodgkinson (2007) highlights that increased recognition of the psychosocial impact of cancer has motivated practitioners to broadly assess individuals' needs in order to provide more supportive care services. It is very important that the medical and psychosocial needs of AYA cancer patients are addressed by practitioners and researchers who understand those needs.

Cancer in AYAs is a major public health concern that has been overlooked by the medical and research communities for years (AYAOPRG, 2006). The recent gains in awareness for AYAs through the AYAOPRG and the LSYAA illustrate that AYA cancer is a unique field that requires attention. AYA patients are in need of cancer-specific, age-appropriate care and

increased awareness campaigns to achieve progress in their treatment outcomes. Reversing the past trend in the approach to AYA cancer care and decreasing the "AYA Gap", consisting of the lack of progress in cancer outcomes as compared to other age groups, must involve comprehensive efforts from multiple stakeholders, including the government, insurance agencies, healthcare providers, and researchers (Ferrari, Montello, Budd, & Bleyer, 2008; Pollock & Birch, 2008).

Significance to Public Health

AYA cancer patients have received inadequate attention in the areas of cancer research, interventions, and awareness. While historically AYAs have typically seen positive survival outcomes as compared to other age groups, there has been a significant lack of progress in the survival rates of AYAs since 1975 (AYAOPRG, 2006; Bleyer, 2002). Over the past 20 years the survival rates for children and older adults have improved significantly, while the survival rates of AYAs have remained stagnant (LSYAA, 2006). Understanding the cancer incidence in AYAs may provide insight into their future cancer burden (Weir et al., 2011). Investigation of AYA cancer has the potential to provide insight into the etiology of certain cancer types, especially since the interval between exposure and diagnosis may be shorter (Weir et al., 2011). Examining the incidence and prevalence of cancer in the AYA population in Tennessee will provide evidence at the state level for understanding the overall cancer burden in this specific population. Using a state-based cancer registry to provide a state profile of AYA cancers will provide a resource for future state-based cancer interventions and cancer control.

Human Subjects Protection

The East Tennessee State University and Veteran's Administration Institutional Review Board (IRB) reviewed this study and it was exempt on the basis of not representing human subjects' research. The data were collected by the state cancer registry and all identifying information on individuals was removed prior to being provided for the current study.

CHAPTER 2

ADOLESCENT AND YOUNG ADULT CANCER INCIDENCE IN TENNESSEE: USE OF A STATE-BASED CANCER REGISTRY

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ABSTRACT

Purpose: Adolescents and Young Adults (AYAs) are an underserved and underrepresented population in cancer care. Understanding the unique cancer burden in this population in Tennessee will help to improve cancer prevention and control efforts. *Patients and Methods:* Tennessee Cancer Registry data for 2004-2008 were used to determine incidence rates of the five most frequently diagnosed cancers in AYAs: breast, lymphoma, melanoma, testicular, and thyroid. Cancers were coded by ICD-O-3 codes. Cancer-specific incidence rates were determined according to age, gender, and year of diagnosis. Age-adjusted rates were calculated by cancer type using the US 2000 Standard Population. *Results:* For 2004-2008, breast cancers (15.0%) were the most common AYA cancers, followed by melanomas (13.7%), thyroid cancers (10.3%), lymphomas (7.7%), testicular cancers (6.1%), and all other cancer types (47.3%). Adjusted incidence rates for melanomas were higher in females than males (AIR 14.01, CI 12.96-15.06 vs. AIR 8.08, CI 7.28-8.88, respectively) as were thyroid cancers (AIR 13.39, CI 12.37-14.42 vs. AIR 3.50, CI 2.98-4.03, respectively). Incidence rates for all cancer types increased with age. *Conclusion:* The types of cancers diagnosed in AYAs in Tennessee are similar to those diagnosed in the United States. The incidence of melanoma and thyroid cancers are higher in Tennessee compared to the United States and both are higher in females than males. Identifying the types of cancer most often diagnosed in AYAs in Tennessee will help focus the direction of future research and provide a basis for the development of cancer prevention and control activities for this population.

Background

Cancer in adolescents and young adults (AYAs) is a major public health concern that has not been effectively addressed by the medical and research communities (AYAOPRG, 2006). The recent increased awareness of AYA cancer resulting from the Adolescent and Young Adult Oncology Peer Review Group (AYAOPRG) and the Live Strong Young Adult Alliance (LSYAA) activities, emphasizes the need for more attention to this area (AYAOPRG, 2006; LYSAA, 2006). Despite the recent attention and recognition of the distinctive health care needs of this population, there is still much to be understood about AYA cancer (Wu et al., 2005). Little is known about the AYA population and factors that play a role in the biologic, epidemiologic, genetic, psychosocial, and economic issues that underlie their morbidity, mortality, and quality of life (AYAOPRG, 2006). Cancer in AYAs has distinct features and the spectrum of malignant disease in this population is much different than for other age groups (Bleyer, 2002). The disruption caused by a cancer diagnosis during this phase of life presents the patients with unique psychosocial, medical, physical, and educational needs (Bleyer, 2002).

Definition of Adolescents and Young Adults

The definition of AYAs has evolved over the years, with many different definitions existing based on age, psychosocial development, and societal influences (AYAOPRG, 2006). The Adolescent and Young Adult Oncology Progress Review Group and the National Cancer Institute have defined AYAs over a wide age range, 15-39 years of age, in order to be include the entire spectrum of cancer patients that continue to experience a lack of improvement in cancer care and survival (AYAOPRG, 2006; NCI, 2012a). Although this age range may seem quite wide, individuals in this population are similar based on extreme differences in the diagnosis and

treatment of cancer as compared to other age groups (Wolfson, 2011). Prior to the development of this AYA definition, individuals in this age range lacked a home in cancer care and research, and were usually treated by either pediatric or adult protocols based solely on their cancer diagnosis (AYAOPRG, 2006). This formal definition of AYAs will help to focus attention and streamline research, interventions, treatment, and awareness efforts in this population (AYAOPRG, 2006).

Epidemiology

The spectrum of tumors seen in AYAs differs from that of either childhood or older adults (Bleyer et al., 2008). The majority of these cancers appear to occur spontaneously and there is not the relationship to environmental carcinogens and family history seen with adult cancers (Bleyer, 2007). About 90% of the tumor types exhibited in AYAs are from ten cancer types: breast, lymphoma, melanoma, ovarian and cervical, thyroid, sarcomas, testicular, colorectal, leukemia, and brain tumors (AYAOPRG, 2006; Bleyer et al., 2008). In addition, approximately two-thirds of AYA cancers are from only six of the aforementioned types: breast, lymphoma, melanoma, thyroid, and male and female gonadal cancers (Johnson, 2011). The incidence of tumor types varies greatly across the AYA age spectrum (AYAOPRG, 2006; Bleyer et al., 2008). Older adolescents (age 15-19 years) suffer more from lymphomas, germ cell tumors, and leukemias as compared to higher levels of carcinomas that occur in young adults (age 20-39) (AYAOPRG, 2006). Males in the 15-29 year old age range are more likely to be diagnosed with cancer compared to females (Bleyer et al., 2006; Bleyer, Viny, & Barr, 2006). Additionally, Caucasians were more likely to be diagnosed with cancer than other ethnicities (AYAOPRG, 2006; Bleyer et al., 2006).

Tennessee

Tennessee (TN) provides a unique opportunity to investigate AYA cancer since the state has distinct geographic and demographic differences. Tennessee encompasses major metropolitan areas, suburban counties, and rural communities located in the Appalachian Mountains and the Mississippi Delta region. Overall, TN is comprised of about 80% Caucasians and has less than 20% African-American people (Erwin et al., 2010). East TN has a relatively homogenous Caucasian population, even in major urban areas like Knoxville (Erwin et al., 2010). Meanwhile, in West TN the percentage of Blacks is proportionally higher than for the overall state with around 50% African-Americans reported (Erwin et al., 2010). Only 27 of TN's 95 counties are considered urban, while 68 are rural (Erwin et al., 2010).

The Tennessee Cancer Registry (TCR) reported that TN has the twenty-second highest age-adjusted cancer incidence rate and the fifth highest cancer mortality rate in the nation (Li et al., 2010). The TCR report shows that children age 0-4 and adolescents age 15-19 have the highest incidence rates for cancers of childhood. However, cancer mortality rates are relatively similar across all cancers that are diagnosed prior to age 20 (Li et al., 2010). There has been no research in TN that has specifically investigated the AYAs, age 15-39 years, to help understand the unique characteristics of cancer in this population. Although TN is well known in cancer control and prevention due to nationally recognized cancer centers such as St. Jude's Children's Research Hospital and Vanderbilt- Ingram Cancer Center, as well as an established state-wide cancer coalition, the burden of cancer in AYAs has not been fully investigated and therefore is not well understood.

Further epidemiologic research focused on AYAs is needed to better understand the cancer burden, patterns and trends and the barriers to progress in cancer prevention and control. This study examines the cancer incidence and patterns for AYAs in TN for 2004 through 2008. The five most common cancers were evaluated, including breast, lymphoma, melanoma, testicular, and thyroid. A better understanding of the types of cancer that affect AYAs along with characteristics of the cancer patients will provide an evidenced-based approach for future cancer research and interventions.

Patients and Methods

Data Source

Data were obtained from the TCR for all new AYA cancer cases in TN from 2004 through 2008. The TCR is part of the National Program of Cancer Registries (NPCR) (CDC, 2012). The NPCR was established in 1992 through the Cancer Registries Amendment Act and works to provide cancer surveillance across the nation (CDC, 2012). Administered by the Centers for Disease Control and Prevention (CDC), state based cancer registries monitor cancer trends over time; determine patterns of cancer incidence and mortality in specific populations, and assist in the planning and evaluation of cancer control programs (CDC, 2012).

The NPCR falls under the jurisdiction of the North American Association of Cancer Registries (NAACR) for standardization of registry data (Thornton, 2010). Standardization of cancer registry data is a vital component of cancer surveillance quality as it provides the basis for having consistent data across cancer registries in North America (Thornton, 2010). The NAACR has developed uniform data standards and an associated data dictionary for the use of all cancer registries in North America. This document serves as a reference to ensure uniform data

collection, assist in the collection of data that is comparable across groups, provide a resource for state based registries, and to reduce redundancy in the coding and collection of data. Furthermore, state registry data must meet NAACR standards of completeness (90% completeness of the data set) in order to be accepted for NAACR/CDC publication (Hofferkamp, 2008).

The TCR met data completeness standards for the first time in 2004 and have continued to produce high quality data since then (Li et al., 2010). Data for the current study, years 2004-2008, met data completeness standards of 95% or higher (Li et al., 2010). The TCR collects data on cancer incidence, including: the type of cancer, primary site of cancer, stage, first course of treatment, vital status, and general demographic information (Li et al., 2010). Data are sent to the TCR from hospitals, pathology labs, physician's offices, and radiation facilities (Li et al., 2010). The information on each case is compiled into the database to provide cancer statistics for the state.

Sample

The sample for this study included all new breast cancer, lymphoma, melanoma, testicular, and thyroid cancer cases (N=4,269) in AYAs from the Tennessee Cancer Registry for the years 2004-2008, inclusive. AYA cases were defined as cancer cases that were diagnosed in individuals ages 15-39 years, inclusive. Both in situ and invasive cancer cases in the AYA population are included. Cancer primary sites were identified by International Classification of Disease for Oncology, Third Edition (ICD-O-3). Hodgkin and non-Hodgkin lymphoma were combined and referred to as lymphomas. General demographic information including gender, age, and insurance status, county of diagnosis, marital status, and race were reported for each

case. Cancer specific information such as primary cancer site, stage at diagnosis, treatment type, and vital status are also reported for each case.

Analyses

Secondary data analysis of the AYA data set was performed using SAS 9.2 (SAS Institute, 2009). Crude incidence rates (CIR), defined as the total number of incident cases divided by the mid-year population, were calculated for each cancer. Age specific incidence rates (ASIRs), the ratio of the number of new cases in a specific age group to the population of that group, were calculated for each cancer by sex. Consistent with current AYA cancer research, ASIRs were calculated for the following five age groups: 15-19, 20-24, 25-29, 30-34, and 35-39. To compare rates across different groups, age adjusted incidence rates (AIR) for each cancer type and year of diagnosis by gender were calculated using the US 2000 standard population. Overall adjusted incidence rates for the 2004-2008 study period for each cancer by gender were calculated using the US 2000 standard population. All rates are expressed per 100,000 population. Confidence intervals (CI 95%) for AIRs were calculated to compare rates across populations and diagnosis years. Rates were not calculated by race due to inadequate information for this variable in the sample.

Results

A total of 8,097 cancers were diagnosed in AYAs in TN from 2004-2008. About half of those cancers (4,269 or 52.7%) were of the five following types: breast, lymphomas, melanoma, testicular, and thyroid. Table 1.1 illustrates the distribution of the top five cancers and the characteristics of those with cancer. The sample included 1,216 breast cancers (15.0%), 1109 melanomas (13.7%), 830 thyroid cancers (10.3%), 623 lymphomas (7.7%) and 491 testicular

cancers (6.1%). The majority of cancer cases were female (66.8%), diagnosed with localized stage cancer (59.3%), and were Caucasian (85.7%).

Table 1.1. Characteristics of the Five Leading AYA Cancers in Tennessee, 2004-2008

N= 4,269	
Characteristics	N (%)
Primary Site*	
Breast	1216 (15.0)
Lymphomas	623 (7.7)
Melanoma	1109(13.7)
Testicular	491 (6.1)
Thyroid	830 (10.3)
Age at diagnosis (years)	
15-19	174 (4.1)
20-24	449 (10.5)
25-29	710 (16.6)
30-34	1151 (27.0)
35-39	1785 (41.8)
Sex	
Female	2851 (66.8)
Male	1416 (33.2)
Race	
Caucasian	3620 (85.7)
Other	602(14.3)
Region	
Non-Appalachian	2353 (55.1)
Appalachian	1916 (44.9)
Stage	
In Situ	172 (9.3)
Local	1093 (59.3)
Regional/Distant	577 (31.3)
Insurance Status	
Not Insured	219 (6.2)
Government Insurance	587 (16.7)
Private/Other	2717 (77.1)
Year of Diagnosis	
2004	793 (18.6)
2005	859 (20.1)
2006	880 (20.6)
2007	882 (20.7)
2008	855 (20.0)

*Based on the total number of cancers in AYAs in TN.
Other cancer types accounted for 52.8% or 3828 cases.

Table 1.2 shows the incidence rates for female breast cancer from 2004-2008. Age-specific breast cancer rates increased as age increased. Age 35-39 had the highest incidence rates while ages 15-19 had the lowest rates. Breast cancer incidence in TN drastically increases with age from 0.30 cases per 100,000 in ages 15-19 to 72.30 cases per 100,000 in 35-39 year olds. The incidence of breast cancer remained consistent throughout the duration of the study period and did not significantly increase from 2004-2008.

Table 1.2. AYA Female Breast Cancer Incidence Rates^ for Tennessee by Age and Year of Diagnosis

Year / **Sex & Age**	**2004**	**2005**	**2006**	**2007**	**2008**	**All**
(N=1209)						
15-19	0.51	1.01	0.0	0.0	0.0	0.30
20-24	1.56	2.56	1.01	2.01	2.00	1.82
25-29	14.06	12.00	11.86	9.21	11.68	11.75
30-34	32.38	30.32	30.80	34.92	31.56	32.00
35-39	66.50	77.78	78.34	67.27	71.68	72.30
All*	**24.56 (21.42-27.71)**	**26.63 (23.33-29.93)**	**26.33 (23.06-29.61)**	**24.35 (21.20-27.49)**	**25.12 (21.92-28.32)**	**25.39 (23.96-26.83)****

^per 100,000, *Age adjusted incidence rate using US 2000 standard population for all age groups, **Age adjusted incidence rate using US 2000 standard population for all age groups and for all five years (2004-2008).

Table 1.3 shows that lymphoma rates in AYAs in TN remained similar and did not significantly increase during the study period. Although males displayed consistently higher incidence rates than females, the differences were not significant at the $p < 0.05$ level. The overall adjusted rate for males was 6.53 (5.82-7.24) and for females was 5.38 (4.73-6.02). In general, incidence rates of lymphoma steadily increased by age for both males and females.

Table 1.3. AYA Lymphoma Incidence Rates^ for Tennessee by Gender, Age, and Year of Diagnosis

Year / Sex & Age	2004	2005	2006	2007	2008	All
Males (N=345)						
15-19	1.94	3.36	3.79	3.29	6.51	3.80
20-24	5.57	7.00	6.92	3.93	4.88	5.65
25-29	5.16	4.65	5.61	5.06	6.02	5.31
30-34	9.90	5.92	7.39	10.89	7.45	8.31
35-39	7.74	12.71	5.34	9.21	10.65	9.13
All*	**6.12 (4.58-7.66)**	**6.92 (5.27-8.56)**	**5.78 (4.30-7.26)**	**6.60 (5.00-8.20)**	**7.25 (5.58-8.92)**	**6.53 (5.82-7.24)****
Females (N=278)						
15-19	3.59	6.09	2.50	3.47	3.43	3.81
20-24	5.70	4.61	4.05	7.54	3.49	5.08
25-29	7.81	5.74	3.09	5.12	4.06	5.15
30-35	4.98	7.96	5.96	4.99	5.51	5.88
35-39	3.82	8.26	8.22	8.71	4.84	6.77
All*	**5.08 (3.69-6.48)**	**6.62 (5.01-8.23)**	**4.89 (3.51-6.28)**	**4.50 (6.03-7.56)**	**4.30 (3.01-5.58)**	**5.38 (4.73-6.02)****

^per 100,000, *Age adjusted incidence rate using US 2000 standard population for all age groups, **Age adjusted incidence rate using US 2000 standard population for all age groups and for all five years (2004-2008).

Table 1.4 illustrates the melanoma cases in TN from 2004-2008 by age and gender. Melanoma rates were higher for females in every age group. Females also displayed higher rates for each year of diagnosis. The overall AIR for males is 8.08 (CI 7.28-8.88) and for females is

14.01 (CI 12.96-15.06), showing statistical significance at the 0.05 level. Melanoma incidence rates increased with age for both males and females increase.

Table 1.4. AYA Melanoma Incidence Rates^ for Tennessee by Gender, Age, and Year of Diagnosis

Year / Sex & Age	2004	2005	2006	2007	2008	All
Males (N=401)						
15-19	2.92	0.96	1.89	2.35	0.93	1.80
20-24	4.05	4.5	2.47	3.44	3.42	3.57
25-29	5.67	7.75	12.76	3.54	6.52	7.24
30-34	8.91	10.84	9.85	9.4	12.42	10.28
35-39	19.34	15.65	15.05	15.03	15.5	16.12
All*	**8.57 (6.72-10.41)**	**8.18 (6.38-9.97)**	**8.56 (6.74-10.39)**	**7.07 (5.40-8.74)**	**8.03 (6.25-9.80)**	**8.08 (7.28-8.88)****
Females (N=707)						
15-19	2.05	2.03	3.5	1.49	1.96	2.20
20-24	10.89	10.77	9.62	11.56	9.98	10.56
25-29	11.46	14.08	17.53	14.32	11.68	13.81
30-34	16.94	16.41	20.87	22.95	16.53	18.74
35-39	17.7	20.42	24.18	28.07	26.64	23.39
All*	**11.96 (9.80-14.12)**	**12.92 (10.67-15.17)**	**15.38 (12.93-17.83)**	**16.05 (13.54-18.56)**	**13.76 (11.43-16.09)**	**14.01 (12.96-15.06)****

^per 100,000, *Age adjusted incidence rate using US 2000 standard population for all age groups, **Age adjusted incidence rate using US 2000 standard population for all age groups and for all five years (2004-2008).

Testicular cancer rates are displayed in Table 1.5. Testicular cancer rates were consistent over the 5 year study period and did not significantly differ from 2004-2008. As with the other

cancers previously discussed, testicular cancer incidence increases with age. However, testicular cancer seems to peak at the 25-29 and 30-34 age groups, with those rates at 12.24 and 12.56 per 100,000, respectively. Incidence rates of testicular cancer are low in 15-19 year olds (2.66), but increase markedly as age increases, with rates roughly four times higher in 30-34 year old age group (12.56).

Table 1.5. AYA Testicular Cancer Incidence Rates^ for Tennessee by Age and Year of Diagnosis

Year / Sex & Age	2004	2005	2006	2007	2008	All
(N=491)						
15-19	2.43	1.92	1.42	3.75	3.72	2.66
20-24	8.11	9.50	4.45	11.79	11.23	9.03
25-29	15.48	13.44	10.72	12.15	9.53	12.24
30-34	8.91	16.76	12.81	11.38	12.92	12.56
35-39	8.71	13.69	14.08	10.67	12.59	11.94
All*	**8.59 (6.78-10.40)**	**11.08 (9.01-13.15)**	**8.84 (6.99-10.69)**	**9.89 (7.95-11.82)**	**10.04 (8.09-12.00)**	**9.69 (8.83-10.55)****

^per 100,000, *Age adjusted incidence rate using US 2000 standard population for all age groups, **Age adjusted incidence rate using US 2000 standard population for all age groups and for all five years (2004-2008).

Table 1.6 displays thyroid cancers in TN by gender and age from 2004-2008. Females were roughly 4 times more likely to be diagnosed with thyroid cancer compared to males, 12.37 (CI 13.39-14.42) and 3.50 (CI 2.98-4.03), respectively. These findings are significant at the 0.05 level. Females were more likely to be diagnosed with thyroid cancer at every age as compared with males. Males and females both experienced increased incidence of thyroid cancer with

increased age. Females in the 30-34 and 35-39 year old age brackets are almost twice as likely to be diagnosed with thyroid cancer compared to any other age group.

Table 1.6. AYA Thyroid Cancer Incidence Rates^ for Tennessee by Gender, Age, and Year of Diagnosis

Year / Sex & Age	2004	2005	2006	2007	2008	All
Males (N=173)						
15-19	0.49	1.44	0.0	0.47	0.0	0.47
20-24	1.52	1.00	1.98	1.47	1.46	1.49
25-29	5.16	2.58	3.06	6.58	2.51	3.98
30-34	3.46	3.94	4.43	5.93	6.46	4.85
35-39	4.35	6.84	5.34	8.24	6.78	6.31
All*	3.00 (1.93-4.08)	3.30 (2.15-4.44)	3.03 (1.94-4.12)	4.63 (3.29-5.97)	3.57 (2.38-4.75)	3.50 (2.98-4.03)**
Females (N=657)						
15-19	1.54	1.52	1.00	0.99	3.92	1.80
20-24	5.70	7.18	8.61	8.55	6.99	7.41
25-29	8.85	12.52	14.95	11.25	14.72	12.47
30-34	17.44	19.89	21.86	20.96	21.04	20.24
35-39	21.05	15.56	28.53	26.62	25.18	23.39
All*	11.27 (9.16-13.38)	11.45 (9.33-13.56)	15.40 (12.94-17.86)	14.10 (12.32-17.13)	14.72 (12.32-17.13)	13.39 (12.37-14.42)**

^per 100,000, *Age adjusted incidence rate using US 2000 standard population for all age groups, **Age adjusted incidence rate using US 2000 standard population for all age groups and for all five years (2004-2008).

Discussion

The types of cancers that affect AYAs in TN are relatively similar to the types that affect AYAs nationally; however, the distribution of those cancers differs slightly in TN. Bleyer (2011) illustrate the distribution of the top five cancers in AYAs to be ranked in the following order: breast, lymphomas, melanomas, female genital tract, and thyroid cancer. The top five most frequently diagnosed cancers in AYAs in TN for 2004-2008 were breast, melanomas, thyroid, lymphomas, and testicular cancers.

According to Bleyer, Viny, and Barr (2006), in the United States, males in the 15-29 age range are more likely to be diagnosed with cancer compared to females. However, in TN for the five cancers most frequently diagnosed, female AYAs (15-39 year old age range) are more likely to be diagnosed with cancer as compared to males. The difference in age ranges examined prevents a valid comparison and the increased cancers diagnosed in females at the upper limits of the AYA age range may explain the difference. Lymphoma diagnoses were relatively similar by gender; however, melanomas and thyroid cancers were diagnosed mostly in females.

In addition, the increased cancer incidence in AYA females compared to males is predominately due to the fact that a large proportion of the cancers diagnosed during this study period were female breast cancers. Incidence rates for female breast cancers in AYAs in TN were higher than the national statistics in all age groups. Females aged 35-39 years in TN reported an incidence rate of 72.30 per 100,000 compared to 59.97 per 100,000 nationally (Surveillance, Epidemiology, and End Results, 2011a).

Melanomas were the second most frequently diagnosed cancer in AYAs in TN and accounted for roughly 25% of the five most common cancers and 13.7% of all cancers diagnosed

in AYAs. However, in the US, melanoma is the third most commonly diagnosed cancer in AYAs (Weir et al., 2011). In all age categories, female AYAs in TN reported higher melanoma incidence rates compared to the nation (Surveillance, Epidemiology, and End Results, 2011b). The greatest difference in incidence rates in TN compared to the nation was for females aged 20-24 years (10.56 vs. 5.80, respectively). Consistent with the current literature, melanoma incidence rates in females proved to be significantly higher than rates for males in AYAs (Bleyer et al., 2006; Weir et al., 2011; Wu et al., 2011). However, this finding is different compared to older age groups where males are more commonly diagnosed, suggesting there may be something unique about melanoma in AYA females (Jemal, Siegal, Xu, & Ward, 2010).

Thyroid cancer accounts for more than 10% of all cancers in the AYA population nationally and is two to three times more common in females (AYAOPRG, 2006; Bleyer, 2005; Tuttle et al., 2010; Wu et al., 2005). Nationally, thyroid cancer is the fifth most frequently diagnosed cancer in females of all ages (Bleyer, 2011). In this sample, thyroid cancer was the third most commonly diagnosed cancer, behind breast cancer and melanoma, respectively and accounted for 10.3% of the cancers diagnosed in AYAs in TN during the study period. Thyroid cancer incidence rates in females in TN ages 30-34 (20.24) and 35-39 (23.39) are slightly higher than national incidence rates for ages 30-34 (18.19) and 35-39 (21.78). Additionally, thyroid cancer was almost four times more common in AYA females compared to AYA males in TN.

Testicular cancer was also more frequently diagnosed in AYAs in TN compared to the nation. Nationally, testicular cancers are the seventh most commonly diagnosed cancer in AYAs (Bleyer, 2011). In this study testicular cancers were the fifth most commonly diagnosed cancer. However, incidence rates for testicular cancer were similar to national rates for all races. Incidence rates in TN from 2004-2008 were only marginally higher compared to national

statistics from 2000-2008 for men 35-39 years of age (11.94 vs. 11.29) (Surveillance, Epidemiology, and End Results, 2011a). Consistent with current literature, testicular cancers were highest in males aged 20-34 (NCI, 2012e).

In conclusion, AYA cancers in TN represent a unique population in cancer occurrence. Cancer types vary by gender and age in this population and are different from cancer types affecting both younger and older age groups. Cancer incidence patterns in this age group are not fully understood, but are more likely to be related to genetic predisposition and explicit health behaviors associated with AYAs. Cancer prevention and control strategies should be age-specific and tailored for the needs of this group.

Strengths and Limitations

The use of the TN Cancer Registry provided high-quality data that met national standards of the North American Association of Cancer Registries. The study provided useful information on the unique characteristics of cancer in the AYA population in TN. This is the first study to use the TN Cancer Registry to look at the distinct features of AYA cancer and to explore the differences of AYAs in TN compared to national data.

As is true of all studies, this study has limitations. There was a lack of sufficient racial diversity in the sample to allow for incidence rates to be calculated by race. These findings do not supply information regarding potential racial disparities in AYA cancer. Future research that includes additional socio-demographic and cancer specific variables related to diagnosis, treatment, and stage will help to identify the barriers to progress in AYA cancers in TN.

Public Health Implications

Identifying the main cancer types affecting AYAs in TN provides the opportunity to adapt and customize cancer prevention and control efforts for this age group based on the types of cancer that predominately occur in this population. Prevention activities should focus on educating AYAs about the most commonly diagnosed cancers in their age range, risk factors, and screening provisions. Four of the five types of cancer most commonly diagnosed in AYAs in TN (breast, melanoma, thyroid, and testicular cancers) have known symptoms and screening procedures that can be used to educate medical practitioners about approaches to incorporate into their practice when treating AYAs. Finally, increasing awareness of the most commonly diagnosed cancers in AYAs and the risk factors associated with those cancers will assist in reducing the disparities connected to cancer among 15-39 year olds.

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CHAPTER 3

PREDICTORS OF LATE STAGE MELANOMA DIAGNOSIS: ADOLESCENT AND YOUNG ADULT CANCER PATIENTS IN TENNESSEE

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ABSTRACT

Purpose: Melanoma is the second most commonly diagnosed cancer in adolescents and young adults (AYAs) aged 15-39 years in the United States. This study's objectives were to understand the unique characteristics of melanoma in AYAs in Tennessee and to identify the predictors of late-stage diagnosis. *Patients and Methods:* All (AYA) melanoma cases in Tennessee (N=1109) were obtained from the Tennessee Cancer Registry for the years 2004-2008. Cases with a confirmed stage of diagnosis (n=327) were included for analysis to determine predictors of late-stage diagnosis, using the proportional odds model. Sex, insurance status, and age of diagnosis served as predictors in the model. *Results:* The majority of melanoma cases (N=1109) were female (63.8%), Caucasian (96.5%), diagnosed with localized stage cancer (69.3%), and were diagnosed between the ages of 35-39 years (37.8%). Government insurance served as the greatest predictor of late-stage melanoma diagnosis. Individuals with government insurance were eight times (OR 8.41, CI 3.04-23.27, $p<0.01$) more likely to be diagnosed with late stage melanoma compared to individuals with private or other types of insurance. Individuals diagnosed with melanoma between ages 15 and 19 were six times (OR 6.30, CI1.74-22.86, $p<0.01$) more likely to be diagnosed with late-stage melanoma compared to individuals in the 35-39 year old age group. *Conclusion:* These data suggest targeted areas for future research regarding insurance status and age at diagnosis as predictors of late stage melanoma and the need for cancer prevention and control activities geared towards AYAs.

Background

Melanoma is an extremely common and chiefly preventable disease; however, it is still the third most commonly diagnosed cancer in the adolescent and young adult (AYA) population (Plescia et al., 2011; Weir et al., 2011). Increasing incidence of melanoma and trends in melanoma mortality in the United States have motivated public health practitioners to focus on early detection and prevention (Purdue, Freeman, Anderson, & Tucker, 2008; Koh & Geller, 2011). Melanoma is defined by the uncontrolled growth of melanocytes that can spread to other parts of the body, potentially resulting in death (American Melanoma Foundation, 2006). Early detection and treatment of melanoma generally yields a favorable prognosis (Bleyer et al., 2006).

The most well known risk factor for melanoma is overexposure to ultraviolet (UV) radiation from sunlight or artificial sources (Gilchrest et al., 1999). Family history of melanoma, light hair/skin color, tendency to develop freckles, and immunosuppression all pose an increased risk for melanoma (Lin et al., 2008; Weir et al., 2011). Incidence of melanoma is highest in Caucasians compared to all other racial groups, regardless of age (SEER, 2011b; Weir et al., 2011). Melanomas in AYAs suggests that early risk factors play an important role, specifically the potential for gene-environment interactions due to increased UV exposure from sunlight or tanning beds/booths and accumulated lifelong UV exposure (Anderson et al., 2009; Weir et al., 2011).

Definition of Adolescents and Young Adults

The definition of AYAs has developed throughout the years, with many different definitions existing based on age, psychosocial development, and societal influences (AYAOPRG, 2006). The Adolescent and Young Adult Oncology Progress Review Group

(AYAOPRG, 2006) opted to define the AYA population with a wide range in order to be inclusive of the entire spectrum of cancer patients that continue to experience a lack of improvement in cancer care and survival (AYAOPRG, 2006). The current definition of AYAs encompasses individuals diagnosed with cancer from 15 through 39 years of age (AYAOPRG, 2006). Although this age range may be quite wide, individuals in this population are unified based on their extreme differences in the cancer journey when compared to other age groups (Wolfson, 2010). Further, prior to this AYA definition, individuals in this age range lacked a home in cancer care and research, typically being treated on pediatric or adult protocols based on their cancer diagnosis (AYAOPRG, 2006). The formal definition of AYAs will help streamline research, interventions, treatment, and awareness efforts in this population (AYAOPRG, 2006).

Tennessee

Tennessee (TN) provides a unique opportunity to investigate AYA cancer in that it is a state that has distinct geographic and demographic differences. It encompasses major metropolitan areas, suburban counties, and several rural communities located in the Appalachian Mountains and the Mississippi Delta region. Tennessee has a predominately Caucasian population (over 80%) and there are less than 20% African-Americans (Erwin et al., 2010). East TN has a relatively homogenous Caucasian population, even in major urban areas like Knoxville (Erwin et al., 2010). Meanwhile, in West TN the percentage of African-Americans is proportionally higher than the overall state percentage, with figures around 50% (Erwin et al., 2010). In addition, only 27 of TN's 95 counties are considered urban, while 68 are rural.

The Tennessee Cancer Registry (TCR) found that TN has the twenty-second highest age-adjusted cancer incidence rate and the fifth highest cancer mortality rate in the nation (Li et al.,

2010). The TCR Annual Report highlights that the majority of the counties that have high incidence and mortality rates are located in the Appalachian region of TN (Li et al., 2010). This finding suggests that Appalachian TN residents may be predisposed to developing cancer due to certain lifestyle factors (Li et al., 2010). However, to date no research has specifically investigated melanoma in AYAs to understand the unique characteristics of cancer in this population in TN. While TN is well known in cancer control and prevention through state of the art cancer centers like St. Jude's and Vanderbilt and an established state-wide cancer coalition, the burden of cancer in AYAs is not fully understood.

This study identifies the characteristics of melanoma in AYAs in TN and examines the predictors of late stage diagnosis of melanoma in this population. Distinguishing the factors that contribute to late stage diagnosis and subsequent poor prognosis compared to early stage diagnosis will help to inform researchers and practitioners when developing melanoma related interventions with the AYA population. Additionally, understanding the burden of melanoma in AYAs in TN will help to target this specific population for cancer control and prevention activities.

Patients and Methods

Data Source

Data were obtained from the Tennessee Cancer Registry (TCR) for all AYA melanoma cases in TN from 2004-2008. The TCR was established in 1983 and collects comprehensive information on all TN residents diagnosed with cancer, as well as individuals treated for cancer in the state (TDOH, 2011). The TCR is part of the National Program of Cancer Registries (NPCR) that was established in 1992 through the Cancer Registries Amendment Act (CDC,

2011). The NPCR works to provide cancer surveillance across the nation (CDC, 2011). Administered by the Centers for Disease Control and Prevention (CDC), state based cancer registries monitor cancer trends over time; determine patterns of cancer incidence and mortality in specific populations, and assist in the planning and evaluation of cancer control programs (CDC, 2011).

The NPCR falls under the jurisdiction of the North American Association of Cancer Registries (NAACR) for standardization of registry data (Thornton, 2010). Standardization of cancer registry data is a vital component of cancer surveillance as it provides the basis for having consistent data across cancer registries in North America (Thornton, 2010). Furthermore, state registry data must meet NAACR standards of completeness (90% completeness of the data set) in order to be accepted for NAACR/CDC publication (Hofferkamp, 2008).

The TCR met data completeness standards for the first time in 2004 and have continued to produce high quality data since then (Li et al., 2010). Data for the current study, years 2004-2008, met data completeness standards of 95% or higher (Li et al., 2010). The TCR collects data on cancer incidence, including: the type of cancer, primary site of cancer, stage, first course of treatment, vital status, and general demographic information (Li et al., 2010). Data are sent to the TCR from hospitals, pathology labs, physician's offices, and radiation facilities (Li et al., 2010). The information on each case is compiled into the database to provide cancer statistics for the state.

Sample

The sample for this study includes all incident melanoma cancer cases (N=1109) in AYAs from the Tennessee Cancer Registry for the years 2004-2008, inclusive. AYA cases were

defined as cancer cases that were diagnosed in individuals of ages 15-39 years, inclusive. Melanoma cases were classified according to the International Classification of Diseases-Oncology (ICD-O-3) site codes C440-C449. Cases with reported stage and insurance status at melanoma diagnosis (N=327) were used for regression analysis.

Analyses

Analysis of melanoma cases in TN was performed using SAS 9.2 software to understand predictors of late-stage diagnosis in AYAs. Stage of diagnosis was defined by SEER Summary Stage and categorized into the following 1) in situ, 2) localized, 3) combined late stage variable for regional and distant stage. Predictor variables included sex, insurance status, and age group. Sex was defined as male and female. Insurance status was defined by the NAACR data dictionary and formatted into not insured, government insurance (Medicare, Medicaid, Tricare, Veteran's Affairs, Indian Health Service and Military), and private insurance/ other (insurance type not specified). Cases with unknown insurance status were excluded from analysis. Age groups were defined according to five year age intervals as follows: 15-19, 20-24, 25-29, 30-34, and 35-39. The analysis did not include race due to the lack of adequate differentiation in the sample. Simple and multiple logistic regression analyses were performed for all predictor variables. The proportional odds model was used due to the multi-level nature of the dependent variable, stage at diagnosis. Odds ratios and corresponding confidence intervals were reported. Descriptive statistics of the overall melanoma sample and those cases with stage at diagnosis were reported using frequencies, percents, and corresponding chi-squared values.

Results

A total of 1109 melanoma cases were diagnosed among AYAs in TN from 2004-2008. Of the 1109 cases reported (Table 2.1): 401 (36.2%) cases were diagnosed in males and 707 (63.8%) cases were diagnosed in females. The majority of the cases were Caucasian (96.5%), diagnosed with localized stage cancer (69.3%), and were diagnosed between ages 35-39 (37.8%). Cases with confirmed stage of diagnosis (Table 2.2) were predominately female (65.2%), had private insurance (90.5%), and were diagnosed between ages 35-39 (36.9%).

Table 2.1. Characteristics of Melanoma Cases in Tennessee for AYAs, 2004-2008

N=1109	
Characteristics	N (%)
Age at diagnosis* (years)	
15-19	42 (3.8)
20-24	143 (12.9)
25-29	208 (18.7)
30-34	297 (26.8)
35-39	419 (37.8)
Sex*	
Female	707 (63.8)
Male	401 (36.2)
Race*	
Caucasian	1039 (96.5)
Other	38 (3.5)
Region	
Non-Appalachia	559 (49.6)
Appalachian	550 (50.4)
Stage*	
In Situ	111 (22.5)
Local	342 (69.4)
Regional/Distant	40 (8.1)
Insurance Status*	
Not Insured	30 (4.5)
Government Insurance	69 (10.5)
Private/Other	560 (85.0)
Year of Diagnosis	
2004	216 (19.5)
2005	207 (18.7)
2006	239 (21.5)
2007	233 (21.0)
2008	214 (19.3)

*$p<0.01$

Table 2.2. Characteristics of Melanoma in Tennessee for AYAs by Stage at Diagnosis, 2004-2008

N=493		**In Situ**	**Localized**	**Regional/Distant**
		N=111	N=342	N=40
Characteristics		N (%)	N (%)	N (%)
Age at Diagnosis	15-19	3 (2.7)	13 (3.8)	4 (10.0)
(years)	20-24	9 (8.1)	57 (16.7)	3 (7.5)
	25-29	22 (19.8)	71 (20.8)	4 (10.0)
	30-34	28 (25.2)	85 (24.9)	12 (30.0)
	35-39	49 (44.1)	116 (33.9)	17 (42.5)
Sex*	Males	27 (24.3)	122 (35.8)	22 (55.0)
	Females	84 (75.7)	219 (64.2)	18 (45.0)
Insurance Status*	Not-Insured	3 (6.8)	5 (2.0)	4 (11.1)
	Government	1 (2.3)	10 (4.1)	8 (22.2)
	Private/Other	40 (90.9)	232 (93.9)	24 (66.7)

*$p<0.01$

Proportional odds analysis (Table 2.3) shows the predictors of late stage diagnosis. Univariate analysis of predictor variables illustrates that government insurance and males are predictors of late stage diagnosis ($p< 0.01$). Age (15-19) is moderately significant ($p=0.06$). Multivariate analysis shows that government insurance, males, and ages 15-19 are all significant predictors of late-stage diagnosis ($p<0.05$).

Table 2.3. Simple and Multiple Logistic Regression of Melanoma Cases in AYAs in Tennessee: Predictors of Late Stage Diagnosis

N=327^			
Variable		**Crude OR [a]**	**Adjusted OR (CI) [b]**
Age at Diagnosis (years)			
(reference: 35-39)	15-19*	2.64	6.30 (1.74-22.86)
	20-24	1.50	2.16 (0.96-4.83)
	25-29*	1.00	0.95 (0.48-1.89)
	30-34	1.23	1.14 (0.57-2.25)
Sex			
	Females vs. Males*	0.48	0.53 (0.30-0.93)
Insurance Status			
(reference: Private/Other)	Not-Insured	2.15	2.12 (0.54- 8.35)
	Government Insurance**	6.85	8.41 (3.04-23.27)

^ Excludes those without known stage at diagnosis or insurance status
[a] OR: odds ratio, [b] CI: 95% confidence interval
*p<0.05, **p<0.01

Government insurance served as the greatest predictor of late-stage melanoma diagnosis. Individuals with government insurance were eight times (OR 8.41, CI 3.04-23.27, p<0.01) more likely to be diagnosed with late stage melanoma compared to individuals with private or other types of insurance. Individuals with no insurance were two times (OR 2.12, CI 0.54-8.35, p 0.66) more likely to be diagnosed with late-stage melanoma compared to those with private or other types of insurance although this finding was not statistically significant. Females were 47% (OR 0.53, CI 0.30-0.93, p=0.03) less likely to be diagnosed with late-stage melanoma compared to men. Individuals diagnosed with melanoma between ages 15 and 19 were six times (OR 6.30, CI1.74-22.86, p<0.01) more likely to be diagnosed with late-stage melanoma compared to individuals in the 35-39 year old age group. Other age groups (20-24, 25-29, and 30-34) were not significant predictors of late-stage diagnosis.

Interaction between insurance status and age of diagnosis was assessed using an interaction term in the logistic regression model. Interaction between insurance status and age of diagnosis was significant ($p=0.01$) in the final regression model. The age groups that showed significant ($p< 0.05$) interaction with insurance status were individuals aged 20-24 who had government insurance and individuals aged 25-29 who were not insured, suggesting that the joint effects of these variables combined is different than their individual effects on predicting late stage diagnosis. The effect of age as a predictor of late stage diagnosis may be influenced by an individual's insurance status. Additionally exploration of interaction between age at diagnosis and insurance status should be explored to fully determine the effects of the independent variables on late stage melanoma diagnosis.

Discussion

Melanoma is the third most commonly diagnosed cancer in the AYA population in the United States (Weir et al., 2011). While melanoma is largely preventable, incidence rates continue to increase in the United States (Weir et al., 2011). Early diagnosis and treatment of melanoma are vital to prognosis (American Melanoma Foundation, 2006).

The majority of melanoma cases diagnosed in TN were Caucasian females, consistent with current literature (Bleyer et al., 2006; Weir et al., 2011; Wu et al., 2011). However, this finding is different compared to older age groups where males are more commonly diagnosed, suggesting there may be something unique about how melanoma behaves in AYAs (Jemal, Siegal, Xu, & Ward, 2010). Additionally, males were found to be more likely to be diagnosed with late stage melanoma; however, females were more likely to be diagnosed with melanoma at any stage. This finding may illustrate a lack of preventive care and regular melanoma screenings by AYA males. Unfortunately, many AYAs do not have a primary care physician that can refer

them to a dermatologist should they notice an abnormal skin lesion (AYAOPRG, 2006; Bleyer, 2007; LSYAA, 2006).

The frequency of melanoma diagnosis increased as age increased and most cases were diagnosed in the 35-39 year old age bracket. However, AYAs in the 15-19 year old age bracket were six times more likely to be diagnosed with late-stage melanoma compared to 35-39 year olds. Melanoma in this age group suggests early life factors are important and may involve a gene-environment interaction with excessive UV radiation exposure (Anderson et al., 2009; Weir et al., 2011). Evidence shows an increase in artificial sources of UV exposure through tanning beds or booths are associated with melanoma (Gallagher, Spinelli, & Lee, 2005; Lazovich et al., 2010; Robinson, Rigel, & Amonette, 1997). More than 30% of Caucasian, adolescent females and 11% of Caucasian, adolescent males have reported using a tanning bed or booth in their lifetime (Demko et al., 2003). The International Agency of Research on Cancer recognizes tanning beds/booths as a known carcinogen to humans (WHO-IARC, 2004). AYA should be cautious of excessive UV radiation in a natural or artificial setting.

Insurance status proved to be the greatest predictor of late-stage melanoma diagnosis. Individuals with government insurance, classified as Medicaid, Military, Veteran's Affairs, Indian Health Service, and Tricare, proved to be eight times more likely to be diagnosed with late-stage melanoma compared to those with no insurance. Those with no insurance did not significantly differ from private or other insurance. The increased risk of late-stage diagnosis in those with government insurance may be due to a lack of preventive care in this population, but additional research must be conducted to determine the implications of insurance status on late stage diagnosis.

Finally, interaction between age of diagnosis and insurance status was present in the final model. The effect of age as a predictor of late stage diagnosis may be influenced by an individual's insurance status. Currently, AYAs are the most underinsured of any age group in the US (Siegal, 2011). Many AYAs do not have consistent, quality health coverage, due to the uniqueness and transitional period that accompanies this life-stage (Siegal, 2011). Additionally exploration on interaction between age at diagnosis and insurance status should be investigated to fully determine the effects of the independent variables on late stage melanoma diagnosis. Further research should be conducted to understand the significance of insurance status and age on late-stage diagnosis, specifically looking at the relationship between the two variables.

Strengths and Limitations

This study is the first to provide an overview of the characteristics of AYAs diagnosed with melanoma in TN from 2004-2008. Additionally, it provides some insight into the predictors of late-stage diagnosis of melanoma in this age group. The use of the TN Cancer Registry provided high-quality registry data that met national completion standards.

This study had several limitations. Incomplete reporting served as a major limitation; with a large percentage of melanoma cases that were either unstaged or missing the SEER Summary stage variable in the data, ultimately limiting the number of cases included that could be included in the final analysis. This emphasizes the need for improved primary data reporting in order to provide a more complete picture of each cancer case. Additionally, characteristics of unstaged cases should be explored to ensure that there are no significant differences in staged and unstaged melanoma cases. Case counts for government insurance, no insurance, and the 15-19 year old group were small, therefore providing wide confidence intervals. Future research

with a larger sample size in those categories should be conducted to corroborate the findings of this study. Additionally, the study only looked at AYA melanoma cases in TN where the sample was relatively homogenous with regard to race. Finally, combining the cancer registry data with other population based demographic databases that include information on percent poverty, education levels, and rural versus urban designations would be helpful to understand more of the socio-demographic factors associated with late-stage melanoma diagnosis in AYAs.

Public Health Implications

Understanding the melanoma burden in AYAs in TN will help to provide a foundation for future interventions and prevention and awareness campaigns in the state. Recognizing the risk factors and predictors of late-stage diagnosis of melanoma in AYAs assists in identifying which groups to target for public health campaigns. Awareness campaigns about the harmful effects of UV exposure (both natural and artificial) have proven successful in reducing incidence rates of melanoma (Weir et al., 2011). This research highlights certain groups in TN to target for increasing awareness of melanoma. AYAs in the 15-19 year age group and those who rely on government insurance should be targeted to understand the risks factors for melanoma, to reduce UV exposure, and to practice regular screenings. This preliminary study provides an initial description of melanoma in TN and predictors of late-stage diagnosis. However, additional research needs to be performed to present a more in-depth look at melanoma in AYAs across the country.

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CHAPTER 4

PREDICTORS OF THYROID CANCER SURGERY TYPES: AN EXAMPLE FROM THE TENNESSEE CANCER REGISTRY

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ABSTRACT

Purpose: Thyroid cancer accounts for roughly 10% of cancers diagnosed in adolescents and young adults (AYAs) age 15-39 years in the United States. Understanding the types of thyroid cancer diagnosed in AYAs, and the factors that predict the approach to treatment will aid in understanding the burden of thyroid cancer in AYAs. *Patients and Methods:* AYA thyroid cancer cases were obtained from the Tennessee Cancer Registry for 2004-2008, inclusive. Thyroid cancer cases and histology were defined according to the International Classification of Diseases- Oncology (ICD-O-3) site codes. Types of surgery were coded from the SEER codebook and dichotomized to 1) total thyroidectomy and 2) non- total thyroidectomy. Histology type, stage at diagnosis, and region (Appalachian vs. non-Appalachian) served as predictor variables. *Results:* The majority of thyroid cancers (N=830) occurred in Caucasians (89.6%), females (79.2%), were diagnosed at a localized stage (77.4%), and were diagnosed when between ages 35-39 (37.0%). Individuals diagnosed with regional or distant stage thyroid cancer compared to localized stage were almost three times (OR 2.80, CI 1.34-5.85) more likely to have a total thyroidectomy. Individuals diagnosed with papillary adenocarcinoma were 3.5 times (OR 3.56, CI1.37-9.19) more likely to have a total thyroidectomy compared to individuals diagnosed with follicular adenocarcinoma. *Conclusion:* Stage at diagnosis and specific histology type were the greatest predictors of total thyroidectomy. Future research studies should use larger sample sizes to better explore the characteristics of thyroid cancer in AYAs. Specific cancer prevention and control activities should target AYAs.

Background

The thyroid gland, located at the front of the lower neck uses iodine to produce several important metabolic hormones (NCI, 2011b). Thyroid hormones are responsible for controlling heart rate, body temperature, metabolism, and calcium levels in the blood (NCI, 2011b). The National Cancer Institute estimates that there will be over 50,000 new cases and almost 2,000 deaths due to thyroid cancer in 2012 (NCI, 2012f). Thyroid cancer is one of the most frequently diagnosed cancers in adolescents and young adults (AYAs) and accounts for roughly 10% of all cases in that age group (AYAOPRG, 2006; Bleyer et al., 2005; Wu et al., 2005). In addition, thyroid cancer is the fifth most commonly diagnosed cancer overall in females (Jemal, Siegal, Xu, & Ward, 2010).

There are three main histology types of thyroid cancer: differentiated, medullary, and anaplastic (Tuttle et al., 2010). Differentiated thyroid cancer (including papillary, follicular, and Hürthle cell) accounts for roughly 95% of all thyroid cancers, medullary for 3% and anaplastic for 2% (NCI, 2011b; Tuttle et al., 2010). Papillary thyroid cancer is the most commonly diagnosed histology type in the United States (NCI, 2011b; Tuttle et al., 2010). Known risk factors for thyroid cancer include: history of having an enlarged thyroid, family history of thyroid cancer or thyroid disease, specific genetic conditions, exposure to radiation, age 25-65 years, being Asian, and being female (NCI, 2011b; PubMed Health, 2011). Prognosis of thyroid cancer is dependent on histology type, size of the nodule or tumor, and stage at diagnosis (NCI, 2011b). While thyroid cancers occur more frequently in females who have more thyroid nodules, death due to thyroid cancer occurs more frequently in males due to diagnosis later in life (Tuttle et al., 2010).

Treatment for thyroid cancer typically varies based on age of the patient, size of the nodule/tumor, histology type, and stage of the cancer (NCI, 2011b). Currently, no prospective randomized treatment trials have been performed to determine the best treatment approach for thyroid cancer (Tuttle et al., 2010). The most common type of treatment for thyroid cancer is surgery (NCI, 2011b). The extent of thyroid surgery can range from a lobectomy to a full thyroidectomy (NCI, 2011b; Tuttle et al., 2010). Total thyroidectomy can be used for all types of thyroid cancer and involves removal of the entire thyroid gland. The thyroidectomy is usually followed by radioactive iodine therapy to kill any remaining cancer cells (NCI, 2011b). The other main surgery type is a lobectomy, where a lobe of the thyroid and the isthmus are removed (NCI, 2011b). Some individuals that initially have a lobectomy will later have a total thyroidectomy due to cancer recurrence and/or complications.

Based on the type of initial treatment, about 30% of patients diagnosed with differentiated thyroid cancer have tumor recurrences. Patients younger than 20 years of age have some of the highest recurrence frequencies (40%) (Mazzaferri & Jhiang, 1994; Sherman et al., 1998). This may be due to the fact that most physicians feel as though the prognosis of thyroid cancer in young people is favorable and therefore the cancer is classified as a low-risk tumor and treated with less invasive surgery (Samuel, Rajashekharrao, & Shah, 1998; Tuttle et al., 2010). Most patients can be cured of thyroid cancer with proper treatment; however, following surgery, thyroid hormone replacement will be necessary for the remainder of their lives (NCI, 2011b; Sherman, 2003). Understanding the types of thyroid cancer diagnosed in AYAs, the extent of the surgery performed, and factors that predict surgery outcomes will help aid in understanding the burden of thyroid cancer in AYAs.

Definition of Adolescents and Young Adults

The definition of AYAs has developed throughout the years, with many different definitions existing based on age, psychosocial development, and societal influences (AYAOPRG, 2006). The Adolescent and Young Adult Oncology Progress Review Group (AYAOPRG, 2006) opted to define the AYA population with a wide range in order to be inclusive of the entire spectrum of cancer patients that continue to experience a lack of improvement in cancer care and survival (AYAOPRG, 2006). The current definition of AYAs encompasses individuals diagnosed with cancer from 15 to 39 years of age (AYAOPRG, 2006). Although this age range may be quite wide, individuals in this population are unified based on their extreme differences in the cancer journey when compared to other age groups (Wolfson, 2010). Further, prior to this AYA definition, individuals in this age range lacked a home in cancer care and research, typically being treated on pediatric or adult protocols based on their cancer diagnosis (AYAOPRG, 2006). The formal definition of AYAs will help streamline research, interventions, treatment, and awareness efforts in this population (AYAOPRG, 2006).

Tennessee

Tennessee (TN) provides a unique opportunity to investigate thyroid cancers in AYAs because it has distinct geographic and demographic differences. It encompasses metropolitan areas and rural communities located in the Appalachian Mountains and the Mississippi Delta region. Only 27 of TN's 95 counties are considered urban, while 68 are rural (Erwin et al., 2010). Over 80% of Tennessee residents are Caucasian; with less than 20% African-Americans (Erwin et al., 2010). East TN has a relatively homogenous Caucasian population, even in major urban areas like Knoxville (Erwin et al., 2010). Meanwhile, in West TN the percentage of

African-Americans is proportionally higher than the overall state percentage, with figures around 50% (Erwin et al., 2010).

There has not been any prior reported research dealing with thyroid cancers in AYAs in TN. TN is well known in cancer control and prevention through state of the art cancer centers like St. Jude's and Vanderbilt and an established state-wide cancer coalition, however, the burden of cancer in AYAs is not fully understood.

Patients and Methods

Data Source

Data were obtained from the TCR for all AYA thyroid cancer cases in TN from 2004-2008. Established in 1983, the TCR collects comprehensive information on all TN residents diagnosed with cancer, as well as individuals treated for cancer in the state (TDOH, 2011). The TCR is part of the National Program of Cancer Registries (NPCR) (CDC, 2012). Administered by the Centers for Disease Control and Prevention (CDC), state based cancer registries monitor cancer trends over time; determine patterns of cancer incidence and mortality in specific populations, and assist in the planning and evaluation of cancer control programs.

The NPCR falls under the jurisdiction of the North American Association of Cancer Registries (NAACR) for standardization of registry data (Thornton, 2010). Standardization of cancer registry data is a vital component of cancer surveillance as it provides the basis for having consistent data across cancer registries in North America (Thornton, 2010). State registry data must meet NAACR standards of completeness (90% completeness of the data set) in order to be accepted for NAACR/CDC publication (Hofferkamp, 2008).

The TCR met data completeness standards for the first time in 2004 and have continued to produce high quality data since then (Li et al., 2010). Data for the current study, years 2004-2008, met data completeness standards of 95% or higher (Li et al., 2010). The TCR collects data on cancer incidence, including: the type of cancer, primary site of cancer, stage, first course of treatment, vital status, and general demographic information (Li et al., 2010). Data are sent to the TCR from hospitals, pathology labs, physician's offices, and radiation facilities (Li et al., 2010). The information on each case is compiled into the database to provide cancer statistics for the state.

Sample

The sample for this study includes all incident thyroid cancer cases (N=830) in AYAs from the Tennessee Cancer Registry for the years 2004-2008, inclusive. AYA cases were defined as cancer cases that were diagnosed in individuals ages 15-39 years, inclusive. Thyroid cancer cases and their histology were defined according to the International Classification of Diseases- Oncology (ICD-O-3) site code, C739. General demographic and descriptive information included gender, age, insurance status, county of diagnosis, marital status, and race. Cancer specific information such as primary cancer site, stage at diagnosis, treatment type, and vital status are also reported for each case.

Analyses

Analysis was performed using SAS 9.2 software (SAS Institute, 2009). Thyroid cancer cases of AYAs in TN were analyzed to understand predictors of a total thyroidectomy used as a surgery treatment option. Surgery of the primary site codes were provided by the NAACR data dictionary and the SEER Program code manual for thyroid cancer specific surgery procedures.

Surgery was dichotomized into total thyroidectomy versus other, less invasive surgical procedures. Individuals that did not receive surgery as a treatment outcome (N=6) were excluded from analysis in order to minimize bias in the sample. The following predictors were included in the final model: histology type, stage at diagnosis, and region. Stage at diagnosis was coded into localized and a combined regional and distant stage due to low counts in the last two categories. Region was coded into Appalachian and Non-Appalachian by county of diagnosis codes. Sex, race, and 5-year age groups were evaluated but were not included in the final model as they were not significant predictors of a thyroidectomy in either univariate or multivariate analysis. Univariate and multivariate analysis were performed for the predictor variables. Odds ratios and corresponding confidence intervals were reported. Descriptive statistics of the overall thyroid cancer sample and those cases included in the final model were reported using frequencies, percents, and corresponding chi-squared values.

Results

A total of 830 thyroid cancer cases were diagnosed among AYAs in TN from 2004-2008. Of the 830 cases reported (Table 3.1): 173 (20.8%) cases were in males and 657(79.2%) were in females. Most cases were Caucasian (89.6%) and were diagnosed with localized stage cancer (77.4%). Thyroid cancer occurred most commonly between the ages 35-39 (37.0%). The most common histology type of thyroid cancer diagnosed was papillary adenocarcinoma, 320 cases (38.6%). Cases that received a total thyroidectomy as a treatment outcome (Table 3.2) were predominately female (77.6%), were diagnosed with localized stage thyroid cancer (72.8%), and were diagnosed with papillary adenocarcinoma (42.2%).

Table 3.1. Characteristics of Thyroid Cancer Cases in Tennessee for AYAs, 2004-2008

N=830	
Characteristics	N (%)
Age at diagnosis* (years)	
15-19	23 (2.8)
20-24	88 (10.6)
25-29	160 (19.3)
30-34	252 (30.3)
35-39	307 (37.0)
Sex*	
Female	657 (79.2)
Male	173 (20.8)
Race*	
Caucasian	741 (89.6)
Other	86 (10.4)
Region*	
Appalachian	363 (43.7)
Non-Appalachian	467 (56.3)
Stage*	
Localized	270 (77.4)
Regional/Distant	79 (22.6)
Year of Diagnosis**	
2004	140 (16.9)
2005	145 (17.5)
2006	181 (21.8)
2007	184 (22.2)
2008	180 (21.7)
Histology Type*	
Follicular Adenocarcinoma	49 (5.9)
Papillary Adenocarcinoma	320 (38.6)
Papillary Carcinoma	171 (20.6)
Papillary & Follicular Carcinoma	248 (29.9)
Other	42 (5.1)

*$p<0.01$ **$p<0.05$

Table 3.2. Characteristics of Thyroid Cancer in Tennessee for AYAs by Surgery Type, 2004-2008

N=824		Total Thyroidectomy	Other
Characteristics		N=618	N=206
		N (%)	N (%)
Histology Type*			
	Follicular Adenocarcinoma	25 (4.1)	24 (11.7)
	Papillary Adenocarcinoma	261 (42.2)	57 (16.7)
	Papillary Carcinoma	118 (19.1)	71 (20.8)
	Papillary & Follicular Carcinoma	183 (29.6)	85 (24.9)
	Other	31 (5.0)	116 (33.9)
Sex	Females	480 (77.7)	173 (83.5)
	Males	138 (22.3)	34 (16.5)
Stage*	Localized	182 (72.8)	88 (89.8)
	Regional/Distant	68 (27.2)	10 (10.2)

*$p<0.01$

Logistic regression analyses (Table 3.3) were performed to determine the predictors of a having a total thyroidectomy for treatment. Simple logistic regression analysis illustrates that localized stage at diagnosis, non-Appalachian region, and papillary adenocarcinoma histology type are predictors of total thyroidectomy procedure ($p< 0.01$). Multiple logistic regression analysis shows that stage at diagnosis and non-Appalachian region are the strongest predictors of total thyroidectomy. Papillary adenocarcinoma and papillary carcinoma compared to follicular adenocarcinoma are associated with an increased risk of a total thyroidectomy.

Table 3.3. Predictors of Total Thyroidectomy in AYAs in Tennessee:

Simple and Multiple Logistic Regression

N=348^			
Variable		**Crude OR [a]**	**Adjusted OR (CI) [b]**
Histology Type (reference: Follicular Adenocarcinoma)			
	Papillary Adenocarcinoma	4.40	3.56 (1.37-9.19)*
	Papillary Carcinoma	2.27	2.64 (1.02-6.83)**
	Papillary & Follicular Carcinoma	2.70	2.10 (0.84-5.28)
	Other	2.98	3.68 (0.78-17.4)
Region (reference: Appalachian)	Non-Appalachian	1.37	2.07 (1.26-3.42)*
Stage (reference: Localized)	Regional/Distant	3.29	2.80 (1.34- 5.85)*

^Includes cases that had known stage at diagnosis and histology type
[a] OR: odds ratio, [b] CI: 95% confidence interval
*p<0.01, ** p<0.05

Histology type is a major and significant predictor of total thyroidectomy. Individuals diagnosed with papillary adenocarcinoma were 3.5 times (OR 3.56, CI1.37-9.19, p<0.01) more likely to have a total thyroidectomy while those with papillary carcinoma were two times (OR 2.64, CI 1.02-6.83, p<0.05) more likely to have a total thyroidectomy compared to individuals diagnosed with follicular adenocarcinoma. Other histology types did not significantly predict total thyroidectomy as compared to follicular adenocarcinoma. Stage also served as a predictor of a total thyroidectomy procedure. Individuals diagnosed with regional or distant stage thyroid cancer were almost three times (OR 2.80, CI 1.34-5.85, p<0.01) more likely to have a total thyroidectomy compared with those diagnosed with localized stage thyroid cancer. Individuals living in the non-Appalachian region of TN were two times (OR 2.07, CI 1.26-3.42, p<0.01)

more likely to have a total thyroidectomy performed compared to those living in the Appalachian region of TN.

Discussion

Thyroid cancer accounts for more than 10% of all cancers in the AYA population and disproportionately affects females (AYAOPRG, 2006; Bleyer, 2005; Wu et al., 2005). Thyroid nodules, typically benign lumps found in the thyroid, are roughly four times more common in women than men and thyroid cancer is two to three times more common in women than men (Tuttle et al., 2010). The current study represents the first to evaluate thyroid cancer in AYAs in TN and to determine the predictors of total thyroidectomy. Almost 80% of thyroid cancers in TN AYAs were diagnosed in females, consistent with current literature (AYAOPRG, 2006; Bleyer, 2005; Tuttle et al., 2010; Waguespack, Wells, Ross, & Bleyer, 2006; Wu el al., 2005). About 90% of the cases were in Caucasians, which is also consistent with the current literature (Tuttle et al., 2010; Waguespack et al., 2006). Asian/Pacific Islanders are at a greater risk for developing thyroid cancer (NCI, 2011b; Waguespack et al., 2006); however, the small sample size of this race in the current study did not allow for evaluation of this variable for TN.

The results of this study reveal several important observations. Differentiated thyroid cancer types accounted for 95% of the thyroid cancers in AYAs in TN. The majority of differentiated thyroid cancers (89.1%) were some type of papillary carcinoma (papillary carcinoma, papillary adenocarcinoma, and papillary and follicular carcinoma). These findings are consistent with the existing literature (NCI, 2011b; Tuttle et al., 2010; Waguespack et al., 2006).

Specific histology types were found to be a significant predictor of total thyroidectomy. Papillary adenocarcinoma was the strongest significant predictor and was three times more likely to be associated with total thyroidectomy as compared to follicular adenocarcinoma. Papillary carcinoma and papillary adenocarcinoma were the only histology types that significantly predicted total thyroidectomy as a surgical outcome. Interestingly, follicular tumors are considered to be more aggressive than papillary tumors (Tuttle et al., 2010) and it might be assumed they would be treated by more a more aggressive surgical procedure. However, the number of follicular adenocarcinomas in the sample were small. Additional research to identify the reasons for surgical choice as based on histology type would be beneficial. Additionally, understanding the type of surgeon and the experience level of the surgeon would assist in predicting future complications (Tuttle et al., 2010).

Tumor stage at diagnosis was a major predictor of total thyroidectomy. While the majority of the sample were diagnosed with localized stage cancer, those diagnosed with regional or distant stage cancer were two times more likely to have a total thyroidectomy. Unfortunately, due to the slow growth and lack of obvious symptoms of differentiated thyroid cancers, there are often long delays in diagnosis that could result in a later stage cancer at diagnosis and substantial worse outcomes (Mazzaferri & Jhiang, 1994; Tuttle et al., 2010). Because delays in diagnosis generally exist in the AYA population, awareness of thyroid cancer symptoms should be increased for AYAs and medical practitioners who see this age group.

Individuals living in the non-Appalachian region of TN were two times more likely to undergo a total thyroidectomy compared to those living in the Appalachian region. There was a slightly higher frequency in the number of thyroid cancer cases diagnosed in the non-Appalachian region versus the Appalachian region (467 cases vs. 363 cases). The increased

probability of a total thyroidectomy procedure in the non-Appalachian region could signify several things. First, individuals diagnosed in non-Appalachian regions of TN may have more access to specialized surgeons and oncologists who would use a more aggressive treatment plan. Another explanation might be that individuals in non-Appalachian regions may present with later stage cancers or different histology types that would more likely to be treated with a total thyroidectomy. Further research should be conducted to understand the difference between thyroid cancer treatment and outcomes in the Appalachian and non-Appalachian regions of TN.

Strengths and Limitations

The use of the TN Cancer Registry provided high-quality data that met national standards of the North American Association of Cancer Registries. The study served as a preliminary study to gain more information on the specific characteristics of thyroid cancer in the AYA population in TN. This is the first study to use the TN Cancer Registry to look at the distinct features of thyroid cancer in AYAs and those factors that predict total thyroidectomy in this population.

There are some limitations in this study. Lack of racial heterogeneity does not allow these findings to be generalized to populations with more racial and ethnic diversity. Incomplete reporting of stage at diagnosis was also a limitation and many cases were either unstaged or unreported. This research was conducted using only TN data and can provide information on AYA thyroid cancer cases only for TN. Future research that includes additional socio-demographic variables that may provide insight into access to qualified medical practitioners and cancer facilities would help to further inform predictors of a patient receiving a total thyroidectomy as a surgical treatment option.

Public Health Implications

Investigating cancer in the AYA population is important to understanding the overall cancer burden in TN. AYAs are currently an understudied population and this study provides the first step into identifying the characteristics of thyroid cancer in AYAs. Thyroid cancer is one of the most commonly diagnosed cancers in AYAs, specifically in females. Female AYAs in TN and general medical practitioners that serve this population should be targeted to increase awareness of thyroid cancer signs and symptoms and screenings. Finally, researchers need to take the additional steps to understand and decrease disparities in thyroid cancer morbidity based on region and type of surgery received.

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CHAPTER 5

DISCUSSION AND CONCLUSION

The recent expanded definition of the AYA age group to cover 15 to 39 years by the Adolescent and Young Adult Oncology Peer Review Group and the National Cancer Institute (2006) has provided a basis for an increased focus on cancer research in this age group. This expanded definition provides an opportunity to study an under-served, under-represented population in cancer research. The types of cancers affecting AYAs and the associated risk factors are not fully understood. In addition, there are distinct psychosocial and survival issues that impact this age group and that deserve further exploration and study.

Use of state cancer registries to provide an in-depth picture of AYA cancer at the state-level is the first step in understanding the cancer burden for this population as the state level. Identifying cancers that specifically affect AYAs will help to target cancer prevention and control activities for this group. Prior to this study, very few AYA cancer research projects have focused on a specific state; instead most have used national data. Prior research on cancer in AYAs has not focused solely on TN. The current research study explored the characteristics of AYAs with cancer in TN and provides a foundation for future research in this field. Focusing specifically on TN provided the opportunity for an in-depth look at AYA cancers as a basis of better understanding the cancer burden at the state level. In order to effectively target public health prevention and awareness for AYAs, health practitioners need data regarding the cancer burden based in their state in order to know which groups to target for those efforts. This profile of AYA cancers in TN will help to develop and implement prevention and awareness efforts for the state.

Several key findings resulted from this research study. The knowledge that breast cancer, melanoma, lymphomas, thyroid cancer, and testicular cancer are the most frequently diagnosed cancers in AYAs in TN should help to develop age-specific awareness and screening campaigns based on cancer type. Knowledge of the increased incidence rates for breast cancer and melanoma in AYA females in TN provides a basis for developing age-specific prevention and interventions based on the risk factors for those cancers. In addition, knowing that there are disparities in late-stage melanoma diagnosis based on age and insurance status will help practitioners focus on those groups to promote early detection. Finally, distinguishing the histology types and other predictors of a having a total thyroidectomy as a surgery treatment option should help understand the reasons for the type of treatment that AYAs receive.

Additional future research concentrated on the AYA population will help to provide a greater evidence base for this field. Understanding the AYA cancer experience will assist in eliminating disparities in cancer care and research in this age group. Future research that links the TN Cancer Registry data base with socio-demographic characteristics such as poverty levels, educational attainment, and rural- urban designations will assist in providing a greater understanding of socio-demographic risk factors for AYA cancer. Insurance status and type of insurance should also be investigated to determine if AYAs are being marginalized due to a lack of consistent and sufficient insurance. Also, comprehending where AYAs in TN are being treated and by what types of practitioners will offer insight into the AYA cancer journey. Finally, research on the AYA cancer burden in TN will help to inspire public health interventions and campaigns emphasized on AYAs.

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APPENDIX

HUMAN SUBJECTS PROTECTION

ETSU

East Tennessee State University
Office for the Protection of Human Research Subjects • Box 70565 • Johnson City, Tennessee 37614-1707 • (423) 439-6053
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September 23, 2011

Megan Quinn
405 W. Pine Street, Apt. 1
Johnson City, TN 37604

Dear Ms. Quinn,

Thank you for recently submitting information regarding your proposed activity entitled, " Adolescent and Young Adult Cancer: A Profile of Tennessee ".

I have reviewed the information, which includes a description of the proposed activity.

The determination is that this proposed activity meets neither the FDA nor the DHHS definition of research involving human subjects. Therefore, it does not fall under the purview of the ETSU/VA IRB and does not require ETSU/VA IRB approval.

Thank you for bringing this proposed activity forward to the ETSU/VA IRB for evaluation and for your commitment to excellence.

Sincerely,

George Youngberg, M.D.
Chair, ETSU/VA IRB

Association for the Accreditation of Human Research Protection Programs, Inc.
Full AAHRPP Accreditation

Accredited Since December 2005

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